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Activation chimiosélective et dérivatisation d'amides et d'alcools: Synthèse de plusieurs groupements fonctionnels et hétérocycles

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Résumé

Un objectif majeur en chimie organique est le développement de méthodes de synthèses générales, simples et peu coûteuses permettant la modification efficace des ressources naturelles en différents produits d'intérêt public. En particulier, la recherche de méthodes chimiosélectives et de méthodes dites « vertes » représente un intérêt croissant pour le secteur industriel (dont le domaine pharmaceutique). En fait, l'application en synthèse sur grande échelle de procédés catalytiques, sélectifs et utilisant des conditions douces permet de réduire le volume de déchets et la demande énergétique, minimisant ainsi les coûts de production et les effets néfastes sur l'environnement. Dans ce contexte, le groupe de recherche du Professeur André B. Charette de l'Université de Montréal s'intéresse au développement de méthodes générales et chimiosélectives permettant la transformation de fonctionnalités aisément accessibles tels que les amides et les alcools. La fonction amide, aussi appelée liaison peptidique dans les protéines, est présente dans diverses familles de molécules naturelles et est couramment employée comme intermédiaire synthétique dans la synthèse de produits d'intérêt pharmaceutique. Le groupement alcool est, quant à lui, l'une des fonctionnalités les plus abondantes dans la nature, intrinsèquement et largement utilisé en chimie de synthèse.

Dans le cadre de cette thèse, des transformations simples, générales et chimiosélectives ont été réalisées sur des amides secondaires et tertiaires, ainsi que sur des alcools primaires et secondaires. La première partie de ce manuscrit se penche sur l'activation de la fonction amide par l'anhydride triflique (Tf_2O), suivie de l'addition nucléophile de différents réactifs permettant ainsi la formation de plusieurs groupements fonctionnels versatiles, parfois indispensables, couramment employés en chimie organique tels que les aldimines, les aldéhydes, les amines, les cétones, les cétimines et des dérivés de la fonction amidrazone. Cette dernière fonctionnalité a également été utilisée dans des réactions successives vers la formation d'hétérocycles. De ce fait, des 1,2,4-triazoles ont été formés suite à une cyclodéshydratation initiée en conditions thermiques et faiblement acides. D'autre part, des 3-

aminoindazoles ont été synthétisés par une fonctionnalisation C–H catalysée par un sel de palladium (II).

La deuxième partie de la thèse est consacrée à la réaction de Mitsunobu en conditions acides, permettant ainsi la substitution nucléophile d'alcools en présence de carbamines (ou amines ne possédant pas de groupement électro-attracteurs). Ce type de nucléophile, basique lorsqu'utilisé comme base libre (avec un p*K*a se situant au-dessus de 13 dans le DMSO), n'est intrinsèquement pas compatible dans les conditions standards de la réaction de Mitsunobu. Contrairement aux conditions usuelles multi-étapes employant la réaction de Mitsunobu, la méthode développée au cours de cette étude permet la formation d'amines substituées en une seule étape et ne requiert pas l'emploi de groupements protecteurs.

Mots-clés : amide, alcool, activation, anhydride triflique, réaction de Mitsunobu, réduction, addition nucléophile, substitution nucléophile, chimiosélectivité, généralité, praticabilité.

Abstract

A major objective in organic chemistry is the development of methods for general, simple and cost-effective transformations allowing for the efficient modification of natural resources into different products of public interest. In particular, the research of chemoselective and "green" methods represents a growing interest for the industrial sector. In fact, the synthetic application on large-scale of catalytic and selective processes using mild conditions allows the reduction of wastes and energy usage, minimizing the cost of production and the harmful effects to the environment. In this context, the research group of Professor André B. Charette from Université de Montréal is interested in the development of general and chemoselective methods for the derivatization of readily available functionalities, such as amides and alcohols. The amide function, also named peptide bond in proteins, is identified in diverse families of natural products and is commonly used as synthetic intermediate in the synthesis of pharmaceutical leads. The alcohol function is one of the most abundant functionalities in nature, intrinsically and largely used in synthetic chemistry.

In the context of this thesis, simple, general and chemoselective transformations were applied to secondary and tertiary amides, as well as to primary and secondary alcohols. The first part of the thesis relies on the activation of amides mediated by triflic anhydride, followed by the nucleophilic addition of different reagents, allowing for the formation of several key functional groups in organic chemistry, such as aldimines, aldehydes, amines, ketones, ketimines, and amidrazone derivatives. The latter functionality has been used in successive reactions towards the formation of heterocycles, such as 1,2,4-triazoles via a cyclodehydration reaction and 3-aminoindazoles via a palladium-catalyzed C–H functionalization reaction.

The second part of the thesis is based on an acid mediated Mitsunobu reaction allowing the nucleophilic substitution of alcohols in the presence of free carbamines (which doesn't contain any electron-withdrawing substituents), normally basic entities with p*K*a over 13 (in DMSO), which are intrinsically unaccepted in standard Mitsunobu conditions. Contrary to the

usual multi-step synthesis of amines using the Mitsunobu reaction, this method allows the formation of substituted amines in a single step without the need of protecting groups.

Keywords : amide, alcohol, activation, triflic anhydride, Mitsunobu reaction, reduction, nucleophilic addition, nucleophilic substitution, chimioselectivity, generality, pratical.

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Liste des abréviations

$[\alpha]_D$	rotation optique; raie D du sodium
°C	degrés Celsius
®	marque enregistrée
Ac	acétyle
aq.	aqueux
Bn	benzyle
Boc	carbonate de *tert*-butyle
Bu	butyle
Bz	benzoyle
cat.	catalyseur ou quantité catalytique
Cbz	carboxybenzyle
CCR1	chemokine receptor type 1
CDI	carbonyldiimidazole
2-ClPyr	2-chloropyridine
Cp	cyclopentadiényl
Cy	cyclohexyle
d	doublet
DCC	*N,N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroéthane
DCM	dichlorométhane
dd	doublet de doublet
DCC	*N,N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroéthane
DEAD	diéthylazodicarboxylate
DIPEA	di-*iso*-propyléthylamine
1,4-DHP	1,4-dihydropyridine
DMAP	4-diméthylaminopyridine

DME	1,2-diméthoxyéthane
DMF	diméthylformamide
DMSO	sulfoxide de diméthyle
DTBMP	2,6-di-*tert*-butyl-4-méthylpyridine
DTBP	2,6-di-*tert*-butylpyridine
dt	doublet de triplet
E+	électrophile
EDA	diazoacétate d'éthyle
EDC	1-éthyl-3-(3-diméthylaminopropyl)carbodiimide
ee	excès énantiomère
équiv.	équivalent
Et	éthyle
Ent	énantiomère
es	excès d'énantiospécificité
FCI	fondation canadienne pour l'innovation
2-FPyr	2-fluoropyridine
g	gramme
GEA	groupement électroattracteur
GED	groupement électrodonneur
gem	géminal
GP	groupement protecteur
h	heure
HEH	hydrure de l'ester de Hantzsch
HOBt	*N*-hydroxybenzotriazole
HRMS	spectre de masse haute résolution
HWE	Horner-Wadsworth-Emmons
Hz	hertz
I	*iso*
i. e.	*id est*
in situ	sur place
IR	infra rouge

J	constante de couplage
λ_{em}	longueur d'onde d'émission optimale
L	ligand
LCMS	liquid chromatography-mass spectrometry
M	concentration molaire
m	méta
m	masse
Me	méthyle
2-MeOPyr	2-méthoxypyridine
mg	milligramme
MHz	mégahertz
min	minute
mL	millilitre
MM	masse moléculaire
mmHg	millimètres de mercure (pression)
mmol	millimole
mol%	pourcentage molaire
Ms	mésyle
MS	tamis moléculaire
N	normalité de la solution
NADP	nicotinamide adénine dinucléotide phosphate
naphth	naphtyle
nOe	effet nucléaire Overhauser
Nu	nucléophile
o	*ortho*
OLED	diodes organiques émettant de la lumière
p	*para*
Φ_F	rendement de fluorescence quantique
Piv	pivaloate
Ph	phényle
PMP	*para*-méthoxyphényle

ppm	partie par million
Pr	propyle
psi	pounds per square inch
PTAs	polytriazoles
PTSA	acide *para*-toluènesulfonique
q	quadruplet
R	substituant quelconque
rac.	racémique
r.d.	ratio diastéréomérique
r.e.	ratio énantiomérique
rdt.	rendement
réf.	référence
R_f	rapport frontal
RMN	résonance magnétique nucléaire
r.r.	ratio régioisomérique
sat.	saturé
SFC	chromatographie en phase super critique
S_N2	substitution nucléophile bimoléculaire
Solv.	solvant
t	triplet
T	température
t.a.	température ambiante
TBDMS/TBS	*tert*-butyldiméthylsilyl
TBAB	bromure de tétrabutylammonium
TDMPP	tris(2,6-dimethoxyphenyl)phosphine
TDMS	tétraméthyldisiloxane
TEA	triéthylamine
TES	triéthylsilyl
Tf	trifluorométhanesulfonyl
TFA	acide trifluoroacétique
TFAA	anhydride de l'acide trifluoroacétique

THF	tétrahydrofurane
TIPS	tri-*iso*-propylsilyl
TMS	triméthylsilyle
trig	trigonale
Ts	tosyle
UV	ultra violet
vs	versus
vide infra	voir plus bas
vide supra	voir plus haut
δ	déplacement chimique
µW	micro-ondes

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« La grandeur des êtres humains ne réside pas tant dans leur capacité de refaire le monde... que dans leur aptitude à se réformer eux-mêmes »
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Chapitre 1: Introduction

1.1 La chimiosélectivité

Inspirée par la diversité des produits naturels et afin de répondre à la demande pharmaceutique actuelle de nouvelles cibles moléculaires thérapeutiques, la communauté scientifique, plus spécialement les chimistes de synthèse, s'intéressent de plus en plus aux structures moléculaires complexes et hautement fonctionnalisées.[1] Afin d'accéder rapidement et rentablement à une complexité moléculaire par voie synthétique, les chimistes organiciens ont recours à plusieurs approches dont la biosynthèse, la dérivatisation sélective de produits naturels, ou la synthèse totale. Cette dernière approche est attrayante lorsqu'elle peut être réalisable en peu d'étapes et avec un rendement global acceptable. Ces balises sont cependant rarement respectées, surtout considérant l'échelle nécessaire au niveau industriel. Par conséquent, les chimistes doivent méticuleusement considérer l'efficacité de chaque étape d'une synthèse totale dans le but de se rapprocher de ces critères d'efficacité.[2] Tel qu'énoncé par Hendrickson et Baran, une synthèse totale efficace ou dite « idéale » peut être définie par « la construction moléculaire d'une cible complexe où les fonctionnalités sont directement installées à leur place respective en minimisant le nombre d'étapes synthétiques et en évitant les séquences d'oxydation-réduction et la fonctionnalisation d'intermédiaires (ex : protection et déprotection) ».[3] Plusieurs concepts ont été développés par les chimistes organiciens afin d'améliorer l'efficacité des voies synthétiques, en l'occurrence le concept d'économie d'atomes,[4] le concept d'économie d'étapes[5] et le concept de chimiosélectivité.[6]

Le concept d'économie d'atomes vise à maximiser l'inclusion des atomes provenant des réactifs dans le produit final, alors que le concept d'économie d'étapes vise à minimiser le nombre d'étapes lors de la synthèse d'une cible. Parmi les différents types de sélectivité retrouvés en chimie organique (ex : la régiosélectivité, la diastéréosélectivité et

l'énantiosélectivité), la chimiosélectivité est définie par la réaction préférentielle d'un réactif avec un groupe fonctionnel sur un substrat de départ en présence d'autres groupes fonctionnels portant des propriétés électroniques similaires, et par ce fait même, susceptibles de réagir dans les mêmes conditions réactionnelles.[7] Par exemple, une réaction chimiosélective peut avoir lieu sur un groupement fonctionnel (décrit ici par GF^4) d'une molécule comportant trois autres groupements fonctionnels (GF^1, GF^2, GF^3) non-protégés (**Figure 1**). Cette dernière permet ainsi la formation exclusive d'un nouveau groupement fonctionnel GF^5, et ce, sans observer de réactions secondaires sur les autres groupements.

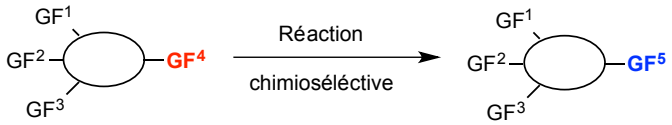


Figure 1. Réaction chimiosélective : fonctionnalisation sélective d'un groupement fonctionnel en présence d'autres

Le niveau de chimiosélectivité observé normalement lors de transformations chimiques dans les systèmes biologiques diffère considérablement des processus synthétiques.[8] Dans le cas des systèmes biologiques, les réactions biochimiques ont lieu dans le site actif des enzymes, aussi appelé poche de reconnaissance.[9] Ce site actif est assemblé de façon à reconnaître et à interagir spécifiquement avec un substrat donné, acheminant des transformations chimiques avec des niveaux élevés de stéréosélectivité, de régiosélectivité et de chimiosélectivité. Le site actif d'une enzyme est une partie intégrante d'une protéine possédant une structure tertiaire idéale pour la/les transformations à accomplir. Ces dernières se produisent normalement à l'interface entre la cavité du site actif et le substrat (ou ligand) ainsi activé. Brièvement, les réactions biochimiques impliquent une combinaison complexe de réactions en cascade et incluent normalement divers acides aminés spécifiques au site actif. La conformation (de plus basse énergie) et l'orientation de ces acides aminés sont gouvernées par plusieurs interactions stabilisatrices présentes dans la protéine telles que les pont-hydrogènes, la conformation *trans* des amides, les empilements π, les interactions hydrophobes et les interactions électrostatiques. Ces

dernières permettent une approche optimale du substrat dans le site actif afin de catalyser la réaction désirée.

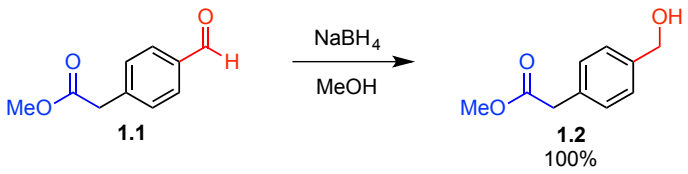
Or, il existe un problème majeur et récurrent lorsque l'on a recours à une méthode dite biochimique. En effet, au niveau de la sélectivité, les enzymes sont maîtres lorsqu'il est temps d'effectuer une réaction donnée avec un substrat donné. Malheureusement (ou heureusement pour l'ingénierie de notre corps !), lorsque la structure de ce dernier est modifiée, il est courant d'observer une baisse et parfois une absence de réactivité et/ou sélectivité pour la transformation voulue. Contrairement aux systèmes biologiques, ce type de spécificité pour un substrat n'est habituellement pas une propriété souhaitable en synthèse organique. En effet, la généralité, c'est-à-dire le fait qu'une large variété de substrats soit compatible avec les conditions réactionnelles d'une transformation spécifique, représente un des facteurs les plus recherchés lors de la mise en place d'un procédé de synthèse organique.

Dans ce contexte, les nouvelles méthodes synthétiques développées à ce jour proposent normalement un équilibre (ou un compromis) entre la chimiosélectivité pour un groupement fonctionnel donné ainsi qu'une généralité visant à maximiser la diversité des substrats qui peuvent être utilisés. Idéalement, en chimie organique, les niveaux de chimiosélectivité et de généralité d'une méthode doivent être maximisés. Une méthode employant des conditions réactionnelles très chimiosélectives envers un groupement fonctionnel donné permet l'application de celle-ci à plusieurs substrats et en présence de différents groupements fonctionnels.

Afin de prédire ou d'expliquer la chimiosélectivité de réactions organiques, les chimistes ont habituellement recours à la modulation des propriétés stéréoélectroniques et/ou stériques des substrats et des réactifs.[10] À partir d'une optimisation réactionnelle minutieuse, les organiciens s'appuient également, dans la mesure du possible, sur l'emploi de réactions dont le mécanisme est cinétiquement favorable à la formation du produit désiré. De plus, il est préférable d'utiliser des conditions réactionnelles douces (pression et température ambiantes) afin de défavoriser les réactions secondaires sur d'autres groupements fonctionnels. Généralement, la chimiosélectivité d'une méthode synthétique

peut être simplement atteinte en exploitant la différence entre la vitesse de réactivité de deux (avec des constantes k_a et k_b) (ou plusieurs) groupes fonctionnels versus un réactif (où $k_{rel} = k_a/k_b$, un indice de chimiosélectivité pour le produit A). Par exemple, la réduction d'une fonction aldéhyde d'un substrat **1.1** en utilisant le $NaBH_4$ (borohydrure de sodium) est chimiosélective en présence de divers groupements fonctionnels électrophiles susceptibles de réagir dans des conditions réductrices, tels que la fonction ester (**Schéma 1**).[11] Dans ce cas-ci, le $NaBH_4$ est une source d'hydrure faible et ne réagit donc pas avec la fonction ester.[12]

Schéma 1. Réduction d'aldéhyde chimiosélective en présence d'un ester

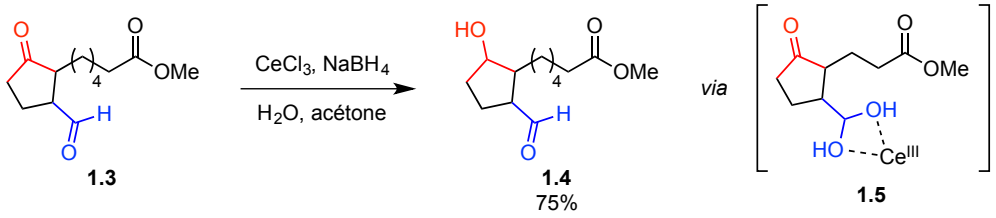


1.1 **1.2** 100%

L'incorporation d'additifs dans des conditions réactionnelles représente également une approche attrayante permettant l'atteinte de niveaux élevés de chimiosélectivité. Certains additifs peuvent augmentent la réactivité d'un groupement fonctionnel donné. D'autre part, d'autres exemples d'additifs procurent une protection temporaire d'une partie réactive de la molécule de départ. Un exemple de ce dernier concept peut être illustré par la réduction d'un cyclopentanone possédant un groupement aldéhyde (**1.3**), et ce, à l'aide de la méthode classique de réduction de Luche (**Schéma 2**). Plus précisément, la réduction chimiosélective de la cétone versus deux groupements réactifs envers les hydrures est possible grâce au $CeCl_3$ (trichlorure de cérium). Le succès de cette méthode complétement chimiosélective se base sur la protection *in situ* de l'aldéhyde en présence de Ce(III) *via* la formation d'un hydrate stable dans les conditions réactionnelles. Par conséquent, la fonction cétone libre, le groupement le plus électrophile encore accessible, peut ainsi réagir avec le réducteur $NaBH_4$ pendant que la fonction aldéhyde est masquée jusqu'au parachèvement de la réaction. Malgré la perte en économie d'atomes engendrée par l'incorporation stœchiométrique d'un additif, ici le $CeCl_3$, cette réaction chimiosélective est plus rentable qu'un processus multi-étape impliquant la protection et la déprotection de la

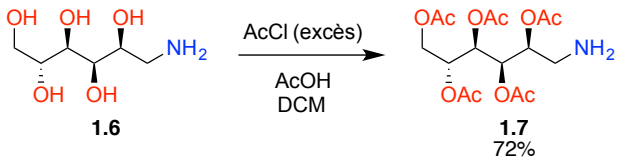
fonction aldéhyde. En fait, cet exemple démontre également que, dans certains cas, les réactions chimiosélectives permettent l'exclusion de groupes protecteurs[3] et contribuent globalement au concept d'économie atomes[4] et au concept d'économie d'étapes.[5]

Schéma 2. Réduction de Luche chimiosélective pour une cétone



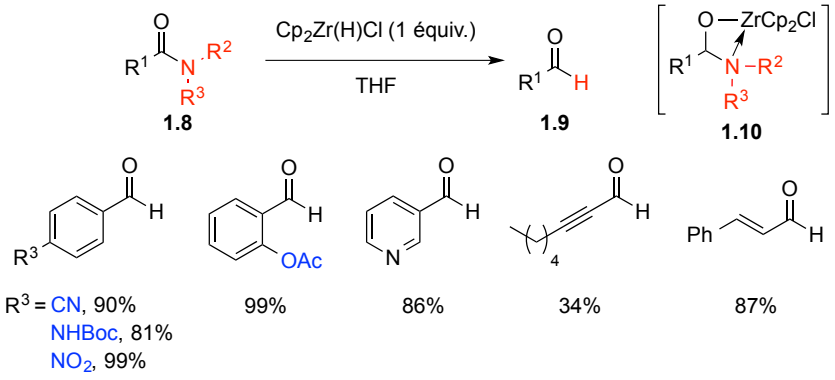
La chimiosélectivité représente également une facette importante à considérer lors de l'élaboration et la fonctionnalisation de dérivés de sucres.[13] En fait, la présence des plusieurs fonctionnalités alcools et amines libres rendent les processus de synthèse difficiles lesquels sont souvent non-sélectifs, dû à la nucléophilie comparable de ces fonctionnalités. Par conséquent, le processus de fonctionnalisation des sucres et des aminosucres s'appuie habituellement sur des séquences de synthèse multi-étapes nécessitant la protection et la déprotection orthogonale de différents groupements fonctionnels.[14] Par exemple, la synthèse de sucres *O*-acétylés tels que le composé **1.7**, requiert normalement la protection de la fonction amine primaire du composé **1.6** avant de pouvoir effectuer la fonctionnalisation des alcools primaire et secondaires (**Schéma 3**). Afin de développer une méthode de fonctionnalisation chimiosélective d'aminosucres, le groupe d'Hamilton a tiré profit de la basicité innée de la fonction amine, pour effectuer une acylation sélective des polyols.[15] En réalisant la réaction en présence d'acide acétique comme additif, l'amine est temporairement masquée dans les conditions réactionnelles, permettant l'acétylation sélective des groupements alcools en une étape avec un bon rendement de 72%.

Schéma 3. *O*-Acétylation sélective d'aminosucres



Parallèlement à la technique des additifs, la chimiosélectivité d'une réaction peut également être modulée par la diminution ou l'augmentation de la réactivité d'un des réactifs nécessaire à la transformation. Un exemple concret et pertinent aux travaux illustrés dans cette thèse vient des groupes de Ganem [16] et Georg [17] qui ont développé indépendamment une stratégie chimiosélective de réduction d'amides secondaires et tertiaires (**1.8**) en imines ou aldéhydes (**1.9**) en présence du réactif de Schwartz (Cp_2ZrHCl).[18] Ils ont notamment démontré que ce type d'hydrozirconation peut être très général tout en étant chimiosélectif, puisque le réactif de Schwartz est inactif en présence de différents groupements fonctionnels électrophiles tels des nitriles, nitro, esters et des carbamates tout en étant disponible pour plusieurs types d'amides (**Schéma 4**). De plus, des études mécanistiques par analyse IR et RMN ^{1}H indiquent que la formation quantitative de l'intermédiaire **1.10** explique le contrôle réactionnel qui mène à la formation de l'imine et l'absence de réduction additionnelle indésirable qui donnerait des produits saturés tels que l'amine tertiaire ou l'alcool correspondants. Lors du parachèvement de la réaction en présence d'eau, l'intermédiaire **1.10** permet ainsi la formation efficace et sélective d'aldéhydes (**1.9**) correspondants.

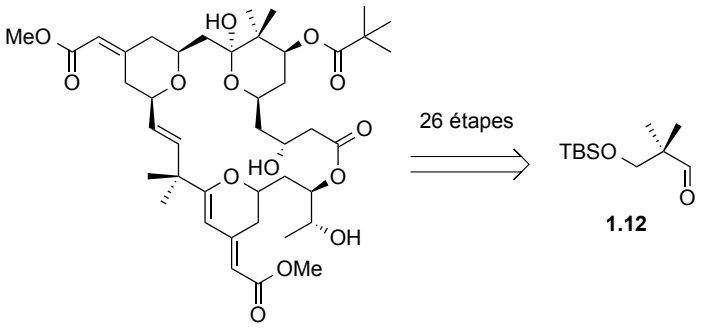
Schéma 4. Réduction chimiosélective d'amides avec le réactif de Schwartz



Plusieurs autres stratégies permettant d'atteindre des niveaux élevés de chimiosélectivité, comparables à celui illustré précédemment, ont été développées au cours de la dernière décennie. Malgré les difficultés inhérentes reliées aux études mécanistiques de certaines de ces réactions, le succès remporté par plusieurs méthodes chimiosélectives peut être corrélé à plusieurs concepts déjà répertoriés dans la littérature tels que le potentiel redox d'un catalyseur (par exemple dans le domaine de la chimie photoredox avec des catalyseurs de $Ru(bpy)_3PF_6$),[19] le p*K*a des réactifs employés, ainsi que les concepts d'acide/base, mou ou dur des groupements fonctionnels.[6]

Cependant, la synthèse totale de produits naturels ou pharmaceutiques très fonctionnalisés représente une plateforme exigeante afin d'explorer et exploiter au maximum le principe de sélectivité. Ceci est d'autant plus important lorsque la réaction chimiosélective à effectuer est en fin de synthèse, alors qu'une grande partie des groupements fonctionnels et des centres stéréogènes sont déjà installés. En effet, une dimension des effets « match » et « mismatch » entre en compte, en même temps que la nécessité d'avoir un niveau élevé de chimiosélectivité. Dans la plupart des cas, l'intermédiaire avancé d'une synthèse totale possède déjà une conformation tridimensionnelle spécifique et les conditions chimiosélectives développées sur des molécules simples ne s'appliquent pas nécessairement sans problème. En effet, le défi qui est de se rapprocher (ou de mimer) la biochimie effectuée par les enzymes, afin d'obtenir un seul stéréoisomère d'une molécule complexe en présence de plusieurs autres fonctionnalités, représente alors un objectif beaucoup plus exigeant à franchir. Malgré ces obstacles potentiels, certains exemples ont été rapportés, dont entre autres la synthèse totale de la bryostatine 16 par le groupe de Trost (**Schéma 5**).[20] En seulement 26 étapes linéaires et à partir des produits commercialement disponibles, cette contribution représente à ce jour la synthèse totale la plus courte de la littérature pour la famille des bryostatines; en comparaison, la deuxième synthèse totale la plus courte comporte 40 étapes linéaires.[21]

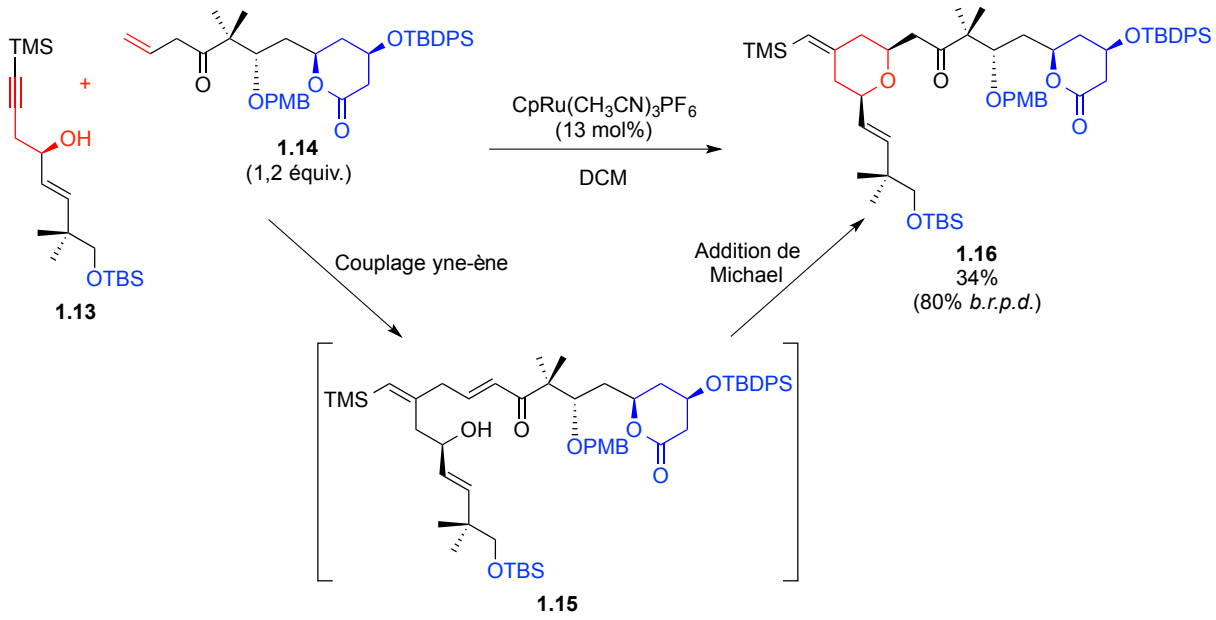
Schéma 5. Structure et simple rétrosynthèse de la bryostatine 16



Bryostatine 16 (**1.11**)

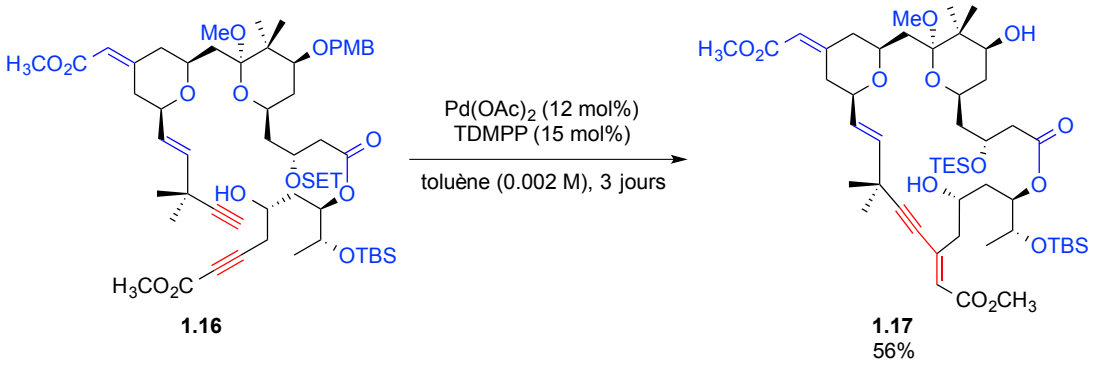
Cette synthèse totale du groupe de Trost repose sur le développement et l'application de deux étapes clés sélectives digne de mention.[22] La première réaction implique un couplage alcène-alcyne (ou enyne) catalysée par un complexe de ruthénium entre les intermédiaires **1.13** et **1.14** formant l'intermédiaire **1.15** (**Schéma 6**). Cette réaction génère un accepteur de Michael disponible pour une addition conjuguée intramoléculaire, formant ainsi le tétrahydropyrane **1.16** désiré avec un rendement de 34%. Il est important d'observer que la réaction donne un rendement de 80% basé sur la récupération du substrat de départ. La faible conversion de cette réaction peut être expliquée par le fait que celle-ci est effectué à 23 °C, atténuant ainsi la vitesse de réaction entre le complexe métallique et d'autres groupements fonctionnels tels que l'acène disubstitué du substrat **1.13**. Une température plus élevé pourrait favoriser la réaction de couplage, mais entraîne davantage la formation de produits secondaires, n'augmentant pas le rendement de la réaction. En effet, la réaction se déroule en présence de plusieurs groupes fonctionnels tels que deux éthers silylés, une cétone et une lactone. Malgré la chimiosélectivité de cette réaction, la protection préalable de trois groupements alcools est toutefois inévitable.

Schéma 6. Couplage alcène-alcyne suivie d'une réaction d'addition de Michael



La deuxième étape clé de la synthèse de la bryostatine 16 est une macrocyclisation du substrat **1.16** formant le produit désiré **1.17** en 56% de rendement en présence de $Pd(OAc)_2$ (**Schéma 7**). Cette réaction avait été précédemment optimisée sur des molécules simples,[20] et il est remarquable de constater que cette carbopalladation donne un rendement élevé considérant la fonctionnalisation dense du substrat **1.16**. Toutefois, les auteurs ne commentent ni sur la chimiosélectivité obtenue suite à cette réaction, ni sur la formation potentielle de produits secondaires expliquant un rendement moyen 56%. Par contre, il est important d'observer que la réaction a lieu à température ambiante, et ce, durant 3 jours! De plus, les conditions très diluées permettent de favoriser la réaction intramoléculaire versus la réaction intermoléculaire.

Schéma 7. Couplage alcène-alcyne suivie d'une réaction d'addition de Michael



1.16 **1.17**
56%

Malgré les avancées récentes exploitant le concept de chimiosélectivité, l'étude et le développement de nouveaux processus sélectifs évitant l'utilisation des groupements protecteurs est encore désirable et représente un domaine en expansion. En effet, seulement en étant conscient de cette problématique, les chimistes contemporains pourraient augmenter d'avantage l'efficacité de nouvelles voies synthétiques et, de ce fait, obtenir des synthèses totales plus efficaces. Il serait aussi intéressant de revisiter certaines méthodes de synthèse classiques mais non-sélectives; elles seraient encore plus utiles si elles étaient chimiosélectives (par exemple : la réduction des esters en aldéhydes par des hydrures de bore ou d'aluminium tel le DIBAL).[23] De plus, l'atteinte de ce but permettrait sûrement d'apporter des pistes et des solutions à certains mécanismes non élucidés. La disponibilité limitée des matières premières, (par exemple : certains métaux de transition), combinée avec des préoccupations environnementales grandissantes, exigent également la mise en évidence de ces objectifs et leurs applications aux futurs procédés industriels.

1.2 Activation et dérivatisation d'amides

Le groupe de recherche du Prof. André B. Charette s'intéresse depuis plusieurs années au développement de nouvelles méthodes d'activation et de dérivatisation d'amides à l'aide de l'agent activateur Tf_2O (anhydride trifluorométhanesulfonique).[24,25] Ces projets se basent le fait que la *O*-triflation des amides est rapide, quantitative et chimiosélective, et ce, même à de basses températures. Comme il sera décrit à plusieurs reprises dans cette

thèse, les amides sont la fonctionnalité de choix pour générer, par réaction avec le Tf_2O, un électrophile très réactif en présence d'autres groupements électrophiles classiques. Normalement, l'amide est une fonctionnalité très stable et peu électrophile. Cette propriété découle de la forte résonance du doublet d'électrons non-liant de l'atome d'azote dans le système π du carbonyle (**Figure 2**).[26] La résonance confère une augmentation de la nucléophilie et de la basicité de l'atome d'oxygène et une diminution de la nucléophilie de l'atome d'azote. Cet effet électronique explique ainsi la faible réactivité des amides observée en présence de plusieurs réactifs nucléophiles utilisés en chimie organique.

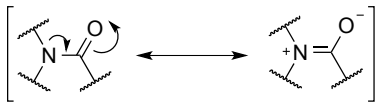


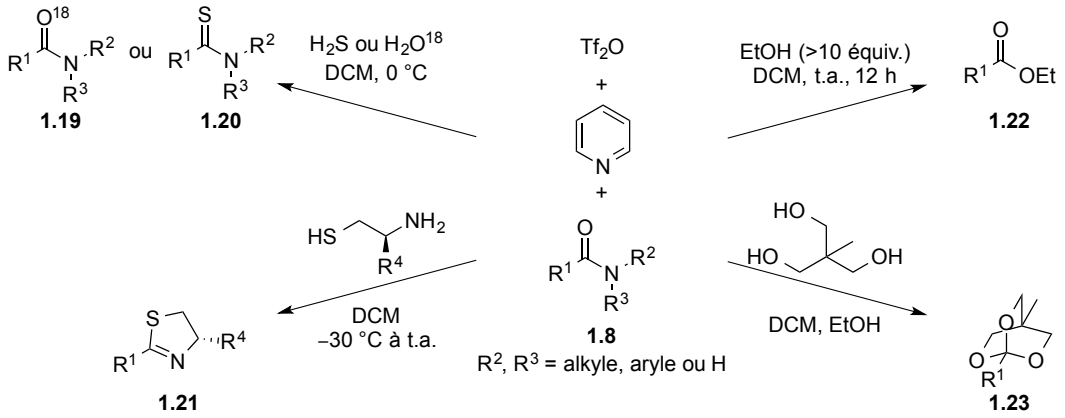
Figure 2. Formes de résonance de l'amide

De ce fait, la basicité accrue de l'oxygène peut être exploitée avantageusement en présence d'un agent activateur afin d'abaisser la stabilité de l'amide. En effet, la réaction entre un amide et un agent activateur permet de former un nouveau lien covalent, de polariser les liens C−O et C−N, de perturber la résonance et de former un produit considérablement plus électrophile[27] Dans ce contexte, divers agents activateurs permettant la formation d'halogénures d'imidoyle/iminium ont été rapportés : $POCl_3$,[28] $COCl_2$,[29] $(COCl)_2$, [30] $SOCl_2$, [31] PCl_3/Cl_2, [32] $PhPCl_4$, [33] PCl_5 [34] et PBr_3/Br_2.[35] Par contre, un excès d'agent activateur et/ou des températures élevées sont souvent nécessaires afin que la réaction d'activation soit efficace. Une approche alternative emploie le réactif de Meerwein, Et_3OBF_4 (tétrafluoroborate de triéthyloxonium), permettant la formation d'imidates d'alkyle ou d'esters d'iminium à de basses températures.[36] Par contre, ces derniers sont moins électrophiles que les halogénures d'imidoyle/iminium.

Depuis les travaux pionniers de Ghosez,[37] l'emploi de l'anhydride triflique en présence de dérivés de pyridine s'est avéré une méthode d'activation d'amides de choix.[38]

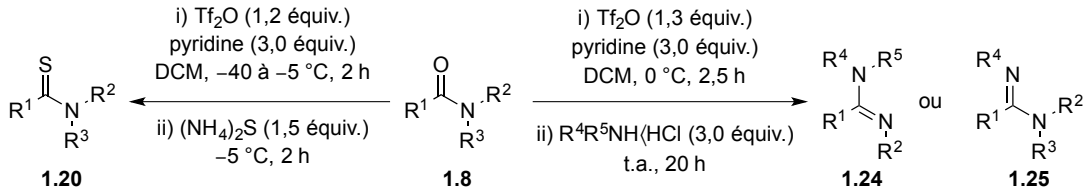
Cette approche permet la formation de triflates d'imidoyle/iminium dans des conditions douces (basses températures), tout en employant des quantités stœchiométriques équimolaire en Tf_2O. Au cours de ses études de doctorat dans le groupe du Prof. Charette, Peter Chua a employé la stratégie d'activation d'amides (**1.8**) en présence de Tf_2O et de pyridine pour former différents groupements fonctionnels *via* l'addition nucléophile de différents réactifs sur l'espèce activée (**Schéma 8**). En fait, les méthodes développées permettent la formation d'amides portant un isotope 18 de l'oxygène (**1.19**), de thioamides (**1.20**), de thiazolines (**1.21**), d'esters (**1.22**) et d'ortho-esters (**1.23**).[39,25b]

Schéma 8. Dérivatisation d'amides secondaires et tertiaires en différentes fonctionnalités



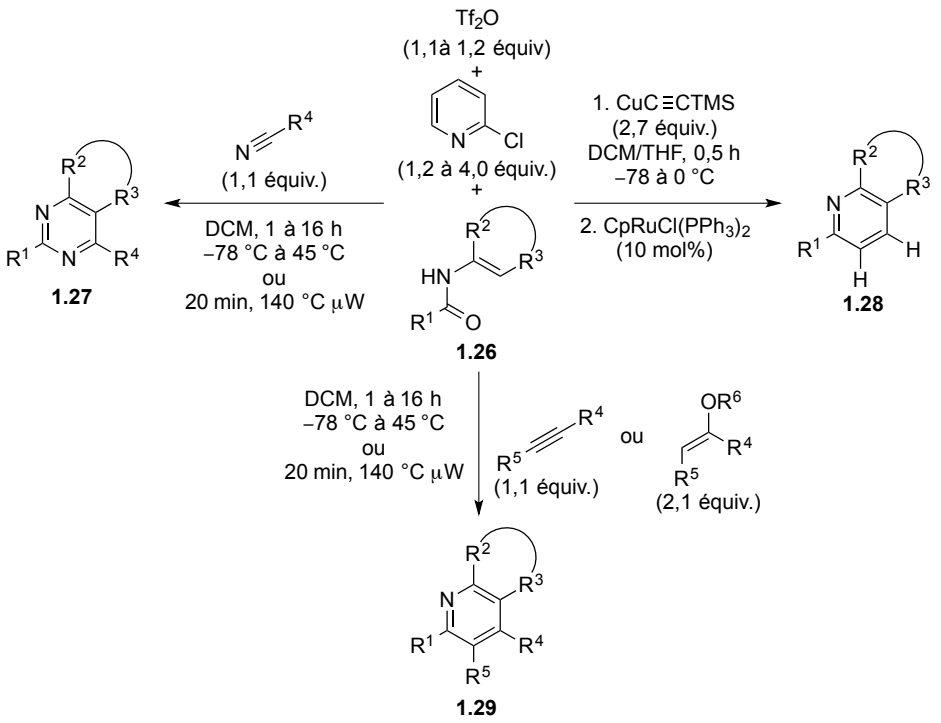
Suivant les travaux de Peter Chua, Michel Grenon, a développé des méthodes de dérivatisation d'amides permettant la formation d'amidines (**1.24** ou **1.25**) (**Schéma 9**).[40] De plus, il a amélioré les conditions de formation de thioamides (**1.20**) en employant le réactif $(NH_4)_2S$ au lieu du H_2S, un réactif toxique.[41]

Schéma 9. Formation d'amidines et de thioamides



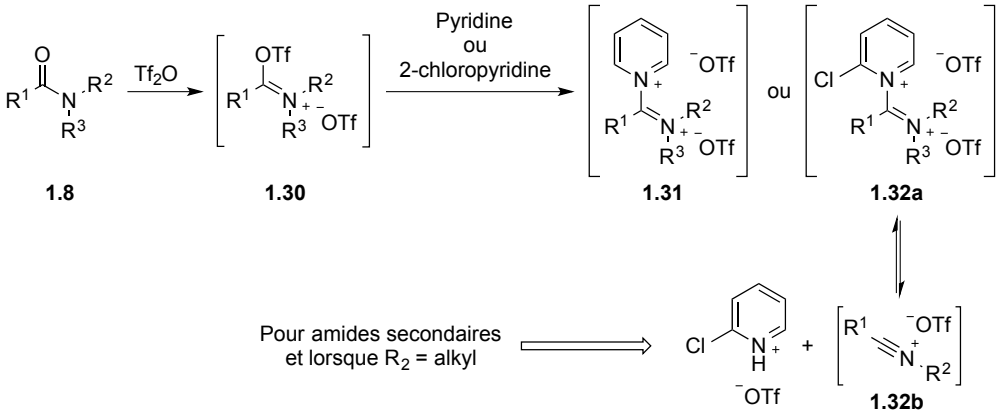
Parallèlement aux travaux du groupe du Prof. Charette, le groupe du Prof. Myers a découvert que des bases peu nucléophiles, telles la 2,6-di-*tert*-butylpyridine (DTBP) et la 2-chloropyridine (2-ClPyr),[42] donnent de meilleurs résultats que l'emploi de la pyridine dans certains cas.[43] Par la suite, le groupe du Prof. Movassaghi a exploité ce concept d'activation d'amides (**1.26**) en présence de 2-chloropyridine afin de synthétiser plusieurs hétérocycles azotés substitués tels que des pyrimidines (**1.27**) et des pyridines (**1.28** et **1.29**) (**Schéma 10**).[44]

Schéma 10. Synthèse de pyrimidines et pyridines par activation électrophile d'amides



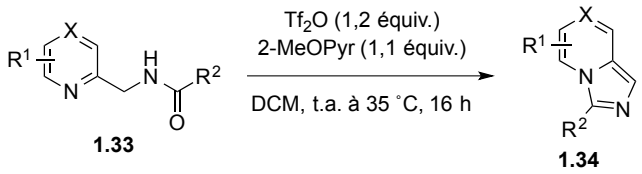
Le groupe du Prof. Movassaghi s'est également penché en détails sur l'étude mécanistique d'activation d'amides en présence de 2-chloropyridine ou 2-fluoropyridine (**Schéma 11**).[44c, 45] En effet, l'identification et la caractérisation de certains intermédiaires réactionnels a été rendu possible grâce à la technique de « React-IR », ce qui a permis d'observer la présence de sels de pyridinium et de nitrilium formés suite à l'activation d'amide. Il a émis l'hypothèse selon laquelle les transformations procédant par l'activation d'amides en présence de 2-halopyridine résultent de la formation d'intermédiaires pyridinium plus électrophiles (**1.32**) qu'en présence de pyridine (**1.31**). Par corrélation de l'intensité IR de chacun des intermédiaires formés dans le temps, il a également proposé que la 2-chloropyridine soit nettement moins nucléophile que la pyridine (donc que le 2-chloropyridinium est un meilleur nucléofuge que le pyridinium correspondant) en observant que l'intermédiaire **1.32a** est en équilibre avec une espèce nitrilium **1.32b** avant l'ajout de nucléophile, ce qui n'est pas vrai pour **1.31**. Ceci est appuyé par le fait que l'acide conjugué de la 2-chloropyridine (pK_a = 0.73 dans DMSO) est nettement plus fort que l'acide conjugué de la pyridine (pK_a = 5.33 dans DMSO).

Schéma 11. Activation d'amides en présence de pyridine et de 2-halopyridine



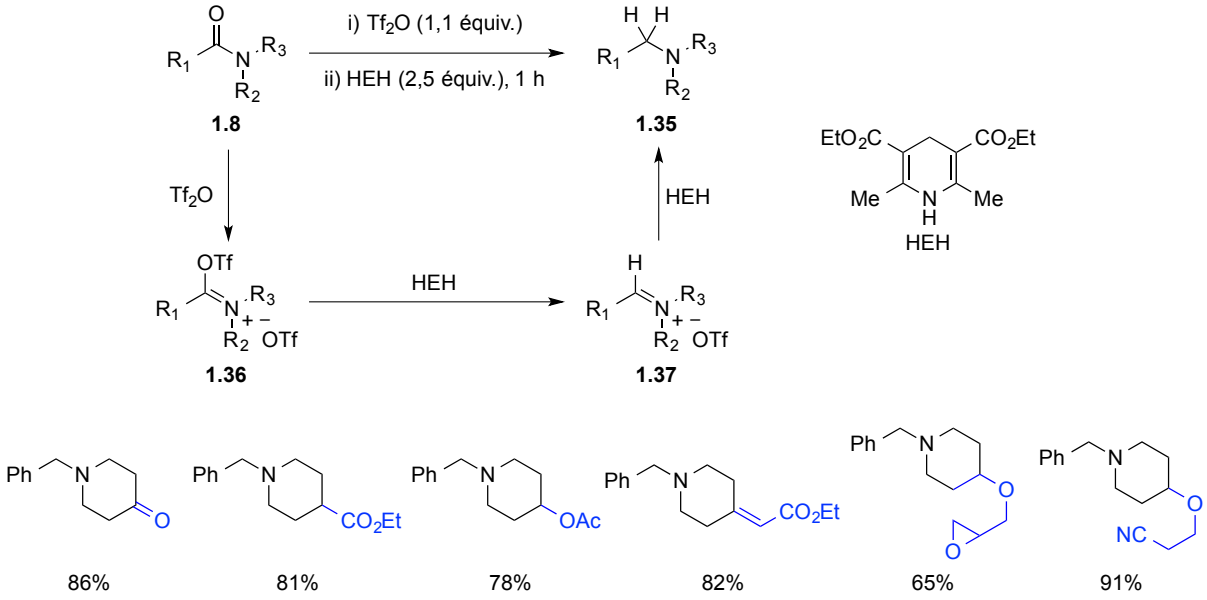
Suite aux contributions des groupes de Myers et Movassaghi, notre groupe et plusieurs autres ont également profité de l'effet bénéfique qu'apporte les pyridines C-2 substituées comme additifs basiques.[46] Par exemple, au cours de ses études doctorales, Guillaume Pelletier a développé une méthode de synthèse des imidazo[1,5-a]azines **1.34** *via* l'activation de l'amide **1.33** suivie d'une séquence de cyclodéhydration/aromatisation à 35 °C (**Schéma 12)**.[47] Les conditions de cette réaction supposent la formation d'intermédiaires similaires à ceux produits dans les conditions développées par le groupe de Movassaghi à l'exception que la 2-méthoxypyridine est ici employée. En effet, cette base possède des propriétés adéquates de basicité (pK_a = 3.06 dans le DMSO) et de nucléophilie. La 2-méthoxypyridine est aussi peu nucléophile en comparaison à la pyridine dû au fait que le doublet non-liant de l'oxygène force le groupement méthyle, par effet inductif de minimisation des dipôles, à adopter une conformation *syn* au doublet non-liant de l'azote de la pyridine.[48] Cet effet stéréoélectronique a pour effet d'augmenter l'encombrement stérique autour de l'azote de la pyridine, ce qui diminue son caractère nucléophile.

Schéma 12. Synthèse d'imidazo[1,5-a]azines



Le groupe de recherche du Prof. Charette s'est également intéressé au développement de méthodes d'activation et de dérivatisation d'amides chimiosélectives en présence d'autres fonctionnalités possédant un caractère de base de Lewis. Un exemple concret de ce concept a été initialement développé par Guillaume Barbe. Durant ses études doctorales, il a notamment développé une méthode de réduction sans métal (facilitant la purification) de fonctions amides tertiaires (**1.8**) en différentes amines (**1.35**) en présence d'une variété de groupements fonctionnels (**Schéma 13**).[49] La méthode est basée sur l'activation d'amides tertiaires (**1.8**) suivie de l'addition de deux équivalents de l'hydrure de l'ester de Hantzsch (HEH). Le premier équivalent d'hydrure permet la réduction du triflate d'iminium (**1.36**) en iminium (**1.37**), qui est ensuite réduit en amine (**1.35**) en présence d'un deuxième équivalent de HEH. Dans ce cas-ci, aucun additif de type pyridine n'est nécessaire à l'étape d'activation. La chimiosélectivité de cette méthode dépend de l'utilisation d'une source d'hydrure non métallique et peu nucléophile (HEH). Une étude portant sur le pouvoir de réduction de différents agents réducteurs révèle que le HEH est une source d'hydrure moins nucléophile que le $NaBH_3CN$.[12] Le HEH est d'ailleurs connu pour réduire des groupements fonctionnels tels que les aldéhydes et les imines en conditions acides.[50] Dans ce cas-ci, le HEH est un hydrure suffisamment nucléophile pour réduire les intermédiaires cationiques de la réaction (**1.36** et **1.37**), mais reste inerte en présence de plusieurs autres fonctionnalités. Par conséquent, cette méthode tolère la présence de cétones, d'esters, d'alcènes, d'époxydes et de nitriles, connus pour réagir en présence de réducteurs couramment utilisés en chimie organique tels que les dérivés d'aluminium ou de bore.

Schéma 13. Réduction chimiosélective d'amides tertiaires activés en présence de HEH

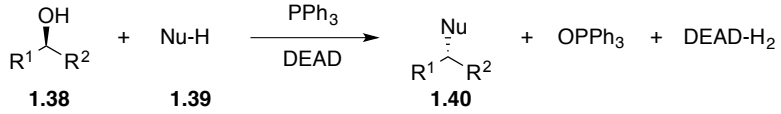


Les chapitres 2 à 5 résument nos efforts pour étendre ce concept d'activation et de réduction à plusieurs autres amides pour obtenir des produits différents de ceux illustrés dans le **Schéma 13**. En effet, en combinant une base et un agent réducteur faible, il a été possible d'étendre cette approche aux réductions d'amides secondaires tout en gardant un niveau élevé de chimiosélectivité (**Chapitre 2**). L'emphase sur le concept de contrôle réactionnel sera également mise de l'avant puisqu'il a également été possible d'arrêter la réduction à différents états d'oxydation envisageables (aldéhyde, imine, amine). Étonnamment, ce concept de contrôle réactionnel a été également observé et exploité lorsque nous avons substitué l'hydrure faible par un réactif organométallique nucléophile. Cette transformation a permis la synthèse d'une panoplie de cétones et de cétimines, tout en gardant le même niveau exceptionnel de chimiosélectivité observé pour les réductions (**Chapitre 3**). Suite à ces travaux, nous nous sommes intéressés à la synthèse d'hétérocycles azotés complexes suite à une séquence d'addition/cyclodéshydratation similaire à celle présentée dans le **Schéma 12**. En effet, plusieurs 1,3,4-triazoles (**chapitre 4**) et 3-aminoindazoles (**chapitre 5**) ont été synthétisés par une voie alternative aux imidazo[1,5-*a*]pyridines, et ce, par l'entremise d'addition intermoléculaire d'hydrazides suite à l'activation d'amides.

1.3 La réaction de Mitsunobu

Le groupe de recherche du Prof. Charette s'intéresse également au développement de méthodes de synthèse d'amines à partir de groupements fonctionnels couramment utilisés en chimie organique. Deux fonctions de départs ont été explorés antécédemment, tels que les imines[51] et les amides[49]. Nous avons ensuite envisagé la synthèse d'amines à partir des alcools, des fonctionnalités présentes en abondance dans les produits naturels et/ou dans les produits commercialement disponibles. Une méthode de synthèse permettant ce type de conversion est la réaction de Mitsunobu. Depuis sa découverte en 1967, la réaction de Mitsunobu a gagné en popularité au sein de la communauté scientifique en raison de son efficacité à activer et substituer la fonction alcool (**1.38**) (**Schéma 14**). En effet, suite à l'addition d'une quantité stœchiométrique d'un réactif de type azodicarboxylate et d'une phosphine, il est possible d'initier une réaction de S_N2 stéréospécifique en présence d'une grande variété de réactifs (**1.39**) permettant la formation de liens C–C, C–N, C–O, C–S, et C–halogénure. Le succès de cette méthode y est attribuable à sa généralité, ses conditions douces et l'inversion stéréospécifique observée pour les alcools secondaires. La réaction de Mitsunobu est classiquement reconnue pour avoir lieu en présence d'un réactif pro-nucléophile acide (**1.39**), de la PPh_3 (triphénylphosphine) et un dérivé de DEAD (azodicarboxylate de diéthyle). La réaction permet la formation d'une nouvelle fonctionnalité désirée (**1.40**), l'oxyde de triphénylphosphine et le réactif de DEAD réduit.

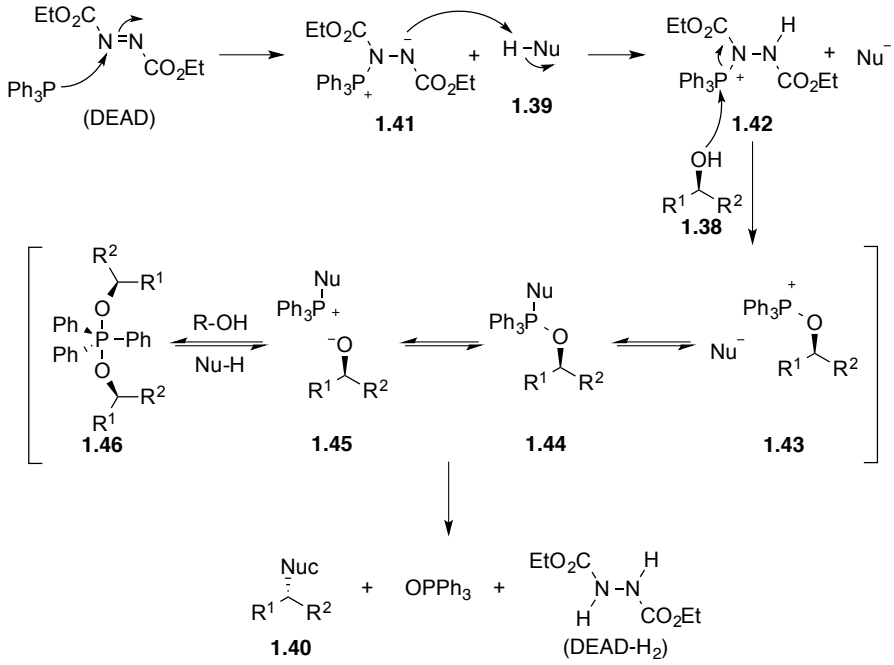
Schéma 14. Réaction de Mitsunobu



La première étape du mécanisme de la réaction de Mitsunobu communément acceptée[52] est la réaction rapide entre PPh_3 et DEAD pour former un adduit P–N zwitterionique (**1.41**), communément appelé « bétaïne de Mitsunobu » (**Schéma 15**).

Ensuite, il y a protonation de l'anion **1.41** en présence d'un acide, utilisé comme pro-nucléophile (Nu–H) (**1.39**), pour donner le sel de phosphonium **1.42**. Or, un désavantage connu de la réaction de Mitsunobu provient du fait que le pro-nucléophile (**1.39**) doit posséder un p*K*a inférieur à 13 (dans le DMSO). Si ce n'est pas le cas, celui-ci n'est pas suffisamment acide pour protoner l'adduit **1.41** et la réaction ne peut pas avoir lieu de façon productive. Lors de l'étape de l'activation de l'alcool (**1.38**) en présence du phosphonium **1.42**, quatre intermédiaires différents (**1.43**, **1.44**, **1.45**, **1.46**) ont été proposés. Ils sont en équilibre dans le milieu réactionnel selon un ratio dépendant de l'acidité du pro-nucléophile et de la polarité du solvant. Une fois l'alcool activé, la base conjuguée de l'acide (Nu^-) réagit selon une réaction de S_N2, plus probablement *via* l'intermédiaire **1.43**, conduisant au produit d'inversion stéréospécifique **1.40**. [53]

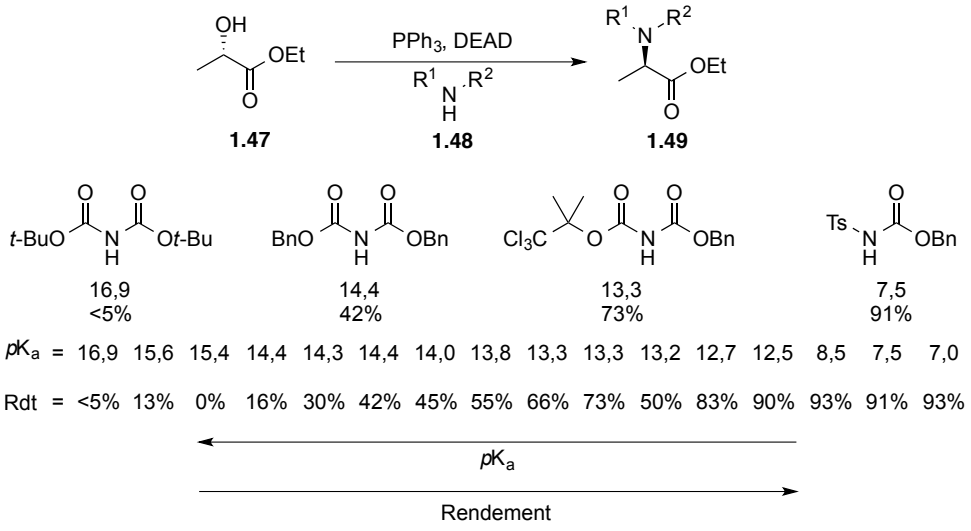
Schéma 15. Mécanisme de la réaction de Mitsunobu



Une étude permettant de faire une corrélation directe entre le pK_a du pro-nucléophile et le rendement de la réaction standard de Mitsunobu a été réalisée à partir de plusieurs imidodicarbonates et tosylcarbamates (**1.48**) en présence de lactate d'éthyle (**1.47**) (**Schéma 16**). Il est intéressant d'observer que les rendements de réactions pour des

composés avec un pK_a supérieur à 14,0 sont bas et ou presque nuls. Pour les composés ayant un pK_a entre 13 et 14, la réaction peut avoir lieu avec des rendements entre 45 et 73%, alors qu'avec un pro-nucléophile possédant une valeur de pK_a en dessous ou égal à 13, l'efficacité de la réaction varie avec des rendement de bons à excellents.[54]

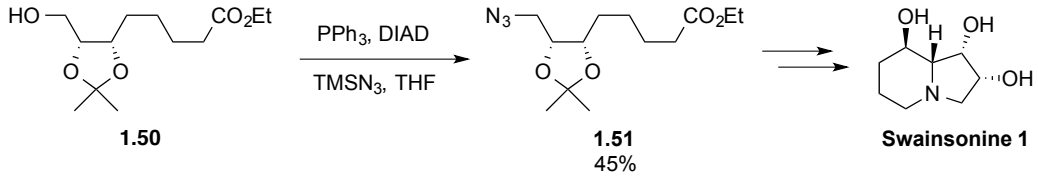
Schéma 16. Étude comparative entre le pK_a du pro-nucléophile et le rendement de la réaction de Mitsunobu.



La réaction de Mitsunobu a également été amplement utilisée par la communauté scientifique pour la synthèse d'amines. Par contre, en raison des limitations mentionnées ci-dessus en termes de pK_a, la synthèse d'amines utilisant la réaction de Mitsunobu nécessite intrinsèquement un processus multi-étapes utilisant des pro-nucleophiles azotés suffisamment acides tels que les azotures, les sulfonamides et les phthalimides. Ainsi, les produits de ces réactions requièrent inévitablement des étapes de déprotection et de fonctionnalisation de l'amine libre afin d'obtenir une amine substituée. Malgré cette limitation, la réaction de Mitsunobu a tout de même été amplement utilisée en synthèse totale, et ce, autant dans le domaine académique qu'industriel. Un exemple d'utilisation de la réaction de Mitsunobu à échelle industrielle a été réalisé par la compagnie GLYCO Design Inc. lors de la synthèse de la Swainsonine 1, une indolizidine polyhydroxylée possèdant des activités biologiques variées telles que des propriétés anti-HIV et anti-cancéreuses (**Schéma 17**). La compagnie emploie l'alcool primaire **1.50** en présence de

PPh_3, DIAD (azodicarboxylate de diisopropyle) et $TMSN_3$ (azoture de triméthylsilyle) permettant la synthèse du produit désiré **1.51** avec 45% de rendement.[55]

Schéma 17. Synthèse sur grande échelle vers la synthèse de la Swainsonine 1



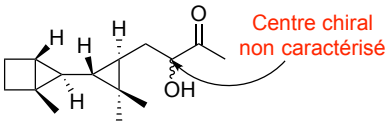
1.50 **1.51** 45% **Swainsonine 1**

Au cours de nos études, nous nous sommes penchés sur ce problème d'inefficacité de la réaction de Mitsunobu en présence de nucléophiles basiques (pK_a >13). Plus précisément, nous avons émis l'hypothèse que si ces derniers ne possèdent pas de protons disponibles pour former des intermédiaires tels **1.42**, l'ajout d'un équivalent d'acide dans le milieu devrait remédier à ce manque. Or, la subtilité importante de cette approche provient explicitement dans le choix de cet acide exogène. En effet, ce-dernier doit posséder un contre-anion non-nucléophile (ou moins nucléophile que le pro-nucléophile basique choisi) afin de ne pas perturber la distribution des produits désirés. Ici, grâce à notre connaissance précédente sur le pouvoir activant et électrophile du Tf_2O sur les amides, nous proposons d'utiliser l'acide triflique comme additif externe dans la réaction de Mitsunobu. Cette supposition vient du fait que le triflate est un excellent nucléofuge possédant une base conjuguée extrêmement faible (pK_a TfOH = -17.0).

1.4 Antécédents de recherche

En août 2008, l'auteur de cette thèse a rejoint le groupe du Prof. André B. Charette qui lui a offert de travailler sur un projet de synthèse totale d'un nouveau sesquiterpène (**1.52**) isolé en 2006 du corail *Clavularia inflata var. luzonia* (**Schéma 18**).[56] L'activité biologique de cette molécule vis-à-vis de certains agents pathogènes en fait une cible synthétique de choix. En effet, il a été découvert que l'extrait du corail contenant cette molécule naturelle possède un effet cytotoxique important sur les cellules tumorales HT-29 et P-388, impliquées respectivement dans le cancer du colon humain et dans la leucémie lymphoïde chez la souris. Contenant six carbones asymétriques et deux cyclopropanes très substitués, le sesquiterpène **1.52** représente un défi synthétique important pour les chimistes organiciens.

Schéma 18. Nouveau sesquiterpène contenant deux cyclopropanes très substitués

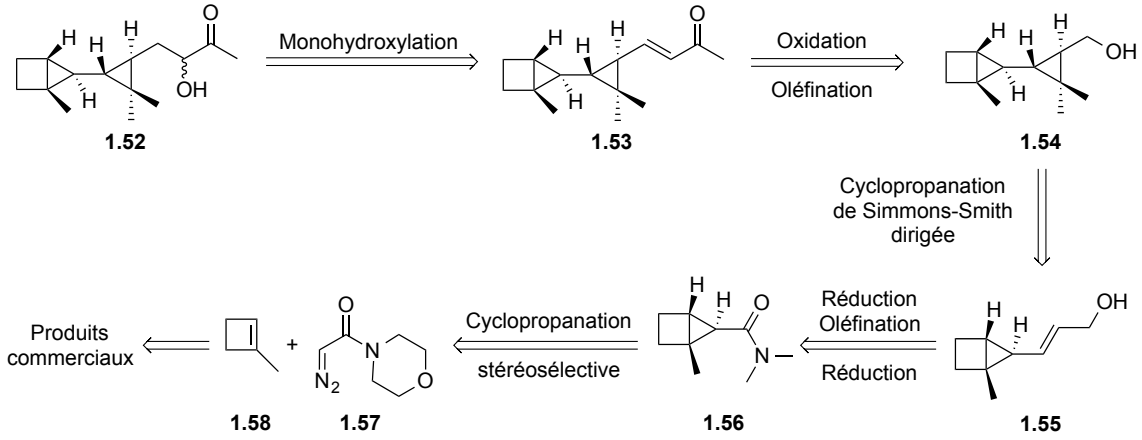


1.52

Jusqu'à présent, cette molécule naturelle n'a jamais été synthétisée et la configuration absolue du centre asymétrique en α de l'alcool est encore inconnue. Par conséquent, le but de ce projet consistait à synthétiser les deux diastéréoisomères possibles du sesquiterpène, c'est-à-dire la molécule dont le carbone en question est de configuration *R* et celle dont le carbone est de configuration *S*. Avec les deux diastéréoisomères caractérisés, il serait possible de comparer leurs propriétés physiques avec celles de la molécule isolée, permettant de déterminer la configuration stéréochimique absolue du sesquiterpène naturel. La synthèse totale de cette molécule a été débutée par David Marcoux, avec qui l'auteur de cette thèse élaboré une nouvelle analyse rétrosynthétique par rapport à celle initialement développée au cours de ses études de doctorat (**Schéma 19**). Afin de synthétiser l'hydroxycétone **1.52**, il devrait être possible de faire une réaction de

monohydroxylation de la cétone α,β-insaturée **1.53**. Cet intermédiaire pourrait être produit par une réaction d'oléfination d'Horner-Wadsworth-Emmons à partir de l'aldéhyde correspondant. Ce dernier pourrait être obtenu par une oxydation de l'alcool **1.54**. Le *gem*-diméthylcyclopropane **1.54** pourrait être synthétisé par une réaction de cyclopropanation de Simmons-Smith dirigée sur l'alcool allylique **1.55**. Ensuite, ce dernier pourrait être obtenu à partir de l'aldéhyde correspondant par une réaction d'Horner-Wadsworth-Emmons, suivie de la réduction de la fonction ester obtenue. L'aldéhyde en question pourrait être obtenu par réduction de l'amide **1.56**. Finalement, l'intermédiaire **1.56** pourrait être synthétisé par une réaction de cyclopropanation énantiosélective et diastéréosélective du cyclobutène **1.58** en présence du composé diazoïque **1.57** (**Schéma 19**).

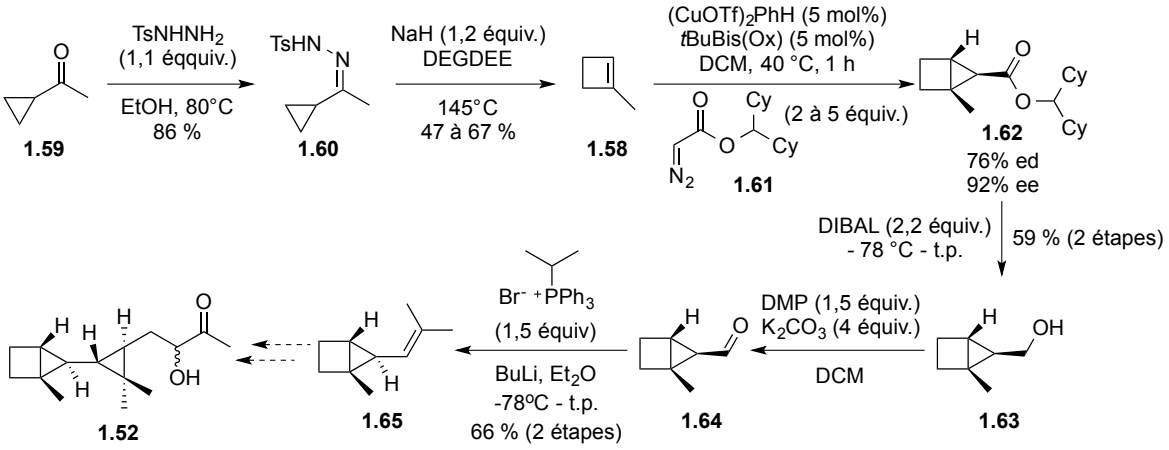
Schéma 19. Analyse rétrosynthétique du nouveau sesquiterpène



La synthèse totale initialement élaborée par David Marcoux et le Prof. André B. Charette comprenait quelques limitations. Après avoir synthétisé les réactifs de départ **1.58** et **1.61**,[57] David Marcoux a été en mesure d'obtenir le composé bicyclo [2.1.0] (**1.62**) par une réaction de cyclopropanation catalysée par un sel de cuivre (II) et un ligand chiral, soit la *t*-BuBis(Ox) (**Schéma 20**).[58] À cause des difficultés reliées à la purification de cette molécule, celle-ci a été réduite à l'alcool correspondant **1.63** en présence de DIBAL. David a obtenu 69% de rendement (en deux étapes), 76% e.d. (d'excès diastéréoisomérique) et 92% e.e. (d'excès énantiomérique). Malgré que David ait réussi à avancer la synthèse jusqu'à l'alcène **1.65**, la stratégie posait plusieurs problèmes, dont des réactions non-

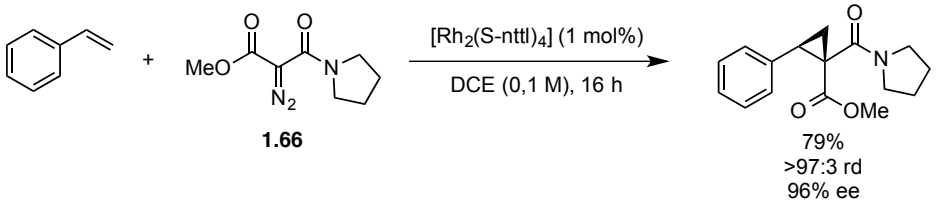
reproductibles à différentes échelles. Premièrement, les composés **1.58**, **1.62**, **1.64** et **1.65** sont très volatiles et leur purification très difficile. Ils restent contaminés par le produit de l'étape précédente, et ce, au point où nous n'avons jamais réussi à avoir assez de ces composés suffisamment purs pour les caractériser. De plus, la stéréosélectivité de la première réaction de cyclopropanation pour préparer le composé **1.62** était moyennement acceptable pour une synthèse totale de plus de 15 étapes.

Schéma 20. Voie de synthèse initiale



Pendant ses études, David Marcoux a démontré que les diazoamides permettent d'obtenir de meilleurs excès diastéréoisomérique et énantiomérique lors des cyclopropanations catalysées par des dimères de rhodium (II) (**Schéma 21**). [59]

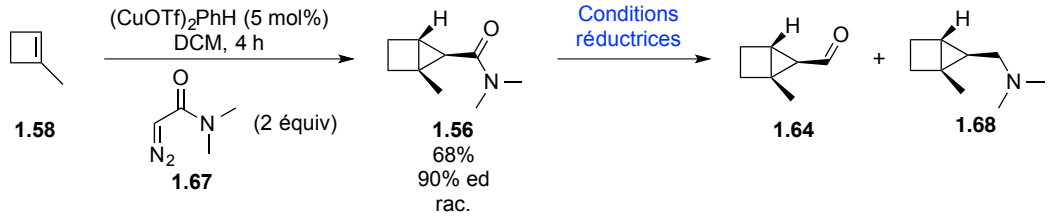
Schéma 21. Cyclopropanation à partir de composés diazoïques dérivés de malonamide monoester



Par conséquent, après avoir reformulé la rétrosynthèse, l'auteur de cette thèse a réessayé la cyclopropanation à partir du diazoamide **1.67**, ce qui a permis d'obtenir le composé **1.56** avec 68% de rendement et 90% e.d., comparativement à 76% e.d.

initialement obtenu par David. Cependant, lors de la poursuite de la synthèse totale via la réduction de l'amide **1.56** en aldéhyde **1.64**, différents problèmes ont été rencontrés (**Tableau 1**). Malgré plusieurs tentatives de réduction, des rendements bas ont été obtenus et de la sur-réduction de l'amide a été observée menant à la formation de l'amine **1.68** non-désirée.

Table 1. Réaction de cyclopropanation et différentes conditions de réduction d'amide tertiaire

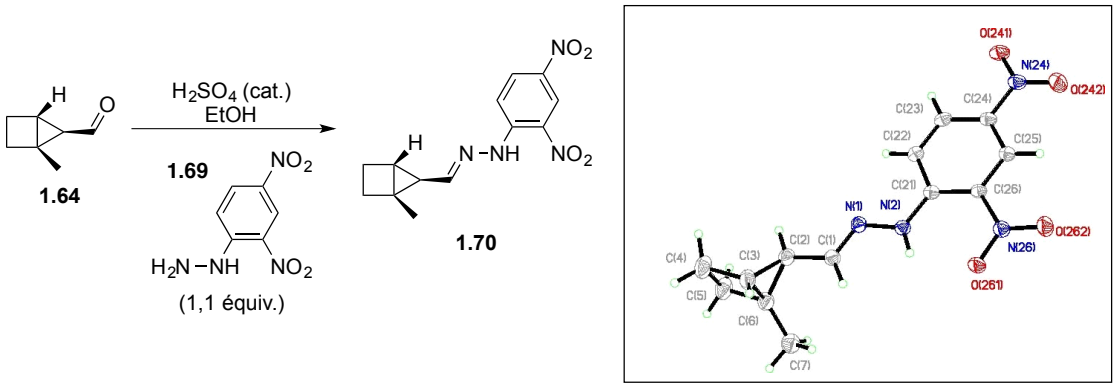


Entrée	Réducteur	Équiv.	Solvant	Température	Rendement Isolé de 1.64	Observations
1	$LiAlH_2(OEt)_2$	1,0	Et_2O	0 °C	31 - 55%	présence de **1.68**
2	$LiAlH(OEt)_3$	1,0	Et_2O	0 °C	28%	présence de **1.56**
3	$LiAlH(OEt)_3$	2,0	Et_2O	0 °C	25%	présence de **1.56** et **1.68**
4	Cp_2ZrHCl	1,5	THF	t.p.	20%	présence de **1.56**
5	Tf_2O HEH	1,1 1,5	DCM	0 °C	29%	présence de **1.68**

Des quantités appréciables de l'aldéhyde **1.64** ont tout de même été obtenus. Il a été possible de le faire réagir avec l'arylhydrazine **1.69** pour obtenir l'hydrazone **1.70**, lequel

donne des cristaux qui ont été résolus par diffraction des rayons-X. Cette structure a permis de confirmer la présence du bicyclo[2.1.0]pentane, un motif ayant une tension de cycle élevée.

Schéma 22. Confirmation du motif bicyclo [2.1.0] par diffraction des rayons-X de cristaux du dérivé **1.70**



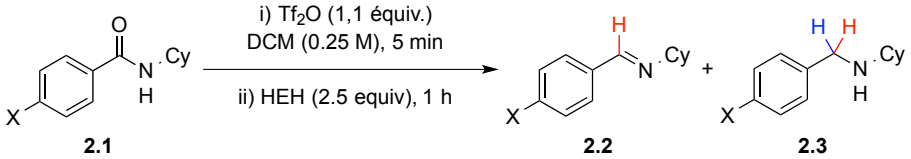
Malgré l'obtention de la structure par diffraction des rayons-X, beaucoup de limitations ont été observées avec la synthèse du sesquiterpène **1.52**, entre autres, des produits très volatiles, des rendements réactionnels très bas et surtout des purifications suffisamment difficiles rendant la caractérisation des produits obtenus impossible. Par conséquent, ce projet a été abandonné. Toutefois, il a motivé l'auteur de cette thèse à s'intéresser aux réactions impliquant le Tf_2O et le TfOH. Ainsi, nous avons décidé de développer des nouvelles réactions de dérivatisation chimiosélectives d'amides (**Chapitre 2, 3, 4 et 5**) et de développer une approche générale de synthèse d'amines en une étape à partir de la réaction de Mitsunobu (**Chapitre 6**).

Chapitre 2. Controlled and Chemoselective Reduction of Secondary Amides

2.1 Introduction

La méthode de réduction chimiosélective développée par Guillaume Barbe (**Schéma 13, Chapitre 1**) a été originalement optimisée et appliquée aux amides tertiaires uniquement. Les premiers travaux de recherche de l'auteur dans ce domaine ont été réalisés en collaboration avec Guillaume Pelletier, un étudiant au doctorat du Prof. André B. Charette, et ont porté sur l'application de cette dernière méthode aux amides secondaires. Lors des premiers essais, des produits provenant de la mono- et de la double réduction ont été obtenus, soit l'imine et/ou l'amine correspondante et ce, pour différents amides secondaires (**Table 2**). Pour la réduction de dérivés du *N*-cyclohexylbenzamide **2.1** contenant différents groupements en position *para* (Cl, OMe ou H), la réactivité s'est avérée être fonction des effets inductifs (ou électroniques) du substrat. Contrairement aux réductions d'amides tertiaires, la réduction d'un amide secondaire dont la fonction amide est appauvrie en électrons par effet inductif (X = Cl) donne seulement l'amine **2.3** (Entrée 1, **Table 2**). Dans le cas du *N*-cyclohexylbenzamide (X = H), un mélange d'imine **2.2** et d'amine **2.3** a été observé avec un ratio de 1,5:1 (Entrée 2, **Table 2**). Finalement, la réduction d'un substrat riche en électrons donne également un mélange, mais cette fois-ci avec une distribution de produits de 8,8:1 en faveur de l'imine versus l'amine (Entrée 3, **Table 2**).

Table 2. Réductions d'amides secondaires en présence de HEH



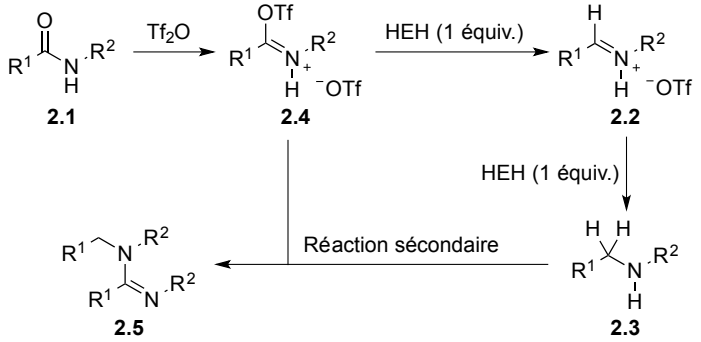
2.1 **2.2** **2.3**

Entrée	X	Rendement **2.2** (%)[a]	Rendement **2.3** (%)[a]
1	Cl	0	31
2	H	23	15
3	OMe	53	6

[a] Rendement obtenu par analyse du brut par RMN ^{1}H utilisant le Ph_3CH comme standard interne.

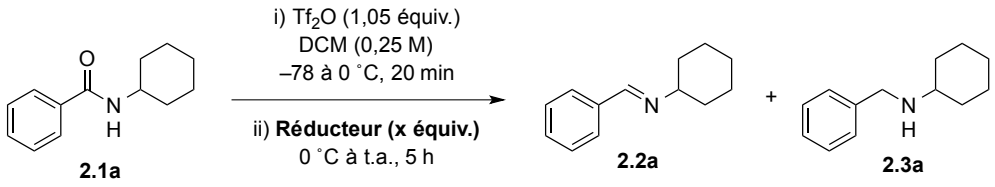
Afin d'améliorer cette transformation pour obtenir une sélectivité envers l'imine ou l'amine, nous avons entrepris une optimisation du temps réactionnel et de la quantité de HEH. Malgré différentes tentatives, la réduction d'amides secondaires en présence de HEH était très limitée, soit avec des rendements bas, soit avec la formation d'un mélange de produits. Nous avons alors cherché à comprendre les réactions secondaires possibles de cette transformation. En effet, en isolant tous les produits obtenus dans les réactions avec le HEH, nous avons observé la formation des dérivés de l'amidine **2.5** provenant d'une réaction secondaire entre le produit amine **2.3** et l'amide activé **2.4** (**Schéma 23**). Tel que démontré par Michel Grenon, un amide secondaire activé par Tf_2O réagit facilement en présence d'amines pour former les amidines **1.25** correspondantes (**Schéma 9**).[40]

Schéma 23. Réaction secondaire de la réduction d'amides secondaires



Afin d'éviter cette réaction secondaire et améliorer les conversions de cette transformation, nous avons envisagé employer un agent réducteur moins nucléophile que le HEH. Cette hypothèse est basée sur le fait que l'intermédiaire triflate d'imidoyle **2.4** est plus électrophile que l'imine **2.2**. Donc, en présence d'un réducteur peu nucléophile, il devrait être possible de contrôler la séquence de réduction en défavorisant la réduction de l'imine **2.2**. De plus, l'utilisation d'un tel réducteur devrait tolérer la présence de plusieurs groupements fonctionnels, permettant ainsi le développement d'une méthode chimiosélective. Par conséquent, nous avons étudié la réduction d'amides secondaires en présence de plusieurs agents réducteurs (**Table 3**). Pour ce faire, nous nous sommes basés sur l'étude comparative de la nucléophilie de différentes sources hydrures effectuée par Mayr.[12] Par exemple, le réducteur $NaBH_3CN$ est plus nucléophile que le Bu_3SnH, qui est plus nucléophile que le HEH. Par contre le Et_3SiH est une source d'hydrure moins nucléophile que le HEH. Nous avons également limité la quantité de réducteur à 1,5 équivalents afin de favoriser la mono-réduction de l'intermédiaire de triflate d'imidoyle **2.4**.

Table 3. Variation de la source d'hydrure dans la réduction de l'amide secondaire **2.1a**



Entrée	Réducteur	Ratio **2.2a**:**2.3a**	Rendement **2.2a** (%)[a]	Rendement **2.3a** (%)[a]
1	$NaBH_3CN$	0:100	0	38
2	Bu_3SnH	3:97	1	37
3	HEH	47:53	17	19
4	Et_3SiH	100:0	77	0

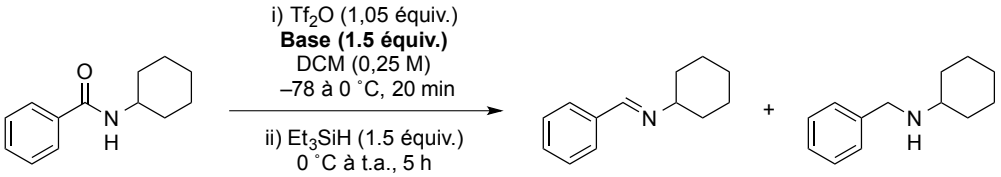
[a] Rendement obtenu par analyse du brut par RMN ^1H utilisant le Ph_3CH comme standard interne.

Tel que prévu, l'optimisation de la réduction du benzamide **2.1a** a révélé que l'emploi des réducteurs plus nucléophiles que le HEH donne majoritairement l'amine **2.3a** (Entrées 1 et 2). En présence de 1,5 équivalents de HEH, un ratio de 47:53 a été obtenu pour l'imine **2.2a** versus l'amine **2.3a** (Entrée 3). Lorsque le Et_3SiH a été utilisé, l'imine **2.2a** a été obtenue avec un rendement surprenant de 77% et une sélectivité complète pour le produit partiellement réduit **2.2a** (Entrée 4). À partir de ce résultat, il a été possible de constater que le Et_3SiH semble être suffisamment nucléophile pour réagir avec l'amide activé, mais pas assez nucléophile pour réduire l'iminium formé, confirmant l'hypothèse de départ. Par conséquent, nous avons procédé à une optimisation systématique de cette réaction afin de maximiser les rendements pour la formation de l'imine **2.2a**.

La première partie de l'optimisation consiste à étudier l'effet d'une base externe dans la réaction (**Table 4**). Cette étude a permis d'obtenir un excellent rendement pour l'imine **2.2a** en présence de dérivés de pyridine non-nucléophiles, comme découvert par Myers et Movassaghi.[43,44,45] Les meilleurs rendements ont été obtenus avec la 2,6-

dichloropyridine, la 2-chloro-5-bromopyridine et la 2-fluoropyridine, et parmi ces pyridines, nous avons choisi d'utiliser la 2-fluoropyridine (entrées 3, 9 et 12). Ce choix est basé sur le fait que la 2-fluopyridine est une base volatile (point ébullition : 126 °C à 753 mmHg), facilitant l'étape de purification du produit désiré. De plus, celle-ci est une base peu dispendieuse vis-à-vis du prix des autres dérivés de pyridine.[60]

Table 4. Optimisation de la base externe



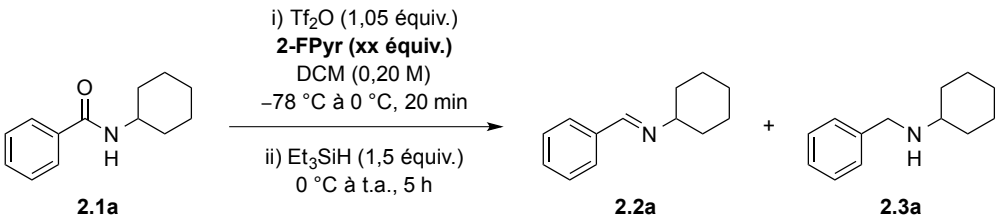
2.1a **2.2a** **2.3a**

Entrée	Base	Rendement **2.1a** (%)[a]	Rendement **2.2a** (%)[a]
1	Aucune	14	77
2	MgO	29	56
3	2,6-dichloropyridine	0	90
4	pyrazine	5	67
5	2,6-lutidine	89	4
6	3-chloropyridine	23	18
7	3-bromopyridine	34	15
8	DIPEA	86	4
9	2-chloro-5-bromopyridine	0	94
10	pyridine	20	25
11	2,4,6-collidine	80	13
12	2-fluoropyridine	10	92
13	2-bromopyridine	18	68
14	2-chloropyridine	15	74

[a] Rendement obtenu par analyse du brut par RMN ^{1}H utilisant le Ph_3CH comme standard interne.

Nous avons tout d'abord vérifié la quantité de 2-fluoropyridine idéale pour cette transformation (**Table 5**). L'étude d'optimisation a révélé que 1,1 équivalent de base est suffisant pour atteindre une conversion complète de l'amide **2.1a** en imine **2.2a**.

Table 5. Optimisation de la quantité de 2-fluoropyridine



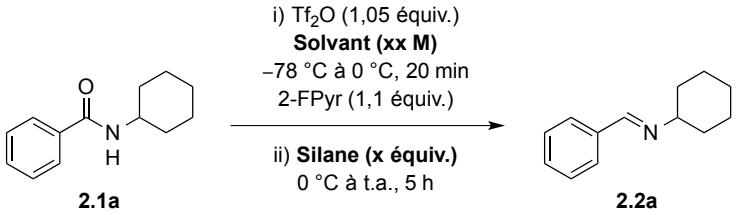
2.1a **2.2a** **2.3a**

Entrée	2-Fluoropyridine (équiv.)	Rendement **2.1a** (%)[a]	Rendement **2.2a** (%)[a]
1	0	14	77
2	0,5	5	86
3	1,1	0	91
4	1,2	0	92
5	1,5	0	92
6	2,0	0	92
7	4,0	0	88

[a] Rendement obtenu par analyse du brut par RMN ^{1}H utilisant le Ph_3CH comme standard interne.

Nous avons ensuite optimisé la concentration du substrat dans le solvant, ainsi que la quantité et la nature du silane (**Table 6**). Cette étude nous a permis de conclure que la réaction est optimale à 0,25 M de dilution en présence de dichlorométhane et de 1,1 équivalent de Et_3SiH.

Table 6. Optimisation du solvant et de la source de silane



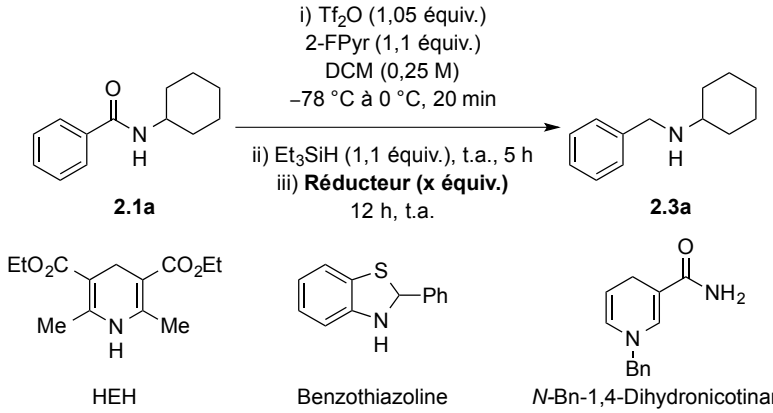
2.1a **2.2a**

Entrée	Solvant (M)	Silane (équiv.)	Rendement **2.2a** (%)[a]
1	DCM (0,50 M)	Et_3SiH (1,5 équiv.)	95
2	DCM (0,25 M)	Et_3SiH (1,5 équiv.)	98
3	DCM (0,20 M)	Et_3SiH (1,5 équiv.)	92
4	DCM (0,10 M)	Et_3SiH (1,5 équiv.)	89
5	DCM (0,05 M)	Et_3SiH (1,5 équiv.)	74
6	DCE (0,20 M)	Et_3SiH (1,5 équiv.)	85
7	toluène (0,20 M)	Et_3SiH (1,5 équiv.)	0
8	DME (0,20 M)	Et_3SiH (1,5 équiv.)	0
9	DCM (0,25 M)	Et_3SiH (1,25 équiv.)	98
10	DCM (0,25 M)	Et_3SiH (1,1 équiv.)	98
11	DCM (0,25 M)	Et_3SiH (1,05 équiv.)	88
12	DCM (0,25 M)	Et_3SiH (3,5 équiv.)	30
13	DCM (0,25 M)	$PhMe_2SiH$ (1,5 équiv.)	87
14	DCM (0,25 M)	$PhSiH_3$ (1,5 équiv.)	30

[a] Rendement obtenu par analyse du brut par RMN ^1H utilisant le Ph_3CH comme standard interne.

Par la suite, nous avons effectué l'optimisation de la réduction de l'imine **2.2a** en amine **2.3a** *in situ* par l'addition séquentielle d'une source d'hydrure plus nucléophile. Bien que d'autres hydrures organiques peu nucléophiles comme la benzothiazoline[61] ou le *N*-Bn-1,4-dihydronicotinamide[62] ont été testés, le HEH s'est avéré le réducteur de choix pour cette étape.

Table 7. Optimisation de la réduction de l'amide secondaire à l'amine



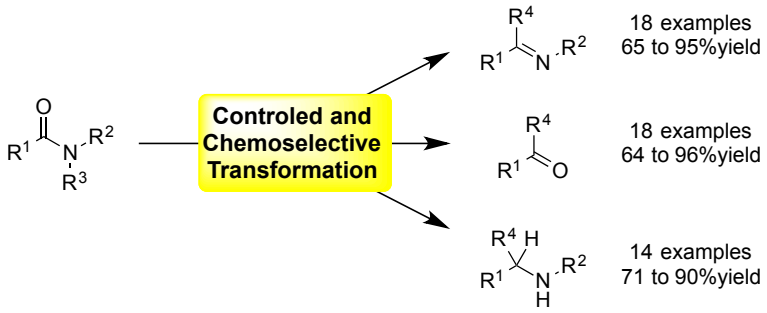
Entrée	Réducteur	Quantité H^- (équiv.)	Additif (équiv.)	Rendement **2.3a** (%)
1	HEH	1,0	Aucun	68
2	HEH	1,1	Aucun	77
3	HEH	1,2	Aucun	82
4	HEH	1,3	Aucun	96
5	HEH	1,4	Aucun	96
6	HEH	1,5	Aucun	97
7	HEH	1,7	Aucun	97
8	HEH	2,0	Aucun	97
9	HEH	1,1	Et_3N (0,2 équiv.)	93
10	HEH	1,1	Pyr (0,2 équiv.)	94
11	Benzothiazoline	1,5	Aucun	0
12	*N*-Bn-1,4-dihydronicotinamide	1,5	Aucun	0

[a] Rendement obtenu par analyse du brut par RMN ^1H utilisant le Ph_3CH comme standard interne.

2.2 Abstract

This communication describes a metal-free methodology involving an efficient and controlled reduction of secondary amides to imines, aldehydes, and amines in good to excellent yields under ambient pressure and temperature. The process includes a chemoselective activation of a secondary amide with triflic anhydride in the presence of 2-fluoropyridine. The electrophilic activated amide can then be reduced to the corresponding iminium using triethylsilane, a cheap, rather inert, and commercially available reagent. Imines can be isolated after a basic workup or readily transformed to the aldehydes following an acidic workup. The amine moiety can be accessed via a sequential reductive amination by the addition of silane and Hantzsch ester hydride in a one-pot reaction. Moreover, this reduction tolerates various functional groups that are usually reactive under reductive conditions and is very selective to secondary amides.

Schéma 24. Chemoselective and controlled reduction of secondary amides to imines, aldehydes and amines



2.3 Reference

Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817.

2.4 Article

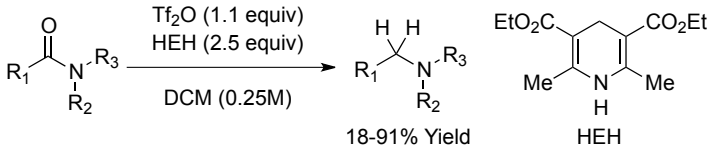
The issue of chemoselectivity in carboxamide reduction has recently been a topic of marked interest due to its step-economical potential and cost effectiveness.[63] Finding mild, chemoselective, and general conditions for the reduction of amides is of great importance for pharmaceutical chemistry as this moiety could serves as a template for the direct formation of compounds possessing basic nitrogens or aldehydes.[64] In contrast, the high stability of carboxamides originates from its strong resonance, and accounts for its low propensity to react with hydrides.[65] Thus, the most common approaches to their reduction employ nucleophilic metallic hydride donors, such as aluminum[66] and boron[67] reagents. Despite the fact that they are reliable for the synthesis of amines, the access to imines and aldehydes can be problematic due to the intrinsic high reactivity of the hydrides needed to effect the reduction. Moreover, low functional group tolerance, by-product formation, costly purifications, and poor reduction control to different oxidation states impair their applications.

To address these issues, direct reduction methods have been described to yield the corresponding aldehyde or imine. Among these, the use of Weinreb amides[68] or morpholine-derived amides[69] in combination with DIBAL are known to control the reduction outcome to aldehydes. Also, Buchwald reported a more general and chemoselective reduction of α-enolizable amides to aldehydes in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ and Ph_2SiH_2.[70] Alternatively, the use of stoechiometric or excess amounts of Schwartz's reagent (Cp_2ZrHCl) can lead to the formation of a variety of aldehydes[71] or imines[72] with great functional group tolerance.

Recently, our group has reported a metal-free chemoselective reduction of tertiary amides to amines mediated by the activation with triflic anhydride (Tf_2O) and reduction with Hantzsch ester hydride (HEH) (**Scheme 25**).[73] In contrast, tertiary amines can be obtained by the catalytic hydrosilylation of amides in the presence of transition metals, such as Rh,[74a,b] Ru,[74c,d] Mo,[74e] Ti,[74f] Pt,[74g,h] Pd,[74h] and Fe[74i,j]. The most recent examples were

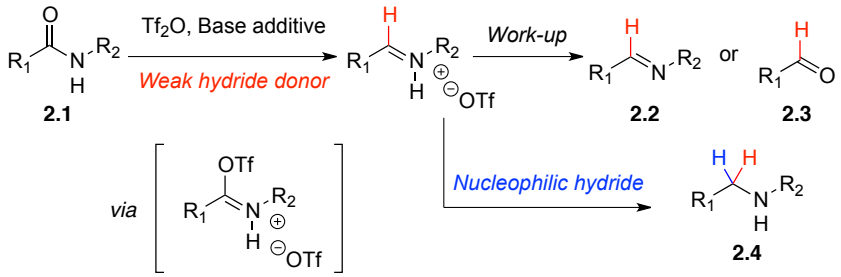
published by Beller and exhibit a notable chemoselectivity level when the reduction of tertiary amides is catalyzed by $Zn(OAc)_2$ in presence of $(EtO)_3SiH$ at ambient temperature.[74k]

Scheme 25. Reduction of tertiary amides to amines mediated by HEH



While the majority of these methods were shown to be effective for a large array of substituted tertiary amides, only scarce examples of secondary amides underwent a controlled reduction to different oxidation states and with an appreciable level of functional group selectivity. To address this issue, we report herein a versatile and highly functional group tolerant reduction methodology of secondary amides (**2.1**) giving access to imines (**2.2**), aldehydes (**2.3**), or amines (**2.4**) without the use of any metallic hydride (**Scheme 26**).

Scheme 26. Strategy for the Controlled Reduction of Secondary Amides

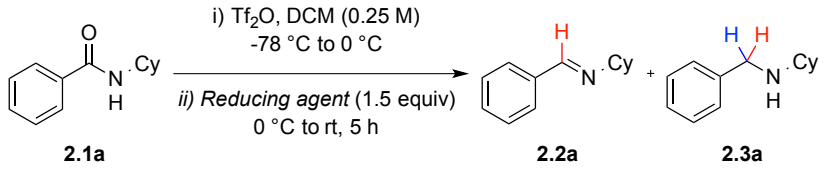


During the exploration of different reduction conditions,[75] we found that treating *N*-cyclohexylbenzamide **2.1a** under our previously reported HEH reduction conditions (Scheme 24) lead to a sluggish reaction that gave a mixture of products and was non-reproducible for different secondary amides. By lowering the amount of HEH in the reaction mixture to 1.5 equiv and by performing the activation process from –78 °C to 0 °C, we observed a 47:53 mixture of imine **2.2a** versus amine **2.4a** (**Table 8**, entry 3). We then hypothesized that if the reaction was performed with a less nucleophilic hydride source

than HEH, the reaction could be controlled in favor of the formation of imine **2.2a**. In 2009, Mayr demonstrated that organosilanes were weaker hydride donors than 1,4-dihydropyridine derivatives in DCM.[76] We then verified this by performing the reaction in the presence of Et_3SiH. To our delight, the crude mixture exclusively showed the presence of imine **2.2a** in 77% yield (Table 8, entry 4).

Afterwards, we recognized the need to buffer the resulting acidic mixture of this reaction. As demonstrated in many Tf_2O-mediated electrophilic activation conditions suited for secondary amides,[77] the incorporation of 2-halopyridine derivatives as non-nucleophilic and slightly basic additives in the reaction media was found to be crucial to achieve an appreciable level of efficiency.[78,79] We thus explored base additives, finding that 2-fluoropyridine (2-FPyr) was the optimal choice for ease of purification.[75]

Table 8. Effect of the Reductant



2.1a **2.2a** **2.3a**

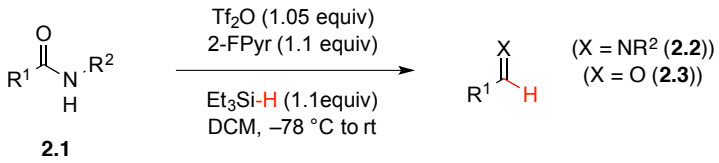
entry	reducing agent	ratio **2.2a**:**2.3a**[a]	yield **2.2a** (%)[a]	yield **2.3a** (%)[a]
1	$NaBH_3CN$	0:100	0	38
2	Bu_3SnH	3:97	1	37
3	HEH	47:53	17	19
4	Et_3SiH	100:0	77	0
5	Et_3SiH[b]	100:0	98	0
6	Et_3SiH/HEH[b,c]	0:100	0	96

[a] Obtained by analysis of the crude mixture by ^1H NMR using Ph_3CH as an internal standard. [b] Reduction was performed with 1.1 equiv of Et_3SiH and 1.1 equiv of 2-fluoropyridine as base additive. [c] Reduction was performed with 1.1 equiv of Et_3SiH for 5 h followed by 1.4 equiv of HEH for 12 h.

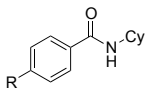
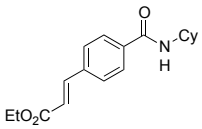
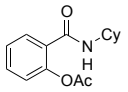
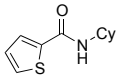
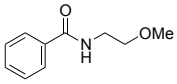
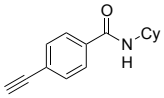
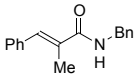
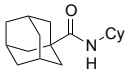
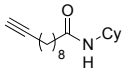
By further optimizing the amount of base, solvent, concentration, and the silane's nature, we were pleased to find that treating amide **2.1a** in the presence of 1.1 equiv of 2-fluoropyridine, 1.05 equiv of Tf_2O and 1.1 equiv of Et_3SiH gave an optimal 98% yield for imine **2.2a** without the observation of amine **2.4a** by ^1H NMR analysis of the crude mixture (**Table 8**, entry 5).[75]

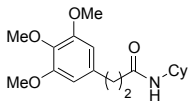
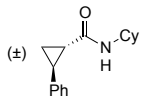
We next investigated the chemoselectivity of the reaction by substituting the aryl of the benzamide by various functional groups susceptible to be reduced with strong nucleophilic hydride donors (**Table 9**). The reaction was found to be very effective for the formation of imines when the media is quenched in basic conditions and aldehydes when the crude mixture is hydrolyzed in the presence of an aqueous buffer of citric acid and THF. As shown in Table 2, the reaction is high yielding for amides containing an electron-withdrawing substituent on the aryl group such as a cyano (entry 2), a nitro (entry 3), an ester (entry 5) and an α,β-unsaturated ester (entry 9). The optimized conditions were also applied to amides bearing the even more electrophilic azido (entry 4), aryl acetate (entry 10) and aldehyde (entry 6) substituents, achieving high yields and an unprecedented chemoselectivity for these groups. Another remarkable result is the complete selectivity obtained for the secondary amide versus a tertiary amide when the electrophilic activation step was performed at –20 °C instead of 0 °C (entry 8).[75] The electron-rich *N*-cyclohexylthiophene-2-carboxamide **2.1k** (entry 11) afforded good yields for the reduction to imine **2.2k** and aldehyde **2.3k**. Alternatively, deuterated aldehydes could be obtained when Et_3SiD was used instead of Et_3SiH (entry 13).[71b] The methodology can also be extended to conjugated vinylic and aliphatic secondary amides (entries 14-18). In certain cases, the imines were found to be unstable, and their corresponding iminium compounds were analyzed by crude ^1H NMR.[75] All these reductions were found to be very selective for the secondary amide moiety by ^1H NMR analysis of the crude mixture, as no over-reduction by-products derived from the other functionalities present were observed.

Table 9. Reduction of Secondary Amides to Imines and Aldehydes



2.1

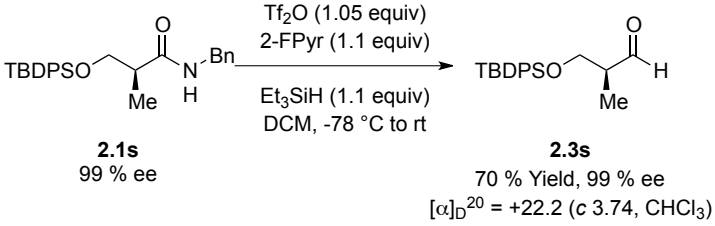
Entry	amide		yield imine (%)[a,b,c]		yield aldehyde (%)[a,d]	
1		**2.1a** R=H	**2.2a**	81	**2.3a**	89
2		**2.1b** R=CN	**2.2b**	88	**2.3b**	89
3		**2.1c** R=NO_2	**2.2c**	84	**2.3c**	81
4		**2.1d** R=N_3	**2.2d**	88	**2.3d**	89
5		**2.1e** R=CO_2Me	**2.2e**	95	**2.3e**	90
6		**2.1f** R=CHO	**2.2f**	(81)[e]	**2.3f**	84[e]
7		**2.1g** R=$PO(OEt)_2$	**2.2g**	(65)	**2.3g**	64
8		**2.1h** R=$CONEt_2$	**2.2h**	99[f]	**2.3h**	95[f]
9		**2.1i**	**2.2i**	96	**2.3i**	96
10		**2.1j**	**2.2j**	80[e]	**2.3j**	84[e]
11		**2.1k**	**2.2k**	85	**2.3k**	80
12		**2.1l**	**2.2l**	79	**2.3a**	85
13		**2.1m**	**2.2m**	95	**2.3m** **2.3m'**	94 90[g]
14		**2.1n**	**2.2n**	(75)	**2.3n**	92
15		**2.1o**	**2.2o**	78[h]	**2.3o**	70[h]
16		**2.1p**	**2.2p**	(80)	**2.3p**	72

17		**2.1q**	**2.2q**	(75)	**2.3q**	70
18		**2.1r**	**2.2r**	(83)	**2.3r**	84

[a] Isolated yields. [b]Yield in parentheses obtained by ^{1}H NMR using Ph_3CH as internal standard. [c] Work-up performed with aq. $NaHCO_3$. [d] Work-up performed with aq. citric acid/THF. [e] Reduction with Et_3SiH was performed at 0 °C for 5 h. [f] Activation of the amide was done at –78 °C for 1 h, followed by –20 °C for 1 h, and 0 °C for 10 min. [g] Reduction was performed with Et_3SiD instead of Et_3SiH. [h] 1.3 equiv of Et_3SiH was used instead of 1.1 equiv of Et_3SiH.

The optimized reduction conditions can also be applied to an enantioenriched secondary amide (**2.1s**) derived from the commercially available (*S*)-Roche's ester (**Scheme 27**). Indeed, aldehyde **2.3s** was isolated with a 70% yield and 93% ee, showing that a racemization pathway *via* the formation of an enamine intermediate is not predominent. This observation is consistent with preliminary results obtained by Movassaghi *et al.* during their studies on the formation of pyridine and pyrimidine substrates with amides possessing an α-enolizable chiral center.[78,79a]

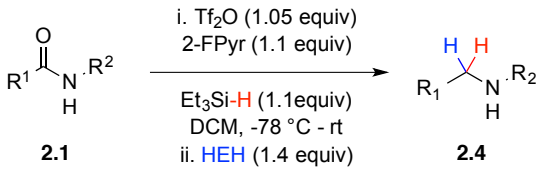
Scheme 27. Metal-free chemoselective reduction of secondary amide derived from (*S*)-Roche's ester



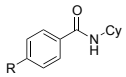
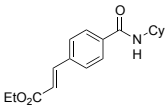
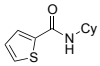
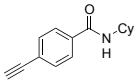
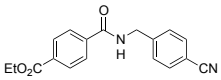
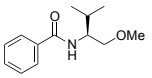
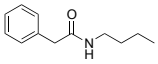
We were also interested in accessing a variety of secondary amines with high chemoselectivities comparable to those observed in the imine or aldehyde syntheses (**Table 10**). After investigating different reduction conditions and hydride sources,[75] we observed that a subsequent addition of 1.4 equiv of HEH *in situ* gave an excellent 96% yield for

amine **2.4a** by ^{1}H NMR (**Table 9**, entry 6).[80] Interestingly, HEH is known as a stoechiometric and non-metallic alternative in hydrogen transfer reactions.[81,73] In our case, the tandem Et_3SiH/HEH reduction was successfully applied to a variety of substrates, as shown in **Table 10**. Indeed, the reaction tolerates the presence of sensitive groups, such as a nitrile, nitro, azido, ester, tertiary amide, α,β-unsaturated ester, and an alkyne (entries 2-6, 8 and 10). The nitrogen branch can also be varied without affecting the efficiency of the reaction: a substituted *N*-benzyl amide and a hindered valine-derived amide reacted smoothly, leading to the corresponding amines in 77% and 89% yield, respectively (entries 11 and 12). Also, amides possessing alkyl substituents α to the carbonyl reacted well under these conditions (entries 13 and 14). It is noteworthy that all of the amines were isolated by employing a simple acid-base extraction, thereby simplifying the purification step.

Table 10. Reduction of Secondary Amides to Amines



2.1 **2.4**

entry	amide		yield amine (%)[a]	
1		**2.1t** R=Br	**2.4b**	86
2		**2.1b** R=CN	**2.4c**	87
3		**2.1c** R=NO_2	**2.4d**	90
4		**2.1d** R=N_3	**2.4e**	89
5		**2.1e** R=CO_2Me	**2.4f**	90
6		**2.1h** R=$CONEt_2$	**2.4g**	90[b]
7		**2.1u** R=OMe	**2.4h**	81[c]
8		**2.1i**	**2.4i**	71
9		**2.1k**	**2.4j**	86
10		**2.1m**	**2.4k**	90
11		**2.1v**	**2.4l**	77
12		**2.1w**	**2.4m**	89
13		**2.1x**	**2.4n**	85
14		**2.1y**	**2.4o**	75

[a] Isolated yields. [b] Activation of the amide was done at –78 °C for 1 h followed by –20 °C for 1 h and 0 °C for 10 min. [c] 2.0 equiv of HEH was used instead of 1.4 equiv.

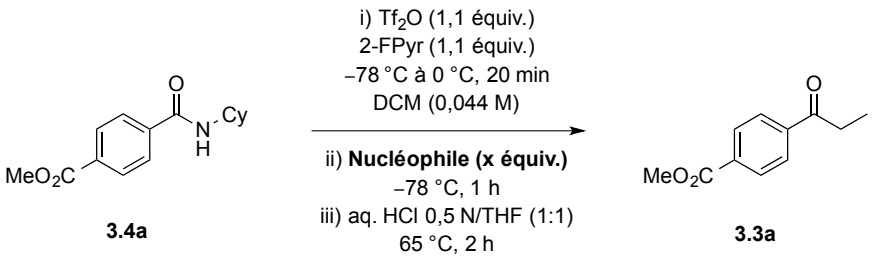
In summary, this work represents an integral and broad complement to the available and efficient tertiary amide reduction methods (*vide supra*). In that sense, general and chemoselective conditions were developed to control the reduction outcome of secondary amides to imine, aldehyde and amine oxidation states. We expect this method to be useful in the total synthesis of more complex molecules by optimizing the step-economy in synthesis planning. Further efforts are ongoing to apply this reduction methodology to other carbonyl moieties and the results will be reported in due course.

Chapitre 3. Chemoselective Synthesis of Ketones and Ketimines by Addition of Organometallic Reagents to Secondary Amides

3.1 Introduction

À la suite du succès obtenu dans le développement de la méthode de réduction contrôlée et chimiosélective d'amides secondaires, nous avons envisagé de développer des conditions similaires pour la synthèse de cétones et de cétimines. Dans ce contexte, nous avons étudié l'emploi de différents réactifs organométalliques en présence de l'amide activé afin de former le lien C–C désiré (**Table 11**). De plus, afin d'étudier la chimiosélectivité de la réaction, nous avons identifié l'amide **3.4a** comportant une fonction ester, comme candidat idéal pour l'étude et pour l'optimisation de la transformation. En fait, la méthode couramment utilisée en chimie organique pour la synthèse des cétones (**3.3a**) à partir d'amides (**3.4a**), a été développée par Weinreb.[82] Cette méthode emploie des réactifs de Grignard et ne tolère pas la présence d'un groupement ester. Nous avons débuté l'optimisation en variant la nature du nucléophile. Tant le réactif de Grignard, que les réactifs organométalliques peu nucléophiles tels que le $(Et)_2CuMgBr$ et le Et_2Zn nous ont permis d'obtenir la cétone désirée (**3.3a**) avec des bons rendement (entrées 1, 5 et 7). De plus, aucune réaction secondaire sur l'ester n'a été observée. Il est important de mentionner que le premier équivalent de réactif de Grignard sert à déprotoner l'acide formé suivant l'activation d'amide. Puis le deuxième équivalent réagit majoritairement avec l'amide activé, lequel est plus électrophile que la fonction ester.

Table 11. Variation de la nature du nucléophile



3.4a **3.3a**

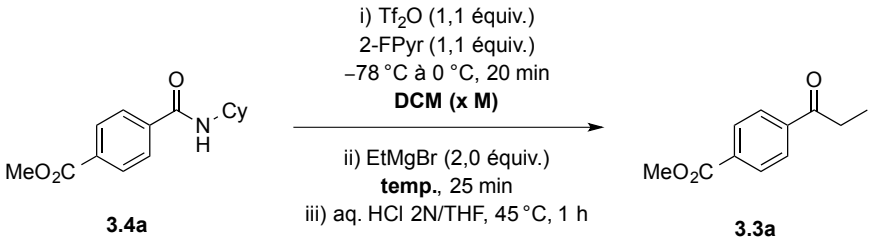
Entrée	Nucléophile	Quantité (équiv.)	Rendement **3.3a** (%)[a]
1	EtMgBr	2,0	87
2	EtLi	2,0	63
3	EtCu[b]	2,0	0
4	$(Et)_2CuMgBr$[c]	1,0	35
5	$(Et)_2CuMgBr$[c]	2,0	82
6	EtMgBr + CuI	2,0 + 0,2	89
7	Et_2Zn	2,0	82[f]
8	EtZnI	2,0	33[f]
9	Et_3In[d]	1,0	30[f]
10	$EtCeCl_2$[e]	2,0	15[f]

[a] Rendement obtenu par analyse du brut par RMN ^1H utilisant le Ph_3CH comme standard interne. [b] Synthétisé à partir de EtMgBr (1,0 équiv.) et CuI (1,0 équiv.). [c] Synthétisé à partir de EtMgBr (2,0 équiv.) et CuI (1,0 équiv.). [d] Synthétisé à partir de $InCl_3$ (1,0 équiv.) et EtLi (3,0 équiv.). [e] Synthétisé à partir de $CeCl_3$ (1,0 équiv.) et EtLi (1,0 équiv.). [f] Réaction effectuée à t.a. plutôt qu'à −78 °C.

Le EtMgBr a été choisi comme réactif organométallique modèle pour la suite de l'optimisation puisqu'il est facilement accessible, stable et commercialement disponible à grande échelle. L'étape suivante consiste à optimiser la base ajoutée lors de l'activation d'amide, de la même manière que ce qui a été fait dans le cadre du développement de la méthode de réduction (**Table 4, Chapitre 1)**. Nous avons de nouveau identifié la 2-fluoropyridine comme la base idéale.

Par la suite, nous avons étudié l'effet de la concentration du substrat dans le solvant et la température de réaction suivant l'addition du nucléophile (**Table 12**). Cette étude nous a permis de constater que des conditions diluées sont nécessaires et que les températures basses permettent d'éviter des réactions secondaires sur la fonction ester (Entrée 12). En effet, nous avons pu observer que des basses températures et des temps de réaction courts jouent un rôle important dans l'obtention de niveaux élevés de chimiosélectivité. De plus, nous avons rapidement identifié que l'hydrolyse de l'intermédiaire cétimine en cétone nécessite 2 h d'hydrolyse à 65 ˚C (Entrée 13).

Table 12. Variation de la concentration et de la température de la réaction



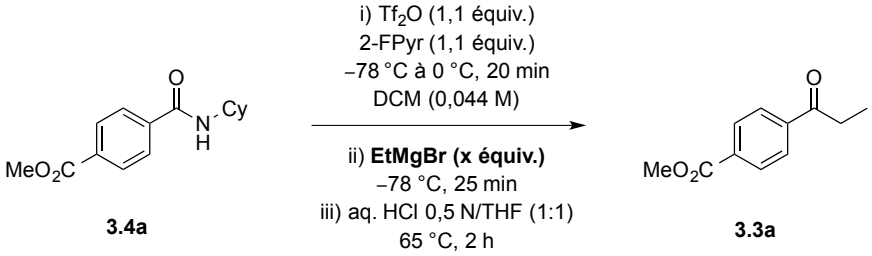
Entrée	Température (°C)	Concentration (M)	Rendement **3.3a** (%)[a]
1	0	0,25	12
2	−20	0,25	26
3	−40	0,25	29
4	−78	0,25	49
5	−95	0,10	75
6	−95	0,25	69
7	−95	0,40	51
8	−95	0,60	38
9	−95	0,80	23
10	−95	1,00	21
11	−78	0,10	71
12	−78	0,044	80
13	−78	0,044	99[b]

[a] Rendement obtenu par analyse du brut par RMN ^{1}H utilisant le Ph_3CH comme standard interne. [b] Hydrolyse effectué pendant 2 h à 65 ˚C.

Nous avons complété l'étude en faisant l'optimisation de la quantité de réactif de Grignard. Étonnamment, cette réaction ne nécessite pas de stœchiométrie stricte de nucléophile (e.g. elle n'est pas limitée à l'ajout d'exactement 2 équivalents pour obtenir des rendements optimaux). En effet, la réaction est très efficace même si un excès de réactif organométallique est ajouté et le produit **3.3a** (ainsi que le produit de départ **3.4**) tolère un

excès de réactif de Grignard dans les conditions optimales (4 équivalents, entrée 4). C'est seulement à partir de 5 équivalents d'EtMgBr que nous pouvons observer des réactions secondaires avec la fonction ester.

Table 13. Variation de la quantité de EtMgBr

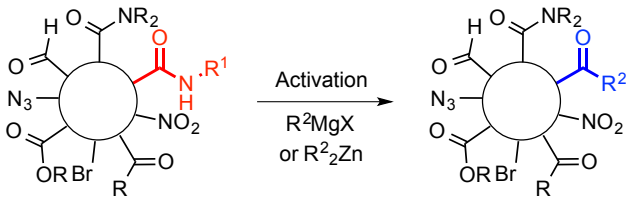


Entrée	EtMgBr (équiv.)	Rendement **3.3a** (%)[a]
1	1,50	74
2	1,75	93
3	2,00	99
4	2,50	99
5	3,00	99
6	4,00	99
7	5,00	99
8	6,00	85

[a] Rendement obtenu par analyse du brut par RMN ^{1}H utilisant le Ph_3CH comme standard interne.

3.2 Abstract

A general and chemoselective method was developed based on an activation/addition sequence on secondary amides allowing the controlled isolation of structurally diverse ketones and ketimines. The generation of a highly electrophilic imidoyl triflate intermediate was found to be pivotal in the observed exceptional functional group tolerance, allowing the facile addition of readily available Grignard and diorganozinc reagents to amides, and avoiding commonly observed over-addition or reduction side-reactions. The methodology has been applied to the formal synthesis of analogues of the antineoplastic agent Bexarotene in excellent yield. Furthermore, combined with the versatility of the Weinreb ketone synthesis, the developed method can be employed in the rapid and efficient synthesis of unsymmetrical diketones from diamides in a one-pot procedure.



3.3 Reference

Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228.

3.4 Article

Chemical synthesis in nature is defined by selective and redox-economical transformations giving rise to complex natural products.[83,84,85,86] The development of synthetic processes with such outstanding chemoselectivity remains a preeminent goal for organic chemists in order to avoid accumulation of unnecessary steps and to allow the extrusion of protecting groups in total synthesis.[87,88,89,90] However, developing widely applicable processes that selectively target a defined functional group is still challenging most particularly in C–C bond forming reactions.[91]

The assembly of the ketone moiety *via* a C–C bond-forming reaction (**Figure 3**) is often featured as a key step in the retrosynthetic analysis of natural and pharmaceutically relevant molecules.[92,93,94,95,96] In this regard, there are abundant examples of ketones synthesized by direct 1,2-addition of organometallic reagents onto electrophilic carboxylic acid derivatives. Unfortunately, these nucleophilic substitutions suffer from limitations involving precarious further additions, poor chemoselectivity, excess use of acylating reagents, or tedious procedures.[97,98] To circumvent these drawbacks, the successful and highly applicable transformation of *N*,*O*-dimethylhydroxyamides (**3.1**) to a variety of functionalized ketones (**3.3**) upon reaction with organolithium or Grignard reagents was developed by Weinreb (**Figure 3b**).[99,100,101] The efficiency of this operation is attributed to the exceptional stability of the 5-membered ring chelate intermediate (**3.2**). Despite the utility and generality of the Weinreb ketone synthesis,[102,103] no comprehensive chemoselectivity study has been reported for this process.[104,105] Interestingly, as pointed out by the pioneer work of Weinreb[99] as well as by a recent example,[105] the addition of Grignard reagents to *N*,*O*-dimethylhydroxyamides containing an ester functionality is not trivial as it results in polyalkylated adducts. Ideally, one would like to obtain various ketones from amides while having the liberty to include unprotected and electrophilic functional groups (ex: esters, ketones, aldehydes, alkyl halides) that are often avoided when using hard nucleophiles.[106,107]

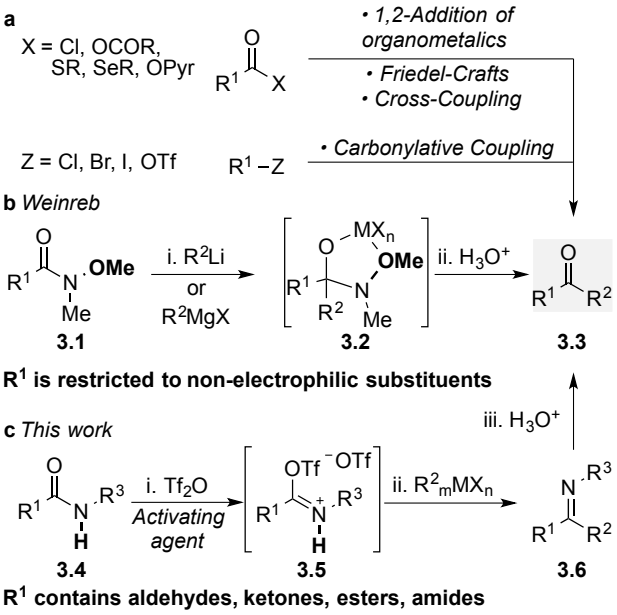
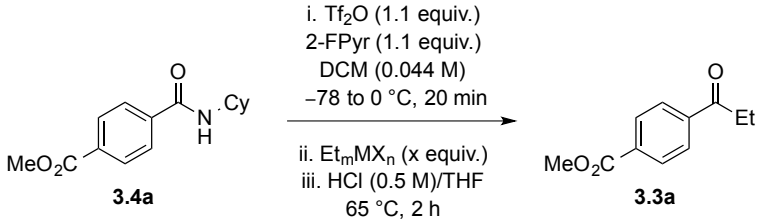


Figure 3. Strategies for the conversion of carboxylic acid derivatives to ketones. **a**. Synthesis of ketones by C–C bond forming reactions. **b.** Conversion of Weinreb amides (**3.1**) to ketones (**3.3**). **c.** Sequential activation/addition on 2° amides (**3.4**) to ketimines (**3.6**) and ketones (**3.3**).

A chemoselective and conceptually distinct approach consists of the *in situ* generation of a highly electrophilic intermediate (**3.5**) from a bench-stable secondary amide (**Figure 3c**). This intermediate may play a dual role: 1) enable an 1,2-addition of organometallics at a faster rate than to other functionalities; 2) prevent further addition by forming initially a stable 2° ketimine (**3.6**) unmasking the ketone moiety (**3.3**) after subsequent acidic work-up. Indeed, the lower electrophilicity of ketimines, as well as their isomerization to an unreactive enamine moiety in basic conditions, prevents over addition at low temperatures.[108,109] Furthermore, such a strategy would considerably be more versatile as it would not be restrained to a certain substituent on the nitrogen amide component. Considering the vast utility of structurally diverse amides as directing[110,111,112] and protecting groups,[107] we hereby report the development of general conditions allowing the controlled conversion of an array of 2° amides (**3.4**) to ketones (**3.3**) and ketimines (**3.6**) with unprecedented functional group tolerance.

Our group has been interested in developing general methods for the controlled reduction of 2° and 3° amides to imines, aldehydes and amines in presence of a variety of functional groups.[113,114] Cognizant of the Lewis basicity of amides, these reductions were enabled by chemoselective activation with triflic anhydride (Tf_2O) in presence of 2-fluoropyridine,[115,116,117,118] and successive addition of Et_3SiH and/or Hantzsch ester hydride (HEH) as poor hydride donors. The incorporation of 2-fluoropyridine as a 2-halopyridine base buffer was found to be mandatory for secondary amides in order to procure acceptable conversion and stability for the imidoyl triflate, as found in many Tf_2O-mediated activation methodologies.[115] Inspired by our precedent success, we next investigated the possibility of developing a sequential activation/addition with various hard organometallic nucleophiles for the synthesis of ketones (**3.3**). To directly address the problem of alkylating *N*,*O*-dimethylhydroxyamide in presence of an electrophilic ester moiety, we decided to establish that amide **3.4a** bearing an methyl ester functionality should be our chemoselectivity benchmark (**Table 14**). In a chemoselective standpoint, the use of hard organometallic nucleophiles is counter-intuitive and contrasts with the choice of Et_3SiH and HEH in the reduction series, which were shown to be inert versus many electrophilic functional groups.[114] Initial attempts with $EtCeCl_2$, Et_3In, or EtLi as alkylating reagents resulted in moderate and sluggish conversion to the corresponding ketone **3.3a** (entries 1-3). However, Et_2CuMgI and Et_2Zn provided good results within 1 h of reaction (82% yield, entries 4 and 5). The addition of a commercially available EtMgBr solution in Et_2O was found to be more practical and provided ketone **3.3a** in a reproducible 87% yield after hydrolysis (entry 6). Shorter reaction times and maintaining the reaction at −78 °C were optimal for the formation of **3.3a** (99% yield, entry 8) as neither over-alkylation on the ketimine intermediate nor on the ester functionality was observed by ^1H NMR analysis of the crude mixture. Stringent experimental precautions are unnecessary since up to 4 equiv of Grignard reagent can be employed without compromising the excellent efficiency and chemoselectivity of the reaction (entry 9). It should be noted that a diluted DCM media (0.044 M) and rapid addition of the nucleophile are recommended as they avoid homocoupling of the enamine intermediate with the activated imidoyl triflate.

Table 14. 1,2-Addition on activated secondary amides to ketones in presence of various organometallic reagents



Entry	Et_mMX_n	Equiv	Et_mMX_n Addition conditions	Yield **3.3a** (%)[a]
1	$EtCeCl_2$	2	–78 °C to rt, 1 h	15
2	Et_3In	1	–78 °C to rt, 1 h	30
3	EtLi	2	–78 °C to rt, 1 h	63
4	Et_2CuMgI	2	–78 °C to rt, 1 h	82
5	Et_2Zn	2	–78 °C to rt, 1 h	82
6	EtMgBr	2	–78 °C to rt, 1 h	87
7	EtMgBr	1.5	–78 °C, 25 min	74
8	EtMgBr	2	–78 °C, 25 min	99
9	EtMgBr	4	–78 °C, 25 min	99
10	EtMgBr	6	–78 °C, 25 min	85

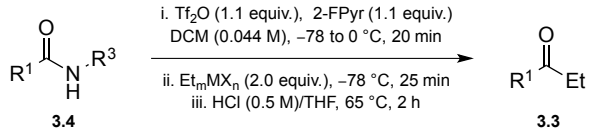
[a] The yields were obtained by 1H NMR analysis of the crude mixture using Ph3CH as an internal standard.

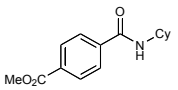
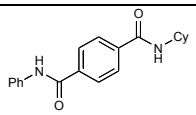
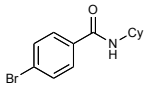
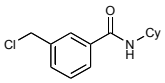
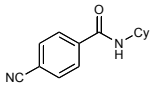
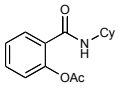
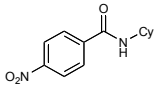
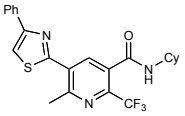
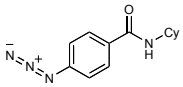
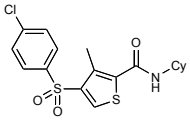
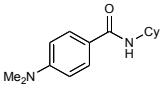
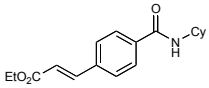
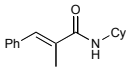
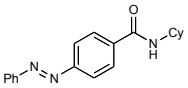
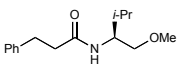
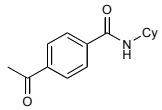
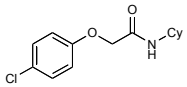
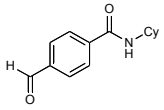
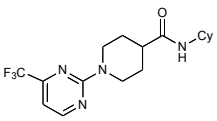
The standard optimized conditions were applied to a large variety of secondary amides (**3.4**) with readily available EtMgBr for a practical set-up procedure to evaluate the functional group tolerance (**Table 15**). High levels of chemoselectivity were achieved with amides bearing substituents known to react with hard nucleophilic organometallic reagents such as esters, aryl and alkyl halides, nitriles, azides, azo, and ketones (entries 1-3, 5, 7-9 and 14). Tertiary and Weinreb amides were also tolerated due to chemoselective activation

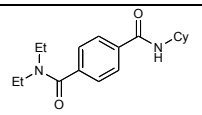
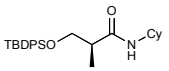
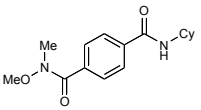
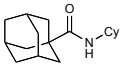
of secondary amides after a longer reaction period with Tf_2O (entries 11 and 12).[114] Alternatively, the concept of selective monoalkylation of a doubly activated *N*-aryl-*N'*-alkyl secondary diamide was explored with substrate **3.4m** (entry 13). It is important to note that the addition of 2 equiv of EtMgBr to activated *N*-aryl secondary amide resulted in low conversion to the desired ketone. Since **3.4m** is poorly soluble in DCM, it required a prolonged activation time and an excess of EtMgBr (3.5 equiv) in order to selectively alkylate the activated *N*-alkyl segment furnishing a reasonable 60% yield for **3.3m**. Interestingly, the starting amide **3.4m** was the major contaminant observed by ^{1}H NMR of the crude mixture, indicating that partial Tf_2O activation occurred.

The methodology was also applied with success to heterocyclic and more complex amides with a drug-like framework[119,120] containing Lewis basic pyridine, sulfone, or pyrimidine (entries 16, 17, and 21). Enolizable aliphatic activated amides were tolerated in which competitive ketenimine or enamine formation could have been an issue (entries 19-22). To support this observation, an enantioenriched secondary amide **3.4v** derived from the commercially available (*S*)-Roche's ester was submitted to the reaction conditions and showed no racemization after hydrolysis (entry 22). Moreover, the reaction can be scaled-up without significant loss of efficiency (see entry 20 on 13.5 mmol scale). Hindered amides also proceeded smoothly to the activation/alkylation step by warming the reaction to room temperature during the activation sequence (75 % yield, entry 23). When the process involved more sensitive functional groups, diorganozinc reagents were ideal alternatives and provided a broader scope of compatible functional groups. By employing the less nucleophilic Et_2Zn, detrimental over-alkylation was suppressed as opposed to EtMgBr addition on azides, ketones, aldehydes, and aryl acetates (compare entries 5, 9, 10, and 15) and expanded the chemoselectivity to amides carrying an aryl nitro functionality (entry 4).

Table 15. Nucleophilic 1,2-addition with EtMgBr or Et_2Zn on activated secondary amides for the preparation of 1-propanone derivatives



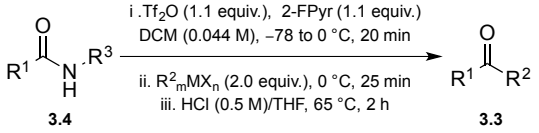
Entry	Amide		Et_mMX_n	Yield **3.3** (%)[a]	Entry	Amide		Et_mMX_n	Yield **3.3** (%)[a]
1		**3.3a**	EtMgBr	96	13		**3.4m**	EtMgBr	60[d]
2		**3.3b**	EtMgBr	74	14		**3.4n**	EtMgBr	88
3		**3.3c**	EtMgBr	92	15		**3.4o**	EtMgBr Et_2Zn	55 75[b]
4		**3.3d**	Et_2Zn	62[b]	16		**3.4p**	EtMgBr	99[c]
5		**3.3e**	EtMgBr Et_2Zn	72 80[b]	17		**3.4q**	EtMgBr	98
6		**3.3f**	EtMgBr	72					
7		**3.3g**	EtMgBr	84	18		**3.4r**	EtMgBr	95
8		**3.3h**	EtMgBr	72	19		**3.4s**	EtMgBr	84
9		**3.3i**	EtMgBr Et_2Zn	61 79[b]	20		**3.4t**	EtMgBr	87 84[e]
10		**3.3j**	EtMgBr Et_2Zn	6 80[b]	21		**3.4u**	EtMgBr	96

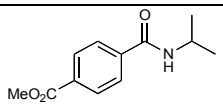
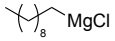
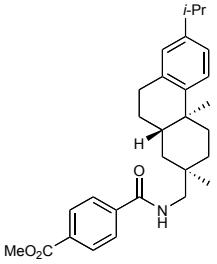
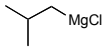
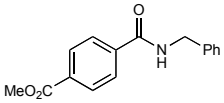
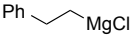
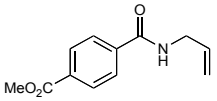
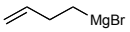
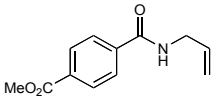
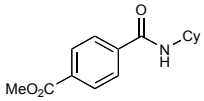
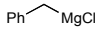
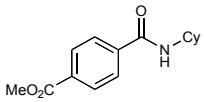
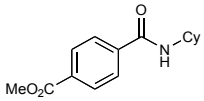
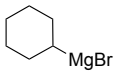
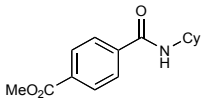
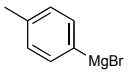
11		**3.3k**	EtMgBr	94[c]	22		**3.4v**	EtMgBr	94[f]
12		**3.3l**	EtMgBr	87[c]	23		**3.4w**	EtMgBr	75[g]

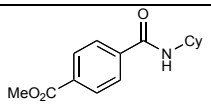
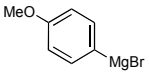
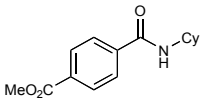
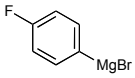
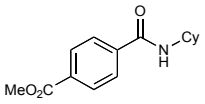
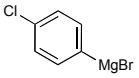
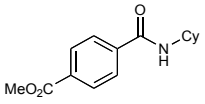
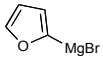
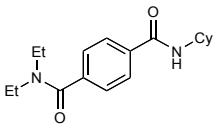
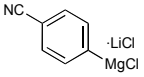
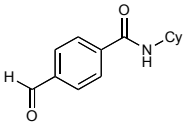
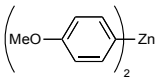
[a] Isolated yields on 1 mmol scale. [b] Et_2Zn (1.5 equiv) added at 0 °C and stirred for 2 h at rt. [c] Amide activated at −78 °C for 1 h, then −20 °C for 1 h, and 0 °C for 10 min. [d] i. Tf_2O (2.2 equiv), 2-FPyr (2.2 equiv), −78 °C to rt for 40 min ii. EtMgBr (3.5 equiv), −78 °C, 25 min. [e] Isolated yield on 13.5 mmol scale. [f] Amide **3.4v** and ketone **3.3v** were found to be >93% ee. [g] Amide activated at −78 °C for 10 min, then rt for 10 min.

After studying the functional group tolerance of the reaction with EtMgBr and Et_2Zn, we considered the reactivity of a range of different Grignard and diorganozinc reagents by simultaneously varying the amide *N*-substituent. Indeed, the nitrogen alkyl branch (R^3) can be varied without affecting the efficiency of the reaction as *N*-*i*-Pr, *N*-Bn, *N*-allyl, and *N*-(+)-dehydroabiethyl behaved similarly to *N*-Cy amides. Following a subsequent optimization with various Grignard reagents, we observed that the addition of more hindered nucleophiles than EtMgBr should be performed at 0 °C or −20 °C instead of −78 °C to obtain ideal conversions to the ketones (**Table 16**). Using these conditions, commercially available Grignard reagents containing a primary or secondary alkyl (entries 1-4, 7 and 8), alkenyl (entry 5), or aryl (entries 9-12) groups lead to the isolation of the corresponding ketones in good to excellent yields after hydrolysis. 2-Furanylmagnesium bromide prepared from the respective lithiated precursor with $MgBr_2 \cdot OEt_2$ also reacted well with **3.4a** affording a 68% yield (entry 13). An example of a functionalized Grignard reagent prepared from 4-bromobenzonitrile and *i*-PrMgCl•LiCl according to Knochel's procedure[121] was added successfully to activated amide **3.4k** (70% yield, entry 14), thus demonstrating the high chemoselectivity of the reaction on both reaction components. Moreover, the addition of diarylzinc species on an aldehyde-containing amide (**3.4j**) provided the desired ketone in good yield without further addition on the aldehyde moiety.

Table 16. Addition of various Grignard and diorganozinc reagents to *N*-alkyl branched amides



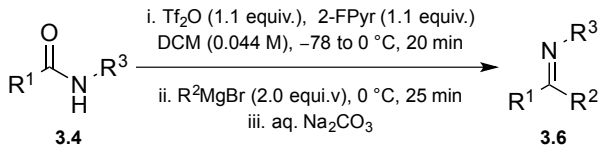
Entry	Amide		$R^2_mMX_n$	Yield **3** (%)[a]
1		**3.4x**		86[b]
2		**3.4y**		94
3		**3.4z**		90
4		**3.4aa**		90
5		**3.4aa**		87
6		**3.4a**		92
7		**3.4a**		92
8		**3.4a**		75
9		**3.4a**		89[c]

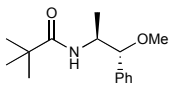
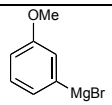
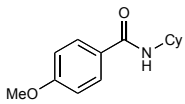
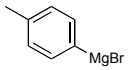
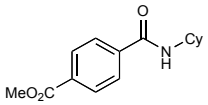
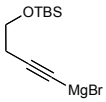
10		**3.4a**		82[c]
11		**3.4a**		99[c]
12		**3.4a**		98[c]
13		**3.4a**		68[c,d]
14		**3.4k**		70[c,d]
15		**3.4j**		80[c,e]

[a] Isolated yields on 1 mmol scale. [b] *n*-DecylMgBr was added at –20 °C and stirred for 25 min. [c] Hydrolysis performed for 3 h. [d] 3.0 equiv of Grignard reagent added. [e] $(PMP)_2Zn$ (1.5 equiv) was added at 0 °C and stirred for 2 h at rt.

We were also interested in controlling the isolation outcome to ketimines considering they are renowned building-block for the generation of ligands[122] and α-chiral amine species.[123] Although enolizable ketimines can be difficult to separate by chromatography due to their fast hydrolysis under acidic conditions,[108] sufficiently stable ketimines were isolated after an aqueous basic work-up with Na_2CO_3 (**Table 17**). In the case of ketimine derived from amide **3.4ac** a mixture of stereoisomers (18:1, *E*:*Z*) was obtained in 84% combined yield (entry 2). Moreover, it is possible to isolate the amine branch following an acid/base work-up after hydrolysis of the corresponding ketimine (see entry 1 and supplementary information Sx to Sx).

Table 17. Secondary ketimines isolation after basic work-up



Entry	Amide		R^3MgBr	Yield **3.6** (%)[a]
1		**3.4ab**		82[b] **3.6a**
2		**3.4ac**		84[c] **3.6b**
3		**3.4a**		88[d] **3.6c**

To contrast the synthetic utility of our methodology with established ketone syntheses, the formal synthesis of analogues (**3.7**-**3.9**) of the antineoplastic agent, bexaroten was explored (**Figure 4a**).[124] The tetrahydronaphthalene **3.7** and dihydronaphthalenes **3.8**-**3.9** have been identified by Eli Lilly as promising retinoid-X receptors (RXR) agonists for the treatment of non-insulin dependent diabetes (type II) mellitus (NIDDM).[124,125] Initial trials by Eli Lilly were performed using the acyl chloride **3.11** or Weinreb amide **3.12** containing an ester functionality affording the desired ketone **3.10** with low yields due to over-addition on the ester moiety with the lithium reagent (**3.13a**) or rapid oxidation of the Grignard nucleophile (**3.13b**) (**Figure 4b**, entries 1-3).[124] To gauge the chemoselectivity of our methodology with the previous results, the addition of the Grignard reagent **3.13b** to the secondary amide **3.4a** was performed and provided the desired ketone **3.10** with an excellent 95% yield without addition on the ester component (**Figure 4b**, entry 4).

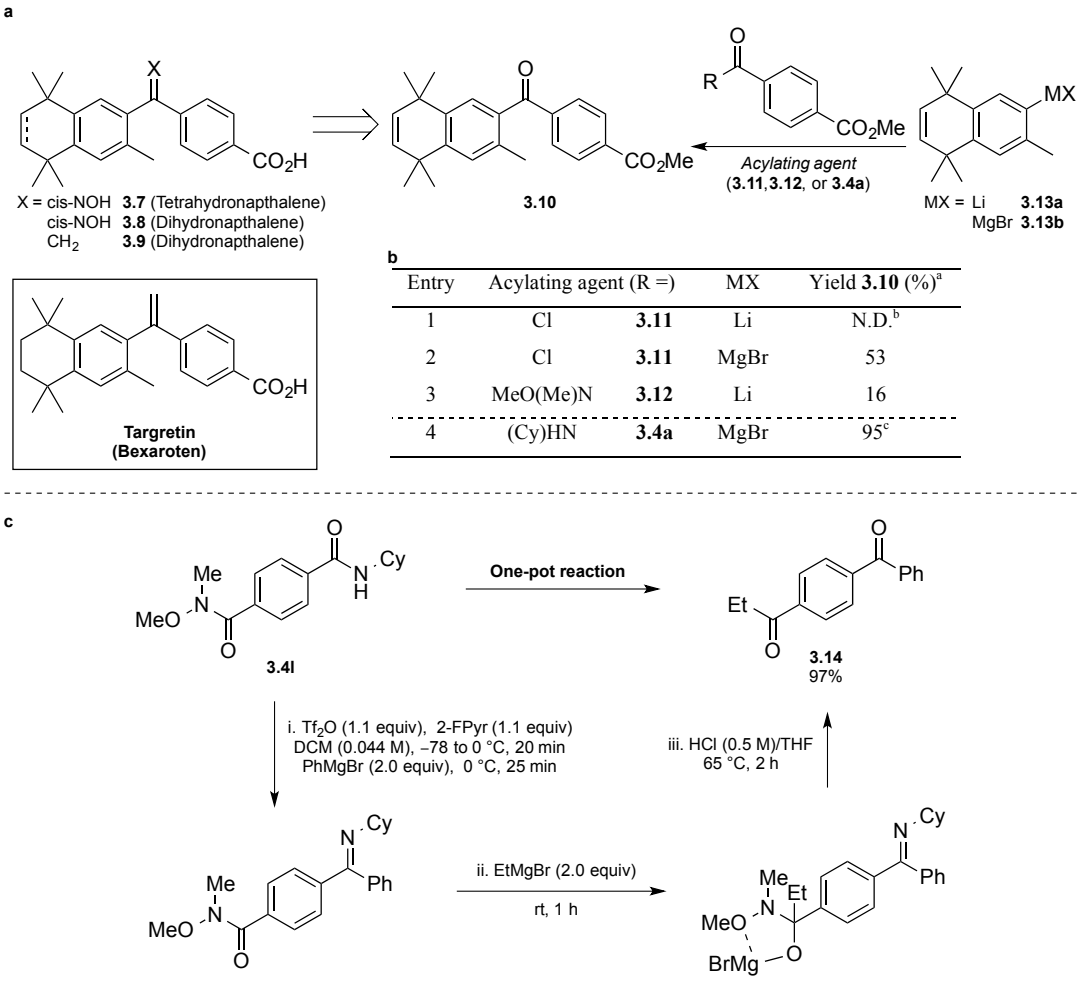


Figure 4. Applications of the methodology. **a**, Formal synthesis of targretin analogues **3.7**-**3.9** with different 1,2-addition strategies. **b**, Comparison of results obtained by Eli Lilly using acyl chloride **3.11** and Weinreb amide **3.12** with the present methodology. [a] Isolated yields [b] Unidentified multiple products obtained. [c] Using reaction conditions illustrated in table 16 on 1 mmol scale with 3.0 equiv of Grignard reagent and performing the hydrolysis for 5 h. **c**, One-pot synthesis of an unsymmetrical diketone. Diamide **3.4l** is converted to the diketone **3.15** by successive addition of two organomagnesium reagents followed by hydrolysis.

Continuous efforts have been directed towards the synthesis of unsymmetrical diketones.[126,127] In this regard, the Weinreb ketone synthesis allows a direct access to these units by successive additions with two different organometallic nucleophiles in a one-pot

procedure.[128,129] Unfortunately, this operation was shown to work with C_2-symmetric substrates and is not chemoselective for a particular amide.[101] To address this problem, the combination of Weinreb amides with secondary amides was explored towards the one-pot synthesis of unsymmetrical diketones (**Figure 4c**). We hypothesized that a double addition could be performed by the successive addition of a Grignard reagent to the activated amide at a low temperature followed by addition of the second nucleophile at room temperature. This strategy was envisioned after observing the chemoselective transformation of amide **3.4l** to the corresponding ketone **3.3l** in presence of a Weinreb amide moiety (see **Table 15**, entry 12). Using this approach, ketone **3.15** was synthesized in 97% isolated yield by successive addition of PhMgBr at 0 °C and EtMgBr at room temperature. The addition of these two Grignard reagents can be inversed without affecting the efficiency of the reaction (95% yield for **3.15,** see supplementary information).

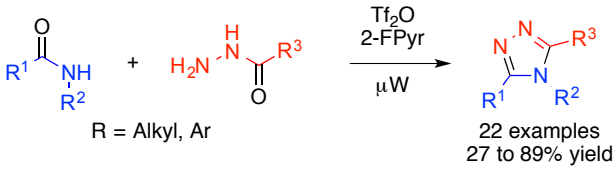
The exceptional chemoselectivity feature studied in the present methodology allows the controlled conversion of secondary amides to structurally diverse ketones and ketimines. A sequential activation/addition with Tf_2O is efficiently performed by the addition of readily available Grignard and diorganozinc reagents. The success of this approach is attributed to the generation of a very reactive intermediate, which reacts in a 1,2-addition at a faster rate and permits control of over-addition by the formation of a ketimine intermediate. The method obviates the need to prepare a specific acylating reagent in order to synthesize ketones. Thus, the results showcase the first comprehensive study that exploited the unique chemoselectivity of the transformation. Other applications illustrating the synthetic potential of this methodology were disclosed through the synthesis of Bexaroten analogues and unsymmetrical diketones. The development of this protocol should allow the late stage and diversified functionalization of secondary amides in total synthesis by sparing the use of unnecessary protecting groups. Efforts are presently directed toward the application of this concept to tertiary amides and peptide derivatives. The results will be reported in due course.

Chapitre 4. One-Pot Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles via the Addition of Hydrazides to Activated Secondary Amides

4.1 Abstract

A general approach has been developed for the one-pot synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from secondary amides and hydrazides via triflic anhydride activation followed by microwave-induced cyclodehydration. In addition, the 1,2,4-triazole moiety is shown to be a useful directing group for Ru-catalyzed C–H arylation. Access to 1,2,4-triazolophenanthridine can be achieved from the reaction products using a Pd-catalyzed intramolecular C–H functionalization reaction.

Scheme 28.



4.2 Reference

Bechara, W. S.; Khazhieva, I. S.; Rodriguez, E.; Charette, A. B. *Org. Lett.* **2015**, *17*, 1184.

4.3 Article

The 1,2,4-triazole motif has attracted considerable interest in the fields of medicinal and coordination chemistry as well as in materials science.[130] For example, this five-membered ring scaffold is found in numerous biologically active compounds[131] and pharmaceuticals, including maraviroc,[132] alprazolam, triazolam[133] and sitagliptin.[134] Notably, this heterocycle is used as amide *cis*-bond isostere for both peptide mimicry and drug design, where it can improve the pharmacological properties of the corresponding lead compound.[135] 1,2,4-Triazoles have also been extensively studied as ligands for mononuclear and oligonuclear metal coordination, exhibiting interesting physical properties.[136] Recent applications illustrate that the incorporation of the 1,2,4-triazole ligand into functional heteroleptic Ir(III) complexes affords a sky-blue emission with attractive quantum yields for potential use in organic light emitting diodes (OLEDs).[137]

Owing to its broad spectrum of functions, a number of synthetic methods have been developed for the synthesis of substituted 1,2,4-triazoles **4.3** (**Figure 5**).[130] The most commonly investigated pathways involve cyclodehydration of *N*-acylamidrazone derivatives **4.2**, which can be formed from various precursors, such as amides **4.1**,[130] amidrazones **4.4**,[138] *N*′-acetyl-*N*,*N*-dimethylhydrazonamides **4.5**,[139] oxadiazoles **4.6**,[140] and *N*-acylhydrazides **4.7**.[141] Substituted 1,2,4-triazole derivatives are also synthesized from dichloroaldazines **4.8** by treatment with anilines at 170 °C.[142] Unfortunately, most of the methods require multistep synthetic procedures as well as the use of non-readily available starting materials and/or are limited to a methyl substituent at the C-5 position (R^3 = Me).[139]

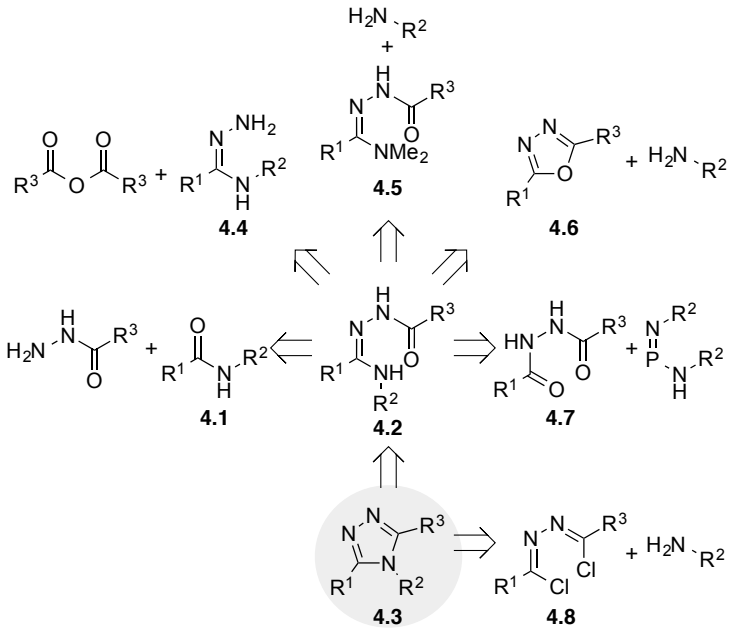
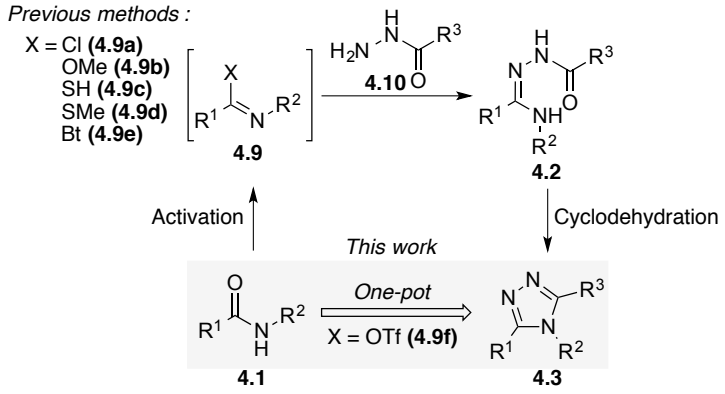


Figure 5. Different synthetic pathways leading to 3,4,5-trisubstituted 1,2,4-triazoles

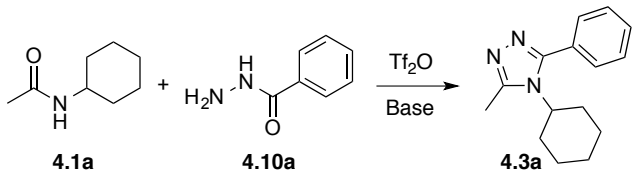
Considering the ubiquity of substituted 1,2,4-triazoles in synthetic and applied chemistry, from both step-economy and medicinal chemistry perspectives, a process that allows the direct synthesis of 1,2,4-triazoles from secondary amides is of high interest. The formation of such heterocycle via the addition of hydrazides to activated amide derivatives have been reported by different research groups (**Figure 6**). These methods include the use of chloromethylene amides[143] **4.9a**, imidates **4.9b**,[144] thioamides **4.9c**,[145] thioimidates **4.9d**[146] and imidoylbenzotriazoles **4.9e**.[147] However, these approaches suffer from various limitations, such as the use of excess activating reagent (which oftentimes must be removed before the cyclodehydration step), the use of toxic metals, the isolation of the activated reactant, long reaction times, sensitivity to steric hindrance of starting materials, and an overall narrow scope in terms of substitution diversity at the C-3, N-4 and C-5 positions. Therefore, developing general and practical one-flask procedures to access multiple 3,4,5-trisubstituted 1,2,4-triazole derivatives from readily available secondary amides is desirable. To address these previous issues, we decided to pursue an operationally simple trifluoromethanesulfonic anhydride (Tf_2O) mediated activation strategy towards **4.3** while employing readily available secondary amides **4.1** and hydrazides **4.10** (**Figure 6**).

Figure 6. Synthesis of 3,4,5-trisubstituted 1,2,4-triazoles via activated amides as intermediates



Various methods based on the chemoselective electrophilic activation of secondary amides with Tf_2O in the presence of 2-halopyridine and a suitable nucleophile have been disclosed by our group[148] and others.[149] These processes allowed the expedient and efficient synthesis of valuable functional groups, including aldehydes, imimes, amines, ketone, ketimines and imidazopyridines.[148] Inspired by these previous achievements, we envisioned that the versatility and the electrophilicity of imidoyl triflate **4.9f** would allow it to be a suitable candidate for the rapid nucleophilic addition of hydrazides at a low temperature, combined with a sequential cyclodehydration of the *N*-acylamidrazone intermediate **4.2**. We first investigated previously reported conditions[148] by performing the activation of amide **4.1a** at 0 °C in DCE in the presence of 2-fluoropyridine (2-FPyr) as a base. The *in situ* addition of hydrazide **4.10a** to the activated species afforded a reasonable 52% yield for triazole **4.3a**, following cyclodehydration at 120 °C for 1 h under microwave irradiation (**Table 18**, entry 2). By performing the cyclodehydration at 140 °C for 2 hours, the corresponding triazole was obtained in 85% yield. The reaction could also be performed successfully when employing DCM as solvent (entry 5).

Table 18. Optimization for the activation/cyclodehydration



4.1a **4.10a** **4.3a**

entry	base [a]	solvent (0.3 M)	μW temp (°C)	time (h)	yield **4.2a** (%) [b]
1	none	DCE	110	1	27
2	2-FPyr	DCE	110	1	52
3	2-FPyr	DCE	140	1	68
4	2-FPyr	DCE	140	2	85
5	2-FPyr	DCM	140	2	81

[a] Conditions: **4.1a** (1.0 mmol), solvent (0.3 M), 2-FPyr (1.1 equiv), Tf_2O (1.1 equiv) at 0 °C for 10 min, then **4.10a** (1.1 equiv) and mW heating for the given time. [b] Yields determined by ^1H NMR analysis using Ph_3CH as an internal standard.

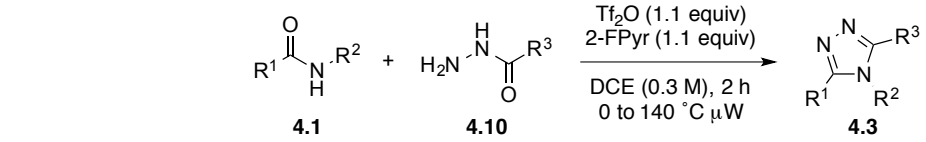
To expand the scope of the one-pot activation/nucleophilic addition/cyclodehydration sequence, various amides and hydrazides were evaluated under our optimized reaction conditions (**Table 19**). To our delight, the triazole synthesis is applicable to a wide variety of substitution patterns at the C-3, N-4 and C-5 positions. Triaryl triazoles **4.3b-4.3d** are obtained in moderate to good yields, as observed with other methods. *N*-Alkyl substituted triazoles **4.3e-4.3l** bearing different functional groups are well tolerated in the methodology. The combination of *N*-alkyl with other C-aryl/alkyl substituents **4.3a** and **4.3m-4.3t** is also possible, in which different amides and hydrazides can be employed with success. The procedure can also be extended to the synthesis of trialkyl substituded triazole **4.3u** in 54% yield. Even substrates with a steric bias that are difficult to obtain by previous methods (such as **4.3g**, **4.3n**, and **4.3o**), are currently produced in moderate to good yields under our optimized conditions. Moreover, the described method allows the synthesis of

chiral 1,2,4-triazoles **4.3k** and it tolerates some heterocycles, such as a thiophenyl (**4.3h, 4.3i, 4.3t**) and a benzothiophenyl group (**4.3l**).

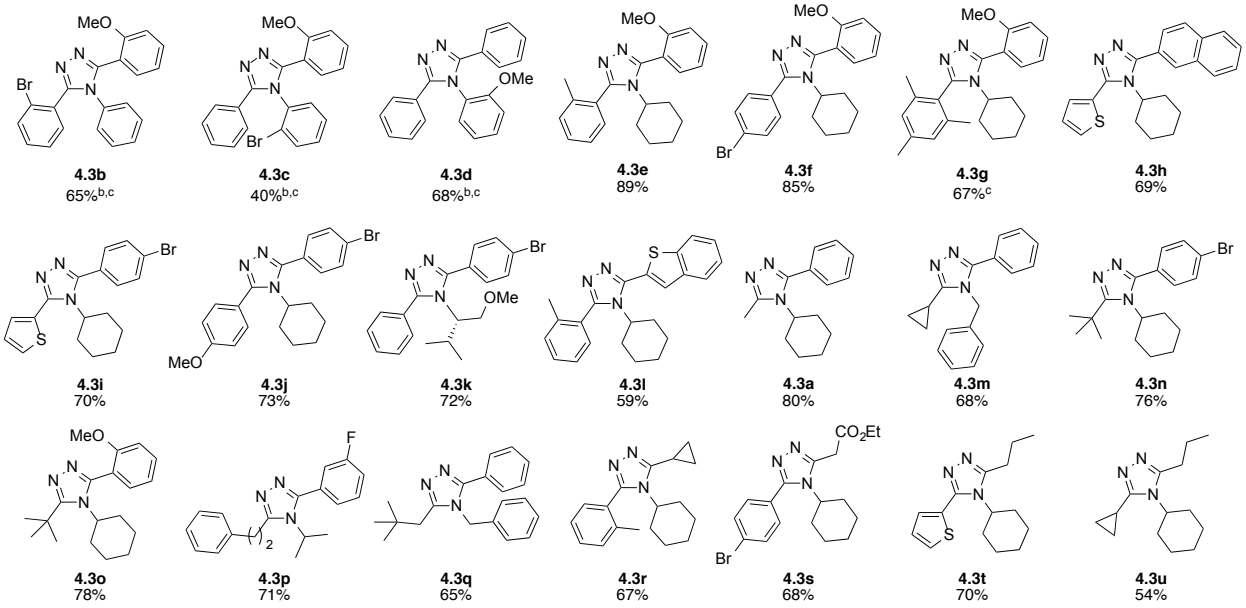
Given the plethora of methodologies that exploit nitrogen-based chelating groups for transition metal-catalyzed C–H functionalization,[150] we sought to take advantage of the two contiguous nitrogen atoms at N-1 and N-2 of the 1,2,4-triazole to selectively perform a Ru-catalyzed C–H arylation at the *ortho* position of the C-3 aryl substituent (**Scheme 29**).[151] Non-optimized conditions using $[RuCl_2(p\text{-cymene})]_2$ complex as the catalyst, were applied to triazole **4.3v** in the presence of bromoacetophenone as the coupling partner. The monoaryl product **4.3v** was obtained in moderate yield (59%), demonstrating the efficiency of 1,2,4-triazole motif as a directing group for C–H arylations.

To further expand the elaboration of 1,2,4-triazoles towards the synthesis of more complex heterocycles, a Pd-catalyzed intramolecular C–H activation reaction was carried out (**Scheme 29**).[152] Starting from triazoles **4.3b** and **4.3c**, 1,2,4-triazolophenanthridine **4.3x** was isolated in 41% and 28% yield correspondingly. Although the phenanthridine scaffold is found in bioactive natural alkaloids and medicinally relevant compounds,[153] there are only scarce examples of processes allowing the synthesis of 1,2,4-triazolophenanthridines.[154]

Table 19. Tf_2O-Mediated One-pot Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles[a]



4.1 + **4.10** → **4.3**



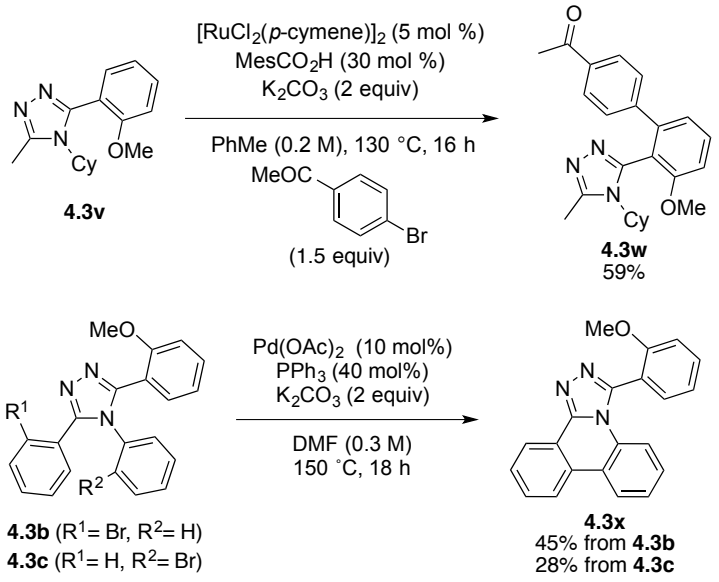
4.3b 65%[b,c] | **4.3c** 40%[b,c] | **4.3d** 68%[b,c] | **4.3e** 89% | **4.3f** 85% | **4.3g** 67%[c] | **4.3h** 69%

4.3i 70% | **4.3j** 73% | **4.3k** 72% | **4.3l** 59% | **4.3a** 80% | **4.3m** 68% | **4.3n** 76%

4.3o 78% | **4.3p** 71% | **4.3q** 65% | **4.3r** 67% | **4.3s** 68% | **4.3t** 70% | **4.3u** 54%

[a] Isolated yields [b] Activation performed with DCM from –78 to 0 °C. [c] Cyclodehydration was performed for 4 h.

Scheme 29. Novel metal-catalyzed C–H functionalization of 3,4,5-trisubstituted 1,2,4-triazoles



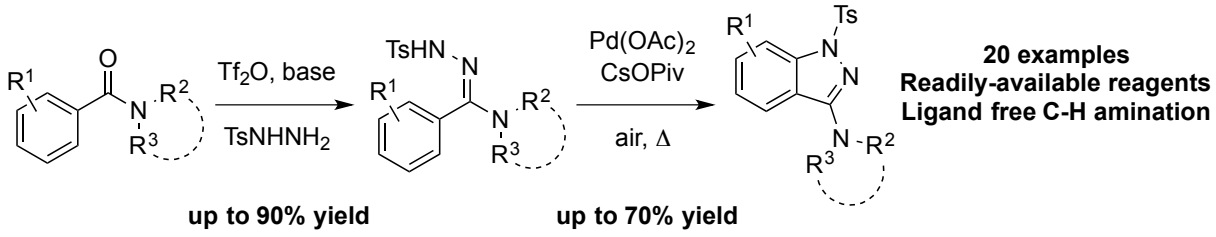
In summary, we successfully developed a general one-pot synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from readily available secondary amides and hydrazides via triflic anhydride activation followed by microwave-induced cyclodehydration. The method is effective at relatively short reaction times while using minimal amounts of activating reagent. The conditions were applied to the synthesis of a variety of 3,4,5-trisubstituted 1,2,4-triazoles with different alkyl/aryl substitution patterns. Moreover, trisubstituted triazoles were proved to be useful handles for both intramolecular Pd-catalyzed and intermolecular Ru-catalyzed C–H functionalization reactions towards the synthesis of triazolophenanthridine and highly substituted triazole. Current efforts in our group are directed toward the expansion of the scope of such C–H functionalization reactions and the results will be reported in due course.

Chapitre 5. An Intramolecular C–H Amination Strategy Applied to the Rapid Synthesis of 3-Aminoindazoles

5.1 Abstract

A step synthesis of structurally diverse 3-aminoindazoles from readily available starting materials was developed. This sequence includes a one-pot chemoselective Tf2O activation of tertiary amides and nucleophilic addition of hydrazides to form aminohydrazones. These precursors then participate in an intramolecular ligand-free Pd-catalyzed C–H amination. The azaheterocycles synthesized via this approach were further diversified by subsequent deprotection/alkylation or transition metal-catalyzed arylations.

Scheme 30.



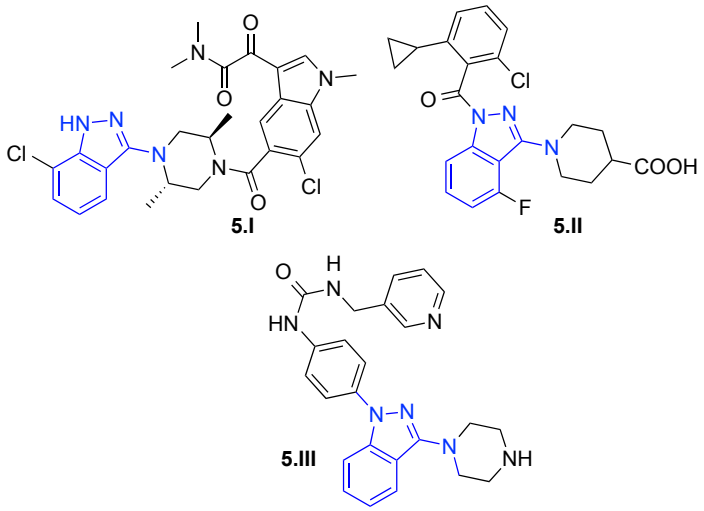
5.2 Reference

Cyr, P.; Régnier, S.; Bechara, W. S. Charette, A. B. *Org. Lett. accepted*.

5.3 Article

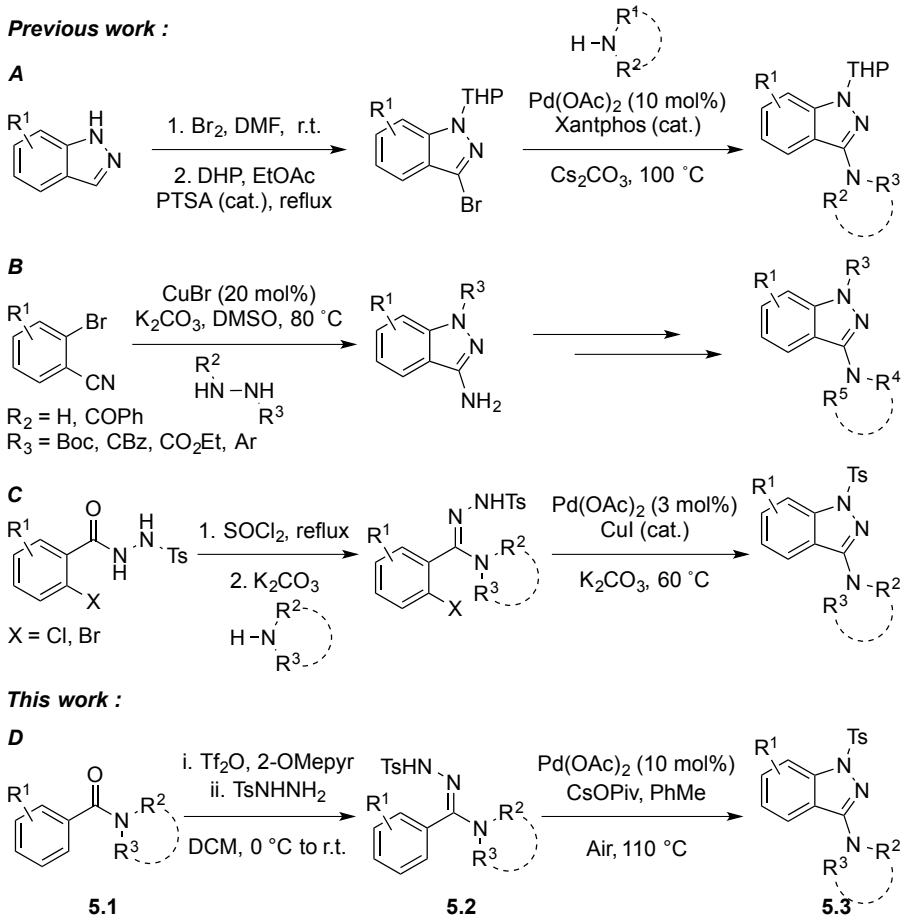
The omnipresence of bioactive nitrogen-containing heterocycles in recently approved drugs continues to inspire organic chemists to develop modular synthetic methodologies toward members of this large family.[155] For example, a recent increasing interest in the indazole scaffold stems in part from the natural rarity of this bicyclic motif and to its potential to act as a successful active bioisostere for various drug designs.[156,157,158] In this context, the 3-aminoindazole scaffold has particularly found broad applications in medicinal chemistry.[159] As such, pharmaceutical leads incorporating this privileged heterocycle were shown to display a wide range of biological responses including anti-psoriasis (**5.I**),[159a] anti-inflammatory (**5.II**),[159c] and anti-cancer (**5.III**)[159a,b] activities (illustrated in blue, Figure 7). Considering their expanded incorporation in important therapeutic leads, intensive efforts have been dedicated toward finding general synthetic operations for the assembly and functionalization of 3-aminoindazoles.[160]

Figure 7. Clinically active pharmaceutical leads bearing substituted 3-aminoindazoles.



With this goal in mind, various metal-catalyzed amination strategies towards 3-aminoindazole were recently disclosed. For example, a 3-step amination protocol based on a preformed indazole subunit was optimized in order to include a Buchwald-Hartwig cross-coupling between secondary amines and a 3-bromoindazole unit (**Scheme 8A**).[161] With the advantage to be operationally simple, the efficacy of this pathway suffers from the requirement to prepare the initial free base indazole, low overall yields, limited functional group tolerance, and narrow scope. A different approach to 3-aminoindazoles involves a sequential intermolecular C–N bond forming step, via either aromatic nucleophilic substitution or metal-catalyzed cross-coupling of 2-halobenzonitriles with hydrazides, followed by a condensation reaction (**Scheme 8B**).[162] However, these reactions are intrinsically limited to costly starting materials and require further synthetic functionalization of free primary amine product, for which limited examples have been reported in the literature.[163] A more convergent and combinatorial approach towards *N*',*N*'-disubstituted 3-aminoindazoles proceeds via intramolecular Pd-catalyzed cross-coupling of *ortho*-halogenated *N*-tosylamidrazones (**Scheme 8C**).[164] Unfortunately, the latter is likewise limited to prefunctionalized and non-commercially available tosylated hydrazides and requires tedious synthetic operations involving purification issues for each intermediate.[165] Thus far, most approaches suffer from lengthy syntheses of specific aromatic halides, which limits the synthetic availability of substituted 3-aminoindazoles.[166]

Figure 8. Strategies towards the formation of substituted 3-aminoindazoles.



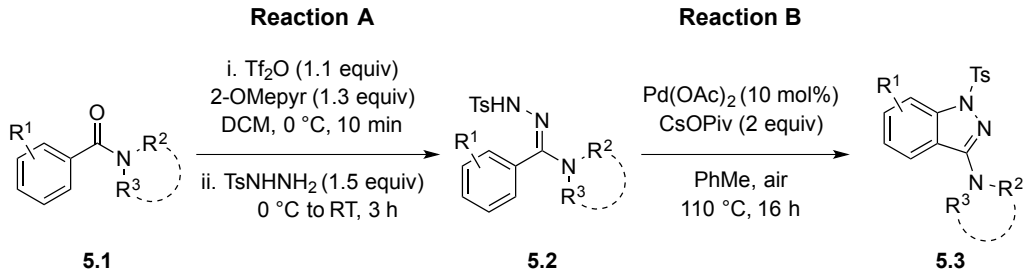
Our group has a long-standing interest in triflic anhydride (Tf_2O) activation and derivatization of amides[167] as well as in metal-catalyzed C–H functionalizations.[168] We sought to reunite both of these chemical processes in a step-economic and operationally simple procedure that is amenable to substituted 3-aminoindazoles (**5.3**) starting from readily available shelf-stable building blocks (**Scheme 8D**). Our envisioned strategy includes a novel intramolecular Pd-catalyzed C–H amination reaction of hydrazonamides (**5.2**), themselves derived from readily available tertiary amides (**5.1**) and hydrazides.

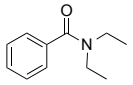
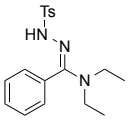
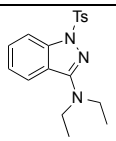
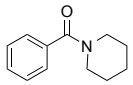
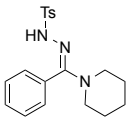
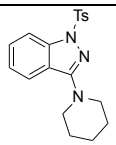
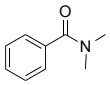
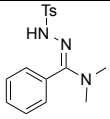
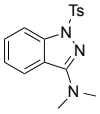
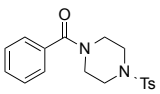
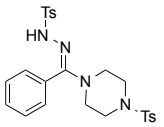
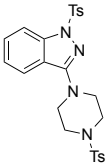
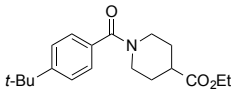
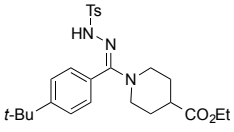
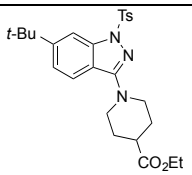
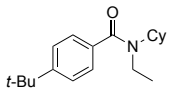
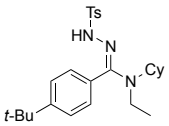
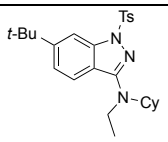
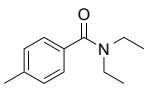
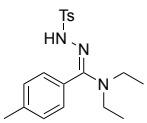
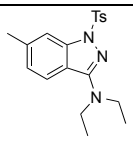
Initially, we had to carefully refine each parameters associated to the amide activation step as well as for the unprecedented *in situ* nucleophilic addition of the *N*-

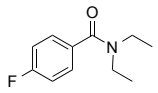
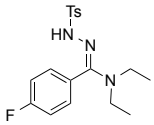
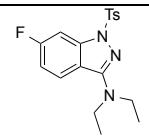
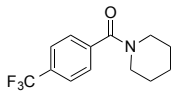
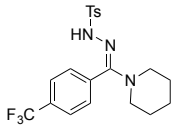
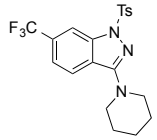
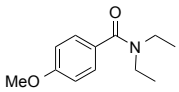
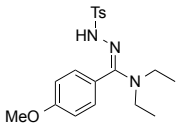
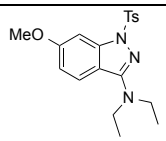
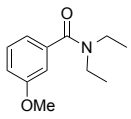
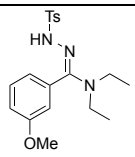
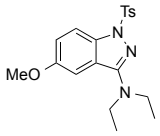
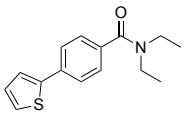
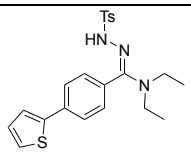
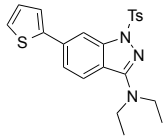
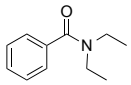
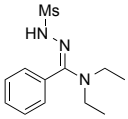
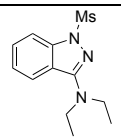
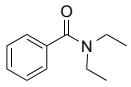
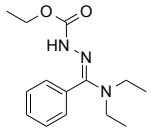
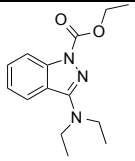
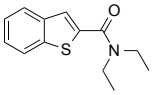
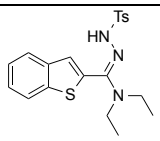
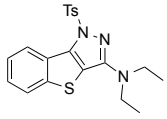
tosylhydrazide nucleophile.[169] Following other well-established chemoselective Tf_2O activation protocols,[170] a base screen was envisioned for the activation of **5.1a** in presence of 1.1 equiv of Tf_2O in DCM at low temperatures. This tuning turned out to be essential as the incorporation of 2-methoxypyridine (2-MeOPyr), a mild base additive, was mandatory in order to achieve an appreciable yields for **5.2a** (90%). As a proof of concept, the stable hydrazonamide **5.2a** was then submitted to different transition metal-catalyzed C–H amination conditions in presence of external oxidizing agents.[169] Inspired by extensive developments in oxidative C–H functionalizations,[171] we were delighted to find that the desired C–N bond forming reaction was achieved when the reaction was run under air and in presence of catalytic $Pd(OAc)_2$ with CsOPiv in refluxing toluene.

As the previous reaction conditions were found optimal for the efficacy of both the amide derivatization and the intramolecular catalytic C–H amination reactions, the substrate scope was studied (**Table 20**). The overall process was shown to be effective in presence of various amides and tolerates different substitution patterns on both the aryl and nitrogen substituents of the benzamide (entries 1-12). Cyclic and acyclic amines can be incorporated at the C-3 position of the desired indazole with consistency in yields for the activation step (Reaction A), although with a more variable efficacy for the C–H functionalization step (Reaction B). Indeed, variation of the electronic properties of the aryl ring on the benzamide displayed marginal influence for the first activation step (Reaction A), whereas the lower conversions were observed for the C–H amination step in presence of strongly electron donating or withdrawing groups at the *para* or *meta* positions (reaction B, entries 9-11). With substrate **5.1l** containing a *meta* substituent on the aryl ring, the cyclization reaction produced a 19:5 mixture of regioisomers (**Table 20**, entry 11). The tosylhydrazide nucleophile can also be replaced by other hydrazides with different electron-withdrawing protecting groups at the N-1 position; however, the desired product were produced in lower yields (**Table 20**, entries 13 and 14). Remarkably, the transformation is also productive in presence of amides bearing heteroaryl groups allowing for the formation of more complex 3-aminoindazobenzothiophene heterocycle (**Table 20**, entry 15).

Table 20. Two-step synthesis of 3-*N'.N'*-disubstituted amino-*N*-tosylindazoles



Entry	Amide **5.1**		Tosylhydrazide **5.2**		3-Aminoindazole **5.3**		Yield **5.2** [%][a]	Yield **5.3** [%][b]
1		**5.1a**		**5.2a**		**5.3a**	90	65
2		**5.1b**		**5.2b**		**5.3b**	71	67
3		**5.1c**		**5.2c**		**5.3c**	82	20
4		**5.1d**		**5.2d**		**5.3d**	65	39
5		**5.1e**		**5.2e**		**5.3e**	76	44
6		**5.1f**		**5.2f**		**5.3f**	82	59
7		**5.1g**		**5.2g**		**5.3g**	69	70

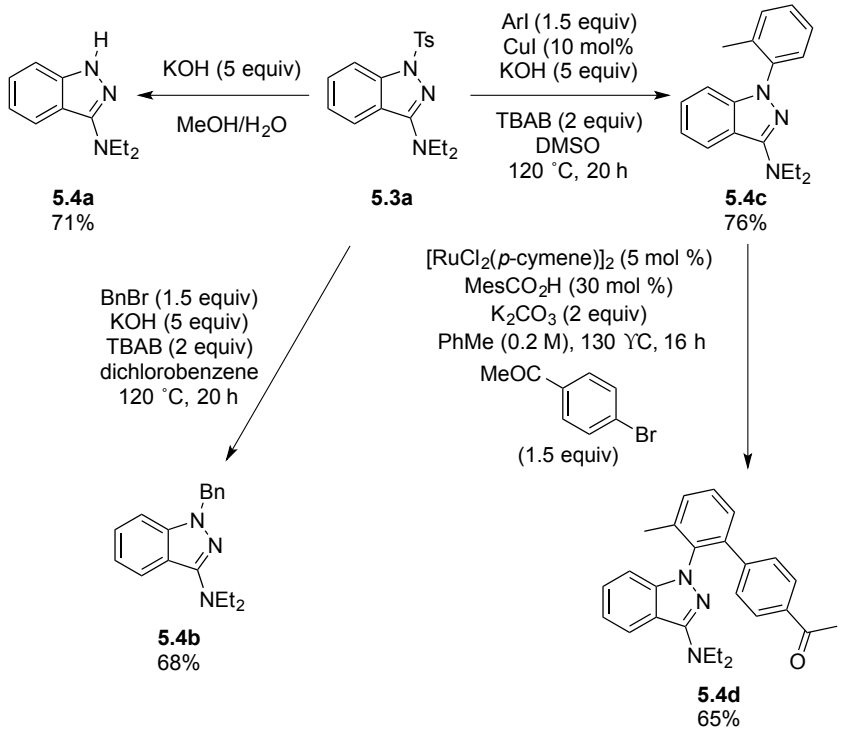
8		**5.1h**		**5.2h**		**5.3h**	79	55
9		**5.1i**		**5.2i**		**5.3i**	73	35
10		**5.1j**		**5.2j**		**5.3j**	74	15
11		**5.1k**		**5.2k**		**5.3k**	44	30[d]
12		**5.1l**		**5.2l**		**5.3l**	67	62
13		**5.1a**		**5.2m**		**5.3m**	70[c]	44
14		**5.1a**		**5.2n**		**5.3n**	84[c]	15
15		**5.1o**		**5.2o**		**5.3o**	86	27

[a] Isolated yields on 0.56 mmol scale. [b] Isolated yields on 0.28 mmol scale. [c] 1.3 equiv of $TsNHNH_2$ was used. [d] A 19:5 mixture of regioisomers was observed (major isomer illustrated in the table).

We were also eager to demonstrate that the *N*-Ts-3-aminoindazole moiety is a versatile stepping-stone for subsequent functionalization. To do so, we focused our attention on diversifying the sp^3 nitrogen position (N-1 position) by applying useful

synthetic transformations on **5.3a** as a benchmark (**Scheme 31**). For example, the *N*-Ts protecting group was easily cleaved under basic conditions to yield the free 3-aminoindazole **5.4a** in 71% yield**.**[172] Furthermore, a sequential one-pot deprotection-functionalization could be performed by either incorporating an alkylating reagent (BnBr) in the previous conditions, or performing a Cu-catalyzed Buchwald-Hartwig coupling to generate compounds **5.4b** and **5.4c** respectively.[173] We also recognized the synthetic potential of the Schiff base present in 3-aminoindazoles to direct Ru-catalyzed C–H *ortho* arylations on the newly installed *N*-Ar substituent of **5.4c**.[174] Following Ackermann's reported conditions,[174a] bis-aryl containing 3-aminoindazoles **5.4d** was generated in good 65% yield .

Schéma 31. Diverse Functionalizations of *N*-Ts-3-Diethylaminoindazole **5.3a**.



In summary, we have developed a two-step process for the rapid conversion of readily available tertiary amides into valuable 3-aminoindazoles. The disclosed synthetic strategy includes a triflic anhydride-mediated chemoselective derivatization which furnishes *N*-Ts amidrazone intermediates poised for subsequent intramolecular palladium catalyzed C–H

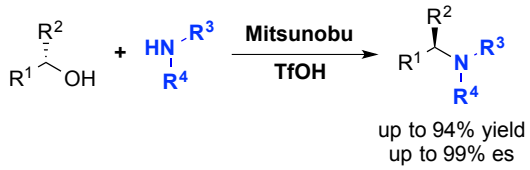
aminations. The optimized conditions allowed for the synthesis of substituted 3-aminoindazoles with broad substitution patterns. Moreover, the resulting azole product can take part in various other useful transition metal-catalyzed functionalizations. These reactions provide a rapid access to complex heterocyclic scaffolds, and thus, we think our proposed synthetic strategy could be useful in both pharmaceutical and agrochemical industries wherein nitrogen containing bioactive compounds are widespread.

Chapitre 6. Direct Alkylation of Amines with Alcohols via Triflic Acid Mediated Mitsunobu Reaction

6.1 Abstract

The direct conversion of alcohols to structurally diverse amines employing the Mitsunobu reaction is achieved with high efficiency in acidic conditions. The incorporation of an external and non-nucleophilic acid, such as TfOH, to the general DEAD/PPh3 substitution conditions is the key parameter that allows the use of basic nucleophilic amines as coupling partners. Inversion of configuration is obtained when optically active secondary alcohols are submitted to the reaction conditions as observed in classical Mitsunobu reactions.

Scheme 32.



6.2 Reference

Bechara, W. S.; Jarvis, S. B. D.; Aubé, A.; Charette, A. B. *Org. Lett. To be submitted.*

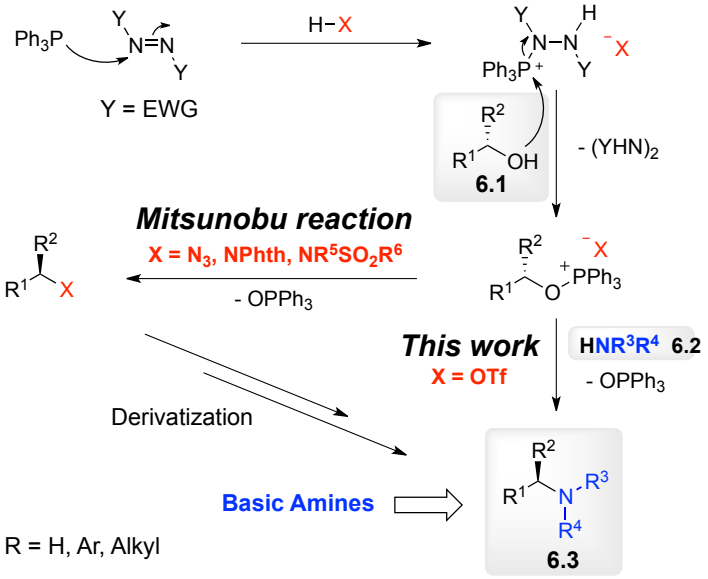
6.3 Article

The unprotected and basic amine moiety is an essential and omnipresent functionality found in nature. Synthetic chemists utilize such functional group in the production of pharmaceutical leads,[175] agrochemicals,[176] ligands,[177] polymers,[178] and dyes.[179] To contribute to the flourishing evolution of these fields, the development of powerful and operationally simple methods for the synthesis of amines is still a prominent aspiration for academic and industrial researchers.[180] A number of C–N bond forming reactions have emerged as venerable and long-standing methods for the synthesis of alkylamines. Such processes include the nucleophilic substitution of halides,[181] reductive aminations,[182] and the Mitsunobu reaction.[183] However, limitation of such methods typically involves the manipulation of alkyl halides, polyalkylation side reactions and/or multistep procedures. Despite the great and recent developments in the field of amine synthesis,[184] a direct and single-step conversion of alcohols to amines remains a highly desirable transformation, more specifically if it allows the use of enantioenriched alcohol precursors for the synthesis of a-chiral amines.

The Mitsunobu reaction is a well-established transformation in organic synthesis for the activation and nucleophilic substitution of alcohols for the formation of C–C, C–N, C–O, C–S, and C–halide bonds.[185] It has attracted increasing attention[186] and has found widespread applications in the synthesis of complex structures.[187] Its success has been attributed to its generality, mild conditions and stereospecific inversion observed for secondary alcohols.[188] Unfortunately, standard Mitsunobu activation conditions are restricted to relatively acidic pronucleophiles with a p*K*a barrier below 13 (in DMSO) in order to be productive.[188b,189] Because of this specific mechanistic requirement, amines synthesized by a C–N bond forming Mitsunobu reaction have been necessarily derived from a two-step procedure using moderately acidic pronucleophiles such as azides, sulfonamides, and phthalimides.[188b, 190] Thus, the nitrogen-containing products formed require further derivatization in order to obtain the basic amine (Figure 1). Ideally, a step-

economic approach to the Mitsunobu reaction would allow the direct use of unprotected and unmasked amines as nucleophiles. We hypothesized that ammonium salts would be acceptable acidic pronucleophiles, as they meet the p*K*a requirements of the standard Mitsunobu conditions.[191] The development of such a strategy would rationally imply the incorporation of a strong acid from which the conjugated base (X^-) is not itself acting as a nucleophile. There are yet few reports illustrating the utility of an external acid in the Mitsunobu reaction.[192] These methods are restricted to specific starting materials, while acid-free methodologies only allow intramolecular cyclisation of amino alcohols.[193]

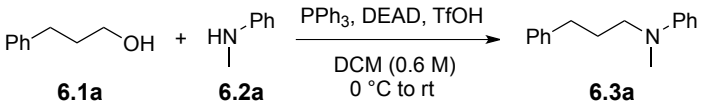
Figure 9. Amine synthesis via the Mitsunobu reaction.



Our interests in developing mild conditions for the synthesis of amines[194] encouraged us to explore the Mitsunobu reaction[195] in acidic conditions using free and basic amines as nucleophiles. We first screened different strong acids with variable p*K*a in classical Mitsunobu conditions. Interestingly, the addition of triflic acid (TfOH) to the reaction employing 3-phenyl-1-propanol (**6.1a**) and *N*-methylaniline (**6.2a**) gave an observable but low yield of the corresponding tertiary amine **6.3a** (24% yield, **Table 21**, entry 1).[196] We further optimized the reaction and found that performing the reaction for 18

hours in the presence of 1.5 equiv of both PPh_3 and diethyl azodicarboxylate (DEAD), 1.2 equiv of TfOH, and 2 equiv of amine **6.2a** provided an excellent 87% yield for tertiary amine **6.3a** (entry 2). The activation step using PPh_3 and DEAD gave a cleaner and faster amination of **6.1a** compared to other phosphine and azo derivatives (entries 4 and 5).[197] Unfortunately, the acid-catalyzed process employing 0.5 equiv of TfOH was not achieved (entry 6), even under extended reaction periods (entry 7). The reaction is normally run in anhydrous DCM for optimal conversions, but anhydrous THF, MeCN and DMF are acceptable non-chlorinated solvent alternatives (entries 8-10). The order of addition of reagents was found to be important (PPh_3, DEAD, TfOH, alcohol and amine were added consecutively). The initial mixture of PPh_3, DEAD, TfOH allows the formation of the activating species before the addition of the alcohol and the amine.[198] Additionally, it is crucial to avoid the direct reaction between azo reagents and amines as it results in the formation of the imine side product.[199]

Table 21. Reaction Opimization



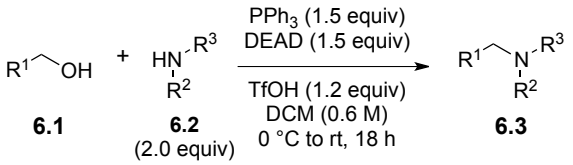
6.1a **6.2a** **6.3a**

entry	PPh_3/ DEAD (equiv)	**6.2a** (equiv)	TfOH (equiv)	solvent	time (h)	yield **6.3a** (%)[a]
1	1.0	1.0	1.0	DCM	18	24
2	1.5	2.0	1.2	DCM	18	87
3	1.5	2.0	1.2	DCM	42	89
4	1.5	2.0	1.2	DCM	18	67[b]
5	1.5	2.0	1.2	DCM	18	42[c]
6	1.5	2.0	0.5	DCM	18	32
7	1.5	2.0	0.5	DCM	42	30
8	1.5	2.0	1.2	THF	18	85
9	1.5	2.0	1.2	MeCN	18	84
10	1.5	2.0	1.2	DMF	18	80

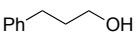
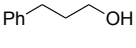
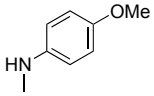
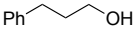
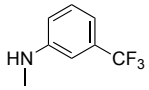
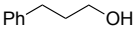
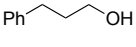
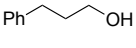
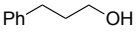
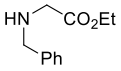
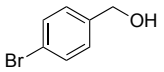
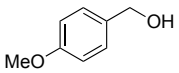
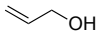
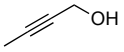
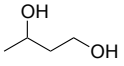
[a] Yields were calculated *via* ^{1}H NMR using triphenylmethane as internal standard on 1.5 mmol scale. [b] Reaction conducted with DIAD instead of DEAD. [c] Reaction conducted with PBu_3 instead of PPh_3.

The optimized conditions depicted in **Table 21** were applied to a variety of primary alcohols **6.1** and secondary amines **6.2** using TfOH as the acidic promoter (**Table 22**). The method proved to be general for the formation of tertiary amines **6.3** from anilines (entries 1-3) and *N*-alkyl amines (entries 4-13). The amine could be used as the limiting reactant when 2 equiv of the alcohol (MeOH) were added (entry 8). Benzylic (entries 9-11), allylic (entry 12) and propargylic (entry 13) alcohols also reacted smoothly leading to the structurally diverse amines in good to excellent yields. Interestingly, the chemoselective substitution of the primary alcohol of (±)-1,3-butanediol was achieved in the presence of the unprotected secondary alcohol (64%, entry 14).

Table 22. Synthesis of Tertiary Amines



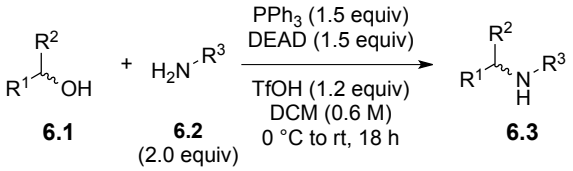
6.1 + **6.2** (2.0 equiv) → **6.3**

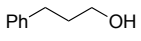
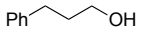
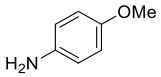
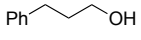
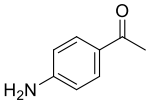
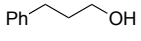
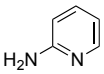
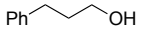
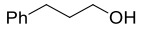
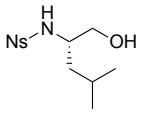
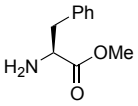
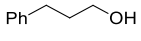
entry	alcohol **6.1**	amine **6.2**	yield **6.3** (%)[a]	
1			**6.3a**	80
2			**6.3b**	80
3			**6.3c**	78
4			**6.3d**	85
5			**6.3e**	84
6			**6.3f**	82
7			**6.3g**	81
8			**6.3h**	92[b]
9			**6.3i**	91
10			**6.3j**	94
11			**6.3k**	82
12			**6.3l**	81
13			**6.3m**	88
14			**6.3n**	64

[a] Isolated yields. Reaction performed on a 1.5 mmol scale. [b] Reaction performed with 1.0 equiv of amine (1.5 mmol), 2.0 equiv of MeOH, 1.5 equiv of PPh_3, 1.5 equiv of DEAD and 1.2 equiv of TfOH.

The conditions were further extended to the synthesis of secondary amines (**Table 23**). Anilines (entries 1-3) and benzyl amines (entries 5-6) were found to be productive coupling partners. Even less nucleophilic 2-aminopyridine provided the desired secondary amine albeit in low yield (entry 4). However, we observed the minor formation of tertiary amines for these exemples, resulting from an undesired over substitution side reaction on the product (entries 1-6). In contrast, the process was successfully applied to the synthesis of peptidoic structure **6.3u** in the presence of *N*-protected amino alcohol **6.1u** and amino ester **6.2u** (entry 7).[200] Interestingly, the transformation was chemoselective in the presence of 2-nitrobenzenesulfonylamide moiety and no over-substitution side reaction was observed.[192d] In the other hand, bulky *tert*-butyl amine provided the desired secondary amine with lower yield and no bis-alkylation (entry 8).

Table 23. Synthesis of Secondary Amines

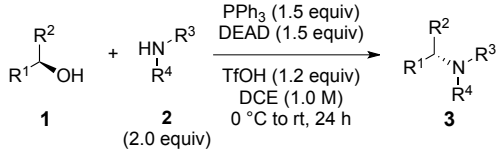


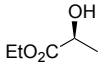
entry	alcohol **6.1**	amine **6.2**	yield **6.3** (%)[a]
1			**6.3o** 75 (16)
2			**6.3p** 68 (20)
3			**6.3q** 50 (3)
4			**6.3r** 27 (15)
5			**6.3s** 83 (17)
6			**6.3t** 71 (8)
7			**6.3u** 88 (0)
8			**6.3v** 38 (0)
9			**6.3w** 25 (0)
10			**6.3x** 0 (0)

[a] Isolated yields on a 1.5 mmol scale. Yield in parentheses is for the doubly substituted amine as determined by ^{1}H NMR analysis using Ph_3CH as an internal standard.

In order to gain preliminary insights into the mechanism of this transformation, we conducted the reaction using cyclohexanol and benzyl amine (**Table 23**, entry 10). As expected, the equatorial alcohol did not undergo substitution suggesting that the previous examples proceeded via a predominant S_N2 inversion, as commonly observed in the Mitsunobu reaction.[188b-d,190a,201] Furthermore, we decided to apply the optimized conditions to enantioenriched secondary alcohols toward the synthesis of α-chiral amines. The efficient synthesis of functionalized α-chiral amines remains an important task, as this motif is ubiquitous in nature and in high demand by the pharmaceutical industry.[180b,184b,202] We verified the stereospecificity (es)[203] of the reaction by submitting enantioriched alcohols to concentrated conditions (1 M) using the less polar solvent DCE (dichloroethane) (**Table 24**).[204] We were pleased to find that (*R*)-(−)-2-octanol reacted well with both aniline and benzyl amine providing the corresponding products **6.3y** and **6.3z** with inversion of configuration and no bis-alkylation (entries 1-2). The reaction was also applicable to (−)-ethyl *L*-lactate and dibenzyl amine for the synthesis of tertiary α-chiral amine **6.3aa** (entry 3). Additionally, ammonium triflate could be directly employed as a pronucleophile, thus increasing the versatility of the reaction by allowing the synthesis of primary α-chiral amine **6.3ab** (entry 4). When this reaction was performed with racemic mixture of alcohol **6.1ab** in DCM (0.6M), the corresponding primary amine was obtained with 74%.

Table 24. Synthesis of Enantiomerically Enriched α-Chiral Amines



entry	alcohol **6.1**	ee (%)	amine **6.2**	yield **6.3** (%)[a]		ee (%)	es (%)
1		99		**6.3y**	60	95	96
2		99		**6.3z**	74	85	86
3		98		**6.3aa**	66	97	99
4[b]		100		**6.3ab**	51 (74)[c]	92	92

[a] Isolated yields on 1.5 mmol scale. [b] No TfOH additive used. 2 equiv of H_4NOTf were used. [c] DCM (0.6 M) instead of DCE was used for the reaction of racemic mixture of alcohol **6.1ab**.

In conclusion, we have disclosed a step-economic acid-mediated Mitsunobu reaction that allows the synthesis of structurally diverse primary, secondary and tertiary amines from alcohols. The reaction is also applicable to the synthesis of α-chiral amines.

Chapitre 7. Conclusion

7.1 Conclusions générales

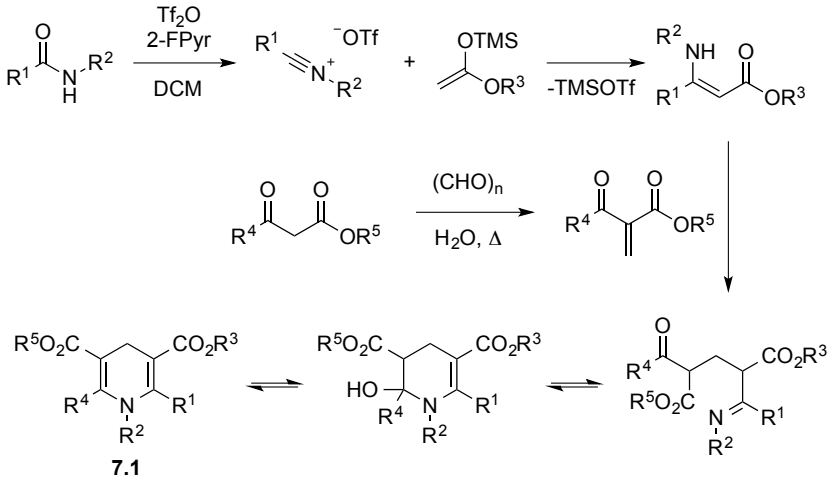
En conclusion, l'auteur de cet ouvrage a eu l'opportunité de travailler sur plusieurs projets reliés à la l'activation et à la dérivatisation des fonctionnalités amides secondaires et tertiaires. En premier lieu, nous avons réussi à développer une méthode de réduction chimiosélective et contrôlée des amides secondaires en aldéhydes, imines et amines. Le succès de cette méthode est attribué à l'utilisation de sources d'hydrures peu nucléophiles qui réagissent de façon sélective avec les intermédiaires obtenus dans la transformation. De plus, l'emploi des ces réducteurs permet la présence d'une diversité de produits fonctionnels. Ces concepts ont également été appliqués à la synthèse de cétones et de cétimines par l'entremise de réactifs de Grignard et d'organozinciques. L'implication d'un nitrilium très réactif permet l'emploi des réactifs organométalliques dans des réactions rapides et à basses températures, en absence de réaction secondaires sur des groupements fonctionnels habituellement sensibles aux réactifs organométalliques. Alternativement, nous nous sommes attardés à la synthèse de la fonction amidrazone à partir des amides secondaires et tertiaires. Ce dernier nous a ainsi permis de former des 1,2,4-triazoles suite à une cyclodéshydratation initiée en condition thermique et des 3-aminoindazoles par une fonctionnalisation C–H catalysée par un sel de palladium (II). Dans la dernière partie de cette thèse, nous avons démontré la possibilité de synthétiser des amines structurellement diversifiées en une seule étape en absence de groupements protecteurs à partir de la réaction standard de Mitsunobu en présence de l'acide triflique.

7.2 Perspectives

Les hétérocycles azotés sont d'une très grande importance pour l'industrie pharmaceutique. Inspiré des méthodes de synthèse de 1,2,4-triazoles (Chapitre 4) et de 3-aminoindazoles (Chapitre 5), il est possible d'envisager la synthèse de 1,4-dihydropyridines et d'imidazoles par l'activation d'amide secondaires suivie par l'addition nucléophile de différents réactifs.

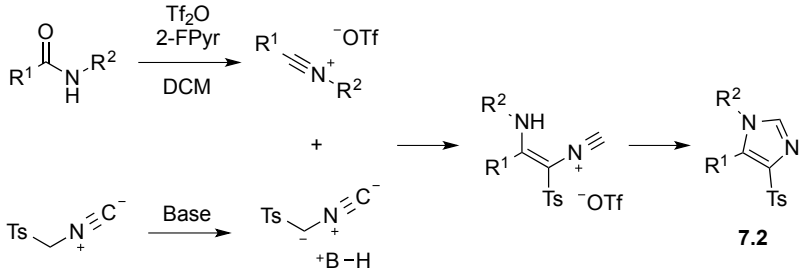
Les groupes de recherche du Prof. Bélanger et du Prof. Huang ont rapporté que des amides activés peuvent réagir par addition nucléophile d'éthers d'énols silylés dans la synthèse d'amides vinylogues.[205] Par conséquent, la synthèse des 1,4-dihydropyridines **7.1** de Hantzsch non symétriques peut être envisagé suivant l'addition *in situ* d'un β-cétoester et du paraformaldéhyde sur l'amide vinylogue formé **(Schéma 33)**.[206]

Schéma 33. Synthèse de 1,4-dihydropyridines non symétriques à partir d'amides secondaires



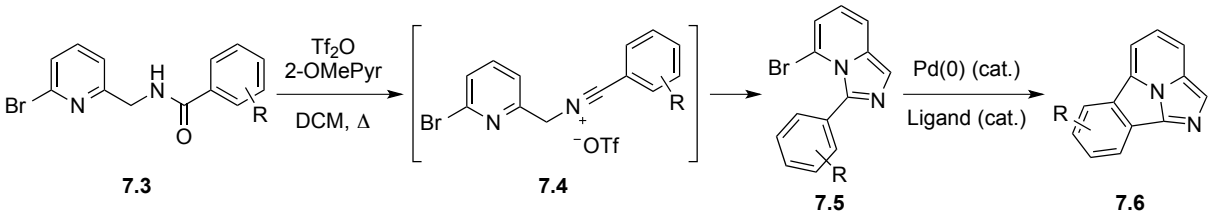
La synthèse d'imidazoles peut être inspiré de la réaction de Van Leusen.[207] Un isonitrile possédant un groupement électroattracteur, tel que le réactif TosMIC, peut être préalablement déprotoné et par la suite, ajouté au nitrilium obtenu par l'activation d'un amide secondaire. Une cyclisation de type 5-*endo*-*dig* de l'intermédiaire obtenu permettrait la formation d'imidazoles trisubstitués **7.2** (**Schéma 34**).

Schéma 34. Synthèse d'imidazoles par l'addition d'un ylure d'isonitrile sur un amide activé.



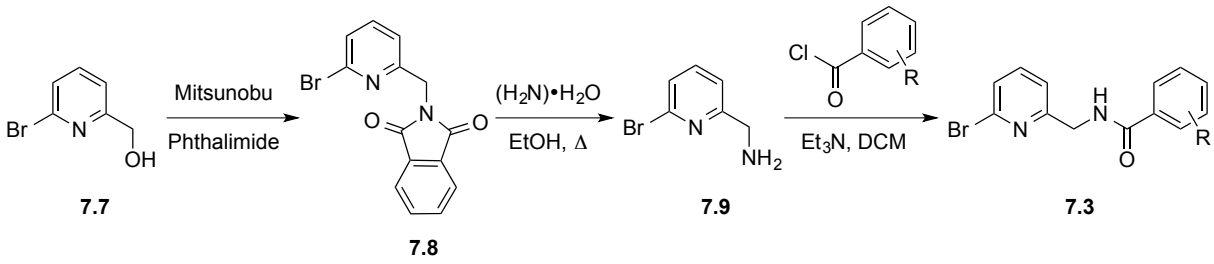
En collaboration avec Éric Lévesque, Léa Constantineau-Forget et Guillaume Pelletier, l'auteur de cette thèse participe présentement dans le développement d'une méthode de synthèse de benzo[a]imidazo[2,1,5-c,d]indolizines (**7.6**) en deux étapes à partir d'amides secondaires **7.3** (**Schéma 35**). La première étape est l'activation de l'amide **7.3** suivie d'une séquence de cyclodéhydration/aromatisation développé par Guillaume Pelletier (**Schéma 12**).[47] La deuxième étape est une réaction de fonctionnalisation C-H intramoléculaire catalysé par un complexe de palladium qui permet la formation d'un cycle à 5 membres. Ce nouvel hétérocycle (**7.6**) présente des propriétés de fluorescence intéressantes et les résultats seront publiés prochainement.

Schéma 35. Synthèse de benzo[a]imidazo[2,1,5-c,d]indolizines



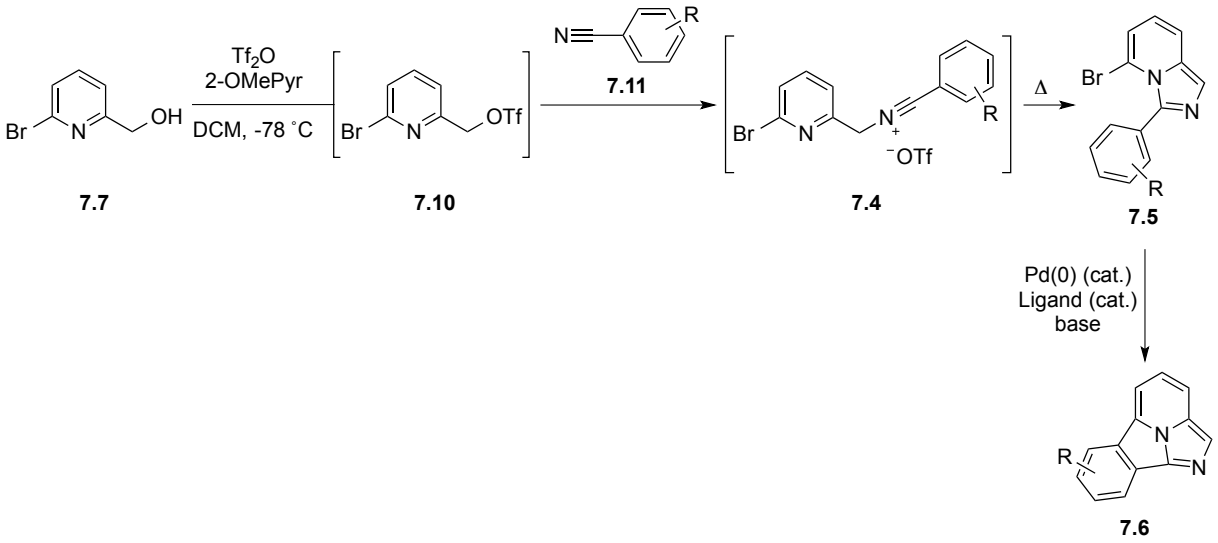
Un désavantage de la méthode précédente est le nombre d'étapes nécessaires pour la synthèse des amides secondaires **7.3** à partir des produits commercialement disponibles, tel que l'alcool **7.7** (**Schéma 36**). En fait, la synthèse est composée d'une réaction de Mitsunobu en présence de phthalimide pour donner le produit **7.8**, suivie d'une réaction de déprotection pour donner l'amine libre **7.9**, qui peut réagir en présence de dérivées de chlorures d'acyles pour donner les amides secondaires en 3 étapes. Au total, la synthèse de benzo[a]imidazo[2,1,5-c,d]indolizines (**7.6**) (**Schémas 35 et 36**) est effectué en cinq étapes.

Schéma 36. Synthèse d'amides secondaires **7.3**



Les groupes de recherche du Prof. Martinez et du Prof. Hanack ont rapporté une modification de la réaction de Ritter *via* la triflation d'alcools en présence de Tf_2O pour former des triflates qui peuvent réagir avec les nitriles. [208] Par conséquent, il serait possible d'envisager la formation du nitrilium **7.4**, obtenu par l'activation d'amides **7.3**, par l'addition du nitrile **7.11** sur le triflate benzylique **7.10** formé *in situ* et à basse température. Cette stratégie permettrait de raccourcir de 2 étapes la synthèse des benzo[a]imidazo[2,1,5-c,d]indolizines (**7.6**) à partir de l'alcool **7.7** (**Schéma 37**).

Schéma 37. Synthèse de benzo[a]imidazo[2,1,5-c,d]indolizines via une réaction de type Ritter.



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Annexe

Partie expérimentale

Experimental section of Chapter 2

General Information

Unless otherwise stated, reactions were run under an argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[1] All glassware was flame-dried prior to use. Dichloromethane, toluene, THF, acetonitrile and DMF were obtained by filtration through drying columns on a filtration system. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel. Visualization of the developed chromatogram was performed by UV, aqueous potassium permanganate, dinitrophenol (DNP) for aldehydes and ninhydrine for amines. Flash column chromatography was performed using 230-400 mesh silica. Melting points were obtained on a melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a 300 MHz or a 400 MHz (^{1}H, ^{13}C, F^{19}, P^{31}, DEPT 135, COSY, HMQC, HMBC) spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, d = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.23 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on a FTIR. Analytical Supercritical Fluid Chromatography analysis was performed on an instrument equipped with a diode array UV detector setted at 210 nm. Carbon dioxide was used as a carrier gas (150 psi). Data are reported as follows: (column type, column length, eluent, run time, flow rate, pressure, rate : retention time (t_r)).

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Reagents

Unless otherwise stated, commercial reagents were used without purification. Trifluoromethanesulfonic (triflic) anhydride was distilled over phosphorous pentoxide and was stored for no more than five days before redistilling. Triethylsilane, 2-Bromopyridine, 2-Chloropyridine and 2-Fluoropyridine were distilled over 4Å Molecular sieves before use and kept under argon before use. Triethylamine (Et_3N), Diisopropylethylamine (DIEPA), Dichloroethane (DCE), 1,2-Dimethoxyethane (DME) and pyridine were distilled over sodium and kept under argon before use. Hantzsch ester hydride (HEH) was synthesized according to literature procedures. [2] 1,4-Dihydro-1-(phenylmethyl)-3-pyridinecarboxamide (*N*-Bn-1,4-Dihydropyridine) was synthesized according to literature procedures.[3] 2,3-Dihydro-2-phenyl-benzothiazole (Benzothiazoline) was synthesized according to literature procedures.[4]

2. Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18-19.
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Amide 2.1a-2.1y synthesis:

4-Azidobenzoic acid (used in the synthesis of amide **2.1d**) was synthesized according to literature procedures.[5]

4-(Diethylphosphoryl)-benzoic acid (used in the synthesis of amide **2.1g**) was synthesized according to literature procedures.[6]

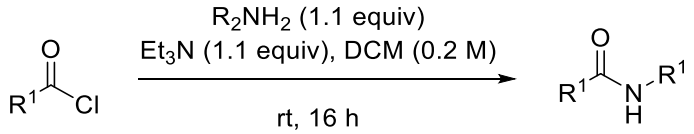
4-Ethynylbenzoic acid (used in the synthesis of amide **2.1m**) was synthesized according to literature procedures.[7]

(2*R*)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2-methylpropanoic acid (used in the synthesis of amide **2.1s**) was made according to literature procedures.[8]

Amide **2.1w** was synthesized according to literature procedures.[9]

Amides **2.1a-e**, **2.1g**, **2.1j-v,** and **2.1x-2.1y** were synthesized according to **procedures A** and **B**

Synthesis of amides starting from commercially available acyl chlorides according to **procedure A**:



Procedure A: To a flame-dried round-bottom flask equipped with a septum and under argon was added the amine (1.1 equiv). It was solubilized in dichloromethane [0.20 M] and stirred at room temperature. The solution was cooled to 0 °C and triethylamine (1.1 equiv) was added to the reaction flask. Then, the acyl chloride (1.0 equiv) was slowly added *via* a syringe dropwise (or portionwise if solid). Then, the reaction was slowly warmed up to room temperature and stirred for 16 h. The reaction was quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11 and then diluted with dichloromethane. The biphasic mixture was

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6. Beletskaya, I. P.; Kabachnik, M. M.; Solntseva, M. D. *Russ. J. Org. Chem.* **1999**, *35*, 71-73.
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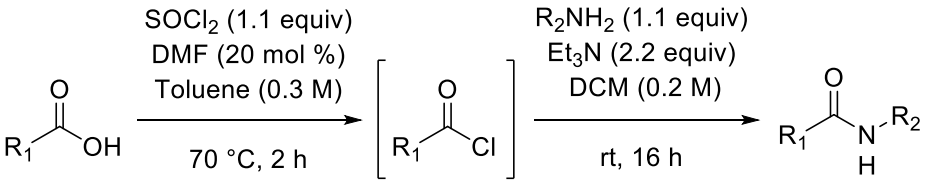
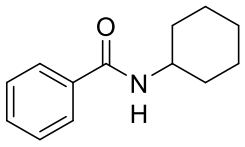
transferred to a separation funnel. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was washed with 1N HCl and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness.

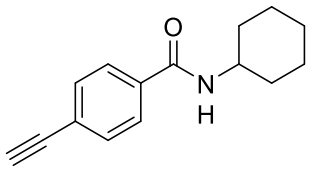
Synthesis of amides starting from carboxylic acids according to **procedure B**:



Procedure B: To a flame-dried round-bottom flask equipped with a condenser and under argon was added the carboxylic acid (1.0 equiv). The acid was diluted with dry toluene ([0.3M]) and 20 mol % dry dimethylformamide (DMF) was added to the reaction flask. Then, the solution was cooled to 0 °C and thionylchloride (1.1 equiv) was added dropwise to the solution *via* a syringe. Upon completion of the addition, the reaction was heated to 70 °C and stirred for 2 h. The reaction was then cooled to 0 °C and was diluted with dry dichloromethane ([0.2M]). The amine (1.1 equiv) and triethylamine (2.2 equiv) were added to the reaction flask at 0 °C *via* a syringe. The reaction was slowly warmed up to room temperature and stirred for 16 h. It was then quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11 and then diluted with dichloromethane. The biphasic mixture was transferred to a separation funnel. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was washed with 1N HCl and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness.

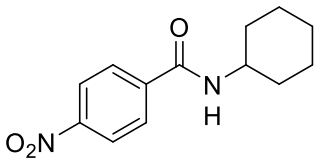


***N*-Cyclohexylbenzamide (2.1a):**[10] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. The solids were filtrated over a Buchner funnel and the product was isolated as an off-white powder (4.90 g, 96% Yield). **mp**: 164-165 °C, litt:[10] 154-156 °C; $\mathbf{R_f}$: 0.8 (50% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.52-7.49 (m, 1H), 7.46-7.42 (m, 2H), 6.00 (br s, 1H), 4.05-3.96 (m, 1H), 2.07-2.04 (m, 2H), 1.80-1.75 (m, 2H), 1.70-1.66 (m, 1H), 1.51-1.40 (m, 2H), 1.31-1.17 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 167.0, 135.5, 131.6, 128.9, 127.2, 49.1, 33.7, 26.0, 25.3; **FTIR** (cm^{-1}) (neat): 3311, 3237, 2928, 2851, 1625, 1535, 1328, 1218; **HRMS** (ESI, Pos): calc. for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388 *m/z*, found: 204.1390 *m/z*.

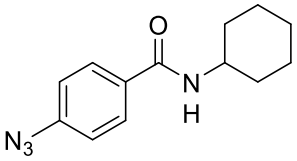


4-Cyano-*N*-cyclohexylbenzamide (2.1b): Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as an off-white powder (4.10 g, 88% Yield). **mp**: 164-165 °C; $\mathbf{R_f}$: 0.85 (50% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.86 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 6.08 (br s, 1H), 4.03-3.94 (m, 1H), 2.07-2.03 (m, 2H), 1.81-1.76 (m, 2H), 1.72-1.66 (m, 1H), 1.50-1.39 (m, 2H), 1.31-1.17 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 164.9, 139.1, 132.5, 127.7, 118.2, 114.9, 49.2, 33.2, 25.5, 24.9; **FTIR** (cm^{-1}) (neat): 3288, 2941, 2857, 2230, 1630, 1541, 1331; **HRMS** (ESI, Pos): calc. for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.1341 *m/z*, found: 229.1314 *m/z*.

[10]. For characterization data, see: Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944-2945.

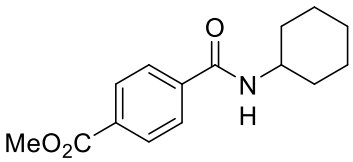


***N*-Cyclohexyl-4-nitrobenzamide (2.1c):**[11] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a yellow powder (1.50 g, 57% Yield). **mp**: 178-179 °C, litt:[11] 156-157 °C; $\mathbf{R_f}$: 0.40 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.29 (d, *J* = 7.0 Hz, 2H), 7.93 (d, *J* = 7.0 Hz, 2H), 6.09 (br s, 1H), 4.04-3.97 (m, 1H), 2.08-2.06 (m, 2H), 1.81-1.78 (m, 2H), 1.71-1.68 (m, 1H), 1.51-1.41 (m, 2H), 1.32-1.19 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 164.3, 149.1, 140.3, 127.7, 123.4, 48.9, 32.8, 25.1, 24.5; **FTIR** (cm^{-1}) (neat): 3317, 2938, 2860, 1631, 1600, 1544, 1519, 1348, 1219; **HRMS** (ESI, Pos) calc. for $C_{13}H_{17}N_2O_3$ $[M+H]^+$: 249.1239 *m/z*, found: 249.1236 *m/z*.

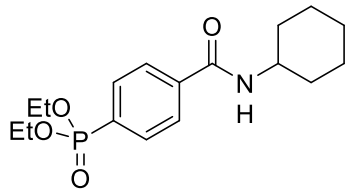


4-Azido-*N*-cyclohexylbenzamide (2.1d): Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 10% EtOAc/Hexanes to 30% EtOAc/Hexanes and fractions containing **2.1d** were concentrated to dryness. It resulted in a brown, crystalline solid (3.30 g, 68 % Yield). **mp**: 158-159 °C; $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.77 (d, *J* = 10 Hz, 2H), 7.06 (d, *J* = 10 Hz, 2H), 5.98 (br d, *J* = 9.0 Hz, 1H), 4.03-3.93 (m, 1H), 2.07-2.02 (m, 2H), 1.81-1.74 (m, 2H), 1.71-1.64 (m, 1H), 1.49-1.39 (m, 2H), 1.30-1.19 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 165.2, 142.7, 131.2, 128.3, 118.6, 48.4, 32.9, 25.2, 24.5; **FTIR** (cm^{-1}) (neat): 3323, 2935, 2853, 2135, 1628, 1604, 1532, 1500, 1329, 1291; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}N_4O$ $[M+H]^+$: 245.1402 *m/z*, found: 245.1387 *m/z*.

[11]. For characterization data, see: Tambade, P. J.; Patil, Y. P.; Bhanushali, M. J.; Bhanage, B. M. *Synthesis* **2008**, 2347-2352.



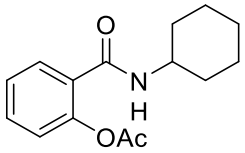
***N*-Cyclohexyl-4-(methoxycarbonyl)benzamide (2.1e):**[12] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a yellow powder (5.80 g, 89% Yield). **mp**: 185-186 °C, litt:[12] 336-337 K; $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.05 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 2H), 6.24 (br d, J = 7.0 Hz, 1H), 4.02-3.91 (m, 1H), 3.91 (s, 3H), 2.05-2.01 (m, 2H), 1.79-1.74 (m, 2H), 1.68-1.63 (m, 1H), 1.47-1.36 (m, 2H), 1.31-1.15 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 166.0, 165.4, 138.7, 132.0, 129.3, 126.6, 52.0, 48.6, 32.7, 25.1, 24.6; **FTIR** (cm^{-1}) (neat): 3305, 2940, 2854, 1720, 1631, 1541, 1435, 1227, 1107; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1443 *m/z*, found: 262.1432 *m/z*.



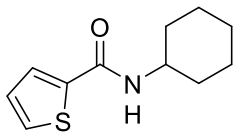
Diethyl-{4-[(cyclohexylamino)carbonyl]-phenyl}-phosphonate (2.1g): Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 80% EtOAc/Hexanes to 10% MeOH/EtOAc and fractions containing **2.1g** were concentrated to dryness. It resulted in a light beige solid (4.00 g, 85% Yield). **mp**: 131-132 °C; $\mathbf{R_f}$: 0.70 (5 % MeOH/EtOAc); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.87-7.78 (m, 4H), 6.52 (br d, J = 5.0 Hz, 1H), 4.17-3.92 (m, 5H), 2.03-1.99 (m, 2H), 1.78-1.73 (m, 2H), 1.67-1.63 (m, 1H), 1.46-1.13 (m, 5H), 1.30 (t, J = 7.0 Hz, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 165.8, 138.8 (d, $J_{P\text{-}C}$ = 3.1 Hz), 131.9 (d, $J_{P\text{-}C}$ = 10 Hz), 131.2 (d, $J_{P\text{-}C}$ = 184.1 Hz), 127.0 (d, $J_{P\text{-}C}$ = 15 Hz), 62.3 (d, $J_{P\text{-}C}$ = 5.5 Hz), 49.0, 33.1, 25.5, 25.0, 16.3 (d, $J_{P\text{-}C}$ = 6.5 Hz); **^{31}P NMR** ($CHCl_3$, 161.9

[12]. For characterization data, see: Jones, P. G.; Kus, P. *Acta. Cryst.* **2004**, *E60*, o1299-o1300.

MHz): d 17.6 **FTIR** (cm^{-1}) (neat): 2935, 1654, 1519, 1239, 1026; **HRMS** (ESI, Pos): calc. for $C_{17}H_{27}NO_4P$ $[M+H]^+$: 340.1678 *m/z*, found: 340.1666 *m/z*.



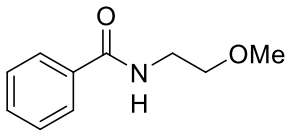
2-[(Cyclohexylamino)carbonyl]phenyl acetate (2.1j): Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (18.50 g, 85% Yield). **mp**: 61-62 °C; $\mathbf{R_f}$: 0.15 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.73 (dd, *J* = 1.5, 7.5, 1H), 7.48-7.43 (m, 1H), 7.33-7.29 (m, 1H), 7.11-7.09 (m, 1H), 6.13 (br d, *J* = 7.5 Hz, 1H), 4.00-3.91 (m, 1H), 2.34 (s, 3H), 2.04-2.00 (m, 2H), 1.78-1.73 (m, 2H), 1.68-1.63 (m, 1H), 1.48-1.38 (m, 2H), 1.26-1.15 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 169.6, 165.2, 148.1, 131.9, 130.1, 129.6, 126.8, 123.5, 48.9, 33.6, 25.9, 25.3, 21.5; **FTIR** (cm^{-1}) (neat): 3284, 2932, 2853, 1765, 1630, 1535, 1194; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1443 *m/z*, found 262.1444 *m/z*.



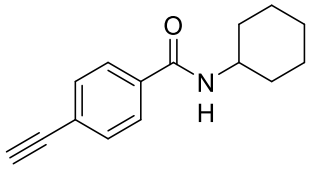
***N*-Cyclohexylthiophene-2-carboxamide (2.1k):**[13] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (5.00 g, 85% Yield). **mp**: 133-134 °C, litt:[13] 161 °C; $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.50 (dd, *J* = 1.0, 3.5 Hz, 1H), 7.46 (dd, *J* = 1.0, 5.0 Hz, 1H), 7.07 (dd, *J* = 3.5, 5.0 Hz, 1H), 5.92 (br s, 1H), 4.00-3.91 (m, 1H), 2.06-2.02 (m, 2H), 1.79-1.74 (m, 2H), 1.70-1.63 (m, 1H), 1.48-1.37 (m, 2H), 1.30-1.16 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 160.6, 139.2, 129.2, 127.3, 127.1, 48.4, 32.9, 25.1, 24.5; **FTIR**

[13]. For characterization data, see: Lee, C. K.; Yu, J. S.; Ji, Y. R. *J. Het. Chem.* **2002**, *39*, 1219-1227.

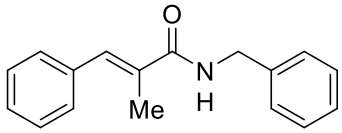
(cm^{-1}) (neat): 3298, 3083, 2931, 2853, 1612, 1551, 1516, 1323, 1289, 1245; **HRMS** (ESI, Pos): calc. for $C_{11}H_{16}NOS$ $[M+H]^+$: 210.0953 *m/z*, found: 210.0947 *m/z*.



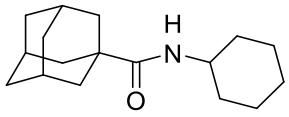
***N*-(2-Methoxyethyl)benzamide (2.1l):** Following **procedure A**, the crude amide was purified by flash chromatography over silica gel using a gradient of 30% EtOAc/Hexanes to 80% EtOAc/Hexanes and fractions containing **2.1l** were concentrated to dryness. It resulted in a translucid oil which solidified to crystals in the freezer (2.45 g, 72% Yield). **mp**: 35-36 °C; **R_f**: 0.20 (50% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.80-7.78 (m, 2H), 7.51-7.48 (m, 1H), 7.45-7.41 (m, 2H), 6.68 (br s, 1H), 3.68-3.64 (m, 2H), 3.58-3.55 (m, 2H), 3.39 (s, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 167.2, 134.2, 131.1, 128.1, 126.6, 70.8, 58.4, 39.3; **FTIR** (cm^{-1}) (neat): 3315, 3062, 2929, 2878, 1636, 1535, 1304, 1195, 1117; **HRMS** (ESI, Pos): calc. for $C_{10}H_{14}NO_2$ $[M+H]^+$: 180.1025 *m/z*, found: 180.1022 *m/z*.



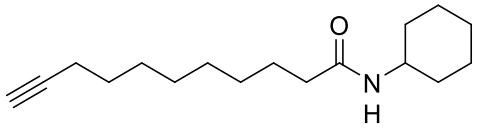
***N*-Cyclohexyl-4-ethynylbenzamide (2.1m):** Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 15% EtOAc/Hexanes to 50% EtOAc/Hexanes and fractions containing **2.1m** were concentrated to dryness. It resulted in a yellow powder (4.00 g, 63% Yield). **mp**: 205-206 °C (dec.); **R_f**: 0.45 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 6.00 (br d, *J* = 7.0 Hz, 1H), 4.03-3.94 (m, 1H), 3.21 (s, 1H), 2.06-2.02 (m, 2H), 1.80-1.75 (m, 2H), 1.70-1.65 (m, 1H), 1.50-1.39 (m, 2H), 1.30-1.17 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 165.4, 134.7, 131.9, 126.5, 124.7, 82.4, 78.9, 48.4, 32.8, 25.2, 24.6; **FTIR** (cm^{-1}) (neat) 3315, 3241, 2925, 2851, 2201, 1621, 1537, 1332; **HRMS** (ESI, Pos): calc. for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1388 *m/z*, found: 228.1380 *m/z*.



***N*-Benzyl-2-methyl-3-phenylacrylamide (2.1n):** Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (1.85 g, 60% Yield). **mp**: 63-64 °C; **R_f**: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.42-7.30 (m, 11 H), 6.28 (br s, 1H), 4.61-4.59 (d, *J* = 6.0 Hz, 2H), 2.14 (s, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 169.5, 138.4, 136.1, 134.2, 131.9, 129.4, 128.8, 128.4, 128.0, 127.9, 127.6, 44.1, 14.4; **FTIR** (cm^{-1}) (neat): 3334, 3030, 2920, 1654, 1608, 1531, 1283, 1011; **HRMS** (ESI, Pos): calc. for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388 *m/z*, found: 252.1386 *m/z*.

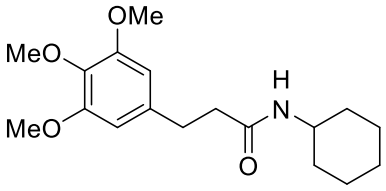


***N*-Cyclohexyladamantane-1-carboxamide (2.1o):** Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (4.10 g, 76% Yield). **mp**: 195-196 °C; **R_f**: 0.70 (30% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 5.42 (br d, *J* = 5.5 Hz, 1H), 3.83-3.73 (m, 1H), 2.06 (s, 3H), 1.93-1.85 (m, 8H), 1.78-1.59 (m, 9H), 1.45-1.33 (m, 2H), 1.24-1.07 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 176.6, 47.2, 40.1, 38.9, 36.2, 32.8, 27.8, 25.3, 24.5; **FTIR** (cm^{-1}) (neat): 3302, 2901, 2851, 1745, 1701, 1625, 1535, 1217; **HRMS** (ESI, Pos): calc. for $C_{17}H_{28}NO$ $[M+H]^+$: 262.2171 *m/z*, found: 262.2162 *m/z*.

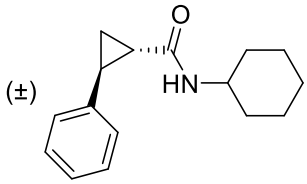


***N*-Cyclohexylundec-10-ynamide (2.1p):** Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 10% EtOAc/Hexanes to 50% EtOAc/Hexanes and fractions containing **2.1p** were concentrated to dryness. It resulted in

a beige powder (2.81 g, 71% Yield). **mp**: 34-35 °C; $\mathbf{R_f}$: 0.40 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 5.87 (br s, 1H), 3.81-3.69 (m, 1H), 2.20-2.14 (m, 4H), 1.94-1.86 (m, 3H), 1.74-1.21 (m, 17H), 1.21-1.07 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 172.1, 84.3, 67.7, 47.9, 36.4, 32.8, 28.8 (2), 28.6, 28.3, 28.0, 25.6, 25.1, 24.5; **FTIR** (cm^{-1}) (neat): 3308, 2929, 2855, 2237, 1631, 1544, 1450, 1251; **HRMS** (ESI, Pos): calc. for $C_{17}H_{30}NO$ $[M+H]^+$: 264.2327 *m/z*, found: 264.2324 *m/z*.



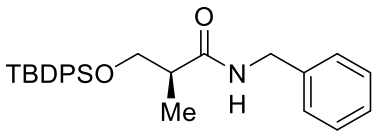
***N*-Cyclohexyl-3-(3,4,5-trimethoxyphenyl)propionamide (2.1q):**[14] Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 30% EtOAc/Hexanes to 80% EtOAc/Hexanes and fractions containing **2.1q** were concentrated to dryness. It resulted in a white powder (4.30 g, 67% Yield). **mp**: 163-164 °C; $\mathbf{R_f}$: 0.70 (90% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 6.43 (s, 2H), 5.25 (br s, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.81-3.71 (m, 1H), 2.91 (t, J = 7.0 Hz, 2H), 2.43 (d, J = 7.0 Hz, 2H), 1.89-1.83 (m, 2H), 1.70-1.56 (m, 3H), 1.41 (m, 2H), 1.19-1.00 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 170.6, 152.8, 136.4, 136.0, 104.9, 60.4, 55.7, 47.7, 38.6, 32.8, 31.9, 25.1, 24.3; **FTIR** (cm^{-1}) (neat): 3290, 2930, 2853, 1639, 1589, 1541, 1508, 1454, 1420, 1237, 1126; **HRMS** (ESI, Pos): calc. for $C_{18}H_{28}NO_4$ $[M+H]^+$: 322.2018 *m/z*, found: 322.2011 *m/z*.



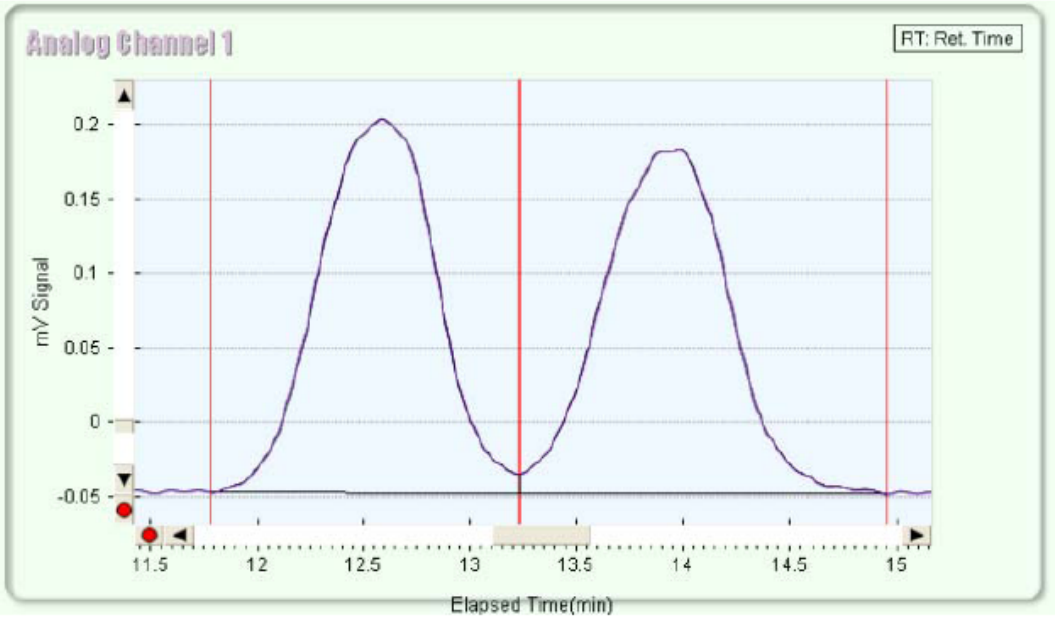
***trans*-*N*-Cyclohexyl-2-phenylcyclopropanecarboxamide (2.1r):** Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (1.10 g, 63% Yield). **mp**: 95-96 °C; $\mathbf{R_f}$: 0.65 (50% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.31-7.27 (m, 2H), 7.23-7.18 (m, 1H), 7.12-

[14]. For characterization data, see: Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055-3057.

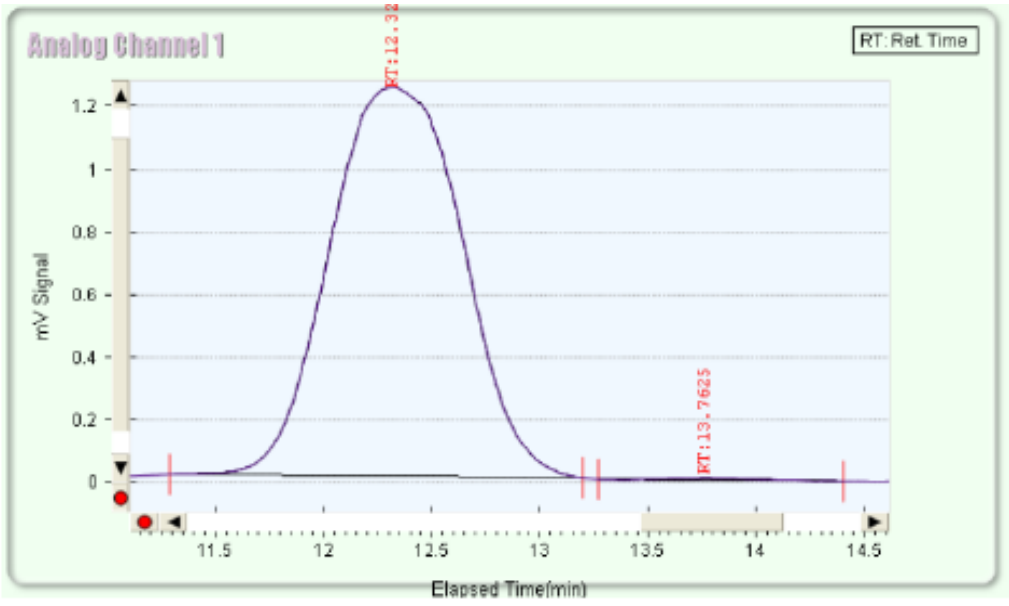
7.09 (m, 2H), 5.55 (br d, J = 7.0 Hz, 1H), 3.87-3.78 (m, 1H), 2.52-2.47 (m, 1H), 1.99-1.92 (m, 2H), 1.76-1.70 (m, 2H), 1.67-1.55 (m, 3H), 1.44-1.33 (m, 2H), 1.25-1.09 (m, 4H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 170.3, 140.7, 128.1, 125.8, 125.6, 48.1, 33.0, 32.9, 26.7, 25.2, 24.5. (2), 15.6; **FTIR** (cm^{-1}) (neat): 3282, 3064, 2930, 2854, 2634, 1547, 1450, 1349, 1230; **HRMS** (ESI, Pos): calc**.** for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1701 *m/z*, found: 244.1685 *m/z*.



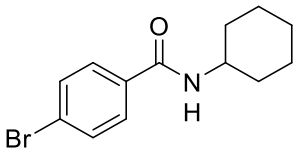
(2*S*)-*N*-Benzyl-3{[*tert*-butyl(diphenyl)silyl]oxy}-2-methylpropanamide (2.1s): Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 10% EtOAc/Hexanes to 50% EtOAc/Hexanes and fractions containing **2.1s** were concentrated to dryness. It resulted in a white powder (7.40 g, 68% Yield). **mp**: 45-46 °C; SFC analysis of the product on a chiral stationary phase (Chiralpak ADH 10 cm, 7% MeOH, 20 min, 3 mL/min, 150 bar, 40 °C isotherm) (*S*)-**2.1s** tr = 12.5 min, *(R)*-**2.1s** tr = 13.9 min; **$[\alpha]_D^{20}$**: +14.1 (*c* 1.37, $CHCl_3$), **R_f**: 0.70 (20 % EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.64-7.60 (m, 4H), 7.48-7.28 (m, 11H), 6.68 (br s, 1H), 4.56-4.45 (m, 2H), 3.81-3.73 (m, 2H), 2.56-2.48 (m, 1H), 1.15 (dd, J = 2.0, 7.0 Hz, 3H), 1.00 (s, 9H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 175.1, 138.8, 136.0, 135.9, 133.3, 133.2, 130.3, 129.1, 128.4, 128.2, 127.8, 66.6, 44.0, 43.5, 27.2, 19.5, 14.1; **FTIR** (cm^{-1}) (neat): 3301, 2910, 2835, 1656, 1540, 1221; **HRMS** (ESI, Pos): calc. for $C_{26}H_{38}NO_2Si$ $[M+H]^+$: 432.2359 *m/z*, found: 432.2363 *m/z*.



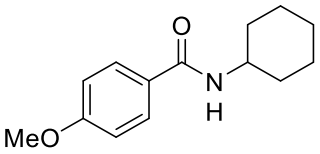
Peak Name	Area %	Area	Retention Time
Peak1	50.2864	9.6706	12.5833 min
Peak3	49.7136	9.5604	13.9833 min



Peak No	Peak Area	% Peak Area	Retention Time
1	52.9865	99.6339	12.3208 min
2	0.1947	0.3661	13.7625 min

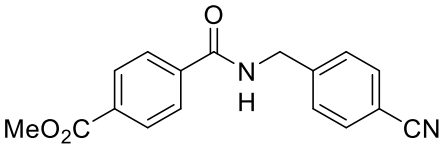


4-Bromo-*N*-cyclohexylbenzamide (2.1t): Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (4.60 g, 82% Yield). **mp**: 180-181 °C; $\mathbf{R_f}$: 0.75 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.64 (d, *J* = 9.5 Hz, 2H), 7.57 (d, *J* = 9.5 Hz, 2H), 5.97 (br d, *J* = 7.5 Hz, 1H), 4.02-3.93 (m, 1H), 2.07-2.01 (m, 2H), 1.81-1.74 (m, 2H), 1.71-1.64 (m, 1H) 1.50-1.39 (m, 2H), 1.30-1.17 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 165.3, 133.6, 131.3, 128.2, 125.4, 48.5, 32.8, 25.2, 24.6; **FTIR** (cm^{-1}) (neat) 3285, 2930, 2853, 1630, 1590, 1540, 1333; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}NOBr$ $[M+H]^+$: 282.0494 and 284.0473 *m/z*, found: 282.0493 and 284.0472 *m/z*.

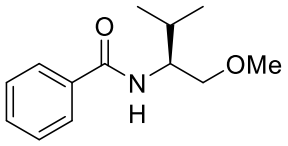


***N*-Cyclohexyl-4-methoxybenzamide (2.1u):**[15] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (9.10 g, 90% Yield). **mp**: 153-154 °C, litt:[15] 159-162 °C; $\mathbf{R_f}$: 0.35 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5, Hz, 2H), 6.17 (br d, *J* = 8.0 Hz, 1H), 4.00-3.89 (m, 1H), 3.62 (s, 3H), 2.01-1.97 (m, 2H), 1.76-1.70 (m, 2H), 1.66-1.60 (m, 1H), 1.44-1.33 (m, 2H), 1.27-1.12 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 166.5, 162.3, 129.1, 127.8, 114.0, 55.8, 49.0, 33.7, 26.0, 25.4; **FTIR** (cm^{-1}) (neat): 3299, 2932, 2853, 1624, 1607, 1533, 1505, 1333, 1252, 1176, 1028; **HRMS** (ESI, Pos): calc. for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494 *m/z*, found: 234.1494 *m/z*.

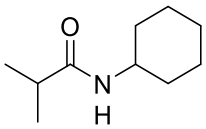
[15]. For characterization data, see: Kang, D. H.; Joo, T. Y.; Chavasiri, W.; Jang, D. O. *Tetrahedron Lett.* **2007**, *48*, 285-287.



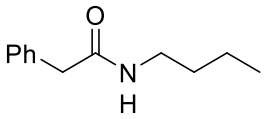
Methyl 4-{[(4-cyanobenzyl)amino]carbonyl}benzoate (2.1v): Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a yellow powder (2.60 g, 80% Yield). **mp**: 124-125 °C; $\mathbf{R_f}$: 0.35 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz), 6.91 (br s, 1H), 4.70 (d, *J* = 6.5 Hz, 2H), 3.96 (s, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 166.4, 165.8, 143.2, 137.3, 132.7, 132.1, 129.5, 127.9, 126.7, 118.3, 111.0, 52.1, 43.3; **FTIR** (cm^{-1}) (neat): 3314, 2952, 2228, 1777, 1720, 1645, 1536, 1321, 1279, 1109; **HRMS** (ESI, Pos): calc. for $C_{17}H_{15}N_2O_3$ $[M+H]^+$: 295.1083 *m/z*, found: 295.1079 *m/z*.



***N*-[(1*S*)-1-(Methoxymethyl)-2-methylpropyl]benzamide (2.1w):**[9] **mp**: 64-65 °C, litt:[9] 67-69 °C; $\mathbf{R_f}$: 0.60 (50% EtOAc/Hexanes); $\mathbf{[\alpha]_D^{20}}$: -40.9 (*c* 1.09, $CHCl_3$), litt:[9] -42.9 (*c* 1.33, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.53-7.43 (m, 3H), 6.42 (br d, *J* = 7.5 Hz, 1H), 4.09-4.03 (m, 1H), 3.63 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.46 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.37 (s, 3H), 2.07-1.95 (m, 1H), 1.03 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 167.6, 135.3, 131.8, 129.0, 127.4, 73.0, 59.6, 54.9, 30.2, 20.0, 19.6; **FTIR** (cm^{-1}) (neat): 3296, 2964, 2873, 1632, 1537, 1490, 1318, 1110; **HRMS** (ESI, Pos): calc. for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1494 *m/z*, found: 222.1492 *m/z*.



***N*-Cyclohexylisobutyramide (2.1x)**:[16] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (4.78 g, 78% Yield). **mp**: 75-76 °C; $\mathbf{R_f}$: 0.70 (50% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 5.46 (br s, 1H), 3.80-3.67 (m, 1H), 2.29 (h, J = 9.0 Hz, 1H), 1.92-1.85 (m, 2H), 1.74-1.55 (m, 3H), 1.42-1.27 (m, 2H), 1.27-1.04 (m, 3H), 1.12 (d, J = 9.0 Hz, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 176.9, 48.8, 36.5, 34.1, 26.4, 25.7, 20.5; **FTIR** (cm^{-1}) (neat): 3287, 1964, 2930, 2854, 1638, 1545, 1446, 1246, 1232; **HRMS** (ESI, Pos): calc. for $C_{10}H_{20}NO$ $[M+H]^+$: 170.1545 *m/z*, found: 170.1536 *m/z*.



***N*-Butyl-2-phenylacetamide (2.1y)**:[17] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a white powder (1.00 g, 70% Yield). **mp**: 37-38 °C, litt:[17] 43-45 °C; $\mathbf{R_f}$: 0.80 (50% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.39-7.26 (m, 5H), 5.48 (br s, 1H), 3.58 (s, 2H), 3.21 (q, J = 7.5 Hz, 2H), 1.45-1.38 (m, 2H), 1.31-1.22 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 170.5, 134.7, 129.1, 128.6, 126.9, 43.5, 39.0, 31.2, 19.6, 13.3; **FTIR** (cm^{-1}) (neat): 3296, 2964, 2873, 1632, 1537, 1490, 1318, 1110; **HRMS** (ESI, Pos): calc. for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1388 *m/z*, found: 192.1388 *m/z*.

Synthesis of amide **2.1f** from 4-formylbenzoic acid:

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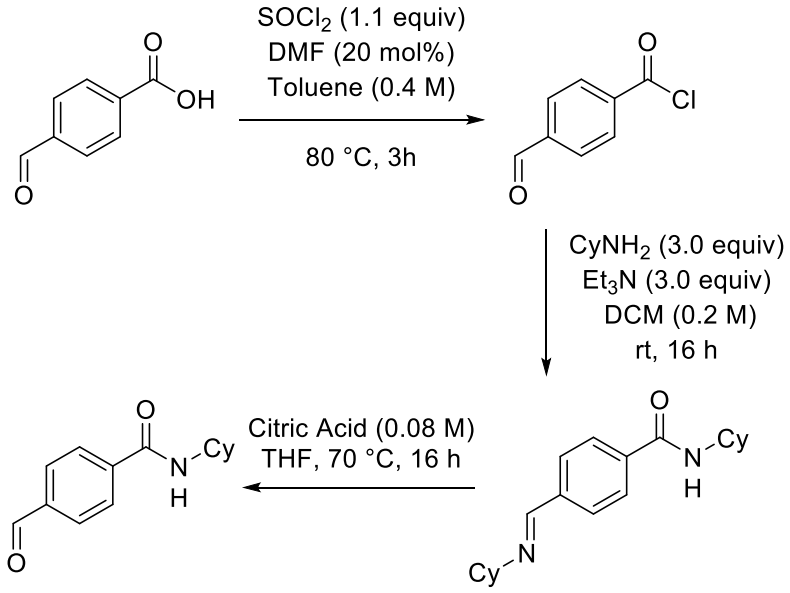
16. For characterization data, see: Maran, F.; *Via*nello, E.; D'Angeli, F.; Cavicchioni, G.; Vecchiati, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 33-38.
17. Katritzky, A. R.; Jiang, R.; Sommen, G. L.; Singh, S. K. *ARKIVOC* **2004**, *9*, 44-51.

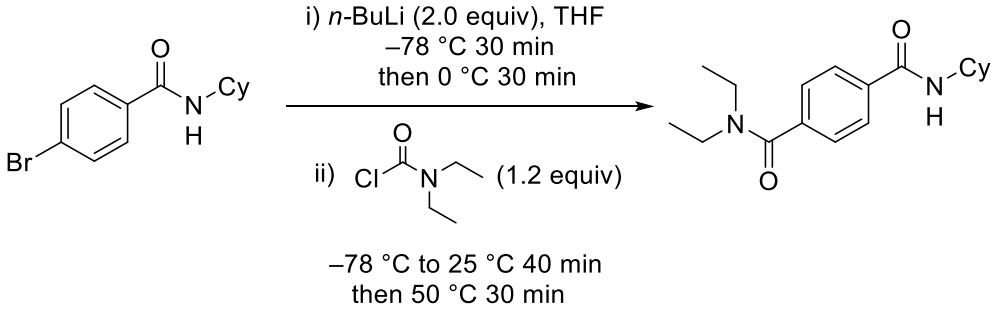


***N*-Cyclohexyl-4-formylbenzamide (2.1f):** To a flame-dried 500 mL round-bottom flask equipped with a condenser and under argon was added 4-formylbenzoic acid (4.70 g, 31.3 mmoles, 1.0 equiv). The acid was diluted with 78.3 mL of dry toluene ([0.4M]) and 484 µL of dry dimethylformamide (DMF) (457 mg, 6.26 mmoles, 0.2 equiv) was added to the reaction flask. Then, the solution was cooled to 0 °C and thionylchloride (4.10 g, 34.4 mmol, 1.1 equiv) was added dropwise to the solution *via* a syringe. Upon completion of the addition, the reaction was heated to 70 °C and stirred for 2 h (during which time the acid was completely solubilized). The reaction was then cooled to 0 °C and was diluted with 156 mL of dry dichloromethane ([0.2M]). Cyclohexylamine (9.31 g, 10.74 mL, 93.9 mmol, 3.0 equiv) and triethylamine (9.50 g, 13.09 mL, 93.9 mmol, 3.0 equiv) were added dropwise to the reaction flask at 0 °C *via* a syringe. The reaction was slowly heated to room temperature and stirred for 16 h (if the suspension is too thick, 30-40 mL of DCM can be added to the reaction mixture to help the stirring). It was then quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11 and then diluted with dichloromethane. The biphasic mixture was transferred to a separation funnel. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with dichloromethane (3x) and the organic layers were combined.

The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness.

The crude imine was then hydrolyzed by diluting it with 312 mL of a mixture (1:1) of an aqueous solution of citric acid [0.08M] and THF. The suspension was heated at 70 °C over 16 h to ensure complete conversion of the imine to the corresponding aldehyde (which is soluble in THF). The reaction was then cooled to room temperature and transferred to a 1-L extraction funnel. It was diluted with 100 mL of EtOAc and 100 mL of water and the aqueous layer was extracted with EtOAc (3x). The organic layers were combined and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness. The crude aldehyde was then purified by flash chromatography using a gradient of 20% EtOAc/Hexanes to 50% EtOAc/Hexanes and fractions containing **2.1f** were concentrated to dryness. It resulted in a white powder (6.44 g, 89% Yield). **mp**: 143-144 °C; $\mathbf{R_f}$: 0.20 (40% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 300 MHz): δ 10.05 (s, 1H), 7.90 (s, 4H), 6.30 (br d, *J* = 7.0 Hz, 1H), 4.03-3.91 (m, 1H), 2.05-2.00 (m, 2H), 1.80-1.63 (m, 3H), 1.48-1.12 (m, 5H); **^{13}C NMR** ($CHCl_3$, 75 MHz): δ 192.5, 166.4, 141.2, 138.8, 130.6, 128.5, 49.9, 33.9, 26.3, 25.8; **FTIR** (cm^{-1}) (neat): 3317, 2930, 2850, 1704, 1626, 1528, 1328, 1204; **HRMS** (ESI, Pos): calc. for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1338 *m/z*, found: 232.1335 *m/z*.

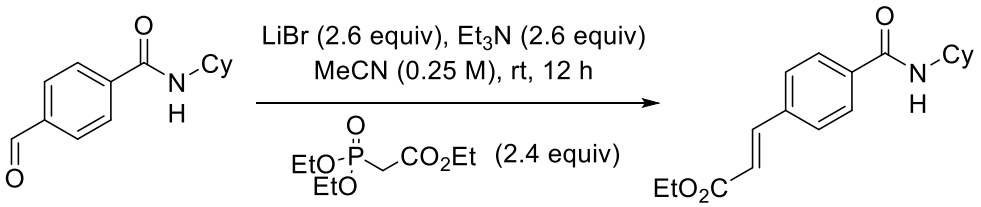
Synthesis of amide **2.1h** from 4-Bromo-*N*-cyclohexylbenzamide (**2.1t**) using a metal-halogen exchange reaction:



***N'*-Cyclohexyl-*N,N*-diethylterephtalamide (2.1h):** To a flame-dried 250 mL round-bottom flask equipped with a septum was added 4-Bromo-*N*-cyclohexylbenzamide (**2.1t**) (5.00 g, 20 mmol, 1.0 equiv). The solid was diluted with anhydrous THF (167 mL, [0.12M]) and the solution was cooled at –78 °C using a dry ice/acetone cooling bath. Then, a BuLi solution in

hexanes ([3.38M]) (11.83 mL, 40 mmol, 2.0 equiv) was added dropwise *via* a syringe over 20 min. The reaction was stirred for 30 min at –78 °C and then heated to 0 °C and stirred for an extra 30 min. The solution was cooled to –78 °C again and *N,N*-diethylcarbamoyl chloride (3.25 g, 3.04 mL, 24.0 mmol, 1.2 equiv) was added dropwise over 10 min. The reaction was slowly heated to room temperature (over 30 min) and stirred at room temperature for 40 min. The reaction was then heated to 50 °C using an oil bath and stirred for 30 min. The reaction was put to room temperature again and quenched by addition of 100 mL of an aqueous solution of HCl [1N]. It was diluted with 150 mL of EtOAc and the biphasic mixture was then transferred to a separation funnel. The layers were separated and the acidic aqueous layer was extracted with EtOAc (3x). The organic layers were combined and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness. The crude diamide was then purified by flash chromatography using a gradient of 30% EtOAc/Hexanes to 90% EtOAc/Hexanes and fractions containing **2.1h** were concentrated to dryness. It resulted in a white powder (3.00 g, 49% Yield). **mp**: 75-76 °C; $\mathbf{R_f}$: 0.40 (90% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.34 (br d, *J* = 7.0 Hz, 1H), 4.02-3.93 (m, 1H), 3.55 (br q, *J* = 7.5 Hz, 2H), 3.20 (d, *J* = 7.5 Hz, 2H), 2.05-2.01 (m, 2H), 1.80-1.75 (m, 2H), 1.69-1.65 (m, 1H), 1.48-1.37 (m, 2H), 1.31-1.07 (m, 9H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 170.6, 166.2, 139.8, 135.9, 127.3, 126.5, 48.9, 43.3, 39.4, 33.3, 25.7, 25.1; **FTIR** (cm^{-1}) (neat): 3312, 2932, 2855, 2241, 1619, 1541, 1450, 1323, 1288, 1098, 905; **HRMS** (ESI, Pos): calc. for $C_{18}H_{27}N_2O_2$ $[M+H]^+$: 303.2073 *m/z*, found: 303.2069 *m/z*.

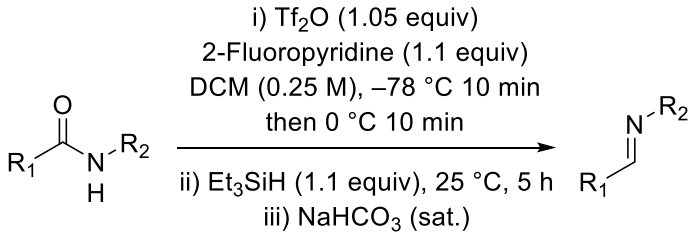
Synthesis of amide **2.1i** from *N*-Cyclohexyl-4-formylbenzamide (**2.1f**) using a Horner-Wadsworth-Emmonds olefination reaction:



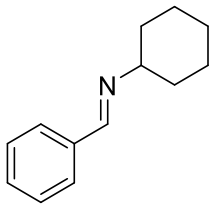
Ethyl (2*E*)-3-{[(cyclohexylamino)carbonyl]phenyl}acrylate (2.1i): To a flame-dried 250-mL round-bottom flask equipped with a septum and under argon was added successively LiBr (2.92 g, 33.8 mmol, 2.6 equiv), MeCN (65.0 mL, [0.20M]), Et_3N (3.42 g, 4.70 mL, 33.8 mmol, 2.6 equiv) and triethylphosphonoacetate (6.98 g, 6.18 mL, 31.2 mmoles, 2.4 equiv). The solution was stirred at room temperature for 5 min and *N*-cyclohexyl-4-formylbenzamide (**2.1f**) (3.00g, 13.0 mmol, 1.0 equiv) was added portion wise at room temperature. The reaction was stirred at room temperature for 16 h. The reaction was quenched by addition of 30 mL of an aqueous saturated sodium carbonate (Na_2CO_3) and was diluted with 30 mL of EtOAc. The biphasic mixture was transferred to a 250 mL extraction funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the organic layers were combined and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness. The crude amide (*E : Z* ratio is > 20 : 1) was then purified by flash chromatography using a gradient of 20% EtOAc/Hexanes to 60% EtOAc/Hexanes and fractions containing **2.1i** were concentrated to dryness. It resulted in a white powder (3.30 g, 84% Yield). **mp**: 175-176 °C; $\mathbf{R_f}$: 0.65 (60% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 16.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 16.5 Hz, 1H), 6.02 (br d, *J* = 7.5 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 4.04-3.95 (m, 1H), 2.07-2.03 (m, 2H), 1.81-1.75 (m, 2H), 1.71-1.65 (m, 1H), 1.50-1.18 (m, 5H), 1.36 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 166.8, 165.9, 143.4, 137.2, 136.5, 128.2, 127.6, 120.1, 60.8, 49.0, 33.3, 25.7, 25.1, 14.4; **FTIR** (cm^{-1}) (neat): 3285, 2937, 2855, 1712, 1627, 1541, 1309, 1174; **HRMS** (ESI, Pos): calc. for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1756 *m/z*, found: 302.1753 *m/z*.

Imine and iminium synthesis (Table #1, entries 1-19, **2.2a-2.2r**):

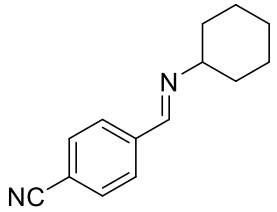
Synthesis of imines **2.2a-2.2f**, **2.2k-2.2m** and **2.2o** according to **procedure C**:



Procedure C: To a flame-dried 50-mL round-bottom flask equipped with a septum was added the amide (2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmoles, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. The reaction was quenched by addition of 1 mL of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) and diluted with 8 mL of dichloromethane. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude imine was purified by evaporation of the 2-fluoropyridine and silane residues in a vaccum oven (1-5 mmHg) at 50 °C for 4 h. **Note**: *The pure imines were then stored in the freezer (–20 °C) under argon.*

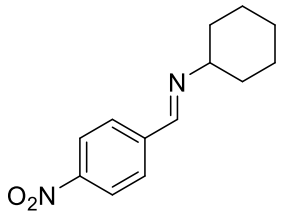


Benzylidenecyclohexylamine (2.2a):[18] Following the **procedure C**, the imine was isolated as a yellow oil (301.7 mg, 81% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.34 (s, 1H), 7.78-7.76 (m, 2H), 7.44-7.42 (m, 3H), 3.27-3.20 (m, 1H), 1.89-1.84 (m, 2H), 1.79-1.58 (m, 5H), 1.45-1.26 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 159.2, 130.9, 129.0, 128.6, 70.3, 34.7, 26.0, 25.2; **FTIR** (cm^{-1}) (neat): 2926, 2852, 1642, 1449, 1217, 964; **HRMS** (ESI, Pos): calc. for $C_{13}H_{18}N$ $[M+H]^+$: 188.1439 *m/z*, found: 188.1431 *m/z.*

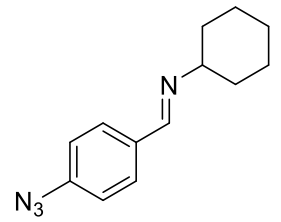


4-[(*E*)-((Cyclohexylimino)methyl)benzonitrile (2.2b): Following the **procedure C**, the imine was isolated as an orange oil (374.0 mg, 88% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.35 (s, 1H), 7.86 (br d, *J* = 7.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 3.33-3.26 (m, 1H), 1.91-1.85 (m, 2H), 1.78-1.57 (m, 5H), 1.45-1.24 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 156.8, 140.7, 132.5, 128.6, 118.8, 113.7, 70.2, 34.3, 25.7, 24.7; **FTIR** (cm^{-1}) (neat): 2928, 2854, 2227, 1642, 1449, 1299, 833; **HRMS** (ESI, Pos): calc. for $C_{14}H_{17}N_2$ $[M+H]^+$: 213.1392 *m/z*, found: 213.1390 *m/z*.

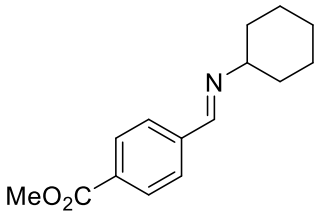
[18]. For characterization data, see: Naeimi, H.; Salimi, F.; Rabiei, K. *J. Mol. Catal. A* **2006**, *260*, 100-104.



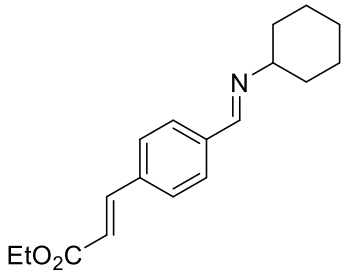
***N*-[(1*E*)-(4-Nitrophenyl)methylene]cyclohexanamide (2.2c):** Following the **procedure C**, the imine was isolated as an orange solid (386.0 mg, 84% Yield). **mp**: 38-39 °C; **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.41(s, 1H), 8.28 (d, *J* = 12.5 Hz, 2H), 7.91 (d, *J* = 12.5 Hz, 2H), 3.35-3.26 (m, 1H), 1.91-1.84 (m, 2H), 1.80-1.69 (m, 3H), 1.67-1.58 (m, 2H), 1.46-1.29 (m, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz): δ 157.1, 149.6, 143.0, 129.5, 124.6, 70.9, 35.0, 26.4, 25.4; **FTIR** (cm^{-1}) (neat): 2927, 2853, 1641, 1599, 1517, 1339, 1107; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}N_2O_2$ $[M+H]^+$: 233.1290 *m/z*, found: 233.1285 *m/z*.



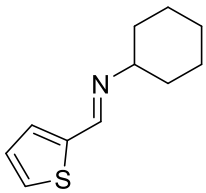
***N*-[(1*E*)-(4-Azidophenyl)methylene]cyclohexanamide (2.2d):** Following the **procedure C**, the imine was isolated as a red oil (400.1 mg, 88% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.29 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 3.24-3.17 (m, 1H), 1.88-1.83 (m, 2H), 1.77-1.68 (m, 3H), 1.64-1.55 (m, 2H), 1.44-1.25 (m, 3H); **^{13}C NMR** ($CHCl_3$, 75 MHz): δ 157.6, 142.2, 134.0, 130.0, 119.4, 70.3, 34.8, 26.1, 25.2; **FTIR** (cm^{-1}) (neat): 2926, 2852, 2115, 1638, 1602, 1504, 1281, 828; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}N_4$ $[M+H]^+$: 229.1453 *m/z*, found: 229.1439 *m/z*.



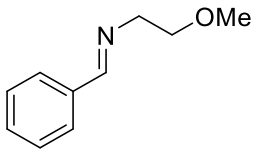
Methyl 4-[(*E*)-(cyclohexylimino)methyl]benzoate (2.2e): Following the **procedure C**, the imine was isolated as a yellow solid (462.3 mg, 95% Yield). **mp**: 49-50 °C; **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.38 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 3.95 (s, 3H), 3.29-3.22 (m, 1H), 1.89-1.84 (m, 2H), 1.78-1.57 (m, 5H), 1.45-1.27 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 166.4, 157.3, 140.2, 131.1, 129.4, 127.6, 69.7, 51.8, 33.9, 25.3, 24.3; **FTIR** (cm^{-1}) (neat): 2927, 2853, 1720, 1639, 1435, 1274, 1109; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494 *m/z*, found: 246.1492 *m/z*.



(*E*)-Ethyl 3-{4-[(*E*)-(cyclohexylimino)methyl]phenyl}acrylate (2.2i): Following the **procedure C**, the imine was isolated as a yellow solid (545.0 mg, 96% Yield). **mp**: 37-38 °C; **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.33 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 16.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 6.49 (d, *J* = 16.5 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.27-3.20 (m, 1H), 1.88-1.56 (m, 7H), 1.45-1.26 (m, 3H), 1.36 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 167.3, 158.2, 144.2, 138.6, 136.7, 128.9, 128.6, 119.5, 70.5, 61.0, 34.7, 26.0, 25.2, 14.7; **FTIR** (cm^{-1}) (neat): 3130, 2984, 2928, 1712, 1637, 1309, 1174; **HRMS** (ESI, Pos): calc. for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1806 *m/z*, found 286.1789 *m/z*.

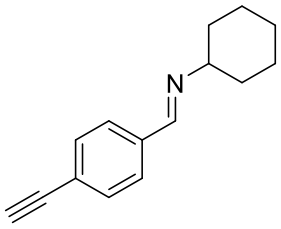


(*E*)-*N*-(Thiophen-2-ylmethylene)cyclohexanamide (2.2k):[19] Following the **procedure C**, the imine was isolated as a yellow oil (329.4 mg, 85% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.42 (s, 1H), 7.39 (d, *J* = 5.0 Hz, 1H), 7.30-7.29 (m, 1H), 7.07 (dd, *J* = 3.5, 5.0 Hz, 1H), 3.22-3.14 (m, 1H), 1.87-1.54 (m, 7H), 1.42-1.23 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 151.9, 143.1, 130.1, 128.5, 127.4, 69.8, 34.5, 25.8, 25.0; **FTIR** (cm^{-1}) (neat): 2927, 2853, 1632, 1449, 1432, 1215, 1074; **HRMS** (ESI, Pos): calc. for $C_{11}H_{16}NS$ $[M+H]^+$: 194.1003 *m/z*, found 194.0992 *m/z*.

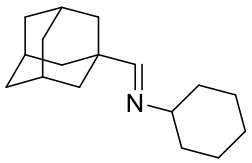


Benzylidene-(2-methoxyethyl)amine (2.2l): Following the **procedure C**, the imine was isolated as a yellow oil (250.1 mg, 78% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.34 (s, 1H), 7.78-7.76 (m, 2H), 7.45-7.42 (m, 3H), 3.83 (t, *J* = 5.5 Hz, 2H), 3.73 (t, *J* = 5.5 Hz, 2H), 3.41 (s, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 163.2, 136.5, 131.1, 129.0, 128.6, 72.6, 61.6, 59.4; **FTIR** (cm^{-1}) (neat) 2887, 1647, 1450, 1121; **HRMS** (ESI, Pos): calc. for $C_{10}H_{14}NO$ $[M+H]^+$: 164.1075 *m/z*, found: 164.1065 *m/z*.

[19]. For characterization data, see: Adrio, L. A.; Antelo, J. M.; Fernández, A.; Pereira, M. T.; Tato, M.; Vila, J. M. *Z. Anorg. Allg. Chem.* **2007**, *633*, 734-740.

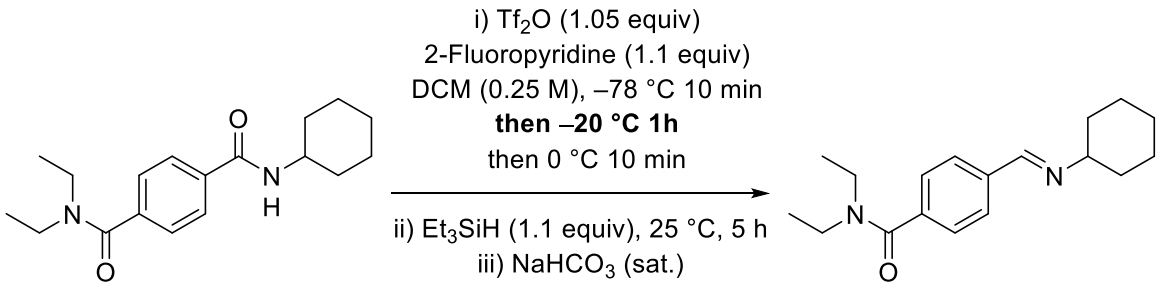


***N*-[(1*E*)-(4-Ethynylphenyl)methylene)cyclohexanamide (2.2m):** Following the **procedure C**, the imine was isolated as a brown solid (399.6 mg, 95% Yield). **mp**: 28-29 °C; **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.32 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 3.27-3.19 (m, 1H), 3.18 (s, 1H), 1.88-1.84 (m, 2H), 1.77-1.68 (m, 3H), 1.65-1.56 (m, 2H), 1.45-1.26 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 157.3, 136.5, 131.2, 127.5, 123.5, 83.1, 78.4, 69.6, 34.0, 25.3, 24.4; **FTIR** (cm^{-1}) (neat) 3293, 2926, 2852, 2107, 1923, 1640, 1448, 1070; **HRMS** (ESI, Pos): calc. for $C_{15}H_{18}N$ $[M+H]^+$: 212.1439 *m/z*, found: 212.1433 *m/z*.



***N*-[(1*E*)-1-Adamantylmethylene]cyclohaxanamide (2.2o):** Following the **procedure C** *with 1.3 equivalent of Et_3SiH instead of 1.1 equiv*, the imine was isolated as a beige gum (381.7 mg, 78% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.38 (s 1H), 2.91-2.84 (m, 1H), 2.03 (s, 3H), 1.86-1.58 (m, 17H), 1.54-1.44 (m, 2H), 1.37-1.18 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 169.0, 69.6, 39.3, 37.2, 36.5, 34.0, 27.7, 25.2, 24.6; **FTIR** (cm^{-1}) (neat) 2901, 2848, 1666, 1450, 1343; **HRMS** (ESI, Pos): calc. for $C_{17}H_{28}N$ $[M+H]^+$: 246.2222 *m/z*, found: 246.2212 *m/z*.

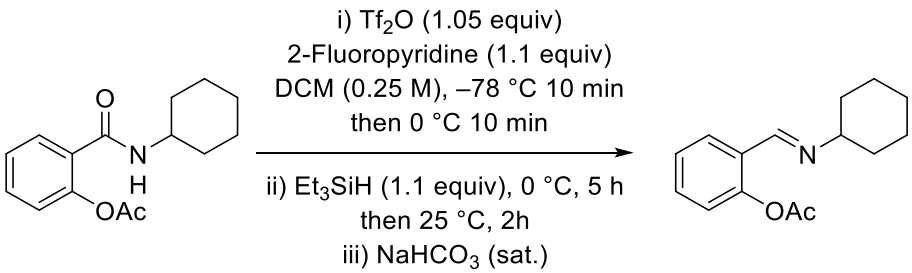
Synthesis of imine **2.2h** by activation of the amide **2.1h** at –20 °C:



4-[(*E*)-(Cyclohexylimino)methyl]-*N*,*N*-diethylbenzamide (2.2h): To a flame-dried 50-mL round-bottom flask equipped with a septum was added *N'*-Cyclohexyl-*N*,*N*-diethylterephtalamide (**2.1h**) (604.1 mg, 2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 5 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was slowly heated to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred at –20 °C for 1 h. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. The reaction was quenched by addition of 1 mL of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) and diluted with 8 mL of dichloromethane. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude imine was purified by evaporation of the 2-fluoropyridine and silane residues in a vaccum oven (1-5 mmHg) at 50 °C for 4 h. It resulted in a yellow oil (564.3 mg, 99% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.35 (s, 1H), 7.76 (d, *J* = 11.0 Hz, 2H), 7.41 (d, *J* = 11.0 Hz, 2H), 3.56 (br s, 2H), 3.28-3.18 (m, 3H), 1.90-1.54 (m, 7H), 1.46-1.07 (m, 9H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 170.4, 157.5, 138.6, 136.9, 127.7, 126.2, 69.6, 42.9, 38.9, 34.0, 25.2, 24.4, 13.8, 12.5; **FTIR** (cm^{-1}) (neat): 3376, 2929, 2854, 1631, 1427,

1287, 1094; **HRMS** (ESI, Pos): calc. for $C_{18}H_{27}N_2O$ $[M+H]^+$: 287.2123 *m/z*, found: 287.2114 *m/z*.

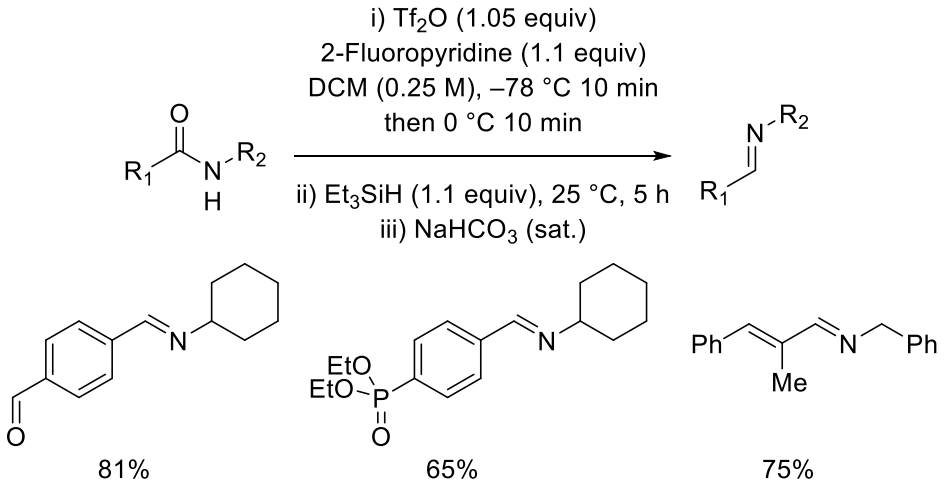
Synthesis of imine **2.2j** by reducing the activated amide **2.1j** at 0 °C for 5 h:



2-[(*E*)-(Cyclohexylimino)methyl]phenyl acetate (2.2j): To a flame-dried 50-mL round-bottom flask equipped with a septum was added 2-[(Cyclohexylamino)carbonyl]phenyl acetate (**2.1j**) (522.3 mg, 2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 5 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 5 h. The solution was heated to room temperature and stirred for an extra 2 h. The reaction was quenched by addition of 1 mL of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) and diluted with 8 mL of dichloromethane. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude imine was purified by evaporation of the 2-fluoropyridine and silane residues in a vaccum oven (1-5 mmHg) at 50 °C for 4 h. It resulted in a yellow oil (419.1 mg, 86% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.38 (s, 1H), 7.90 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.44-7.40 (m, 1H), 7.31-7.26 (m, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 3.22-3.14 (m, 1H), 2.37 (s, 3H), 1.88-1.82 (m, 2H), 1.78-1.67 (m, 3H), 1.64-1.54 (m, 2H), 1.44-1.25 (m, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 168.8, 153.3, 149.4, 130.6,

128.8, 128.1, 125.7, 122.4, 70.1, 34.1, 25.3, 24.3, 20.6; **FTIR** (cm^{-1}) (neat): 2927, 2853, 1766, 1634, 1449., 1367, 1194, 1173; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494 *m/z*, found: 246.1489 *m/z*.

Synthesis of imines **2.2f**, **2.2g** and **2.2n**: Procedure for ^1H NMR analysis of non-isolable imines

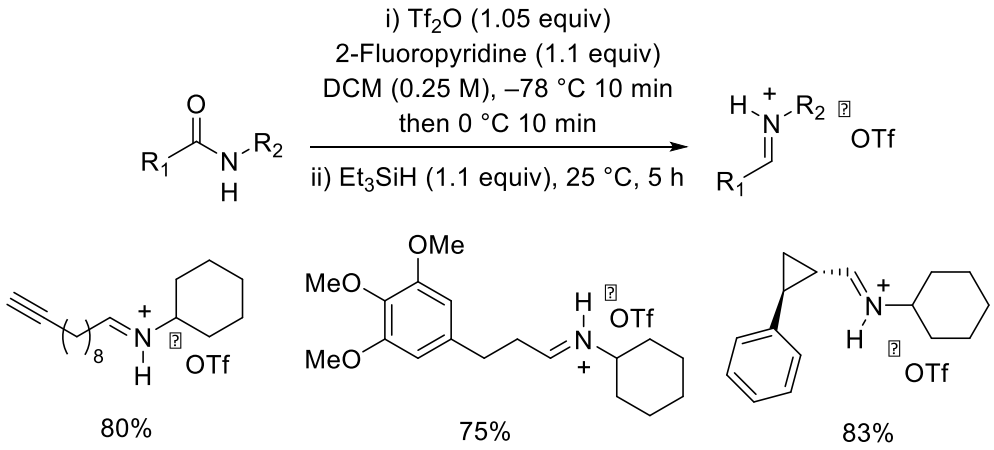


To a flame-dried 50-mL round-bottom flask equipped with a septum was added the corresponding amide (**2.1f**, **2.1g** or **2.1n**) (2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 5 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min.***** The solution was heated to room temperature and stirred for 5 h. Then, triphenylmethane (internal standard) (492.3 mg, 2.0 mmol, 1.0 equiv) was added in the reaction mixture and the reaction was quenched by addition of 1 mL of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) and diluted with 8 mL of dichloromethane. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with

dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude imines were analyzed by ^1H NMR spectroscopy in $CDCl_3$ and the yields were calculated by integration of the imine R-C(***H***)=N-R' signal versus the singlet at 5.56 ppm corresponding to $(Ph)_3C$-***H*** of the internal standard.

***Note**: The reduction of amide **2.1f** was performed at 0 °C for 5 h instead of 5 h at 25 °C.*

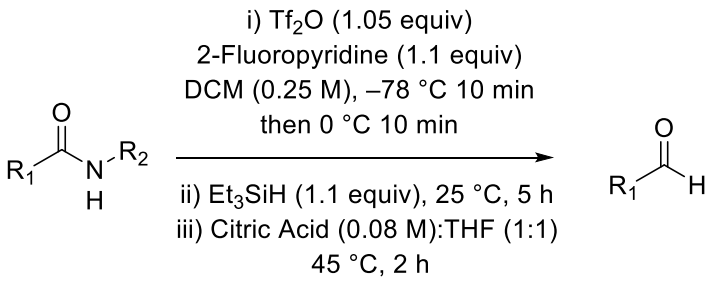
Synthesis of iminiums **2.2p**-**2.2r**: Procedure for ^1H NMR analysis of non-isolable iminiums.



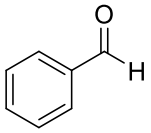
To a flame-dried 50-mL round-bottom flask equipped with a septum was added the corresponding amide (**2.1p**, **2.1q** or **2.1r**) (2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 5 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmoles, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. Then, triphenylmethane (internal standard) (492.3 mg, 2.0 mmol, 1.0 equiv) was added in the reaction mixture and the reaction was evaporated to dryness. The crude iminiums were analyzed by ^1H NMR spectroscopy in $CDCl_3$ and the yields were calculated by integration of the iminium R-C(***H***)=NH^+-R' signal versus the singlet at 5.56 ppm corresponding to $(Ph)_3C$-***H*** of the internal standard.

Aldehyde synthesis (Table #1, entries 1-19, **2.3a-2.3s**):

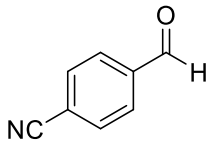
Synthesis of aldehydes **2.3a-2.3e**, **2.3g, 2.3i, 2.3k-2.3r** according to **procedure D**:



Procedure D: To a flame-dried 50-mL round-bottom flask equipped with a septum was added the amide (2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 5 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. Then, the septum was removed and 8 mL of an aqueous solution of citric acid [0.08M] and 8 mL of THF were added to the flask. A reflux condenser was installed on the flask and the reaction was then heated to 45 °C and stirred for 2 h. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. **Note**: *Some synthesized aldehydes were found usually unstable when stored at room temperature on the bench over 1 or 2 days and showed decomposition by ^1H NMR if no special storage precautions were taken. They should be kept under argon in the freezer (–20 °C) or use directly in a further reaction.*



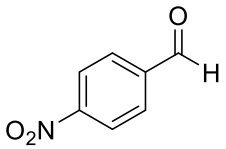
Benzaldehyde (2.3a):[20] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 15% EtOAc/Hexanes and fractions containing **2.3a** were concentrated to dryness. It resulted in a translucid liquid (187.3 mg, 89% Yield). $\mathbf{R_f}$: 0.65 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.05 (s, 1H), 7.92-7.89 (m, 2H), 7.69-7.63 (m, 1H), 7.58-7.53 (m, 2H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 193.2, 137.3, 135.3, 130.6, 129.8; **FTIR** (cm^{-1}) (neat): 3064, 2820, 2737, 1700, 1597, 1311, 1203; **HRMS** (ESI, Pos): calc. for C_7H_7O $[M+H]^+$: 107.0497 *m/z*, found 107.0493 *m/z*.



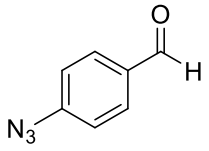
4-Formylbenzonitrile (2.3b):[21] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 15% EtOAc/Hexanes and fractions containing **2.3b** were concentrated to dryness. It resulted in a yellow solid (232.9 mg, 89% Yield). **mp**: 89-90 °C, litt:[21] 97-100 °C $\mathbf{R_f}$: 0.60 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.11 (s, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 190.8, 138.8, 133.0, 130.0, 117.8, 117.7; **FTIR** (cm^{-1}) (neat): 3094, 3047, 2846, 2745, 2229, 1704, 1608, 1572, 1386, 1296, 1202; **HRMS** (ESI, Pos): calc. for C_8H_6NO $[M+H]^+$: 132.0449 *m/z*, found 132.0449 *m/z*.

[20]. For characterization data, see: Rezaeifard, A.; Jafarpour, M.; Kardan, G.; Amini, J. *Bioorg. Med. Chem.* **2007**, *15*, 3097-3101.

[21]. For characterization data, see: Kornblum, N.; Fifolt, M. J. *Tetrahedron* **1989**, *45*, 1311-1322.

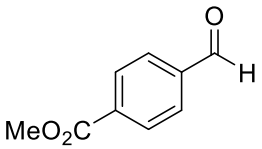


4-Nitrobenzaldehyde (2.3c):[22] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 15% EtOAc/Hexanes and fractions containing **2.3c** were concentrated to dryness. It resulted in a yellow solid (244.0 mg, 81% Yield). **mp**: 103-104 °C, litt:[22] 106-108 °C $\mathbf{R_f}$: 0.30 (10% EtOAc/Hexanes); $^{\mathbf{1}}\mathbf{H}$ **NMR** ($CHCl_3$, 400 MHz): δ 10.19 (s, 1H), 8.42 (d, J = 9.5 Hz, 2H), 8.10 (d, J = 9.5 Hz, 2H); $^{\mathbf{13}}\mathbf{C}$ **NMR** ($CHCl_3$, 100 MHz): δ 190.0, 139.7, 130.1, 124.0; **FTIR** (cm^{-1}) (neat) 3107, 2850, 1706, 1606, 1536, 1346, 1197; **HRMS** (ESI, Pos): calc. for $C_7H_5NO_3$ $[M]^+$: 151.0269 *m/z*, found: 151.0277 *m/z*.

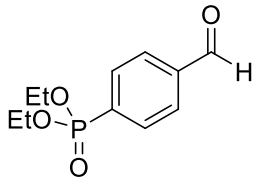


4-Azidobenzaldehyde (2.3d):[23] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 15% EtOAc/Hexanes and fractions containing **2.3d** were concentrated to dryness. It resulted in a yellow oil (244.0 mg, 89% Yield). $\mathbf{R_f}$: 0.50 (10 % EtOAc/Hexanes); $^{\mathbf{1}}\mathbf{H}$ **NMR** ($CHCl_3$, 400 MHz): δ 9.97 (s, 1H), 7.91 (d, J = 10.5 Hz, 2H), 7.18 (d, J = 9.0 Hz, 2H); $^{\mathbf{13}}\mathbf{C}$ **NMR** ($CHCl_3$, 100 MHz): δ 191.0, 146.7, 133.6, 132.0, 119.9; **FTIR** (cm^{-1}) (neat) 3301, 3288, 2117, 1698; **HRMS** (ESI, Pos): calc. for $C_7H_6N_3O$ $[M+H]^+$: 148.0511 *m/z*, found: 148.0510 *m/z*.

22. For characterization data, see: Miao, C.-X.; He, L.-N.; Gao, J. *Synlett* **2009**, 3291-3294.
23. For characterization data, see: Spletstoser, J. T.; Flaherty, P. T.; Himes, R. H.; Georg, G. I. *J. Med. Chem.* **2004**, *47*, 6459-6465.



Methyl 4-formylbenzoate (2.3e):[24] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 20% EtOAc/Hexanes and fractions containing **2.3e** were concentrated to dryness. It resulted in a white solid (294.2 mg, 90% Yield). **mp**: 54-55 °C, litt:[24] 50-51 °C; $\mathbf{R_f}$: 0.40 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.13 (s, 1H), 8.22 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 9.0 Hz, 2H), 3.98 (s, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 191.3, 165.7, 138.8, 134.7, 129.9, 129.2, 52.2; **FTIR** (cm^{-1}) (neat): 3021, 2963, 2888, 1720, 1683, 1280, 1202, 1106; **HRMS** (ESI, Pos): calc. for $C_9H_9O_3$ $[M+H]^+$: 165.0552 *m/z*, found: 165.0544 *m/z*.



Diethyl 4-formylbenzophosphonate (2.3g): [25] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 20% Hexanes/EtOAc to 100% EtOAc and fractions containing **2.3g** were concentrated to dryness. It resulted in a translucid oil (307.1 mg, 64% Yield). $\mathbf{R_f}$: 0.40 (100% EtOAc); **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 10.06 (s, 1H), 7.99-7.94 (m, 4H), 4.21-4.04 (m, 4H), 1.31 (t, J = 7.0 Hz, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz) δ 191.7, 138.7 (d, J_{C-P} = 3.0 Hz), 134.9 (d, J_{C-P} = 184.5 Hz), 132.4 (d, J_{C-P} = 11.0 Hz), 129.4 (d, J_{C-P} = 14.5 Hz), 62.5 (d, J_{C-P} = 5.5 Hz), 16.3 (d, J_{C-P} = 6.5 Hz); **^{31}P NMR** ($CHCl_3$, 161.9 MHz) d 16.69 **FTIR** (cm^{-1}) (neat) 2985, 1707, 1242, 1219, 1015; **HRMS** (ESI, Pos) calc. for $C_{11}H_{16}O_4P$ $[M+H]^+$: 243.0786 *m/z*, found 243.0773 *m/z*.

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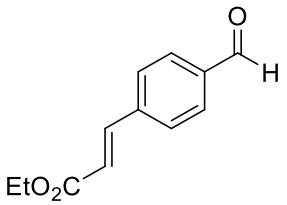
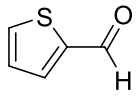
[24]. For characterization data, see: (a) Srogl, J.; Voltrova, S. *Org. Lett.* **2009**, *11*, 843-845. (b) Landesberg, J. M.; Slam, M. A.; Mandel, M. *J. Org. Chem.* **1981**, *46*, 5025-5027.

[25]. For characterization data, see: Morisue, M.; Haruta, N.; Kalita, D.; Kobuke, Y. *Chem. Eur. J.* **2006**, *12*, 8123-8135.

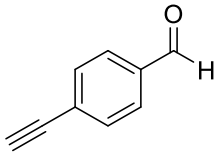


Ethyl 3-(4-formylphenyl)-(*E*)-acrylate (2.3i):[26] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 30% EtOAc/Hexanes and fractions containing **2.3i** were concentrated to dryness. It resulted in a yellow oil (390.5 mg, 96% Yield). $\mathbf{R_f}$: 0.60 (25% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.03 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.73-7.67 (m, 3H), 6.55 (d, *J* = 15.5 Hz, 1H), 4.28 (q, *J* = 7.5 Hz, 2H), 1.35 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 191.1, 166.0, 142.4, 139.7, 136.7, 129.8, 128.1, 121.1, 60.4, 13.9; **FTIR** (cm^{-1}) (neat): 3384, 2981, 2827, 1694, 1637, 1603, 1310, 1201, 1165; **HRMS** (ESI, Pos): calc. for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0865 *m/z*, found: 205.0861 *m/z*.

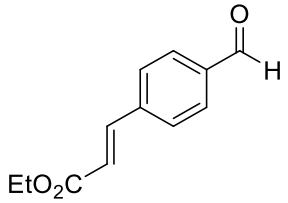


Thiophene 2-carbaldehyde (2.3k):[27] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 20% EtOAc/Hexanes and fractions containing **2.3k** were concentrated to dryness. It resulted in a translucid oil (178.7 mg, 80% Yield). $\mathbf{R_f}$: 0.65 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 9.90 (s, 1H), 7.77-7.73 (m, 2H), 7.18 (dd, *J* = 4.0, 5.0 Hz, 1H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 183.5, 144.4, 136.9, 135.6, 128.8; **FTIR** (cm^{-1}) (neat): 3089, 2820, 1655, 1417, 1211; **HRMS** (ESI, Pos): calc. for C_5H_5OS $[M+H]^+$: 113.0061 *m/z*, found: 113.0059 *m/z*.

[26]. For characterization data, see: Zeitler, K. *Org. Lett.* **2006**, *8*, 637-640.
[27]. For characterization data, see: Xi, B.; Nevalainen, V. *Tetrahedron Lett.* **2006**, *47*, 7133-7135.



4-Ethynylbenzaldehyde (2.3m):[28] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 10% EtOAc/Hexanes and fractions containing **2.3m** were concentrated to dryness. It resulted in a yellow solid (243.9 mg, 94% Yield). **mp**: 59-60 °C, litt:[28] 87 °C; $\mathbf{R_f}$: 0.55 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.04 (s, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.65 (d, *J* = 7.0 Hz, 2H), 3.22 (s, 1H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 191.9, 136.3, 133.1, 129.9, 128.7, 83.1, 81.5; **FTIR** (cm^{-1}) (neat): 3217, 2838, 2741, 2101, 1700, 1684, 1605, 1208; **HRMS** (ESI, Pos): calc. for C_9H_7O $[M+H]^+$: 131.0497 *m/z*, found: 131.0488 *m/z*.



(*E*)-α-Methyl-cinnamaldehyde (2.3n):[29] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 10% EtOAc/Hexanes and fractions containing **2.3n** were concentrated to dryness. It resulted in a translucid oil (266.7 mg, 92% Yield). $\mathbf{R_f}$: 0.70 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 9.62 (s, 1H), 7.58-7.56 (m, 2H), 7.50-7.41 (m, 3H), 7.30 (s, 1H), 2.11 (s, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 195.2, 149.5, 138.0, 134.8, 129.7, 129.2, 128.4, 10.6; **FTIR** (cm^{-1}) (neat): 3335, 3055, 2714, 1677, 1621, 1449, 1187; **HRMS** (ESI, Pos): calc. for $C_{10}H_{11}O$ $[M+H]^+$: 147.0810 *m/z*, found: 147.0801 *m/z*.

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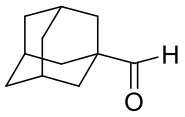
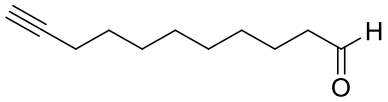
[28]. For characterization data, see: Wautelet, P.; Le Moigne, J.; Videva, V.; Turek, P. *J. Org. Chem.* **2003**, *68*, 8025-8036.
[29]. For characterization data, see: Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471-5474.



Adamantane-1-carbaldehyde (2.3o):[30] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 5% EtOAc/Hexanes and fractions containing **2.3o** were concentrated to dryness. It resulted in a white powder (231.7 mg, 70% Yield). **mp**: 146-148 °C, litt:[30] $\mathbf{R_f}$: 0.65 (5% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 9.28 (s, 1H), 2.04-2.00 (m, 3H), 1.77-1.65 (m, 12H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 205.5, 44.4, 36.2, 35.5, 27.0; **FTIR** (cm^{-1}) (neat) 2903, 2850, 2697, 1720, 1451, 1142; **HRMS** (ESI, Pos): calc. for $C_{11}H_{17}O$ $[M+H]^+$: 165.1279 *m/z*, found: 165.1275 *m/z*.



Undec-10-yn-1-al (2.3p):[31] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 10% EtOAc/Hexanes and fractions containing **2.3p** were concentrated to dryness. It resulted in a translucid oil (238.0 mg, 72% Yield). $\mathbf{R_f}$: 0.70 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 9.77 (t, *J* = 1.5 Hz, 1H), 2.43 (dt, *J* = 2.0, 7.5 Hz, 2H), 2.18 (dt, *J* = 3.0, 7.0 Hz, 2H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.67-1.60 (m, 2H), 1.56-1.49 (m, 2H), 1.43-1.29 (m, 9H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 203.3, 85.1, 68.5, 44.3, 29.6, 29.5, 29.3, 29.0, 28.8, 22.4, 18.8; **FTIR** (cm^{-1}) (neat): 3294, 2929, 2856, 2720, 2117, 1723, 1463, 910; **HRMS** (ESI, Pos): calc. for $C_{11}H_{19}O$ $[M+H]^+$: 167.1436 *m/z*, found 167.1430 *m/z*.

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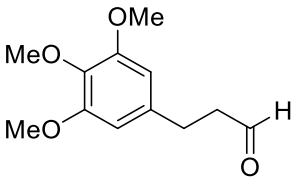
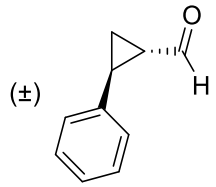
30. For characterization data, see: (a) Quintanilla, E.; Dávalos, J. Z.; Abboud, J.-L. M.; Alcamí, M.; Cabildo, M. P.; Claramunt, R. M.; Elguero, J.; Mó, O.; Yáñez, M. *Chem. Eur. J.* **2005**, *11*, 1826-1832. (b) Wright, J. A.; Gaunt, M. J.; Spencer, J. B. *Chem. Eur. J.* **2006**, *12*, 949-955.
31. For characterization data, see: Hopf, H.; Krüger, A. *Chem. Eur. J.* **2000**, *7*, 4378-4385.



3-(3,4,5-Trimethoxy-phenyl)-propan-1-al (2.3q):[32] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 85% EtOAc/Hexanes and fractions containing **2.3q** were concentrated to dryness. It resulted in a translucid oil (322.6 mg, 72% Yield). $\mathbf{R_f}$: 0.30 (60% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 9.83 (t, *J* = 1.0 Hz, 1H), 6.41 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 2.92-2.89 (m, 2H), 2.81-2.76 (m, 2H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 201.6, 153.4, 136.5, 136.3, 105.3, 61.0, 56.2, 45.6, 28.6; **FTIR** (cm^{-1}) (neat): 2937, 2838, 1721, 1588, 1506, 1456, 1420, 1236; **HRMS** (ESI, Pos): calc. for $C_{12}H_{17}O_4$ $[M+H]^+$: 225.1127 *m/z*, found: 225.1117 *m/z*.



***trans*-2-Phenylcyclopropancarbaldehyde (2.3r)**:[33] Following the **procedure D**, the crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 10% EtOAc/Hexanes and fractions containing **2.3r** were concentrated to dryness. It resulted in a translucid oil (244.4 mg, 84% Yield). $\mathbf{R_f}$: 0.70 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 9.36 (d, *J* = 4.5 Hz, 1H), 7.34-7.24 (m, 3H), 7.16-7.13 (m, 2H), 2.65 (ddd, *J* = 5.0, 7.0, 11.0 Hz, 1H), 2.23-2.18 (m, 1H), 1.77 (dt, *J* = 5.0, 10.0 Hz, 1H), 1.57 (ddd, *J* = 5.0, 7.0, 10.0 Hz, 1H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 200.1, 139.4, 129.1, 127.3, 126.7, 34.3, 27.0, 16.9; **FTIR** (cm^{-1}) (neat) 3030, 2830, 2731, 1698, 1497, 1399; **HRMS** (ESI, Pos): calc. for $C_{10}H_{11}O$ $[M+H]^+$: 147.0810 *m/z*, found: 147.0811 *m/z*.

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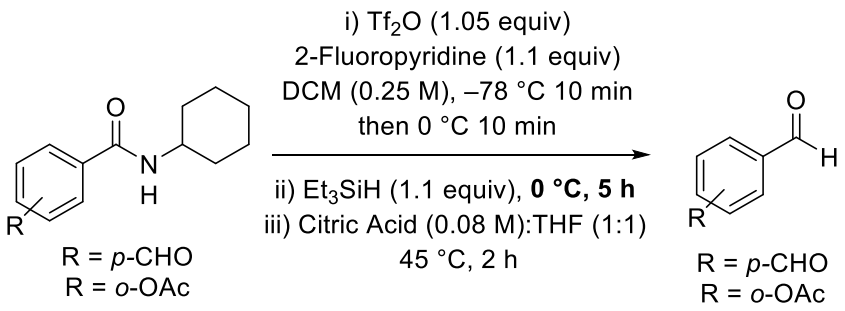
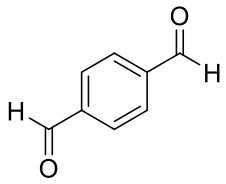
32. For characterization data, see: Bordron, J.; Commeiras, L.; Barbier, P.; Bourgarel-Rey, V.; Pasquier, E.; Vanthuyne, N.; Hubaud, J.-C.; Peyrot, V.; Parrain, J.-L. *Bioorg. Med. Chem.* **2004**, *14*, 5540-5548.
33. For characterization data, see: Cheeseman, M.; Davies, I. R.; Axe, P.; Johnson, A. L.; Bull, S. D. *Org. Biomol. Chem.* **2009**, *7*, 3537-3548.

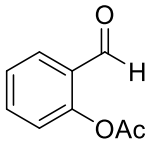
Synthesis of aldehydes **2.3f** and **2.3j** by reduction of amides **2.1f** and **2.1j** at 0 °C for 5 h:



To a flame-dried 50 mL round-bottom flask equipped with a septum was added the amide (2.0 mmol, 1.00 equiv) (**2.1f** or **2.1j**). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 5 h. Then, the septum was removed and 8 mL of an aqueous solution of citric acid ([0.08M]) and 8 mL of THF were added to the flask. A reflux condenser was installed on the flask and the reaction was then heated to 45 °C and stirred for 2 h. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness.



Benzene 1,4-dicarbaldehyde (2.3f): [34] The crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 15% EtOAc/Hexanes and fractions containing **2.3f** were concentrated to dryness. It resulted in a white solid (225.9 mg, 84% Yield). **mp**: 113-114 °C, litt:[34] 114-115 °C $\mathbf{R_f}$: 0.60 (25% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.16 (s, 2H), 8.08 (s, 4H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 191.1, 139.6, 129.8; **FTIR** (cm^{-1}) (neat): 2865, 1685, 1498, 1385, 1300, 1197; **HRMS** (ESI, Pos): calc. for $C_{12}H_{13}O_3$ $[M+H]^+$: 135.0446 *m/z*, found: 135.0434 *m/z*.



Methyl 2-formylbenzoate (2.3j):[35] The crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 15% EtOAc/Hexanes and fractions containing **2.3j** were concentrated to dryness. It resulted in a translucid oil (273.5 mg, 84% Yield). $\mathbf{R_f}$: 0.75 (20% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.14 (s, 1H), 7.91 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.69-7.64 (m, 1H), 7.45-7.41 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 2.43 (s, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 188.4, 168.9, 151.1, 134.9, 131.0, 127.7, 126.1, 123.2, 20.5; **FTIR** (cm^{-1}) (neat): 2859, 1767, 1697, 1604, 1369, 1191; **HRMS** (ESI, Pos) calc. for $C_9H_9O_3$ $[M+H]^+$: 165.0552 *m/z*, found: 165.0550 *m/z*.

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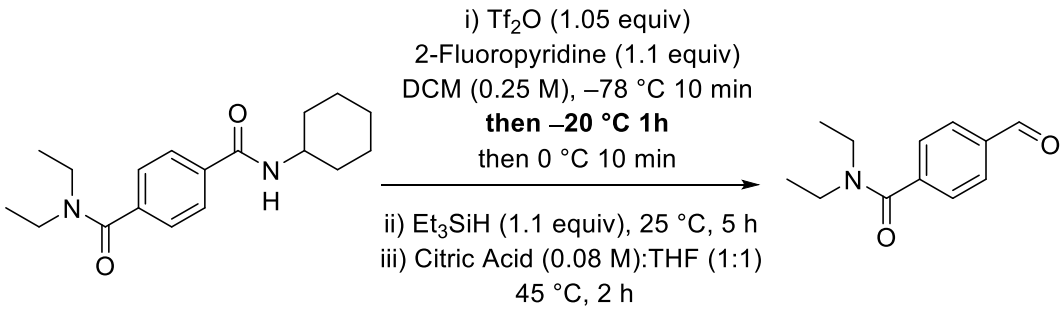
[34]. For characterization data, see: Ghaffarzadeh, M.; Bolourtchian, M.; Gholamhosseni, M.; Mohsenzadeh, F. *Appl. Catal. A* **2007**, *333*, 131-135.

[35]. For characterization data, see: Briard, E.; Zoghbi, S. S.; Imaizumi, M.; Gourley, J. P.; Shetty, H. U.; Hong, J.; Cropley, V.; Fujita, M.; Innis, R. B.; Pike, V. W. *J. Med. Chem.* **2008**, *51*, 17-30.

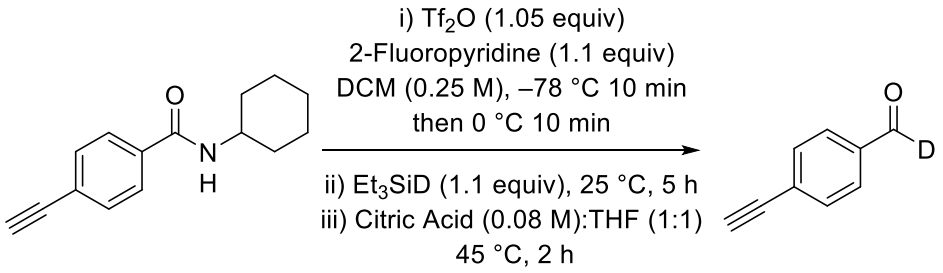
Synthesis of aldehyde **2.3h** by activation of the amide **2.1h** at –20 °C:



***N,N*-Diethyl-4-formylbenzamide (2.3h):** To a flame-dried 50-mL round-bottom flask equipped with a septum was added *N'*-Cyclohexyl-*N,N*-diethylterephtalamide (**2.1h**) (604.1 mg, 2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25 M]) and 2-fluoropyridine (213.5 mg, 190 μL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 μL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was slowly heated to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred at -20 °C for 1 h. The solution was then heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 μL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. The reaction was quenched by addition of 1 mL of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) and diluted with 8 mL of dichloromethane. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. Then, the septum was removed and 8 mL of an aqueous solution of citric acid ([0.08 M]) and 8 mL of THF were added to the flask. A reflux condenser was installed on the flask and the reaction was then heated to 45 °C and stirred for 2 h. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (1x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude aldehyde was purified by flash chromatography

over silica gel using a gradient of 100% Hexanes to 70% EtOAc/Hexanes and fractions containing **2.3h** were concentrated to dryness. It resulted in a translucid oil (388.9 mg, 95% Yield). **^{1}H NMR** ($CHCl_3$, 400 MHz) δ 10.07 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 3.58 (br q, *J* = 7.0 Hz, 2H), 3.24 (br q, *J* = 6.5 Hz, 2H), 1.29 (br t, *J* = 7.0 Hz, 3H), 1.13 (br t, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz) δ 191.2, 169.4, 142.5, 136.1, 129.4, 126.5, 42.8, 38.9, 13.7, 12.4; **FTIR** (cm^{-1}) (neat) 2974, 2936, 1702, 1627, 1594, 1432, 1287, 1219, 1095; **HRMS** (ESI, Pos) calc. for $C_{18}H_{27}N_2O$ $[M+H]^+$: 206.1181 *m/z*, found 206.1176 *m/z*.

Synthesis of aldehyde **2.3m'** by reduction of amide **2.1m** with Et_3SiD:

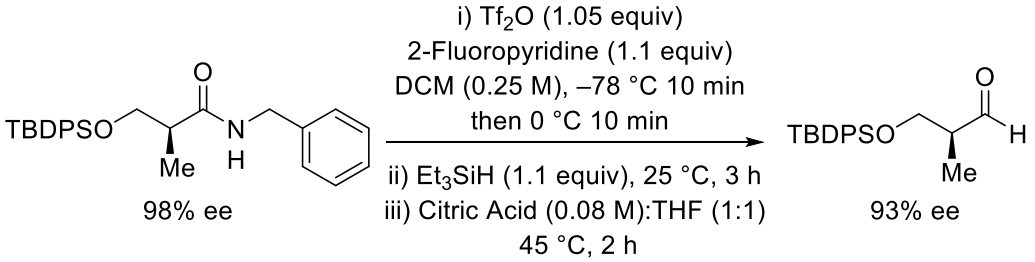


4-Ethynylbenzaldehyde-α-d_1 (2.3m'): To a flame-dried 50 mL round-bottom flask equipped with a septum was added *N*-Cyclohexyl-4-ethynylbenzamide (**2.1m**) (454.3 mg, 2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethyl(silane-d) (Et_3SiD)[36] (257.6 mg, 350 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. Then, the septum was removed and 8 mL of an aqueous solution of citric acid ([0.08M]) and 8 mL of THF were added to the flask. A reflux condenser was installed on the flask and the reaction was then heated to 45 °C and stirred for 2 h. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was

[36]. Triethyl(silane-d) was made according to literature procedures : Caseri, W.; Pregosin, P. S. *J. Organomet. Chem.* **1988**, *356*, 259-269.

extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude aldehyde was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 10% EtOAc/Hexanes and fractions containing **2.3m'** were concentrated to dryness. It resulted in a yellow solid (235.7 mg, 90% Yield). **mp**: 55-56 °C; $\mathbf{R_f}$: 0.55 (10% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.87 (d, *J* = 7.0 Hz, 2H), 7.65 (d, *J* = 7.0 Hz, 2H), 3.22 (s, 1H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 191.9 (t, *J* = 101.6 Hz), 136.3 (t, *J* = 15.6 Hz), 133.1, 129.9, 128.7, 83.1, 81.5; **FTIR** (cm^{-1}) (neat): 3217, 2838, 2741, 2101, 1700, 1684, 1605, 1208; **HRMS** (ESI, Pos): calc. for C_9H_6OD $[M+H]^+$: 132.0559 *m/z*, found: 132.0551 *m/z*.

Synthesis of aldehyde **2.3s** by reduction of amide **2.1s:**



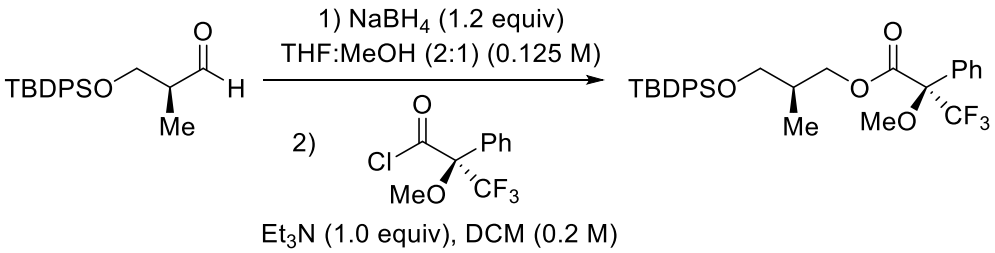
(2*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-methylpropanal (2.3s):[37] To a flame-dried 50-mL round-bottom flask equipped with a septum was added (2*S*)-*N*-Benzyl-3{[*tert*-butyl(diphenyl)silyl]oxy}-2-methylpropanamide (**2.1s**) (862.3 mg, 2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmoles, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C

[37]. For characterization data, see: Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103-106.

and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 3 h. Then, 8 mL of an aqueous solution of citric acid ([0.08M]) was added to the solution and the reaction was stirred for 10 min. The biphasic mixture was transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude aldehyde was purified by flash chromatography over silica gel using an isocratic mixture of 3% EtOAc/Hexanes and fractions containing **2.3s** were concentrated to dryness. It resulted in a translucid oil (450.2 mg, 70% Yield). $\mathbf{R_f}$: 0.75 (10% EtOAc/Hexanes); SFC analysis of the product on a chiral stationary phase (Chiralpak ADH 10 cm, 7% MeOH, 20 min, 3 mL/min, 150 bar, 40 °C isotherm) (*S*)- **2.1q** tr = 12.5 min, *(R)*- **2.1q** tr = 13.9 min; $\mathbf{[\alpha]_D^{20}}$: +22.2 (*c* 3.74, $CHCl_3$), litt[37]: +24.4 (*c* 1.28, CH_2Cl_2), litt:[38] +20.0 (*c* 2.42, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 9.80 (d, *J* = 2.0 Hz, 1H), 7.69-7.67 (m, 4H), 7.50-7.40 (m, 6H), 3.96-3.86 (m, 2H), 2.64-2.56 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 204.1, 135.2, 132.8, 129.5, 127.0, 63.8, 48.5, 26.4, 18.9, 10.0; **FTIR** (cm^{-1}) (neat): 2931, 2857, 1736, 1472, 1427, 1110; **HRMS** (ESI, Pos): calc. for $C_{20}H_{27}O_2SiNa$ $[M+Na]^+$: 349.1600 *m/z*, found 349.1587 *m/z*.

[38]. For characterization data, see: Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2006**, *8*, 3441-3443.

Enantiomeric excess determination *via* reduction of **2.3s** and Mosher ester formation**:**



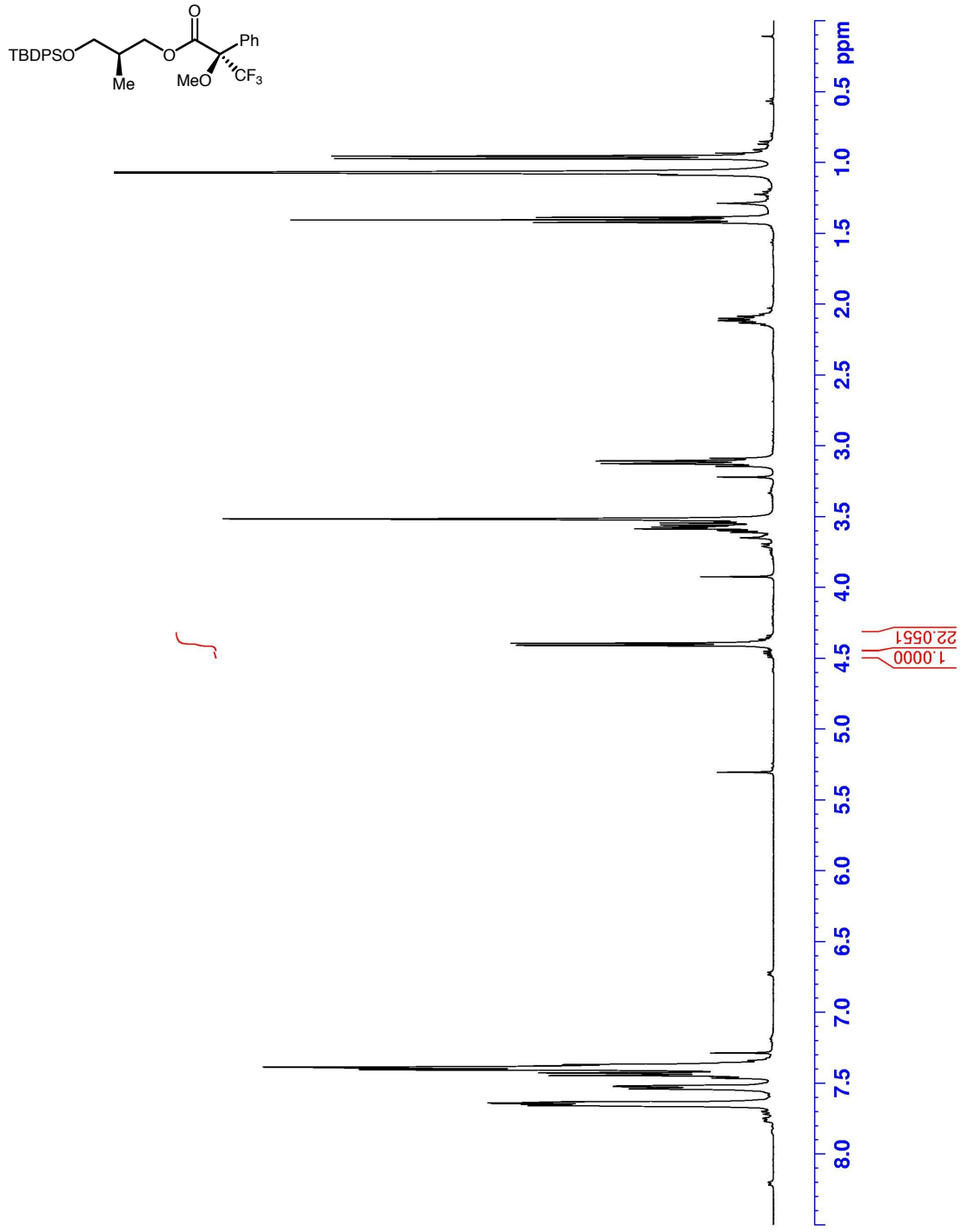
Note: The following reactions were performed on the racemic and enantioenriched aldehyde.

To a flame-dried 100 mL round-bottom flask equipped with a septum was added (2*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-methylpropanal (**2.3s**) (557 mg, 1.71 mmoles, 1.0 equiv). The aldehyde was diluted with a [0.125M] 2:1 mixture of THF (6.83 mL, 0.25M) and MeOH (3.41 mL, 0.50M) and was cooled to 0 °C. Then, $NaBH_4$ (77.5 mg, 2.05 mmoles, 1.2 equiv) was added portionwise at 0 °C and the resulting solution was stirred at 0 °C for 1 h and heated to room temperature over 12 h. The mixture was then quenched by addition of a saturated aqueous solution of NH_4Cl and the mixture was diluted with DCM (50 mL). The mixture was transferred to a 125 mL extraction funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. It resulted in a translucid oil (443.1 mg, 77% Yield). $\mathbf{R_f}$: 0.40 (10% EtOAc/Hexanes); $\mathbf{[\alpha]_D^{20}}$: +6.1 (*c* 0.933, $CHCl_3$), litt:[39] +5.8 (*c* 1.25, $CHCl_3$), litt:[40] (*ent*)-Alcohol at 94 %ee : -6.0 (*c* 1.50, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.70 (d, *J* = 9.5 Hz, 4.0 H), 7.50-7.40 (m, 6H), 3.75 (dd, *J* = 4.5, 10.0 Hz, 1H), 3.70 (d, *J* = 5.5 Hz, 2H), 3.62 (dd, *J* = 7.5, 10 Hz, 1H), 2.45 (br s, 1H), 2.08-1.97 (m, 1H), 1.08 (s, 9H), 0.85 (d, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 135.3 (2), 132.9 (2), 129.5, 127.5, 68.2, 67.1, 37.1, 26.6, 18.9, 12.9; **FTIR** (cm^{-1}) (neat):3385, 2930, 2858, 1472, 1427, 1111, 1039; **HRMS** (ESI, Pos): calc. for $C_{20}H_{29}O_2Si$ $[M+H]^+$: 329.1937 *m/z*, found 329.1928 *m/z*.

To a flame-dried 10 mL round-bottom flask equipped with a septum was added the alcohol (50 mg, 0.152 mmole, 1.0 equiv). The alcohol was diluted with DCM (761 µL, 0.2M) and Et_3N (15.40 mg, 21.2 µL, 0.152 mmole, 1.0 equiv) was added to the flask. Then, (2S)-3,3,3-

[39]. For characterization data, see: Guan, Y.; Wu, J.; Sun, L.; Dai, W.-M. *J. Org. Chem.* **2007**,*72*, 4953-4960.
[40]. (*ent*)-Alcohol : Van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558-2563.

trifluoro-2-methoxy-2-phenylpropanoyl chloride (38.39 mg, 0.152 mmol, 1.0 equiv) was added to the solution and the reaction was stirred at room temperature for 1 h. The solution was then quenched by addition of an aqueous saturated solution of Na_2CO_3 and was diluted with DCM (5 mL). The mixture was transferred to a 60 mL extraction funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was washed with aqueous HCl 1N and dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. It resulted in a translucid oil. The diastereoisomeric mixture of the racemic and enantioenriched Mosher ester were analyzed by ^1H NMR and revealed a 93 %ee for the titled compound (% ee were determined using the diastereotopic protons α to O-C(=O)-R).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MeO
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2.5
3.0
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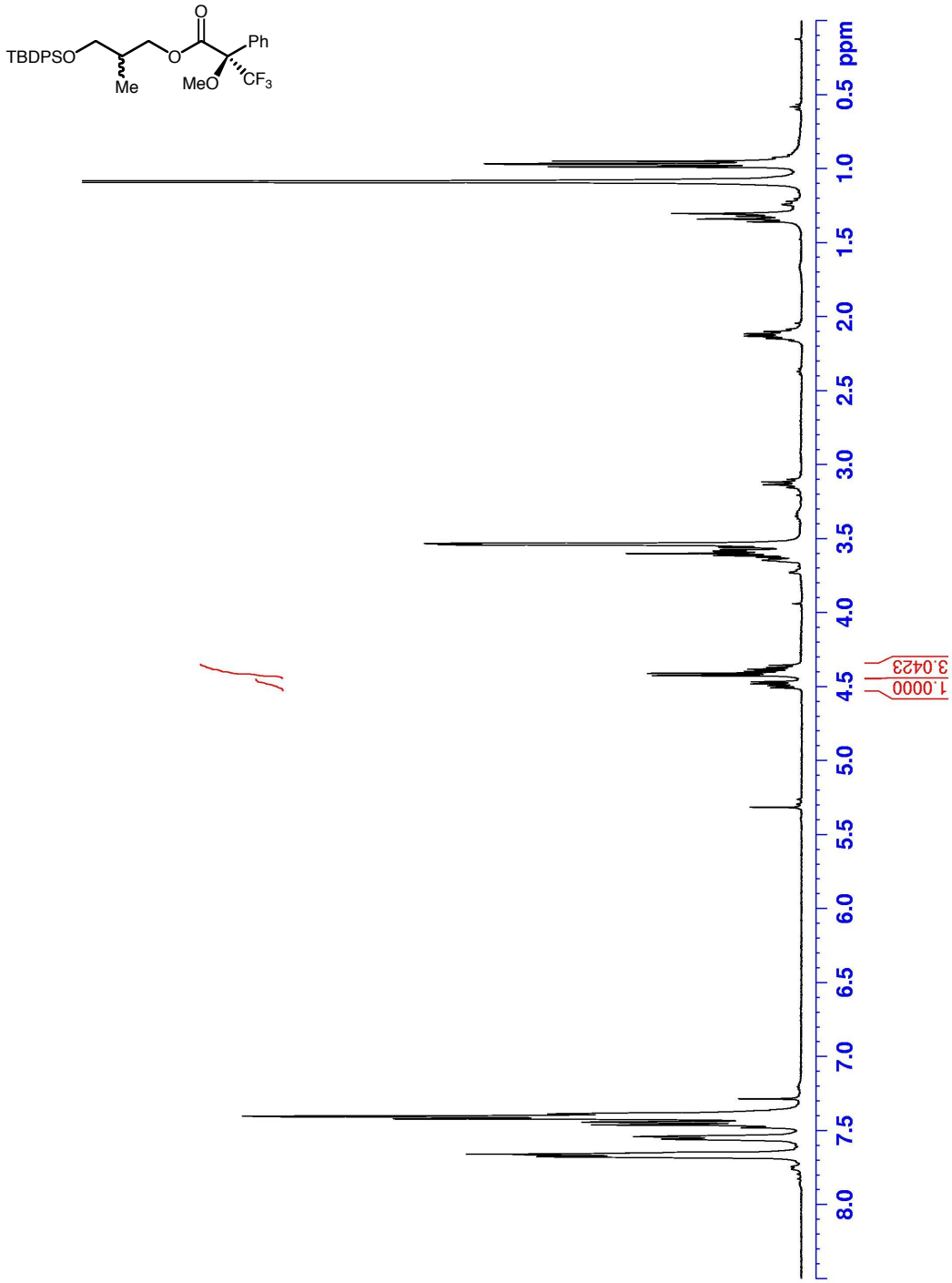
7.0
7.5
8.0
22.0551
1.0000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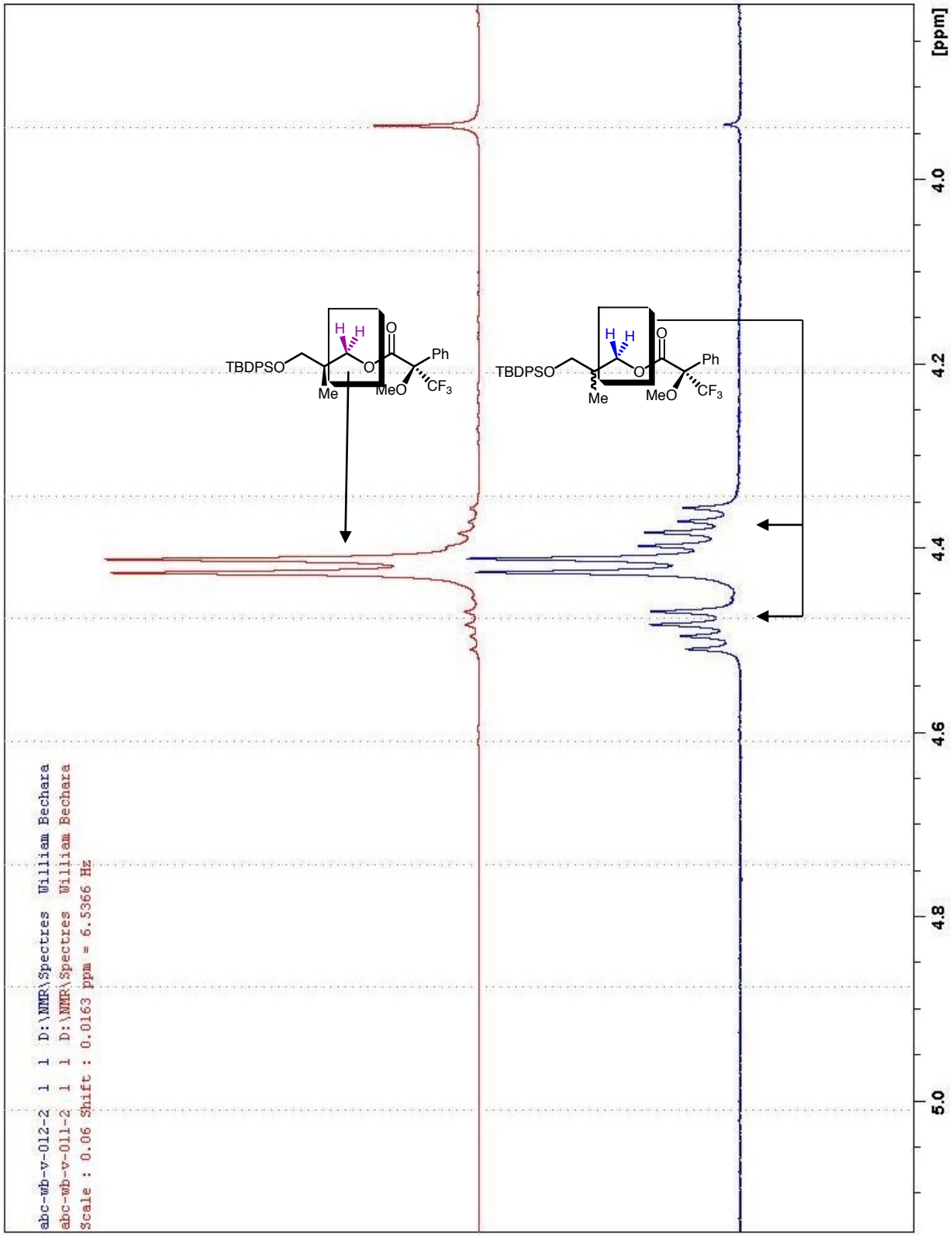
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abc-wb-v-011-2 1 1 D:\NMR\Spectres William Bechara
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5.0
4.8
4.6
4.4
4.2
4.0
[ppm]
TBDPSO
Me
MeO
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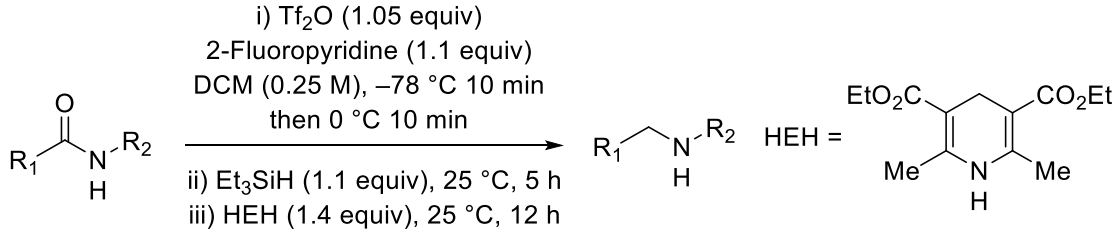
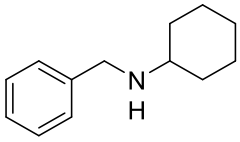
Amine synthesis (Table #2, entries 1-14, **2.4a-2.4o**):

Synthesis of amines **2.4a-2.4f, 2.4i-2.4o** procedure E was followed:

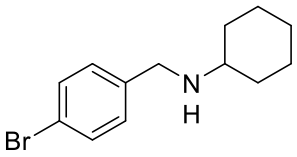


Procedure E: To a flame-dried 50 mL round-bottom flask equipped with a septum was added the amide (2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. Then, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzch Ester Hydride (HEH)) (708.8 mg, 2.8 mmoles, 1.4 equiv) was added to the reaction mixture and the yellow suspension was stirred for 12 h at room temperature. The reaction was quenched by addition of 8 mL of Na_2CO_3 and 20 mL of dichloromethane and the biphasic mixture was stirred for 15 min at room temperature. It was transferred to a 125 mL extraction funnel and the layers were separated. The water layer was extracted with dichloromethane (2x) and the organic layers were combined and dried over anhydrous sodium sulfate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was further purified by acid/base extraction. The residue was diluted with 20 mL of EtOAc and 20 mL of aqueous citric acid ([0.08M]) and transferred to a 250 mL extraction funnel. The layers were separated and the EtOAc layer was extracted with 4x15 mL of citric acid ([0.08M]). The aqueous citric acid layers were combined and washed with 3x15 mL of EtOAc. The last 3 fractions of EtOAc were combined and washed with citric acid ([0.08M]) 1x15mL. All of the citric acid layers were combined and dichloromethane (30 mL)

was added to the citric acid layer which was then made basic (pH ~ 11-12) by addition of a saturated solution of Na_2CO_3 (or NaOH 2M), shaked and let stand for 1 min. The layers were separated, and the now basic aqueous solution was extracted with 4x20mL dichloromethane (*let stand biphasic layers between each extraction*). The dichloromethane layers were combined, dried over anhydrous sodium sulfate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness to afford the pure amines.

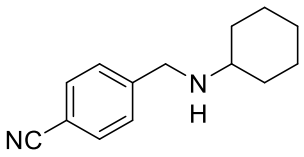


***N*-Benzylcyclohexanamine (2.4a)**:[41] The **procedure E** was followed affording the amine **2.4a** as a yellow oil (340.2 mg, 90% Yield). $\mathbf{R_f}$: 0.50 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.35-7.34 (m, 4H), 7.29-7.24 (m, 1H), 3.84 (s, 2H), 2.55-2.48 (m, 2H), 1.97-1.92 (m, 2H), 1.79-1.73 (m, 1H), 1.41 (br s, 1H), 1.33-1.11 (m, 5H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 140.6, 128.0, 127.8, 126.4, 55.8, 50.7, 33.2, 25.8, 24.7; **FTIR** (cm^{-1}) (neat): 2930, 2850, 2110, 1480, 1439; **HRMS** (ESI, Pos): calc. for $C_{13}H_{20}N$ $[M+H]^+$: 190.1596 *m/z*, found: 190.1599 *m/z*.

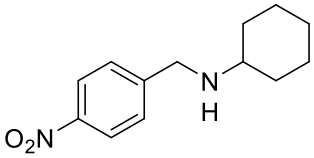


***N*-(4-Bromobenzyl)cyclohexanamine (2.4b)**: The **procedure E** was followed affording the amine **2.4b** as a yellow oil (458.3 mg, 86% Yield). $\mathbf{R_f}$: 0.50 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.45 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 7.0 Hz, 2H), 3.79 (s, 2H), 2.51-2.44 (m, 1H), 1.94-1.90 (m, 2H), 1.78-1.73 (m, 2H), 1.65-1.61 (m, 1H), 1.32-1.08 (m, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 139.4, 131.1, 129.5, 120.2, 55.7, 49.8, 33.1, 25.7, 24.6; **FTIR** (cm^{-1}) (neat): 2927, 2853, 2117, 1486, 1449; **HRMS** (ESI, Pos): calc. for $C_{13}H_{19}BrN$ $[M+H]^+$: 268.0701 and 270.0680 *m/z*, found: 268.0683 and 270.0665 *m/z*.

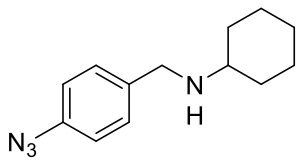
[41]. For characterization data, see: Lee, O.-Y.; Law, K.-L.; Yang, D. *Org. Lett.* **2009**, *11*, 3302-3305.



***N*-[(Cyclohexylamino)methyl]benzonitrile (2.4c)**: The **procedure E** was followed affording the amine **2.4c** as a yellow solid (374.4 mg, 87% Yield). **mp**: 28-29 °C; $\mathbf{R_f}$: 0.30 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 3.89 (s, 2H), 2.50-2.43 (m, 1H), 1.94-1.90 (m, 2H), 1.78-1.73 (m, 2H), 1.65-1.61 (m, 1H), 1.45 (br s, 1H), 1.32-1.07 (m, 5H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 147.4, 132.4, 128.9, 119.3, 110.7, 56.6, 50.9, 34.0, 26.5, 25.3; **FTIR** (cm^{-1}) (neat): 2926, 2852, 2227, 2112, 1725, 1608, 1449; **HRMS** (ESI, Pos): calc. for $C_{14}H_{19}N_2$ $[M+H]^+$: 215.1548 *m/z*, found: 215.1536 *m/z*.

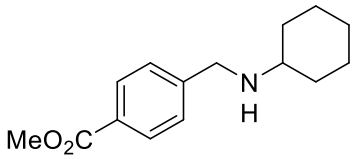


***N*-(4-Nitrobenzyl)cyclohexanamide (2.4d)**: The **procedure E** was followed affording the amine **2.4d** as an orange oil (420.4 mg, 90% Yield). $\mathbf{R_f}$: 0.45 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 3.96 (s, 2H), 2.53-2.46 (m, 1H), 1.95-1.91 (m, 2H), 1.80-1.74 (m, 2H), 1.66-1.61 (m, 1H), 1.32-1.10 (m, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 148.8, 146.4, 128.1, 123.0, 55.9, 49.8, 33.2, 25.7, 24.5; **FTIR** (cm^{-1}) (neat): 2925, 2851, 2117, 1723, 1600, 1515, 1340; **HRMS** (ESI, Pos): calc. for $C_{13}H_{19}N_2O_2$ $[M+H]^+$: 235.1447 *m/z*, found: 235.1433 *m/z*.

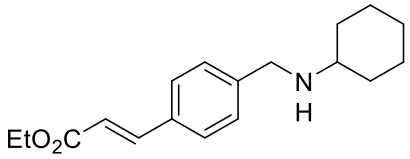


***N*-(4-Azidobenzyl)cyclohexanamide (2.4e)**: The **procedure E** was followed affording the amine **2.4e** as a red oil (374.4 mg, 89% Yield). $\mathbf{R_f}$: 0.35 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.31 (d, *J* = 12.0 Hz, 2H), 6.98 (d, *J* = 12.0 Hz, 2H), 3.80 (s, 2H), 2.51-2.44 (m, 1H), 1.94-1.89 (m, 2H), 1.78-1.72 (m, 2H), 1.65-1.60 (m, 1H), 1.48 (br s, 1H), 1.32-1.08 (m, 5H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 138.9, 138.2, 129.9, 119.4, 56.6, 50.8, 33.9,

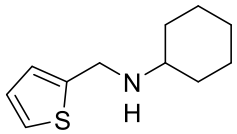
26.6, 25.4; **FTIR** (cm^{-1}) (neat): 2924, 2851, 2103, 1606, 1504, 1283; **HRMS** (ESI, Pos): calc. for $C_{13}H_{19}N_4$ $[M+H]^+$: 231.1610 *m/z*, found 231.1606 *m/z*.



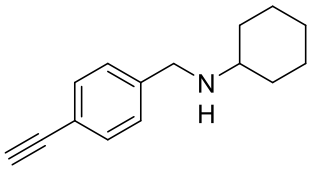
Methyl 4-((cyclohexylamino)methyl)benzoate (2.4f): The **procedure E** was followed affording the amine **2.4f** as a beige solid (420.4 mg, 90% Yield). **mp**: 30-31 °C; $\mathbf{R_f}$: 0.25 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.43 (dd, *J* = 3.0, 8.5 Hz, 2H), 3.93 (s, 3H), 3.90 (s, 2H), 2.53-2.46 (m, 1H), 1.95-1.92 (m, 2H), 1.78-1.74 (m, 2H), 1.65-1.61 (m, 1H), 1.32-1.11 (m, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 146.1, 129.2, 128.2, 127.4, 55.8, 51.5, 50.2, 33.1, 25.7, 24.5; **FTIR** (cm^{-1}) (neat) 2927, 2852, 2115, 1720, 1611, 1449, 1277; **HRMS** (ESI, Pos): calc. for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651 *m/z*, found: 248.1642 *m/z*.



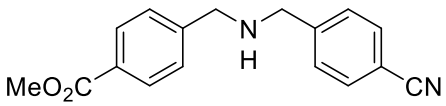
Ethyl (2*E*)-3-{[(cyclohexylamino)carbonyl]phenyl}acrylate (2.4i): The **procedure E** was followed affording the amine **2.4i** as an orange oil (406.8 mg, 71% Yield). $\mathbf{R_f}$: 0.20 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 2H), 2.53-2.46 (m, 1H), 1.95-1.90 (m, 2H), 1.77-1.73 (m, 2H), 1.65-1.61 (m, 1H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.37-1.09 (m, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 167.5, 144.8, 144.1, 133.4, 129.0, 128.6, 118.1, 68.9, 56.6, 51.1, 34.0, 26.6, 25.4, 14.8; **FTIR** (cm^{-1}) (neat): 2924, 2851, 1708, 1635, 1308, 1201, 1163; **HRMS** (ESI, Pos): calc. for $C_{18}H_{26}NO_2$ $[M+H]^+$: 288.1964 *m/z*, found: 288.1956 *m/z*.



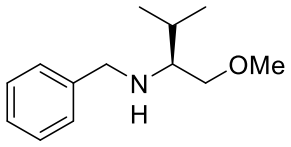
***N*-Cyclohexylthiophen-2-ylmethylamine (2.4j)**: The **procedure E** was followed affording the amine **2.4j** as a translucid oil (335.1 mg, 86% Yield). $\mathbf{R_f}$: 0.70 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.21-7.19 (m, 1H), 6.97-6.92 (m, 2H), 4.03 (s, 2H), 2.58-2.51 (m, 1H), 1.94-1.90 (m, 2H), 1.78-1.73 (m, 2H), 1.66-1.60 (m, 1H), 1.33-1.08 (m, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 144.5, 126.2, 124.1, 123.7, 55.4, 45.1, 33.1, 25.8, 24.6; **FTIR** (cm^{-1}) (neat): 2925, 2851, 1723, 1661, 1448; **HRMS** (ESI, Pos): calc. for $C_{11}H_{18}NS$ $[M+H]^+$: 196.1160 *m/z*, found: 196.1151 *m/z*.



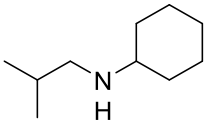
***N*-Cyclohexyl-(4-ethynylbenzyl)-amine (2.4k)**: The **procedure E** was followed affording the amine **2.4k** as a yellow oil (382.2 mg, 90% Yield). $\mathbf{R_f}$: 0.65 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 2H), 3.07 (s, 1H), 2.51-3.44 (m, 1H), 1.94-1.89 (m, 2H), 1.78-1.72 (m, 2H), 1.65-1.60 (m, 1H), 1.32-1.08 (m, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 141.7, 131.8, 127.6, 120.1, 83.4, 76.5, 55.8, 50.3, 33.2, 25.8, 24.6; **FTIR** (cm^{-1}) (neat): 3291, 2924, 2851, 1724, 1505, 1448, 1118; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}N$ $[M+H]^+$: 214.1596 *m/z*, found: 214.1599 *m/z*.



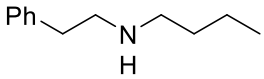
Methyl 4-{[(4-cyanobenzyl)amino]methyl}benzoate (2.4l): The **procedure E** was followed affording the amine **2.4l** as a yellow solid (382.2 mg, 77% Yield). **mp**: 35-36 °C; $\mathbf{R_f}$: 0.80 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 3.94 (s, 3H), 3.89 (d, 4H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 166.6, 145.4, 144.8, 131.9, 129.5, 128.8, 128.3, 127.6, 118.6, 110.5, 52.5, 52.3, 51.7; **FTIR** (cm^{-1}) (neat): 3342, 2950, 2835, 2226, 1714, 1607, 1434, 1275, 1106; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}N$ $[M+H]^+$: 281.1290 *m/z*, found: 281.1282 *m/z*.



(*S*)-*N*-Benzyl-1-methoxy-3-methylbutan-2-amine (2.4m):[42] The **procedure E** was followed affording the amine **2.4m** as a yellow oil (369.1 mg, 89% Yield). $\mathbf{R_f}$: 0.10 (70% EtOAc/Hexanes); $\mathbf{[\alpha]_D^{20}}$: -6.6 (*c* 1.73, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.40-7.32 (m, 4H), 7.28-7.24 (m, 1H), 3.84 (s, 2H), 3.47 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.35 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.35 (s, 3H), 2.63-2.59 (m, 1H), 1.99 (br s, 1H), 1.96-1.88 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 141.4, 128.7, 128.6, 127.2, 73.1, 62.3, 59.3, 52.5, 29.3, 19.4, 18.6; **FTIR** (cm^{-1}) (neat): 2956, 2928, 2872, 2115, 1728, 1452, 1110; **HRMS** (ESI, Pos): calc. for $C_{13}H_{22}NO$ $[M+H]^+$: 208.1701 *m/z*, found: 208.1693 *m/z*.



***N*-Isobutylcyclohexanamide (2.4n)**:[43] The **procedure E** was followed affording the amine **2.4n** as a yellow oil (382.2 mg, 85% Yield). $\mathbf{R_f}$: 0.10 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 2.44 (d, *J* = 7.0 Hz, 1H), 2.43-2.37 (m, 1H), 1.93-1.86 (m, 2H), 1.77-1.70 (m, 3H), 1.65-1.60 (m, 1H), 1.32-1.03 (m, 6H), 0.91 (d, *J* = 6.0 Hz, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 57.3, 55.4, 34.0, 28.9, 26.6, 25.5, 21.1; **FTIR** (cm^{-1}) (neat): 2926, 2853, 2116, 1731, 1464, 1449, 1132; **HRMS** (ESI, Pos): calc. for $C_{10}H_{22}N$ $[M+H]^+$: 156.1752 *m/z*, found: 156.1741 *m/z*.

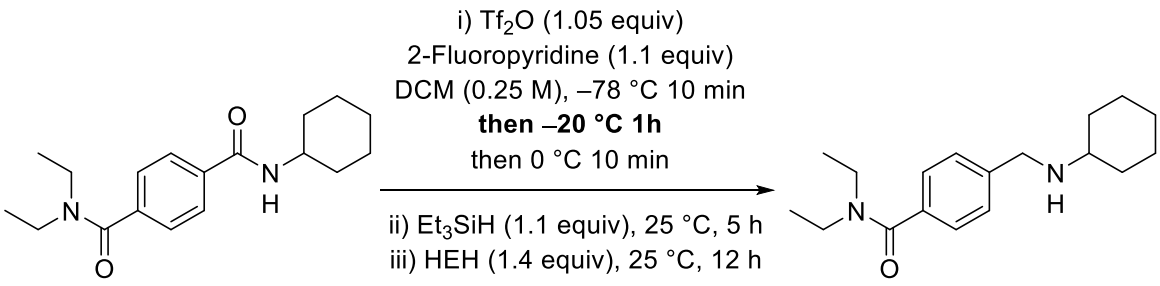


***N*-Butyl-phenethylamine (2.4o)**:[44] The **procedure E** was followed affording the amine **2.4o** as a yellow oil (354.8 mg, 75% Yield). $\mathbf{R_f}$: 0.30 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.37-7.19 (m, 5H), 2.92-2.89 (m, 2H), 2.85-2.80 (m, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 1.51-1.44 (m, 2H), 1.38-1.24 (m, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CHCl_3$, 100

[42]. For characterization data, see: Ando, A.; Shioiri, T. *Tetrahedron* **1989**, *45*, 4969-4988.
[43]. For characterization data, see: Kangasmetsa, J. J.; Johnson, T. *Org. Lett.* **2005**, *7*, 5653-5655.
[44]. For characterization data, see: Das, A. R. *J. Ind. Chem. Soc.* **2009**, *86*, 841-848

MHz): δ 139.9, 128.3, 128.1, 125.7, 51.0, 49.3, 36.1, 31.9, 20.2, 13.7; **FTIR** (cm^{-1}) (neat): 2926, 2853, 2116, 1731, 1464, 1449, 1132; **HRMS** (ESI, Pos): calc. for $C_{12}H_{20}N$ $[M+H]^+$: 178.1593 *m/z*, found: 178.1593 *m/z*.

Synthesis of amine **2.4g** by activation of the amide **2.1h** at –20 °C:

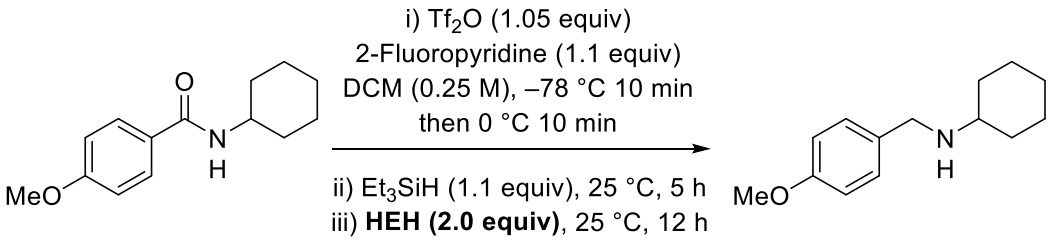


4-((Cyclohexylamino)methyl)-*N,N*-diethylbenzamide (2.4g): To a flame-dried 50-mL round-bottom flask equipped with a septum was added *N'*-Cyclohexyl-*N,N*-diethylterephtalamide (**2.1h**) (604.1 mg, 2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was slowly heated to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred at –20 °C for 1 h. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. Then, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzch Ester Hydride (HEH)) (708.8 mg, 2.8 mmol, 1.4 equiv) was added to the reaction mixture and the yellow suspension was stirred for 12 h at room temperature. The reaction was quenched by addition of 8 mL of Na_2CO_3 and 20 mL of dichloromethane and the biphasic mixture was stirred for 15 min at room temperature. It was transferred to a 125 mL extraction funnel and the layers were separated. The water layer was extracted with dichloromethane (2x) and the organic layers

were combined and dried over anhydrous sodium sulfate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness.

The crude amine was further purified by acid/base extraction. The residue was diluted with 20 mL of EtOAc and 20 mL of aqueous citric acid ([0.08M]) and transferred to a 250 mL extraction funnel. The layers were separated and the EtOAc layer was extracted with 4x15 mL of citric acid ([0.08M]). The aqueous citric acid layers were combined and washed with 3x15 mL of EtOAc. The last 3 fractions of EtOAc were combined and washed with citric acid ([0.08M]) 1x15mL. All of the citric acid layers were combined and dichloromethane (30 mL) was added to the citric acid layer which was then made basic (pH ~11-12) by addition of a saturated solution of Na_2CO_3 (or NaOH 2M), shaked and let stand for 1 min. The layers were separated, and the now basic aqueous solution was extracted with 4x20mL dichloromethane (*let stand the biphasic layers between each extraction*). The dichloromethane layers were combined, dried over anhydrous sodium sulfate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness to afford the amine **2.4g** as a yellow oil (518.8 mg, 90% Yield). $\mathbf{R_f}$: 0.05 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.42-7.32 (m, 4H), 3.86 (s, 2H), 3.56 (br s, 2H), 3.28 (br s, 2H), 2.55-2.48 (m, 1H), 1.96-1.92 (m, 2H), 1.79-1.73 (m, 2H), 1.66-1.61 (m, 1H), 1.32-1.08 (m, 12H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 170.9, 141.7, 135.4, 127.6, 126.1, 55.8, 50.3, 42.9, 38.8, 33.1, 25.8, 24.6, 13.8, 12.5; **FTIR** (cm^{-1}) (neat): 2926, 2852, 2116, 1626, 1450, 1425, 1286, 1094; **HRMS** (ESI, Pos): calc. for $C_{18}H_{29}N_2O$ $[M+H]^+$: 289.2280 *m/z*, found: 289.2262 *m/z*.

Synthesis of amine **2.4h** by reduction with 2.0 equivalents of HEH:



***N*-(4-Methoxybenzyl)cyclohexanamide (2.4h)**: To a flame-dried 50-mL round-bottom flask equipped with a septum was added *N*-Cyclohexyl-4-methoxybenzamide (**2.1u**) (466.3 mg, 2.0 mmol, 1.0 equiv). The amide was diluted with 8 mL of anhydrous dichloromethane ([0.25M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) (592.0 mg, 353 µL, 2.1 mmol, 1.05 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was heated at 0 °C using a water/ice bath and the reaction was stirred for 10 min. Triethylsilane (Et_3SiH) (255.8 mg, 352 µL, 2.2 mmol, 1.1 equiv) was added dropwise at 0 °C and the reaction was stirred for 10 min. The solution was heated to room temperature and stirred for 5 h. Then, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzch Ester Hydride (HEH)) (1.012 g, 4.0 mmol, 2.0 equiv) was added to the reaction mixture and the yellow suspension was stirred for 12 h at room temperature. The reaction was quenched by addition of 8 mL of Na_2CO_3 and 20 mL of dichloromethane and the biphasic mixture was stirred for 15 min at room temperature. It was transferred to a 125 mL extraction funnel and the layers were separated. The water layer was extracted with dichloromethane (2x) and the organic layers were combined and dried over anhydrous sodium sulfate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness.

The crude amine was further purified by acid/base extraction. The residue was diluted with 20 mL of EtOAc and 20 mL of aqueous citric acid ([0.08M]) and transferred to a 250 mL extraction funnel. The layers were separated and the EtOAc layer was extracted with 4x15 mL of citric acid ([0.08M]). The aqueous citric acid layers were combined and washed with 3x15 mL of EtOAc. The last 3 fractions of EtOAc were combined and washed with citric acid ([0.08M]) 1x15mL. All of the citric acid layers were combined and dichloromethane (30 mL)

was added to the citric acid layer which was then made basic (pH ~11-12) by addition of a saturated solution of Na_2CO_3 (or NaOH 2M), shaken and let stand for 1 min. The layers were separated, and the now basic aqueous solution was extracted with 4x20mL dichloromethane (*let stand the biphasic layers between each extraction*). The dichloromethane layers were combined, dried over anhydrous sodium sulfate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness to afford the amine **2.4g** as a yellow oil (355.4 mg, 81% Yield). $\mathbf{R_f}$: 0.20 (70% EtOAc/Hexanes); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 2H), 2.53-2.46 (m, 1H), 1.94-1.91 (m, 2H), 1.77-1.73 (m, 2H), 1.65-1.61 (m, 1H), 1.33-1.09 (m, 6H); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 158.9, 133.6, 129.7, 114.2, 56.5, 55.7, 50.9, 34.0, 26.6, 25.4; **FTIR** (cm^{-1}) (neat): 2923, 2850, 1725, 1610, 1509, 1448, 1242; **HRMS** (ESI, Pos): calc. for $C_{14}H_{21}NO$ $[M+H]^+$: 219.1623 *m/z*, found: 219.1616 *m/z*.

Experimental section of Chapter 3

General Information

Unless otherwise stated, reactions were run under an argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[45] All glassware was flame-dried prior to use. DCM, toluene, THF, MeOH, and DMF were obtained by filtration through drying columns on a filtration system. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV, aqueous potassium permanganate ($KMnO_4$), cerium ammonium molybdate (CAM), or dinitrophenol (DNP) for ketones. Flash column chromatography was performed using 230-400 mesh silica and Merck type E basic alumina (pH ~ 10-11) by hand or performed on an automatic purification system (Teledyne Isco Combiflash® Rf or Sq16x). Prepacked normal phase silica gel column was used for separation of products using Teledyne Isco Redi*Sep*® Rf High Performance Gold or Silicycle Silia*Sep*™ High Performance columns (12g, 24g, 40g, or 80g). Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on an Avance AV400 MHz, Avance AV 300 MHZ, DRX400 MHz, or Avance 700 MHz (^1H, ^{13}C, F^{19}, DEPT 135, COSY) spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard $CDCl_3$ (δ = 7.27 ppm), DMSO-d_6 (δ = 2.50 ppm), CD_2Cl_2 (δ = 5.32 ppm), or CD_3OD (δ = 3.31 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ = 77.23 ppm), DMSO-d_6 (δ = 39.52 ppm), CD_3OD (δ = 49.00 ppm), or CD_2Cl_2 (δ = 53.13 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Bruker Vertex Series FTIR

45. Shriver, D. F. & Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*; 2nd Edition; Wiley: New York, 1986.

(neat) and are reported in reciprocal centimeters (cm^{-1}). Analytical Supercritical Fluid Chromatography (SFC) analysis was performed on samples dissolved in *i*-PrOH with an instrument equipped with a diode array UV detector setted at 210 nm. Carbon dioxide was used as a carrier gas (150 psi). Data are reported as follows: (column type, column length, eluent, run time, flow rate, pressure, rate: retention time (t_r)). Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm. Data are reported as follows: $[\alpha]_\lambda^{temp}$, concentration (*c* in g/100 mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

Reagents

Unless otherwise stated, commercial reagents were used without purification. Trifluoromethanesulfonic (triflic) anhydride was distilled over phosphorous pentoxide and was stored for no more than five days before redistilling. Triethylamine (Et_3N), and diisopropylamine (*i*-Pr_2NH) were distilled over sodium and kept under argon before use. Methyl *tert*-butylether (MTBE) was distilled over 4Å molecular sieves and kept under argon before use. 2-Butanol was distilled over $CaCl_2$ and kept under argon before use. $Et_2CuMgBr$ solution in Et_2O was synthesized according to literature procedures.[46] Ethylzinc iodide solution in DCM/Et_2O was synthesized according to literature procedures.[47] Triethylindium solution in THF was synthesized according to literature procedures.[48] Dichloroethylcerium solution in THF was synthesized according to literature procedures.[49] All Grignard, zinc, and lithium solutions were titrated prior to addition following procedures described in the following section. The following Grignard, lithium and zinc reagents were commercially available in solution (THF, Et_2O, or Benzene:Cyclohexane) or neat from Aldrich, StremChem, FMC Lithium or AkzoNobel:

Ethylmagnesium bromide 3.0 M in Et_2O (Aldrich or StremChem), Ethyllithium 0.5 M in Benzene:Cyclohexane (9:1) (Aldrich), Ethylmagnesium chloride 2.0 M in Et_2O (Aldrich), *n*-Butyllithium 2.5 M in Hexanes (FMC Lithium), Diethylzinc neat (AkzoNobel), *n*-Decylmagnesium chloride 1.0 M in Et_2O (Aldrich), Benzylmagnesium chloride 1.0 M in Et_2O (Aldrich), Isobutylmagnesium chloride 2.0 M in Et_2O (Aldrich), 3-Butenylmagnesium bromide 0.5 M in THF (Aldrich), Isoprenylmagnesium bromide 0.5 M in THF (Aldrich), Phenethylmagnesium chloride 1.0 M in THF (Aldrich), 4-Methoxyphenylmagnesium bromide

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46. Zaparucha, A., Danjoux, M., Chiaroni, A., Royer, J. & Husson, H.-P. Asymmetric synthesis of 3-alkyl pipecolic acids. *Tetrahedron Lett.* **40**, 3699-3700 (1999).

47. Charette, A. B., Gagnon, A. & Fournier, J.-F. First evidence for the formation of a gemial dizinc carbenoid: a highly stereoselective synthesis of 1,2,3-substituted cyclopropanes. *J. Am. Chem. Soc.* **124**, 386-387 (2002).

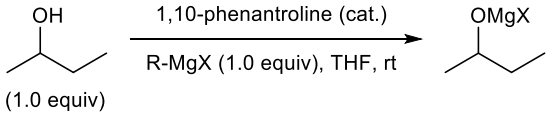
48. Barbero, M., Cadamuro, S., Dughera, S. & Ghigo, G. Reaction of arenediazonium *o*-benzenedisulfonimides with aliphatic triorganoindium compounds *Eur. J. Org. Chem.* 862-868 (2008).

49. Kita, Y.; Matsuda, S.; Kitagaki, S.; Tsuzuki, Y. & Akai, S. Chemistry of silylketene: a one-pot synthesis of α-silyl ketones *Synlett* 401-402 (1991).

0.5 M in THF (Aldrich), 4-Fluorophenylmagnesium bromide 1.0M in THF (Aldrich), 2-Chlorophenylmagnesium bromide 1.0 M in THF (Aldrich), *p*-Tolylmagnesium bromide 0.5 M in Et_2O (Aldrich), Isopropylmagnesium chloride 2.0 M in THF (Aldrich), Cyclohexylmagnesium chloride 2.0 M in Et_2O (Aldrich), Phenylmagnesium bromide 3.0 M in Et_2O (StremChem), Isopropylmagnesium chloride LiCl complex 1.3 M in THF (Aldrich), Methyllithium LiBr complex 1.5 M in Et_2O (Aldrich), 3-Methoxyphenylmagnesium bromide 1.0 M in THF (Aldrich).

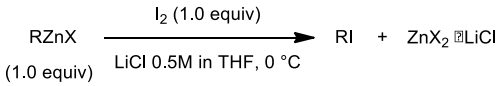
Titration procedures

Titration of Grignard and lithium reagents[50]



To an argon-flushed and flame-dried 10 mL round-bottom flask equipped with a teflon septum and a stirbar was added catalytic amount of 1,10-phenantroline (2 to 5 mg). Then, it was solubilized with 1.0 mL of THF and stirred a room temperature. An accurately syringed volume of Grignard or lithium reagent was added to the 1,10-phenantroline solution using a gaz tight syringe (normally between 0.5 mL to 1.0 mL). A light purple color forms within a 5 minute range indicating the complexation of the 1,10-phenantroline to the Grignard or lithium species. Then, a solution of anhydrous 2-butanol (1 M in toluene) was slowly added dropwise *via* a gaz tight syringe until the end point is reached indicated by a change in color to a yellow or translucid solution. The molarity of the Gringnard or lithium reagent was averaged from a duplicate of the procedure.

Titration of monoorganozinc reagents (for the EtZnI solution)[51]



To an argon-flushed and flame-dried 10 mL round-bottom flask equipped with a teflon septum and a stirbar was added a 0.5 M solution of LiCl in THF (3.0 mL) and the solution was stirred at room temperature. An accurately weighted amount of I_2 (253.8 mg, 1 mmol, 1.0 equiv) was added to the solution forming a dark purple-brown solution and the solution was cooled to 0 °C. The monoorganozinc reagent (1.0 equiv relative to I_2) was added dropwise using a syringe to the iodine solution at 0 °C until the end point is reached indicated by a change in color to a yellow or translucid solution. The molarity of the monoorganozinc reagent was averaged from a duplicate of the procedure.

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50. The titration procedure for Grignard and organolithium reagents was reported previously: Watson, S. C. & Eastham, J. F. Colored indicators for simple direct titration of magnesium and lithium reagents. *J. Organomet. Chem.* **9**, 165-168 (1967).

51. The titration procedure for zinc reagents was reported previously: Krasovskiy, A. & Knochel, P. Convenient titration method for organometallic zinc, magnesium, and lanthanide reagents. *Synthesis*, 890-891 (2006).

Amide 3.4a-3.4ac synthesis

4-Azidobenzoic acid (used in the synthesis of amide (**3.4e**)) was synthesized according to literature procedures.[52]

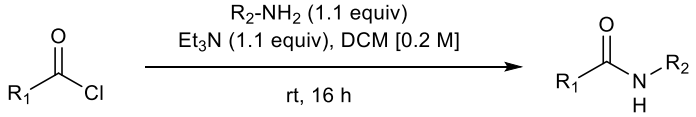
(*S*)-(+)-1-Methoxy-2-amino-3-methylbutane hydrochloride (used in the synthesis of amide (**3.4s**)) was made according to literature procedures.[53]

(2*R*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-methylpropanoic acid (used in the synthesis of amide (**3.4v**)) was made according to literature procedures.[54]

Amides **3.4a-f**, **3.4h-i**, **3.4n-3.4r**, **3.4t-3.4aa**, and **3.4ac** were synthesized according to **procedures A** and **B**.

Amides **3.4g**, **3.4j**, **3.4k** were synthesized according to literature procedures.[55]

*Synthesis of amides starting from commercially available acyl chlorides according to **procedure A**:*



Procedure A: To a flame-dried and argon-flushed round-bottom flask equipped with a septum and a stir-bar was added the amine (1.1 equiv). It was solubilized in anhydrous DCM [0.20 M] and stirred at room temperature. The solution was cooled to 0 °C and triethylamine (1.1 equiv) was added to the reaction flask. Then, the acyl chloride (1.0 equiv) was slowly added *via* a syringe dropwise (or portionwise if solid). The reaction was slowly warmed up to room temperature and stirred for 16 h. The reaction was quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11 and then diluted with DCM. The biphasic mixture was transferred to a separation funnel. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with DCM (2x) and the organic layers were combined.

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52. Liu, Q. & Tor, Y. Simple conversion of aromatic amines into azides. *Org. Lett.* **5**, 2571-2572 (2003).

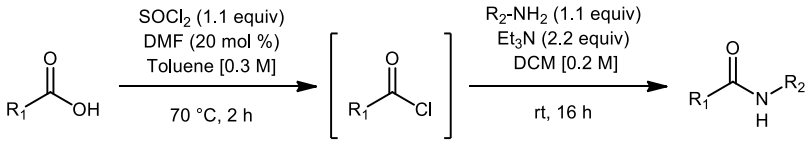
53. Meyers, A. I., Poindexter, G. S. & Brich, Z. Asymmetric synthesis of (+)- or (–)-2-methyloctanal *via* the metalloenamines of chiral alkoxy amines. *J. Org. Chem.* **43**, 892-898 (1978).

54. Parkkari, T. *et al.* Synthesis and CB1 receptor activities of novel arachidonyl alcohol derivatives *Bioorg. Med. Chem. Lett.* **14**, 3231-3234 (2004).

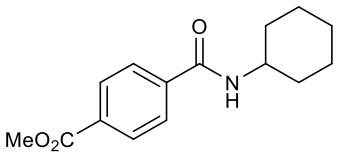
55. Pelletier, G., Bechara, W. S. & Charette, A. B. Controlled and chemoselective reduction of secondary amides *J. Am. Chem. Soc.* **132**, 12817-12819 (2010).

The organic layer was washed with 1 N HCl (3x), aq. NaCl sat. (1x), and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness.

Synthesis of amides starting from carboxylic acids according to ***procedure B****:*

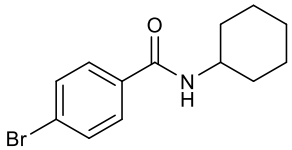


Procedure B: To a flame-dried and argon-flushed round-bottom flask equipped with a stir-bar and a condenser was added the carboxylic acid (1.0 equiv). The acid was diluted with anhydrous toluene ([0.3 M]) and anhydrous dimethylformamide (DMF) (20 mol%) was added to the reaction flask. Then, the solution was cooled to 0 °C and thionylchloride (1.1 equiv) was added dropwise to the solution *via* a syringe. Upon completion of the addition, the reaction was warmed to 70 °C and stirred for 2 h. The reaction was then cooled to 0 °C and was diluted with anhydrous DCM ([0.2 M]). The amine (1.1 equiv) and triethylamine (2.2 equiv) were added to the reaction flask at 0 °C *via* a syringe. The reaction was slowly warmed up to room temperature and stirred for 16 h. It was then quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11 and then diluted with DCM. The biphasic mixture was transferred to a separation funnel. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was washed with 1 N HCl (3x), aq. NaCl sat. (1x), and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness.



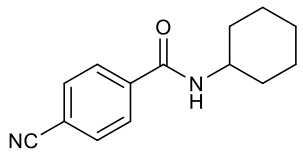
(Table 1, entry 1)

***N*-Cyclohexyl-4-(methoxycarbonyl)benzamide (3.4a):**[55] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4a** was isolated as a white powder (5.80 g, 89% Yield). **mp**: 185-186 °C, $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 2H), 6.24 (br d, *J* = 7.0 Hz, 1H), 4.02-3.91 (m, 1H), 3.91 (s, 3H), 2.05-2.01 (m, 2H), 1.79-1.74 (m, 2H), 1.68-1.63 (m, 1H), 1.47-1.36 (m, 2H), 1.31-1.15 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.0, 165.4, 138.7, 132.0, 129.3, 126.6, 52.0, 48.6, 32.7, 25.1, 24.6; **FTIR** (cm^{-1}) (neat): 3305, 2940, 2854, 1720, 1631, 1541, 1435, 1227, 1107; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1443 *m/z*, found: 262.1432 *m/z*.



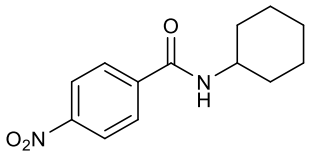
(Table 1, entry 2)

4-Bromo-*N*-cyclohexylbenzamide (3.4b):[55] Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4b** was isolated as a white powder (4.60 g, 82% Yield). **mp**: 180-181 °C; $\mathbf{R_f}$: 0.75 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 9.5 Hz, 2H), 7.57 (d, *J* = 9.5 Hz, 2H), 5.97 (br d, *J* = 7.5 Hz, 1H), 4.02-3.93 (m, 1H), 2.07-2.01 (m, 2H), 1.81-1.74 (m, 2H), 1.71-1.64 (m, 1H) 1.50-1.39 (m, 2H), 1.30-1.17 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.3, 133.6, 131.3, 128.2, 125.4, 48.5, 32.8, 25.2, 24.6; **FTIR** (cm^{-1}) (neat) 3285, 2930, 2853, 1630, 1590, 1540, 1333; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}NOBr$ $[M+H]^+$: 282.0494 and 284.0473 *m/z*, found: 282.0493 and 284.0472 *m/z*.



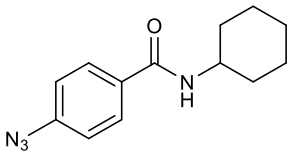
(Table 1, entry 3)

4-Cyano-*N*-cyclohexylbenzamide (3.4c):[55] Following **procedure B** the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4c** was isolated as an off-white powder (4.10 g, 88% Yield). **mp**: 164-165 °C; $\mathbf{R_f}$: 0.85 (50% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 6.08 (br s, 1H), 4.03-3.94 (m, 1H), 2.07-2.03 (m, 2H), 1.81-1.76 (m, 2H), 1.72-1.66 (m, 1H), 1.50-1.39 (m, 2H), 1.31-1.17 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 164.9, 139.1, 132.5, 127.7, 118.2, 114.9, 49.2, 33.2, 25.5, 24.9; **FTIR** (cm^{-1}) (neat): 3288, 2941, 2857, 2230, 1630, 1541, 1331; **HRMS** (ESI, Pos): calc. for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.1341 *m/z*, found: 229.1314 *m/z*.



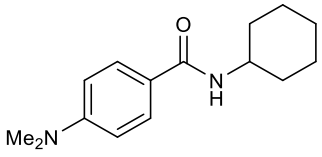
(Table 1, entry 4)

***N*-Cyclohexyl-4-nitrobenzamide (3.4d):**[55] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4d** was isolated as a white powder (10.10 g, 81% Yield). **mp**: 178-179 °C; $\mathbf{R_f}$: 0.40 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 7.0 Hz, 2H), 7.93 (d, *J* = 7.0 Hz, 2H), 6.09 (br s, 1H), 4.04-3.97 (m, 1H), 2.08-2.06 (m, 2H), 1.81-1.78 (m, 2H), 1.71-1.68 (m, 1H), 1.51-1.41 (m, 2H), 1.32-1.19 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 164.3, 149.1, 140.3, 127.7, 123.4, 48.9, 32.8, 25.1, 24.5; **FTIR** (cm^{-1}) (neat): 3317, 2938, 2860, 1631, 1600, 1544, 1519, 1348, 1219; **HRMS** (ESI, Pos) calc. for $C_{13}H_{17}N_2O_3$ $[M+H]^+$: 249.1239 *m/z*, found: 249.1236 *m/z*.



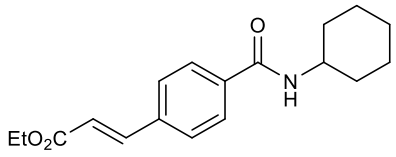
(Table 1, entry 5)

4-Azido-*N*-cyclohexylbenzamide (3.4e):[55] Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 10% EtOAc/Hexanes to 30% EtOAc/Hexanes and fractions containing **3.4e** were concentrated to dryness. It resulted in a brown, crystalline solid (3.30 g, 68 % Yield). **mp**: 158-159 °C; $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 10 Hz, 2H), 7.06 (d, *J* = 10 Hz, 2H), 5.98 (br d, *J* = 9.0 Hz, 1H), 4.03-3.93 (m, 1H), 2.07-2.02 (m, 2H), 1.81-1.74 (m, 2H), 1.71-1.64 (m, 1H), 1.49-1.39 (m, 2H), 1.30-1.19 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.2, 142.7, 131.2, 128.3, 118.6, 48.4, 32.9, 25.2, 24.5; **FTIR** (cm^{-1}) (neat): 3323, 2935, 2853, 2135, 1628, 1604, 1532, 1500, 1329, 1291; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}N_4O$ $[M+H]^+$: 245.1402 *m/z*, found: 245.1387 *m/z*.



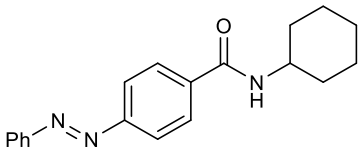
(Table 1, entry 6)

***N*-Cyclohexyl-4-(dimethylamino)-benzamide (3.4f):** Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4f** was isolated as a yellow powder (1.00 g, 62% Yield). **mp**: 160-161 °C; $\mathbf{R_f}$: 0.30 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.70-7.66 (m, 2H), 6.70-6.66 (m, 2H), 5.87 (br d, *J* = 7.0 Hz, 1H), 4.03-3.94 (m, 1H), 3.03 (s, 6H), 2.07-2.01 (m, 2H), 1.80-1.73 (m, 2H), 1.70-1.63 (m, 1H), 1.50-1.39 (m, 2H), 1.29-1.16 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.1, 152.0, 127.9, 121.6, 110.7, 47.9, 39.8, 33.1, 25.3, 24.6; **FTIR** (cm^{-1}) (neat): 3294, 2930, 2850, 1610, 1510, 1325, 1195, 1078; **HRMS** (ESI, Pos): calc. for $C_{15}H_{23}N_2O$ $[M+H]^+$: 247.1810 *m/z*, found: 247.1805 *m/z*.



(Table 1, entry 7)

Ethyl (2*E*)-3-{[(cyclohexylamino)carbonyl]phenyl}acrylate (3.4g):[55] Following the literature procedure described in **reference 55**, the amide **3.4g** was isolated as a white powder (3.30 g, 84% Yield, *E:Z* >20:1). **mp**: 175-176 °C; $\mathbf{R_f}$: 0.65 (60% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 16.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 16.5 Hz, 1H), 6.02 (br d, *J* = 7.5 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 4.04-3.95 (m, 1H), 2.07-2.03 (m, 2H), 1.81-1.75 (m, 2H), 1.71-1.65 (m, 1H), 1.50-1.18 (m, 5H), 1.36 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.8, 165.9, 143.4, 137.2, 136.5, 128.2, 127.6, 120.1, 60.8, 49.0, 33.3, 25.7, 25.1, 14.4; **FTIR** (cm^{-1}) (neat): 3285, 2937, 2855, 1712, 1627, 1541, 1309, 1174; **HRMS** (ESI, Pos): calc. for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1756 *m/z*, found: 302.1753 *m/z*.



(Table 1, entry 8)

***N*-Cyclohexyl-4-(2-phenyldiazenyl)-benzamide (3.4h)**:[56] Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4h** was isolated as red needles (1.01 g, 73% Yield). **mp**: 211-212°C, litt:[56] 228-229 °C; $\mathbf{R_f}$: 0.65 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.97-7.88 (m, 6H), 7.56-7.48 (m, 3H), 6.02 (br d, *J* = 8.5 Hz, 1H), 4.06-3.97 (m, 1H), 2.10-2.04 (m, 2H), 1.82-1.75 (m, 2H), 1.71-1.64 (m, 1H), 1.51-1.40 (m, 2H), 1.32-1.20 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.5, 153.8, 152.2, 136.5, 131.2, 128.8, 127.5, 122.7, 122.5, 48.5, 32.9, 25.2, 24.6; **FTIR** (cm^{-1}) (neat): 3332, 2938, 2844, 1627, 1526, 1324, 1259; **HRMS** (ESI, Pos): calc. for $C_{19}H_{22}N_3O$ $[M+H]^+$: 308.1763 *m/z*, found: 308.1759 *m/z*.

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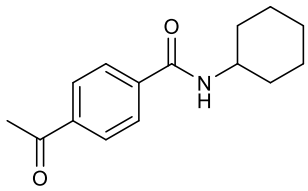
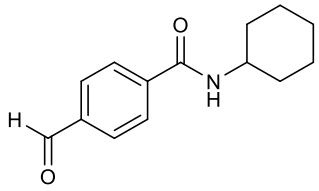
56. For literature characterization data, see: Woolfolk, E. O. & Roberts, E. H. *p*-Phenylazobenzoyl chloride for indentification and chromatographic separation of colorless compounds. II. Amines. *J. Org. Chem.* **21**, 436-438 (1956).



(Table 1, entry 9)

4-Acetyl-*N*-cyclohexylbenzamide (3.4i):[57] Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 10% to 50% EtOAc/Hexanes and fractions containing **3.4i** were concentrated to dryness. The product was isolated as a white powder (10.01 g, 96% Yield). **mp**: 197-198 °C, litt:[57] 209-210 °C; $\mathbf{R_f}$: 0.30 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 6.05 (br d, *J* = 6.5 Hz, 1H), 4.05-3.96 (m, 1H), 2.65 (s, 3H), 2.10-2.04 (m, 2H), 1.82-1.76 (m, 2H), 1.72-1.65 (m, 1H), 1.51-1.40 (m, 2H), 1.32-1.18 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 197.9, 166.0, 139.4, 128.9, 127.6, 49.4, 33.6, 27.2, 25.9, 25.3; **FTIR** (cm^{-1}) (neat): 3311, 2938, 2858, 1682, 1629, 1536, 1265; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494 *m/z*, found: 246.1482 *m/z*.



(Table 1, entry 10)

***N*-Cyclohexyl-4-formylbenzamide (3.4j):** Following the literature procedure described in **reference 55**, the amide **3.4j** was isolated as a white powder (6.44 g, 89% Yield). **mp**: 143-144 °C; $\mathbf{R_f}$: 0.20 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 10.05 (s, 1H), 7.90 (s, 4H), 6.30 (br d, *J* = 7.0 Hz, 1H), 4.03-3.91 (m, 1H), 2.05-2.00 (m, 2H), 1.80-1.63 (m, 3H), 1.48-1.12 (m, 5H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 192.5, 166.4, 141.2, 138.8, 130.6, 128.5, 49.9, 33.9, 26.3, 25.8; **FTIR** (cm^{-1}) (neat): 3317, 2930, 2850, 1704, 1626, 1528, 1328, 1204; **HRMS** (ESI, Pos): calc. for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1338 *m/z*, found: 232.1335 *m/z*.

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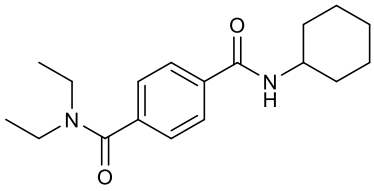
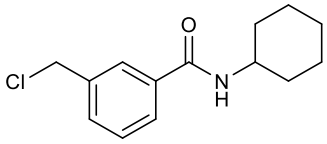
57. For literature characterization data, see: Sigman, M. E., Autrey, T. & Schuster, G. B. Aroylnitrenes with singlet ground states: photochemistry of acetyl-substituted aroyl and aryloxycarbonyl azides. *J. Am. Chem. Soc.* **110**, 4297-4305 (1988).



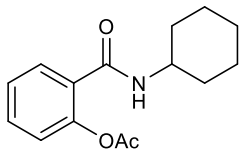
(Table 1, entry 11)

***N'*-Cyclohexyl-*N,N*-diethylterephtalamide (3.4k):**[55] Following the literature procedure described in **reference 55**, the diamide **3.4k** was isolated as a white powder (3.00 g, 49% Yield). **mp**: 75-76 °C; $\mathbf{R_f}$: 0.40 (90% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.34 (br d, *J* = 7.0 Hz, 1H), 4.02-3.93 (m, 1H), 3.55 (br q, *J* = 7.5 Hz, 2H), 3.20 (d, *J* = 7.5 Hz, 2H), 2.05-2.01 (m, 2H), 1.80-1.75 (m, 2H), 1.69-1.65 (m, 1H), 1.48-1.37 (m, 2H), 1.31-1.07 (m, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 170.6, 166.2, 139.8, 135.9, 127.3, 126.5, 48.9, 43.3, 39.4, 33.3, 25.7, 25.1; **FTIR** (cm^{-1}) (neat): 3312, 2932, 2855, 2241, 1619, 1541, 1450, 1323, 1288, 1098, 905; **HRMS** (ESI, Pos): calc. for $C_{18}H_{27}N_2O_2$ $[M+H]^+$: 303.2073 *m/z*, found: 303.2069 *m/z*.



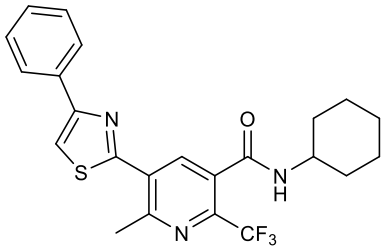
(Table 1, entry 14)

3-(Chloromethyl)-*N*-cyclohexylbenzamide (3.4n): Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. The solids were filtrated over a Buchner funnel and **3.4n** was isolated as a white powder (0.870 g, 65% Yield). **mp**: 150-151 °C; $\mathbf{R_f}$: 0.50 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.79 (t, *J* = 1.5 Hz, 1H), 7.71 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.54 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 6.00 (br d, *J* = 7.0 Hz, 1H), 4.64 (s, 2H), 4.05-3.96 (m, 1H), 2.10-2.03 (m, 2H), 1.83-1.75 (m, 2H), 1.72-1.65 (m, 1H), 1.52-1.41 (m, 2H), 1.32-1.18 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.5, 138.3, 136.1, 131.7, 129.3, 127.6, 127.2, 49.2, 46.1, 33.6, 25.9, 25.4; **FTIR** (cm^{-1}) (neat): 3272, 2937, 2863, 1628, 1534, 1336; **HRMS** (ESI, Pos): calc. for $C_{14}H_{19}ClNO$ $[M+H]^+$: 252.1155 *m/z*, found: 252.1151 *m/z*.



(Table 1, entry 15)

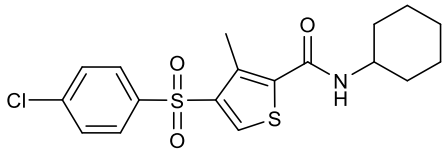
2-[(Cyclohexylamino)carbonyl]phenyl acetate (3.4o):[55] Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4o** was isolated as a white powder (18.50 g, 85% Yield). **mp**: 61-62 °C; $\mathbf{R_f}$: 0.15 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.73 (dd, J = 1.5, 7.5, 1H), 7.48-7.43 (m, 1H), 7.33-7.29 (m, 1H), 7.11-7.09 (m, 1H), 6.13 (br d, J = 7.5 Hz, 1H), 4.00-3.91 (m, 1H), 2.34 (s, 3H), 2.04-2.00 (m, 2H), 1.78-1.73 (m, 2H), 1.68-1.63 (m, 1H), 1.48-1.38 (m, 2H), 1.26-1.15 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 169.6, 165.2, 148.1, 131.9, 130.1, 129.6, 126.8, 123.5, 48.9, 33.6, 25.9, 25.3, 21.5; **FTIR** (cm^{-1}) (neat): 3284, 2932, 2853, 1765, 1630, 1535, 1194; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1443 *m/z*, found 262.1444 *m/z*.



(Table 1, entry 16)

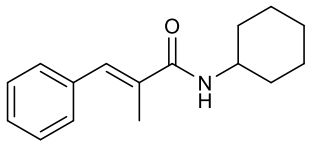
***N*-Cyclohexyl-6-methyl-5(4-phenyl-1,3-thiazol-2-yl)-2-(trifluoromethyl)nicotin amide (3.4p):** Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4p** was isolated as a white powder (0.910 g, 74% Yield). **mp**: 195-196 °C; $\mathbf{R_f}$: 0.50 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.70 (s, 1H), 7.53-7.38 (m, 3H), 5.78 (br d, J = 7.5 Hz, 1H), 4.08-3.98 (m, 1H), 3.03 (s, 3H), 2.13-2.03 (m, 2H), 1.84-1.64 (m, 3H), 1.51-1.40 (m, 2H), 1.33-1.19 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.0, 163.1, 157.7, 157.2, 143.0 (q, J = 33.8 Hz, $J_{C\text{-}F}$), 138.4, 134.2, 131.6, 130.3, 129.3, 129.1, 126.9, 121.7 (q, J = 271.5 Hz, $J_{C\text{-}F}$), 115.3, 49.7, 33.1, 25.8, 25.3, 25.1; **^{19}F NMR** ($CDCl_3$, 375.5 MHz): δ –64.8; **FTIR** (cm^{-1}) (neat): 3293, 2935, 2915,

1641, 1550, 1535, 1445, 1178, 1163, 1136, 1041; **HRMS** (ESI, Pos): calc. for $C_{23}H_{23}F_3N_3OS$ $[M+H]^+$: 446.1514 *m/z*, found: 446.1520 *m/z*.



(Table 1, entry 17)

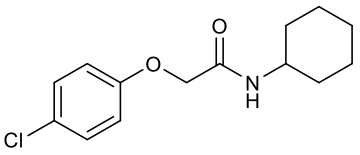
4-[(4-Chlorophenyl)sulfonyl]-*N*-cyclohexyl-3-methylthiophene-2-carboxamide (3.4q): Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4q** was isolated as a white powder (1.10 g, 92% Yield). **mp**: 154-155 °C; $\mathbf{R_f}$: 0.50 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.29 (s, 1H), 7.86 (dt, *J* = 2.5, 9.0 Hz, 2H), 7.53 (dt, *J* = 2.5, 9.0 Hz, 2H), 5.65-5.63 (br d, *J* = 7.0 Hz, 1H), 3.96-3.87 (m, 1H), 2.47 (s, 3H), 2.04-1.98 (m, 2H), 1.79-1.72 (m, 2H), 1.69-1.63 (m, 1H), 1.48-1.37 (m, 2H), 1.28-1.17 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.2, 141.2, 140.7, 139.4, 137.0, 136.6, 134.2, 130.0, 129.6, 49.6, 33.4, 25.8, 25.1, 14.0; **FTIR** (cm^{-1}) (neat): 3295, 2935, 2855, 1613, 1540, 1319, 1154, 1090; **HRMS** (ESI, Pos): calc. for $C_{18}H_{21}ClNO_3S_2$ $[M+H]^+$: 398.0651 *m/z*, found: 398.0646 *m/z*.



(Table 1, entry 18)

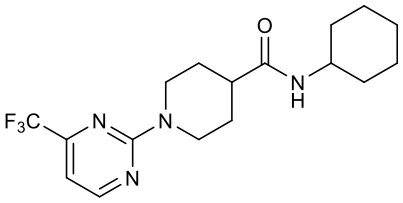
(2*E*)-*N*-Cyclohexyl-2-methyl-3-phenylacrylamide (3.4r): Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4r** was isolated as a white powder (2.67 g, 85% Yield). **mp**: 95-96 °C; $\mathbf{R_f}$: 0.65 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.42-7.29 (m, 6H), 5.75 (br d, *J* = 5.5 Hz, 1H), 3.96-3.87 (m, 1H), 2.11 (d, *J* = 1.5 Hz, 3H), 2.06-1.99 (m, 2H), 1.80-1.73 (m, 2H), 1.71-1.64 (m, 1H), 1.50-1.39 (m, 2H), 1.28-1.17 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.3, 135.9, 133.0, 132.2, 128.9, 127.9, 127.3, 48.1, 32.8, 25.2, 24.5, 14.0; **FTIR** (cm^{-1}) (neat): 3287, 2934, 2854, 1631, 1608,

1534, 1447, 1292; **HRMS** (ESI, Pos): calc. for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1701 *m/z*, found: 244.1703 *m/z*.



(Table 1, entry 20)

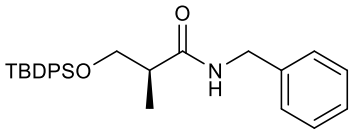
2-(4-Chlorophenoxy)-*N*-cyclohexylacetamide (3.4t): Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4t** was isolated as a white powder (6.40 g, 96% Yield). **mp**: 121-122 °C; $\mathbf{R_f}$: 0.50 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.27 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.37 (br d, *J* = 7.0 Hz, 1H), 4.44 (s, 2H), 3.92-3.83 (m, 1H), 1.96-1.90 (m, 2H), 1.75-1.69 (m, 2H), 1.67-1.60 (m, 1H), 1.44-1.33 (m, 2H), 1.24-1.13 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.1, 156.2, 130.1, 127.5, 116.4, 68.1, 48.3, 33.4, 25.8, 25.2; **FTIR** (cm^{-1}) (neat): 3270, 2921, 2858, 1655, 1560, 1488, 1230; **HRMS** (ESI, Pos): calc. for $C_{14}H_{19}ClNO_2$ $[M+H]^+$: 268.1104 *m/z*, found: 268.1101 *m/z*.



(Table 1, entry 21)

***N*-Cyclohexyl-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidine-4-carboxamide (3.4u):** Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4u** was isolated as a white powder (0.845 g, 82% Yield). **mp**: 200-201 °C; $\mathbf{R_f}$: 0.25 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.49 (d, *J* = 5.0 Hz, 1H), 6.75 (d, *J* = 5.0 Hz, 1H), 5.35 (br d, *J* = 7.0 Hz, 1H), 4.85 (dt, *J* = 3.0, 13.0 Hz, 2H), 3.84-3.74 (m, 1H), 2.99 (dt, *J* = 3.0, 13.0 Hz, 2H), 2.35 (tt, *J* = 3.5, 12.0 Hz, 1H), 1.97-1.90 (m, 4H), 1.78-1.61 (m, 5H), 1.44-1.33 (m, 2H), 1.23-1.08 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 172.9, 161.0, 159.7, 155.9 (q, *J* = 35.4 Hz, $J_{C\text{-}F}$), 120.2 (q, *J* = 273.7 Hz, $J_{C\text{-}F}$), 103.9 (q, *J* = 2.7 Hz,

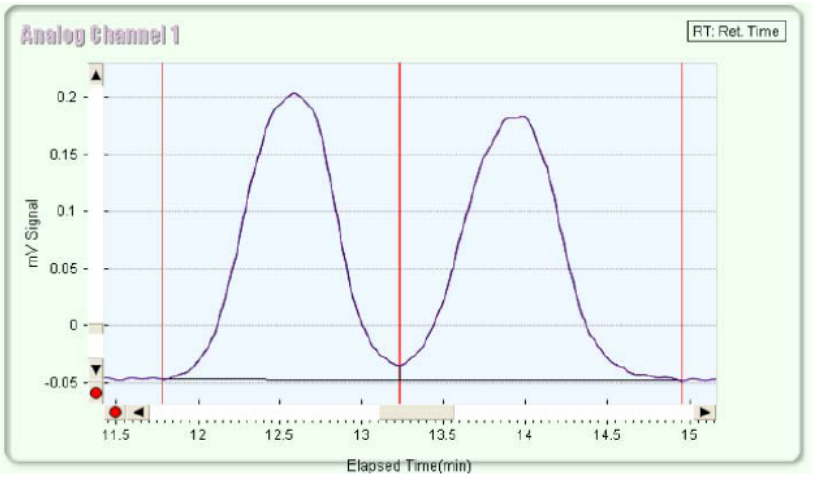
$J_{C\text{-}F}$), 47.6, 43.4, 43.0, 32.8, 28.2, 25.1, 24.5; **^{19}F NMR** ($CDCl_3$, 375.5 MHz): δ –72.3; **FTIR** (cm^{-1}) (neat): 3293, 2939, 2862, 1633, 1593, 1549, 1522, 1331, 1132, 1116; **HRMS** (ESI, Pos): calc. for $C_{17}H_{24}F_3N_4O$ $[M+H]^+$: 357.1902 *m/z*, found: 357.1902 *m/z*.



(Table 2, entry 22)

(2*S*)-*N*-Benzyl-3{[*tert*-butyl(diphenyl)silyl]oxy}-2-methylpropanamide (3.4v):[55]

Following **procedure B**, the crude amide was purified by flash chromatography over silica gel using a gradient of 10% EtOAc/Hexanes to 50% EtOAc/Hexanes and fractions containing **3.4v** were concentrated to dryness. It resulted in a white powder (7.40 g, 68 % Yield, 98 %ee). **mp**: 45-46 °C; SFC analysis of the product on a chiral stationary phase (Chiralpak ADH 10 cm, 7% MeOH, 20 min, 3 mL/min, 150 bar, 40 °C isotherm) (*S*)-**3.4v** tr = 12.5 min, *(R)*-**3.4v** tr = 13.9 min; **$[\alpha]_D^{20}$**: +14.1 (*c* 1.37, $CHCl_3$), **R_f**: 0.70 (20 % EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.64-7.60 (m, 4H), 7.48-7.28 (m, 11H), 6.68 (br s, 1H), 4.56-4.45 (m, 2H), 3.81-3.73 (m, 2H), 2.56-2.48 (m, 1H), 1.15 (dd, *J* = 2.0, 7.0 Hz, 3H), 1.00 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.1, 138.8, 136.0, 135.9, 133.3, 133.2, 130.3, 129.1, 128.4, 128.2, 127.8, 66.6, 44.0, 43.5, 27.2, 19.5, 14.1; **FTIR** (cm^{-1}) (neat): 3301, 2910, 2835, 1656, 1540, 1221; **HRMS** (ESI, Pos): calc. for $C_{26}H_{38}NO_2Si$ $[M+H]^+$: 432.2359 *m/z*, found: 432.2363 *m/z*.



Peak Name	Area %	Area	Retention Time
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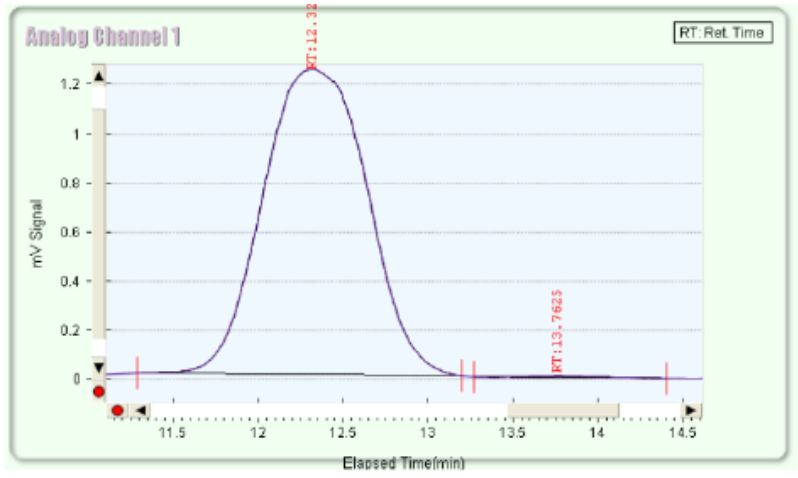
Peak3	49.7136	9.5604	13.9833 min



Peak No	Peak Area	% Peak Area	Retention Time
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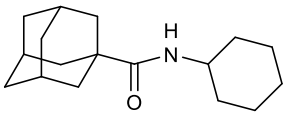
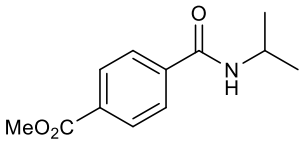
2	0.1947	0.3661	13.7625 min



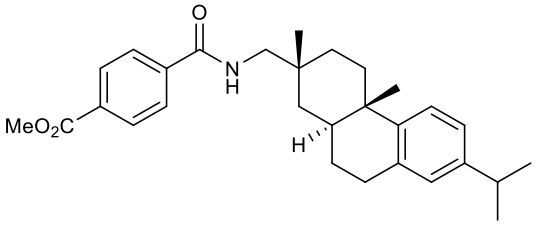
(Table 1, entry 23)

***N*-Cyclohexyladamantane-1-carboxamide (3.4w):**[55] Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4w** was isolated as a white powder (4.10 g, 76% Yield). **mp**: 195-196 °C; $\mathbf{R_f}$: 0.70 (30% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.42 (br d, *J* = 5.5 Hz, 1H), 3.83-3.73 (m, 1H), 2.06 (s, 3H), 1.93-1.85 (m, 8H), 1.78-1.59 (m, 9H), 1.45-1.33 (m, 2H), 1.24-1.07 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 176.6, 47.2, 40.1, 38.9, 36.2, 32.8, 27.8, 25.3, 24.5; **FTIR** (cm^{-1}) (neat): 3302, 2901, 2851, 1745, 1701, 1625, 1535, 1217; **HRMS** (ESI, Pos): calc. for $C_{17}H_{28}NO$ $[M+H]^+$: 262.2171 *m/z*, found: 262.2162 *m/z*.



(Table 2, entry 1)

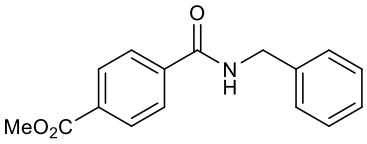
Methyl 4-[(isopropylamino)carbonyl]benzoate (3.4x): Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4x** was isolated as a white powder (1.79 g, 73% Yield). **mp**: 126-127 °C, $\mathbf{R_f}$: 0.25 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* = 9.0 Hz, 2H), 7.81 (d, *J* = 9.0 Hz, 2H), 6.08 (br d, *J* = 5.5 Hz, 1H), 4.31 (h, *J* = 7.0 Hz, 1H), 3.95 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.7, 166.2, 139.3, 132.9, 130.2, 127.3, 52.8, 42.6, 23.2; **FTIR** (cm^{-1}) (neat): 3296, 2959, 2844, 1717, 1629, 1534, 1431, 1273; **HRMS** (ESI, Pos): calc. for $C_{12}H_{16}NO_3$ $[M+H]^+$: 222.1130 *m/z*, found: 222.1127 *m/z*.



(Table 2, entry 2)

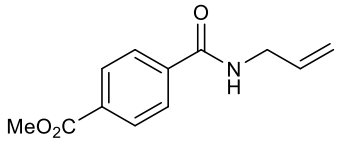
Methyl 4-[({[(2*R*,4a*S*,10a*S*)-7-isopropyl-2,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl]methyl}amino)carbonyl]benzoate (3.4y): Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4y** was isolated as a white powder (2.00 g, 40% Yield). **mp**: 178-179 °C (dec.), $\mathbf{[\alpha]_D^{20}}$: -6.8 (*c* 1.25, $CHCl_3$), $\mathbf{R_f}$: 0.65 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.02 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.91 (s, 1H), 6.29-6.21 (m, 1H), 3.95 (s, 3H), 3.46 (dd, *J* = 6.5, 13.5 Hz, 1H), 3.36 (dd, *J* = 6.5, 13.5 Hz, 1H), 2.96 (dd, *J* = 6.0, 16.0 Hz, 1H), 2.90-2.81 (m, 2H), 2.36-2.31 (m, 1H), 2.03-1.98 (m, 1H), 1.86-1.69 (m, 3H), 1.59-1.50 (m, 2H), 1.46-1.35 (m, 2H), 1.28-1.23 (m, 9H), 1.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.3, 166.7, 147.4, 146.1, 139.2, 135.1, 133.0, 130.3, 127.4, 127.3, 124.6, 124.3, 52.8, 50.9, 46.3, 38.8, 38.2, 38.0, 36.9, 33.8,

30.8, 25.8, 24.4, 19.5, 19.2, 19.0; **FTIR** (cm^{-1}) (neat): 2927, 1724, 1654, 1537, 1435, 1274, 1107; **HRMS** (ESI, Pos): calc. for $C_{29}H_{38}NO_3$ $[M+H]^+$: 448.2852 *m/z*, found: 448.2852 *m/z*.



(Table 2, entry 3)

Methyl 4-[(benzylamino)carbonyl]benzoate (3.4z):[58] Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4z** was isolated as an off-white powder (2.51 g, 84% Yield). **mp**: 150-151 °C; $\mathbf{R_f}$: 0.40 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.14-8.11 (m, 2H), 7.89-7.86 (m, 2H), 7.40-7.32 (m, 5H), 6.43 (br t, *J* = 5.0 Hz, 1H), 4.69 (d, *J* = 5.0 Hz, 2H), 3.97 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.9, 166.7, 138.7, 138.3, 133.2, 130.2, 129.2, 128.4, 128.2, 127.5, 52.8, 44.7; **FTIR** (cm^{-1}) (neat): 3298, 2950, 2844, 1713, 1639, 1553, 1280; **HRMS** (ESI, Pos): calc. for $C_{16}H_{15}NO_3$ $[M+H]^+$: 270.1130 *m/z*, found: 270.1125 *m/z*.



(Table 2, entry 4-5)

Methyl 4-[(allylamino)carbonyl]benzoate (3.4aa):[59] Following **procedure B**, the crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4aa** was isolated as an off-white powder (1.82 g, 75% Yield). **mp**: 105-106 °C; $\mathbf{R_f}$: 0.55 (40% EtOAc/Hexanes); ^{1}H **NMR** ($CDCl_3$, 400 MHz): δ 8.13-8.10 (m, 2H), 7.87-7.84 (m, 2H), 6.34 (br s, 1H), 6.01-5.91 (m, 1H), 5.32-5.21 (m, 2H), 4.14-4.10 (m, 2H), 3.96 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.9, 166.7, 138.8, 134.2, 133.2, 130.3, 127.4, 117.5, 52.8, 43.0; **FTIR** (cm^{-1})

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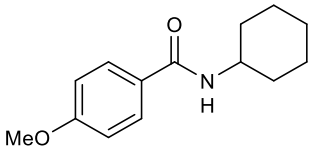
58. For literature characterization data, see: De Sarkar, S. & Studer, A. Oxidative amidation and azidation of aldehydes by NHC catalysis. *Org. Lett.* **12**, 1992-1995 (2010).

59. For literature characterization data, see: Appukkuttan, P., Axelsson, L., Van der Eycken, E. & Larhed, M. Microwave-assisted, $Mo(CO)_6$-mediated, palladium-catalyzed amino-carbonylation of aryl halides using allyl amines: from exploration to scale-up. *Tetrahedron Lett.* **49**, 5625-5628 (2008).

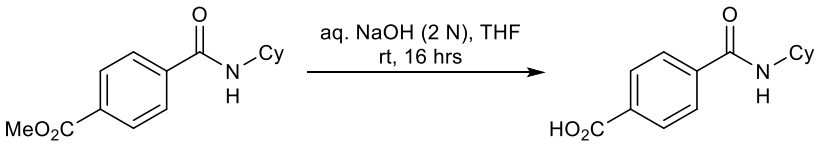
(neat): 3271, 2952, 1719, 1637, 1541, 1434, 1277, 1107; **HRMS** (ESI, Pos): calc. for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0974 *m/z*, found: 220.0969 *m/z*.



(Table 3, entry 2)

***N*-Cyclohexyl-4-methoxybenzamide (3.4ac):**[55] Following **procedure A**, the crude amide was purified by trituration over a mixture of 5% Et_2O/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and **3.4ac** was isolated as a white powder (9.10 g, 90% Yield). **mp**: 153-154 °C; **R_f**: 0.35 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5, Hz, 2H), 6.17 (br d, *J* = 8.0 Hz, 1H), 4.00-3.89 (m, 1H), 3.62 (s, 3H), 2.01-1.97 (m, 2H), 1.76-1.70 (m, 2H), 1.66-1.60 (m, 1H), 1.44-1.33 (m, 2H), 1.27-1.12 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.5, 162.3, 129.1, 127.8, 114.0, 55.8, 49.0, 33.7, 26.0, 25.4; **FTIR** (cm^{-1}) (neat): 3299, 2932, 2853, 1624, 1607, 1533, 1505, 1333, 1252, 1176; **HRMS** (ESI, Pos): calc. for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494 *m/z*, found: 234.1494 *m/z*.

*Synthesis of 4-(methoxycarbonyl)benzoic acid from saponification of N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*

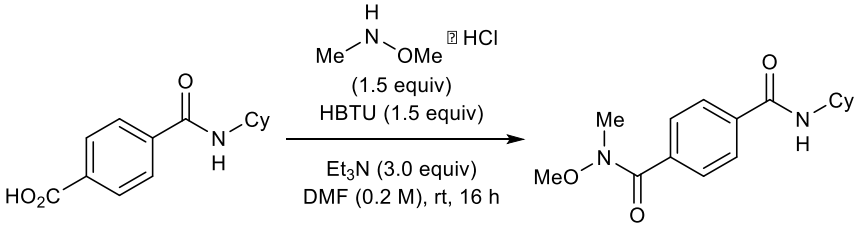


4-(Methoxycarbonyl)benzoic acid:[60] To a 250 mL round-bottom flask equipped with a stir-bar and a septum was added *N*-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**) (4.0 g, 15.31 mmol, 1.0 equiv). The amide was diluted with THF (38.3 mL, [0.4 M]). Then, an aqueous solution of NaOH (2 N) (38.3 mL, [0.4 M]) was added to the organic layer. The biphasic solution was then stirred at room temperature for 16 hours ensuring complete saponification of the ester moiety. Et_2O (40 mL) was then added to the reaction and the mixture was transferred to a 250 mL separatory funnel. The layers were separated and the

60. For literature characterization data, see: Csajági, C. *et al.* High-efficiency aminocarbonylation by introducing CO to a pressurized continuous flow reactor. *Org. Lett.* **10**, 1589-1592 (2008).

basic aqueous layer was washed with Et_2O (2x). The basic aqueous layer was transferred to a 250 mL erlenmeyer equipped with a stir-bar and made acidic by adding an aqueous solution of HCl (2 N) until pH ~ 2-3. The acidic aqueous solution was transferred to a 250 mL separatory funnel and was extracted with DCM (5x). The chlorinated organic layers were combined, dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel, and evaporated to dryness. The acid was isolated as a white powder (3.49 g, 94% Yield). **mp**: 288-289 °C; $\mathbf{R_f}$: 0.55 (80% EtOAc/Hexanes); **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 11.05 (br s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H), 3.81-3.72 (m, 1H), 1.87-1.68 (m, 4H), 1.64-1.56 (m, 1H), 1.37-1.25 (m, 4H), 1.18-1.06 (m, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ 167.7, 165.5, 139.5, 133.6, 130.0, 128.4, 49.4, 33.2, 26.1, 25.8; **FTIR** (cm^{-1}) (neat): 3318, 2938, 2862, 1684, 1632, 1536, 1424, 1259; **HRMS** (ESI, Pos): calc. for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1287 *m/z*, found: 248.1283 *m/z*.

*Synthesis of N'-Cyclohexyl-N-methoxy-N-methylterephtalamide **(3.4l)** from 4-(methoxycarbonyl)benzoic acid (Amine Coupling Reaction)*

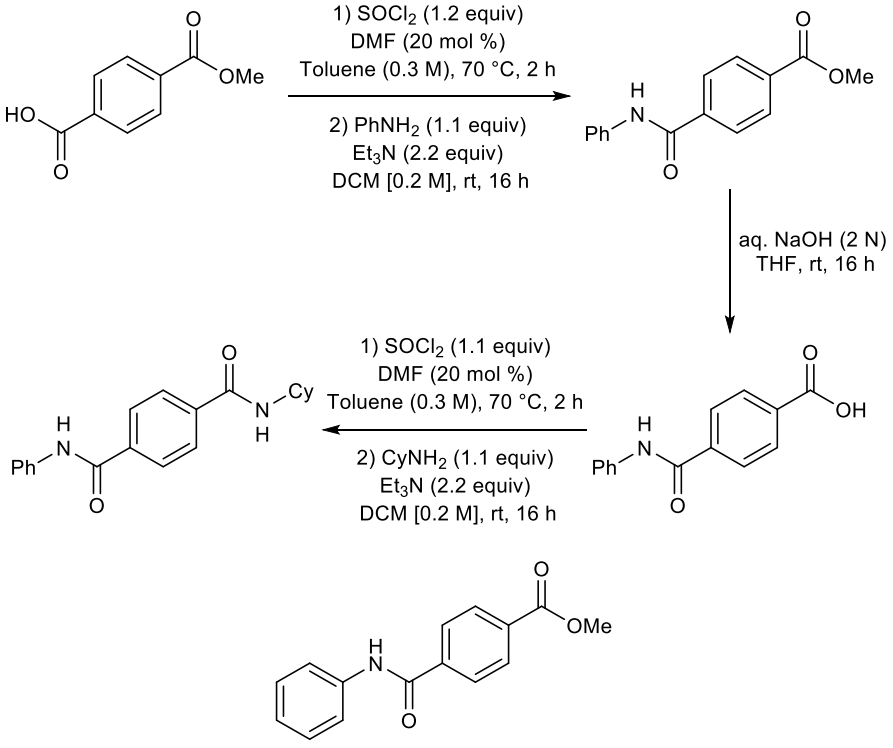


(Table 1, entry 12)

***N'*-Cyclohexyl-*N*-methoxy-*N*-methylterephtalamide (3.4l):** To a flame-dried and argon-flushed 100 mL round-bottom flask equipped with a stir-bar and a septum was added 4-(methoxycarbonyl)benzoic acid (1.50 g, 6.1 mmol, 1.0 equiv). The acid was dissolved in anhydrous DMF (30.3 mL, [0.2 M]) and cooled to 0°C. Then, *N,O*-dimethylhydroxylamine hydrochloride (0.888 g, 9.1 mmol, 1.5 equiv), Et_3N (1.84 g, 2.54 mL, 18.2 mmol, 3.0 equiv), and HBTU (3.45 g, 9.1 mmol, 1.5 equiv) were added successively to the solution and the reaction was slowly warmed to room temperature over 16 hours. The reaction was then quenched by addition of 30 mL of a saturated aqueous solution of $NaHCO_3$. The reaction mixture was transferred to a 250 mL separatory funnel. 50 mL of EtOAc were added to the mixture and the aqueous layer was extracted with EtOAc (3x). The organic layers were combined and washed with brine (3x), dried over anhydrous sodium sulphate (Na_2SO_4),

filtered over a sintered funnel, and evaporated to dryness. The crude Weinreb amide was purified by flash chromatography over silica gel using a gradient of 50% EtOAc/Hexanes to 100% EtOAc and fractions containing **3.4l** were concentrated to dryness. It resulted in a white powder (1.40 g, 74 % Yield). **mp**: 121-122 °C; $\mathbf{R_f}$: 0.40 (80 % EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.80-7.77 (m, 2H), 7.22-7.69 (m, 2H), 6.18 (d, *J* = 7.0 Hz, 1H), 4.04-3.94 (m, 1H), 3.53 (s, 3H), 3.37 (s, 3H), 2.07-2.01 (m, 2H), 1.81-1.74 (m, 2H), 1.71-1.64 (m, 1H), 1.49-1.38 (m, 2H), 1.32-1.16 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.6, 165.6, 136.6, 136.3, 128.0, 126.2, 60.8, 48.5, 33.1, 32.8, 25.2, 24.6; **FTIR** (cm^{-1}) (neat): 3924, 2935, 1722, 1630, 1542; **HRMS** (ESI, Pos): calc. for $C_{16}H_{23}N_2O_3$ $[M+H]^+$: 291.1709 *m/z*, found: 291.1703 *m/z*.

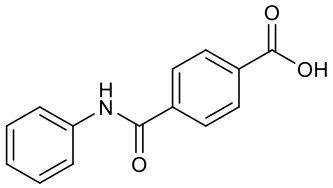
Synthesis of N-cyclohexyl-*N'-phenylterephtalamide (**3.4m**) from 4-(methoxycarbonyl) benzoic acid*



Methyl 4-(anilinocarbonyl)benzoate:[61] To a flame-dried and argon-flushed 100 round-bottom flask equipped with a stir-bar and a condenser was added 4-(methoxycarbonyl)benzoic

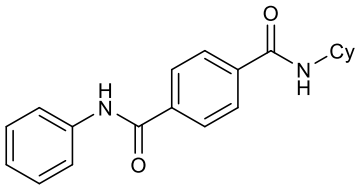
61. For literature characterization data, see : Perry, R. J. & Wilson, D. B. Palladium-catalyzed carbonylation and coupling reactions of aryl chlorides and amines. *J. Org. Chem.* **61**, 7482-7485 (1996).

acid (2.00 g, 11.1 mmol, 1.0 equiv). The acid was diluted with dry toluene (37.1 mL, [0.3 M]) and dry dimethylformamide (DMF) (162.3 mg, 172 µL, 2.22 mmol, 0.2 equiv) was added to the reaction flask. Then, the solution was cooled to 0 °C and thionylchloride (1.585 g, 972 µL, 13.3 mmol, 1.2 equiv) was added dropwise to the solution *via* a syringe. Upon completion of the addition, the reaction was warmed to 70 °C and stirred for 2 h. The reaction was then cooled to 0 °C and was diluted with dry DCM (37.04 mL, [0.2 M]). Aniline (1.136 g, 1.11 mL, 12.2 mmol, 1.1 equiv) and triethylamine (2.469 g, 3.40 mL, 24.4 mmol, 2.2 equiv) were added to the reaction flask at 0 °C *via* a syringe. The reaction was slowly warmed up to room temperature and stirred for 16 h. It was then quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11. The biphasic mixture was transferred to a separatory funnel and then diluted with DCM (40 mL). The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was washed with 1N HCl (2x), aq. NaCl (sat.), and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness. The crude amide was purified by trituration over a mixture of 5% EtOAc/Hexanes for 1-2 h at room temperature. Then, the solids were filtrated over a Buchner funnel and the product was isolated as a beige powder (2.10 g, 74% Yield). **mp**: 182-183 °C; **R_f**: 0.60 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 10.56 (br s, 1H), 8.17-8.14 (m, 2H), 7.95-7.92 (m, 2H), 7.87 (br s, 1H), 7.66 (d, J = 10.0 Hz, 2H), 7.43-7.37 (m, 2H), 7.23-7.16 (m, 1H), 3.97 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.6, 165.2, 139.3, 138.0, 133.4, 130.4, 129.6, 127.5, 125.3, 120.7, 52.9; **FTIR** (cm^{-1}) (neat): 3363, 2949, 1714, 1656, 1599, 1531, 1437, 1277, 1116, 1105; **HRMS** (ESI, Pos): calc. for $C_{15}H_{14}NO_3$ $[M+H]^+$: 256.0974 *m/z*, found: 256.0969 *m/z*.



4-(Anilinocarbonyl)benzoic acid:[62] To a 100 mL round-bottom flask equipped with a stir-bar and a septum was added methyl 4-(anilinocarbonyl)benzoate (1.500 g, 5.9 mmol, 1.0 equiv). The amide was diluted with THF (14.8 mL, [0.4 M]). Then, an aqueous solution of NaOH (2N) (14.8 mL, [0.4 M]) was added to the organic layer. The biphasic solution was then stirred at room temperature for 16 hours ensuring complete saponification of the ester moiety. Et_2O (20 mL) was then added to the reaction and the mixture was transferred to a 125 mL separatory funnel. The layers were separated and the basic aqueous layer was washed with Et_2O (2x). The basic aqueous layer was transferred to a 250 mL erlenmeyer equipped with a stir-bar and made acidic by adding an aqueous solution of HCl (2 N) until pH ~ 2-3. The acidic aqueous solution was transferred to a 250 mL separatory funnel and was extracted with DCM (5x). The chlorinated organic layers were combined, dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel, and evaporated to dryness. The acid was isolated as a white powder (1.31 g, 92% Yield). **mp**: 325-326 °C; litt:[62] >300 °C $\mathbf{R_f}$: 0.25 (10% MeOH/DCM); **^{1}H NMR** (CD_3OD, 400 MHz): δ 8.19-8.16 (m, 2H), 8.05-8.01 (m, 2H), 7.74-7.70 (m, 2H), 7.42-7.37 (m, 2H), 7.21-7.17 (m, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ 167.6, 165.7, 139.8, 139.6, 134.1, 130.1, 129.5, 128.8, 124.8, 121.3; **FTIR** (cm^{-1}) (neat): 3338, 2967, 2963, 2870, 2843, 1679, 1658, 1523, 1436, 1056, 1032; **HRMS** (ESI, Pos): calc. for $C_{14}H_{12}NO_3$ $[M+H]^+$: 242.0817 *m/z*, found: 242.0816 *m/z*.

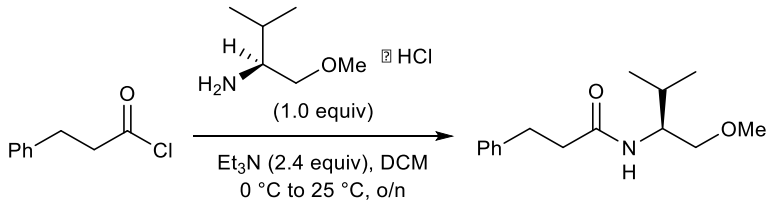
62. For literature characterization data, see : Kagechika, H., Kawachi, E., Hashimoto, Y., Himi, T. & Shudo, K. Retinobenzoic acid. 1. Structure-activity relationships of aromatic amides with retinoidal activity. *J. Med. Chem.* **31**, 2182-2192 (1988).



(Table 1, entry 13)

***N*-Cyclohexyl-*N'*-phenylterephtalamide (3.4m):** To a flame-dried and argon-flushed 100 round-bottom flask equipped with a stir-bar and a condenser was added 4-(anilinocarbonyl)benzoic acid (0.850 g, 3.53 mmol, 1.0 equiv). The acid was diluted with dry toluene (11.8 mL, [0.3 M]) and dry dimethylformamide (DMF) (51.6 mg, 55 μL, 0.710 mmol, 0.2 equiv) was added to the reaction flask. Then, the solution was cooled to 0 °C and thionylchloride (0.462 g, 282 μL, 3.88 mmol, 1.1 equiv) was added dropwise to the solution *via* a syringe. Upon completion of the addition, the reaction was warmed to 70 °C and stirred for 2 h. The reaction was then cooled to 0 °C and was diluted with dry DCM (17.7 mL, [0.2 M]). Cyclohexylamine (0.385 g, 445 μL, 3.88 mmol, 1.1 equiv) and triethylamine (0.786 g, 1.08 mL, 7.77 mmol, 2.2 equiv) were added to the reaction flask at 0 °C *via* a syringe. The reaction was slowly warmed up to room temperature and stirred for 16 h. It was then quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11. The reaction was diluted with Hexanes (40 mL) which created a suspension of the product in the biphasic solution. Then, the solids were filtrated over a Buchner funnel and the product was further dried on a vaccum pump. The product was isolated as a white powder (0.905 g, 80 % Yield). **mp**: 286-288 °C; $\mathbf{R_f}$: 0.50 (10% MeOH/DCM); **^{1}H NMR** (DMSO-d_6, 400 MHz): δ 10.39 (br s, 1H), 8.37 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 8.5 H z, 2H), 7.97 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 3.84-3.74 (m, 1H), 1.89-1.72 (m, 4H), 1.66-1.59 (m, 1H), 1.40-1.26 (m, 4H), 1.20-1.10 (m, 1H); **^{13}C NMR** (DMSO-d_6, 175 MHz): δ 165.4, 165.1, 139.4, 137.9, 137.3, 129.1, 128.0, 127.8, 124.3, 121.0, 50.0, 32.9, 31.2, 25.4; **FTIR** (cm^{-1}) (neat): 3318, 2938, 2926, 2845, 1649, 1627, 1598, 1526, 1499, 1440, 1323, 1288; **HRMS** (ESI, Pos): calc. for $C_{20}H_{23}N_2O_2$ $[M+H]^+$: 323.1760 *m/z*, found: 323.1764 *m/z*.

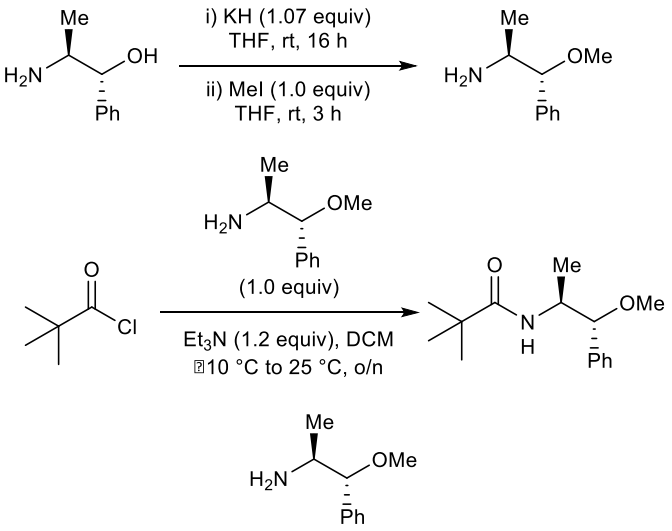
*Synthesis of N-[(1S)-1-(metoxymethyl)-2-methylpropyl]-3-phenylpropanamide (**3.4s**) from (S)-(+)-1-methoxy-2-amino-3-methylbutane hydrochloride*



(Table 1, entry 19)

***N*-[(1*S*)-1-(Methoxymethyl)-2-methylpropyl]-3-phenylpropanamide (3.4s):** To a flame-dried and argon-flushed 250 mL round-bottom flask equipped with a stir-bar and a septum was added (*S*)-(+)-1-methoxy-2-amino-3-methylbutane hydrochloride(**Erreur ! Signet non défini.**) (1.531 g, 10 mmol, 1.0 equiv) and the solid was dissolved in anhydrous DCM (50 mL, [0.2 M]). The reaction was cooled to 0 °C using an ice/water cooling bath and Et_3N (2.428 g, 3.24 mL, 24.0 mmol, 2.4 equiv) was added to the solution. Then, hydrocinnamoyl chloride (1.686 g, 1.483 mL, 10 mmol, 1.0 equiv) was added dropwise via a syringe and the reaction was stirred from 0 °C to room temperature over night. EtOAc (50 mL) was added to the reaction and it was quenched with an aqueous solution of HCl (1N) (40 mL). The biphasic mixture was transferred into a 250 mL extraction funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined and washed with a saturated solution of Na_2CO_3 (2x), brine (2x), dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel, and evaporated to dryness. The crude chiral amide was purified by flash chromatography over silica gel using a gradient of 10% EtOAc/Hexanes to 60% EtOAc and fractions containing **3.4s** were concentrated to dryness. It resulted in a white powder (1.644 g, 66 % Yield). **mp**: 80-81 °C; $\mathbf{[\alpha]_D^{20}}$: -38.5 (*c* 1.36, $CHCl_3$); $\mathbf{R_f}$: 0.45 (40 % EtOAc/Hexanes); ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.19 (m, 5H), 5.56 (br d, *J* = 8.5 Hz, 1H), 3.85-3.79 (m, 1H), 3.47 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.29 (s, 3H), 3.25 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.00 (t, *J* = 7.0 Hz, 2H), 2.52 (t, *J* = 7.0 Hz, 2H), 1.85-1.77 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H); ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 172.0, 142.3, 128.9, 128.8, 126.6, 72.9, 59.4, 54.3, 39.0, 32.2, 29.7, 19.8, 19.4; **FTIR** (cm^{-1}) (neat): 3296, 2973, 2844, 1634, 1541, 1454, 1108; **HRMS** (ESI, Pos): calc. for $C_{15}H_{24}NO_2$ $[M+H]^+$: 250.1807 *m/z*, found: 250.1804 *m/z*.

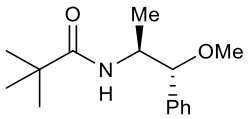
*Synthesis of N-[(1R,2S)-1-Methoxy-1-phenylpropan-2-yl]2,2-dimethylpropanamide (**3.4ab**) from (–)-norephedrine*



(1*R*,2*S*)-1-Methoxy-1-phenylpropan-2-amine:[(63)] To a flame-dried and argon-flushed 250 mL three-neck flask equipped with a stir-bar, an addition funnel, and a septum was added (–)-norephedrine (4.54 g, 30.0 mmol, 1.0 equiv). The aminoalcohol was solubilised with anhydrous THF (62.5 mL, [0.48 M]). Powdered dry KH (1.29 g, 32.1 mmol, 1.07 equiv) was carefully added to the addition funnel and it was suspended in dry THF (25 mL, [1.28 M]). The KH suspension was added dropwise over 45 min on the aminoalcohol solution. The reaction was stirred for 16 hours at room temperature. Then, to a separate 100 mL flask, MeI (4.26 g, 1.87 mL, 30.0 mmol, 1.0 equiv) was solubilised in dry THF (40 mL, [0.75 M]). The MeI solution was canulated dropwise over 30 min at room temperature in the reaction mixture and it was stirred for 3 hours. The reaction was then quenched by addition of 250 mL of a saturated aqueous solution of NaCl. The reaction mixture was transferred to a 500 mL separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3x). The organic layers were combined and dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel, and evaporated to dryness. It resulted in a yellow translucid liquid which was directly submitted to the next step without further purification (4.95 g, 100%

63. For literature characterization data, see: Bertz, S. H., Ogle, C. A. & Rastogi, A. Remarkable effect of silyl groups on asymmetric induction in a conjugate addition reaction with *o*-Methylnorephedrine-based *N*-silylamidocuprates. *J. Am. Chem. Soc.* **127**, 1372-1373 (2005).

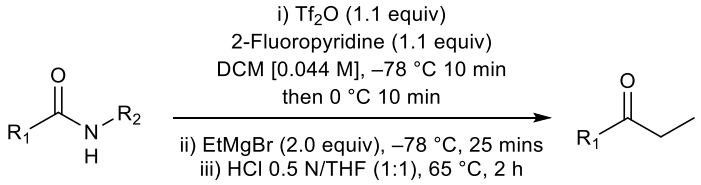
Yield). **$[\alpha]_D^{20}$**: -82.1 (*c* 1.04, EtOH), litt:[63] **$[\alpha]_D^{20}$**: -88.37 (*c* 5.43, EtOH); **R_f**: 0.50 (10% MeOH/DCM); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.39-7.27 (m, 5H), 3.93 (d, *J* = 5.5 Hz, 1H), 3.25 (s, 3H), 3.13 (app qn, *J* = 6.0 Hz, 1H), 1.18 (br s, 2H), 1.06 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 139.4, 128.6, 128.1, 128.0, 89.4, 57.4, 52.1, 19.7; **FTIR** (cm^{-1}) (neat): 3360, 2972, 2823, 1584, 1452, 1373, 1093; **HRMS** (ESI, Pos): calc. for $C_{10}H_{16}NO$ $[M+H]^+$: 166.1232 *m/z*, found: 166.1225 *m/z*.



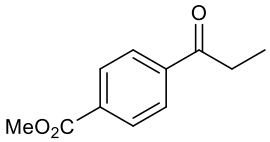
***N*-[(1*R*,2*S*)-1-Methoxy-1-phenylpropan-2-yl]2,2-dimethylpropanamide (3.4ab):** To a flame-dried and argon-flushed 100 mL round-bottom flask equipped with a stir-bar and a septum was added pivaloyl chloride (1.21 g, 1.23 mL, 10 mmol, 1.0 equiv) and it was dissolved in anhydrous DCM (25 mL, [0.4 M]). The reaction was cooled to –10 °C using an acetone/dry ice cooling bath and Et_3N (1.21 g, 1.67 mL, 12.0 mmol, 1.2 equiv) was added to the solution. Then (1*R*,2*S*)-1-methoxy-1-phenylpropan-2-amine (1.65 g, 10 mmol, 1.0 equiv) was added dropwise and the reaction was stirred from –10 °C to room temperature over night. The reaction was worked-up by evaporating the DCM on a rotavap and dissolving the residue with EtOAc (50 mL) and HCl 10% (20 mL). The biphasic mixture was transferred into a 250 mL extraction funnel. The layers were separated and the aqueous layer was extracted with EtOAc (1x). The organic layers were combined and washed with a saturated solution of $NaHCO_3$ (1x), brine (1x), dried over anhydrous magnesium sulphate ($MgSO_4$), filtered over a sintered funnel, and evaporated to dryness. The crude chiral amide was purified by flash chromatography over silica gel using a gradient of 100% Hexanes to 20% EtOAc and fractions containing **3.4ab** were concentrated to dryness. It resulted in a crystalline solid (2.11 g, 85 % Yield). **mp**: 54-55 °C; **$[\alpha]_D^{20}$**: -69.1 (*c* 1.25, $CHCl_3$); **R_f**: 0.35 (20 % EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.40-7.28 (m, 5H), 5.95 (br d, *J* = 8.0 Hz, 1H), 4.33 (d, *J* = 3.5 Hz, 1H), 4.24-4.15 (m, 1H), 3.34 (s, 3H), 1.21 (s, 9H), 0.98 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 178.0, 139.1, 128.8, 128.0, 127.1, 85.7, 58.2, 50.1, 39.0, 28.0, 14.2; **FTIR** (cm^{-1}) (neat): 3338, 2966, 2872, 2824, 1631, 1535, 1452, 1203, 1123, 1094, 1068; **HRMS** (ESI, Pos): calc. for $C_{15}H_{24}NO_2$ $[M+H]^+$: 250.1807 *m/z*, found: 250.1803 *m/z*.

Ketone synthesis (Table #2, entries 1-23, **3.3a-3.3w**):

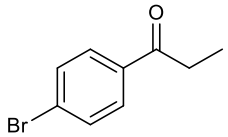
*Synthesis of ketones **3.3a-3.3c, 3.3e-3.3j, 3.3n-3.3o, 3.3q-3.3v** according to **procedure C**:*



Procedure C: To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added the amide (1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. The reaction was then cooled to –78 °C again using an acetone/dry ice cooling bath and stirred for 2 min. A solution of EtMgBr in Et_2O (Aldrich Sure-Sealed (3.0 M) solution) (670 µL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at –78 °C and the reaction was stirred for 25 min at –78 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. ***Note***: *The resulting ketones were found to be stable on the bench over several weeks at room temperature and could be stored without special precautions.*



Methyl 4-propanoylbenzoate (3.3a):[64] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 60% EtOAc/Hexanes and fractions containing **3.3a** were concentrated to dryness. The product was isolated as a white solid (185.2 mg, 96% Yield). **mp**: 75-76 °C, litt:[64b] 80-81.5 °C; $\mathbf{R_f}$: 0.55 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.12-8.09 (m, 2H), 8.01-7.98 (m, 2H), 3.94 (s, 3H), 3.02 (q, J = 7.0, 2H), 1.23 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 199.8, 165.8, 139.7, 133.3, 129.4, 127.5, 52.0, 31.8, 7.7; **FTIR** (cm^{-1}) (neat): 2937, 2844, 1719, 1677, 1434, 1278, 1219, 1194, 1109; **HRMS** (ESI, Pos): calc. for $C_{11}H_{13}O_3$ $[M+H]^+$: 193.0865, found: 193.0859 *m/z*.



1-[4-Bromophenyl]propan-1-one (3.3b):[65] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 70% EtOAc/Hexanes and fractions containing **3.3b** were concentrated to dryness. The product was isolated as crystalline white needles (155.4 mg, 74% Yield). **mp**: 43-44 °C, litt:[65] 47-48 °C; $\mathbf{R_f}$: 0.80 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.86-7.83 (m, 2H), 7.63-7.60 (m, 2H), 2.99 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.1, 136.0, 132.3, 129.9, 128.4, 32.2, 8.5; **FTIR** (cm^{-1}) (neat): 2963, 2931, 1725, 1686, 1585, 1352, 1268, 1215, 1068, 788; **HRMS** (ESI, Pos): calc. for $C_9H_{10}OBr$ $[M+H]^+$: 212.9915 and 214.9894 *m/z*, found: 212.9901 and 214.9890 *m/z*.

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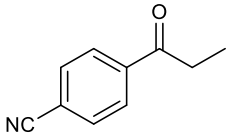
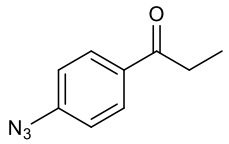
64. For literature characterization data, see: (a) Liu, M., Hyder, Z., Sun, Y., Tang, W., Xu, L & Xiao, J. Efficient synthesis of alkyl aryl ketones & ketals *via* palladium-catalyzed regioselective arylation of vinyl ethers. *Org. Biomol. Chem.* **8**, 2012-2015 (2010). (b) Gangjee, A., Zeng, Y., McGuire, J. J. & Kisliuk, R. L. Synthesis of *N*-[4-[1-ethyl-2-(2,4-diaminofuro[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid as an antifolate. *J. Med. Chem.* **45**, 1942-1948 (2002).

65. For literature characterization data, see: Scheiper, B., Bonnekessel, M., Krause, H. & Fürstner, A. Selective iron-catalyzed cross-croupling of Grignard reagents with enol triflates, acid chlorides, and dichloroarenes. *J. Org. Chem.* **69**, 3943-3949 (2004).

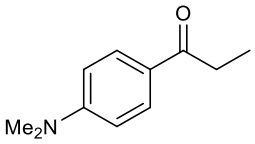


4-Propanoylbenzonitrile (3.3c):[66] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3c** were concentrated to dryness. The product was isolated as a beige solid (147.2 mg, 92% Yield). **mp**: 56-57 °C; $\mathbf{R_f}$: 0.45 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.08-8.04 (m, 2H), 7.80-7.76 (m, 2H), 3.04 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 198.9, 139.4, 132.1, 128.0, 117.6, 115.8, 31.8, 7.6; **FTIR** (cm^{-1}) (neat): 2982, 2227, 1687, 1458, 1400, 1379, 1215, 1081; **HRMS** (ESI, Pos): calc. for $C_{10}H_{10}ON$ $[M+H]^+$: 160.0762, found: 160.0752 *m/z*.

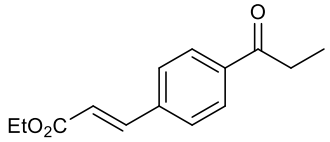


1-(4-Azidophenyl)propan-1-one (3.3e): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3e** were concentrated to dryness. The product was isolated as a gummy orange solid (124.9 mg, 72% Yield). **mp**: 30-31 °C; $\mathbf{R_f}$: 0.70 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.01-7.98 (m, 2H), 7.13-7.09 (m, 2H), 2.99 (q, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 199.6, 145.1, 134.0, 130.3, 119.4, 32.1, 8.6; **FTIR** (cm^{-1}) (neat): 2933, 2091, 1678, 1597, 1281, 1220, 1177; **HRMS** (APCI, Pos): calc. for $C_9H_{10}ON_3$ $[M+H]^+$: 176.0824, found: 176.0821 *m/z*.

66. For literature characterization data, see: Zimbron, J. M., Seeger-Weibel, M., Hirt, H. & Gallou, F. Developpement of a robust and practical process for the Darzens condensation and α-β-epoxide rearrangement: scope and limitations of the methodology. *Synthesis* 1221-1226 (2008).

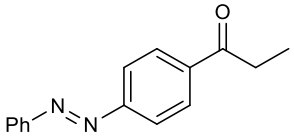


1-[4-(Dimethylamino)phenyl]propan-1-one (3.3f):[67] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 70% EtOAc/Hexanes and fractions containing **3.3f** were concentrated to dryness. The product was isolated as a yellow solid (127.6 mg, 72% Yield). **mp**: 90-92 °C; litt:[67] 94-95 °C; $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.93-7.89 (m, 2H), 6.70-6.65 (m, 2H), 3.08 (s, 6H), 2.93 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 198.8, 152.9, 129.8, 124.6, 110.3, 39.7, 30.6, 8.5; **FTIR** (cm^{-1}) (neat): 2923, 1656, 1594, 1522, 1411, 1231, 1186; **HRMS** (ESI, Pos): calc. for $C_{11}H_{16}ON$ $[M+H]^+$: 178.1232, found: 178.1220 *m/z*.

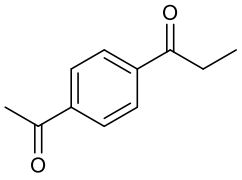


Ethyl (2*E*)-3-(4-propanoylphenyl)prop-2-enoate (3.3g): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 70% EtOAc/Hexanes and fractions containing **3.3g** were concentrated to dryness. The product was isolated as an off-white solid (195.1 mg, 84% Yield). **mp**: 85-86 °C; $\mathbf{R_f}$: 0.55 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 16.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 2H), 6.50 (dd, *J* = 1.5 Hz, 16.5 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 2.99 (q, 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.3, 166.9, 143.4, 139.0, 138.2, 128.9, 128.5, 121.1, 61.1, 32.3, 14.7, 8.5; **FTIR** (cm^{-1}) (neat): 2980, 1702, 1678, 1631, 1315, 1221, 1174; **HRMS** (ESI, Pos): calc. for $C_{15}H_{15}ON_2$ $[M+H]^+$: 233.1178, found: 233.1174 *m/z*.

67. For literature characterization data, see: Cosner, C. C., Cabrera, P. J., Byrd, K. M., Thomas, A. M. A. & Helquist, P. Selective oxidation of benzylic and allylic alcohol using $Mn(OAc)_3$/catalytic 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. *Org. Lett.* **13**, 2071-2073 (2011).

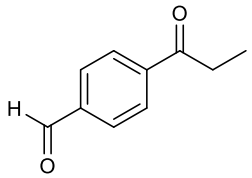


1-{4-[(*E*)-Phenyldiazenyl]phenyl}propan-1-one (3.3h): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 60% EtOAc/Hexanes and fractions containing **3.3h** were concentrated to dryness. The product was isolated as a red solid (170.4 mg, 72% Yield). **mp**: 76-77 °C; $\mathbf{R_f}$: 0.70 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.16-8.12 (m, 2H), 8.01-7.96 (m, 4H), 7.59-7.52 (m, 3H), 3.12-3.05 (m, 2H), 1.31-1.27 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 199.8, 154.6, 152.2, 137.9, 131.4, 128.8, 128.7, 122.8, 122.5, 31.7, 7.9; **FTIR** (cm^{-1}) (neat): 2974, 2931, 1685, 1405, 1211; **HRMS** (ESI, Pos): calc. for $C_{15}H_{15}ON_2$ $[M+H]^+$: 239.1184, found: 239.1182 *m/z*.

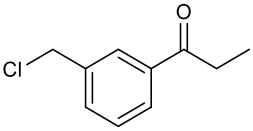


1-(4-Acetylphenyl)propan-1-one (3.3i):[68] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3i** were concentrated to dryness. The product was isolated as a white solid (107.2 mg, 61% Yield). **mp**: 67-68 °C, litt:[68] 71-72 °C; $\mathbf{R_f}$: 0.40 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.04 (s, 4H), 3.05 (q, J = 7.0 Hz, 2H), 2.66 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 199.8, 197.1, 139.7, 139.6, 128.1, 127.8, 31.9, 26.5, 7.7; **FTIR** (cm^{-1}) (neat): 2972, 1672, 1459, 1405, 1263, 1218; **HRMS** (ESI, Pos): calc. for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0916, found: 177.0907 *m/z*.

68. For characterization data, see: Sato, N.; Narita, N. Studies on pyrazine; 38: Acylation of bromopyrazines and 2-bromopyridine *via* copper-cocatalytic Stille reaction. *Synthesis* 1551-1555 (2001).

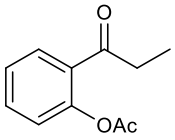


4-Propanoylbenzaldehyde (3.3j): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3j** were concentrated to dryness. The product was isolated as a yellow solid (10.0 mg, 6% Yield). **mp**: 62-63 °C; $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 10.02 (s, 1H), 8.03-8.01 (m. 2H), 7.90-7.88 (m, 2H), 2.98 (q, *J* = 7.0 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.4, 191.2, 141.4, 139.3, 130.1, 128.8, 32.6, 8.3; **FTIR** (cm^{-1}) (neat): 2979, 2844, 1681, 1373, 1355, 1307, 1215, 1201; **HRMS** (ESI, Pos): calc. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163.0759, found: 163.0747 *m/z*.

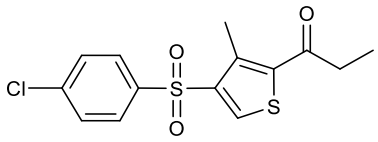


1-[3-(Chloromethyl)phenyl]propan-1-one (3.3n):[69] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 70% EtOAc/Hexanes and fractions containing **3.3n** were concentrated to dryness. The product was isolated as a translucid liquid (160.1 mg, 88% Yield). $\mathbf{R_f}$: 0.70 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 4.62 (s, 2H), 3.00 (q, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.7, 138.4, 137.8, 133.3, 129.5, 128.4, 128.4, 46.0, 32.3, 8.6; **FTIR** (cm^{-1}) (neat): 2978, 1683, 1445, 1242, 1165, 786; **HRMS** (ESI, Pos): calc. for $C_{10}H_{14}OCl$ $[M+H]^+$: 183.0577 *m/z*, found: 183.0566 *m/z*.

69. For literature characterization data, see: Metzger, A., Schade, M. A. & Knochel, P. LiCl-Mediated preparation of highly functionalized benzylic zinc chlorides. *Org. Lett.* **10**, 1107-1110 (2008).

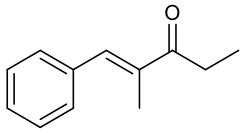


2-Propanoylphenyl acetate (3.3o):[70] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 50% EtOAc/Hexanes and fractions containing **3.3o** were concentrated to dryness. The product was isolated as translucid oil (107.0 mg, 55% Yield). $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.78 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.51 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.03 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.11 (dd, *J* = 1.0, 8.0 Hz, 1H), 2.90 (q, *J* = 7.0 Hz, 2H), 2.34 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 201.1, 169.9, 149.2, 133.4, 131.2, 130.1, 126.4, 124.2, 34.9, 21.5, 8.5; **FTIR** (cm^{-1}) (neat): 2980, 1760, 1687, 1603, 1447, 1367, 1181; **HRMS** (ESI, Pos): calc. for $C_{11}H_{12}O_3Na$ $[M+Na]^+$: 215.0684, found: 215.0682 *m/z*.

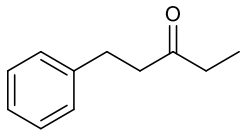


1-{4-[(4-Chlorophenyl)sulfonyl]-3-methylthiophen-2-yl}propan-1-one (3.3q): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 70% EtOAc/Hexanes and fractions containing **3q** were concentrated to dryness. The product was isolated as a white solid (320.0 mg, 98% Yield). **mp**: 135-136 °C; $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H), 7.87-7.83 (m, 2H), 7.52-7.49 (m, 2H), 2.84 (q, *J* = 7.0 Hz, 2H), 2.56 (s, 3H), 1.81 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.3, 142.2, 141.4, 140.7, 139.8, 139.4, 136.2, 130.1, 129.6, 35.9, 14.7, 8.5; **FTIR** (cm^{-1}) (neat): 2973, 2844, 1671, 1318, 1150; **HRMS** (ESI, Pos): calc. for $C_{14}H_{14}O_3S_2Cl$ $[M+H]^+$: 329.0073, found: 329.0074 *m/z*.

70. For literature characterization data, see: Wang, W.-J., Zhang, L., Sun, X., Xu, Y., Krishnamurthy, D. & Senanayake, C. H. Addition of Grignard reagents to aryl acid chlorides: an efficient synthesis of aryl ketones. *Org. Lett.* **7**, 5593-5595 (2005).



(4*E*)-4-Methylhex-4-en-3-one (3.3r):[71] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 40% EtOAc/Hexanes and fractions containing **3.3r** were concentrated to dryness. The product was isolated as a translucid liquid (165.0 mg, 95% Yield). $\mathbf{R_f}$: 0.85 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.55 (s, 1H), 7.49-7.32 (m, 5H), 2.86 (q, *J* = 7.0 Hz, 2H), 2.09 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 202.6, 137.8, 136.8, 135.7, 129.3, 128.1, 128.0, 30.4, 12.8, 8.5; **FTIR** (cm^{-1}) (neat): 2973, 1665, 1625, 1491, 1363, 1206; **HRMS** (ESI, Pos): calc. for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123, found: 175.1116 *m/z*.



1-Phenylpentan-3-one (3.3s):[72] Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 60% EtOAc/Hexanes and fractions containing **3.3s** were concentrated to dryness. The product was isolated as a translucid liquid (136.0 mg, 84% Yield). $\mathbf{R_f}$: 0.80 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.28 (m, 2H), 7.24-7.19 (m, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.43 (q, *J* = 7.0 Hz, 2H), 1.07 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 210.3, 140.8, 128.1, 127.9, 125.7, 43.5, 35.8, 29.5, 7.4; **FTIR** (cm^{-1}) (neat): 2978, 1683, 1444, 1351, 1242, 1165; **HRMS** (ESI, Pos): calc. for $C_{11}H_{15}O$ $[M+H]^+$: 163.1123, found: 163.1113 *m/z*.

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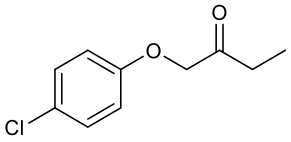
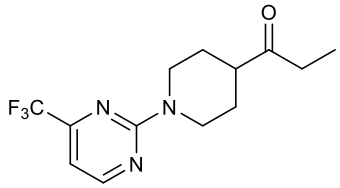
71. For literature characterization data, see: Maji, T., Karma, A., Reiser, O. Visible-light photoredox catalysis: dehalogenation of vicinal dibromo-, α-halo, and α-α-dibromocarbonyl compounds. *J. Org. Chem.* **76**, 736-739 (2011).

72. For literature characterization data, see: Kakusawa, N., Yasuike, S. & Kurita, J. Rhodium-catalyzed conjugate addition of Sb-aryl-1,5-azastibocines to α,β-unsaturated carbonyl compounds. *Heterocycles* **77**, 1269-1283 (2009).

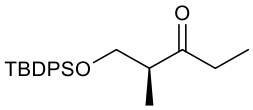


1-(4-Chlorophenoxy)butan-2-one (3.3t): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 60% EtOAc/Hexanes and fractions containing **3.3t** were concentrated to dryness. The product was isolated as a translucid liquid (172.7 mg, 87% Yield). $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.28-7.24 (m, 2H), 6.85-6.80 (m, 2H), 4.55 (s, 2H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.12 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 208.1, 156.9, 130.0, 127.0, 116.3, 73.2, 32.8, 7.5; **FTIR** (cm^{-1}) (neat): 2938, 1719, 1490, 1288, 1244, 823; **HRMS** (ESI, Pos): calc. for $C_{10}H_{12}OCl$ $[M+H]^+$: 199.0526, found: 199.0517 *m/z*.

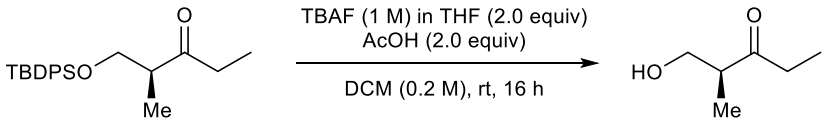
Note: The reaction perfomed on a 13.5 mmol scale of **3.4t** gave the desired ketone **3.3t** in a similar yield (2.250 g, 84% Yield).



1-{1-[4-(Trifluoromethyl)pyrimidin-2-yl]piperidin-4-yl}propan-1-one (3.3u): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 10% EtOAc/Hexanes to 100% EtOAc and fractions containing **3.3u** were concentrated to dryness. The product was isolated as a white powder (275.0 mg, 96% Yield). **mp**: 57-59 °C; $\mathbf{R_f}$: 0.45 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.49 (d, *J* = 5.0 Hz, 1H), 6.75 (d, *J* = 5.0 Hz, 1H), 4.81 (dt, *J* = 3.0, 13.0 Hz, 2H), 3.03 (ddd, *J* = 3.0, 12.5, 13.5 Hz, 2H), 2.65 (tt, *J* = 3.5, 11.0 Hz, 1H), 2.53 (q, *J* = 7.5 Hz, 2H), 1.97-1.91 (m, 2H), 1.69-1.59 (m, 2H), 1.09 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 212.4, 161.0, 159.7, 155.9 (q, *J* = 35.1 Hz, $J_{C\text{-}F}$), 120.2 (q, *J* = 284.9 Hz, $J_{C\text{-}F}$), 104.0 (q, *J* = 2.7 Hz, $J_{C\text{-}F}$), 48.1, 43.0, 33.4, 27.1, 7.3; **^{19}F NMR** ($CDCl_3$, 375.5 MHz): d –71.3; **FTIR** (cm^{-1}) (neat): 2939, 1702, 1590, 1439, 1325, 1131; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}OF_3N_3$ $[M+H]^+$: 288.1324, found: 288.1319 *m/z*.



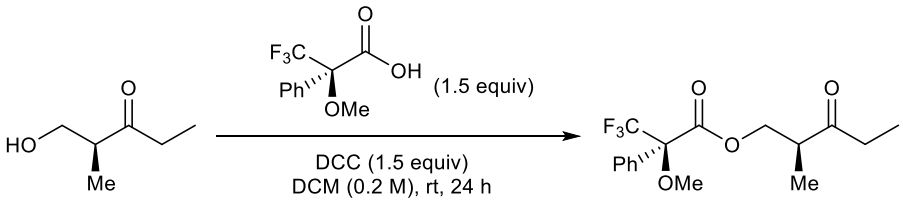
(2S)-1-{(tert-butyl(diphenyl)silyl}oxy-2-methylpentan-3-one (3.3v): Following **procedure C**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 50% EtOAc/Hexanes and fractions containing **3.3v** were concentrated to dryness. The product was isolated as a translucid liquid (352.1 mg, 94% Yield). SFC analysis of the product on a chiral stationary phase did not resolved the enantiomers in two clear and separated peaks; $[\alpha]_D^{20}$: +27.8 (*c* 1.43, $CHCl_3$), R_f: 0.80 (20 % EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.72-7.69 (m, 4H), 7.50-7.41 (m, 6H), 3.87 (dd, *J* = 7.5, 9.5 Hz, 1H), 3.71 (dd, *J* = 5.5 Hz, 9.5 Hz, 1H), 2.93-2.85 (m, 1H), 2.68-2.50 (m, 2H), 1.13-1.06 (m, 15H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 215.1, 136.0, 135.9, 133.9, 133.7, 130.2 (2), 128.2 (2), 66.8, 48.7, 36.2, 27.2, 19.6, 13.5, 8.0; **FTIR** (cm^{-1}) (neat): 2936, 2860, 1714, 1472, 1427, 1388, 1110; **HRMS** (ESI, Pos): calc. for $C_{22}H_{30}NaO_2Si$ $[M+Na]^+$: 377.1913 *m/z*, found: 377.1914 *m/z*.



(2*S*)-1-Hydroxy-2-methylpentan-3-one:[73] To a flame-dried 50 mL round bottom flask was added (2*S*)-1-{(*tert*-butyl(diphenyl)silyl}oxy-2-methylpentan-3-one (225 mg, 0.635 mmol, 1.0 equiv). The ketone was dissolved in anhydrous DCM (3.17 mL, [0.2 M]) and the solution was cooled to 0 °C. AcOH (76.2 mg, 73 µL, 1.270 mmol, 2.0 equiv) and TBAF 1.0 M in THF (1.27 mL, 1.270 mmol, 2.0 equiv) were added successively to the reaction and the reaction was warmed to rt over 16 hours. The reaction was quenched by addition of 8 mL of a saturated aqueous solution of $NaHCO_3$ and transferred to a 125 mL separatory funnel. The layers were separated and the aqueous extracted with DCM (3x). The organic layers were combined and washed with brine (1x), dried over Na_2SO_4, filtered and evaporated to dryness. The crude oil

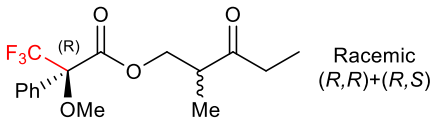
73. For literature characterization data and procedure for the synthesis of Mosher's ester, see: Calter, M. A. Catalytic, asymmetric dimerization of methylketene *J. Org. Chem.* **61**, 8006-8007 (1996).

was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 0% to 90% EtOAc/Hexanes and fractions containing the pure alcohol were concentrated to dryness. The product was isolated as a yellow liquid (51 mg, 70% Yield). $\mathbf{[\alpha]_D^{20}}$: -20.3 (*c* 1.36, $CHCl_3$), litt (for alcohol at 98% ee):[73] $\mathbf{[\alpha]_D^{20}}$: -19.3 (*c* 0.85, $CHCl_3$) and -22.0 (*c* 0.85, $CHCl_3$); $\mathbf{R_f}$: 0.20 (30 % EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.74 (dd, *J* = 7.0, 11.0 Hz, 1H), 3.64 (dd, *J* = 4.0, 11.0 Hz, 1H), 2.80-2.72 (m, 1H), 2.62-2.43 (m, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 216.0, 64.8, 48.2, 35.2, 13.7, 7.9; **FTIR** (cm^{-1}) (neat): 3440, 1710, 1605, 1445, 1309; **HRMS** (ESI, Pos): calc. for $C_6H_{13}O_2$ $[M+H]^+$: 117.0916 *m/z*, found: 117.0911 *m/z*.



(2*S*)-2-methyl-3-oxopentyl-(2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate:[73] To a 20 mL glass vial equipped with a plastic stopper and a small stir bar was added (2*S*)-1-hydroxy-2-methylpentan-3-one (40 mg, 0.344 mmol, 1.0 equiv). The oil was dissolved in anhydrous DCM (6.8 mL, (0.05 M)). Then, (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (99%+) (120.8 mg, 0.516 mmol, 1.5 equiv), DCC (106.4 mg, 0.516 mmol, 1.5 equiv), and DMAP (4.1 mg, 0.034 mmol, 0.1 equiv) were added successively to the reaction at room temperature. The reaction was then stirred for 24 hours at room temperature. The reaction was worked up by evaporating the DCM under reduced pressure and by adding Et_2O to the residue. The suspension was then filtered on a pad of silica gel (~3cm) with Et_2O and EtOAc and the filtrate was evaporated to dryness.

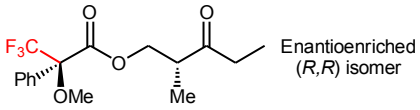
The analysis of the crude (*R,R*) Mosher's ester by ^{1}H NMR (not well resolved) and by ^{19}F NMR (resolved) permited to calculate a ee% value of >93% (see attached Spectra).



Racemic
(*R,R*)+(*R,S*)

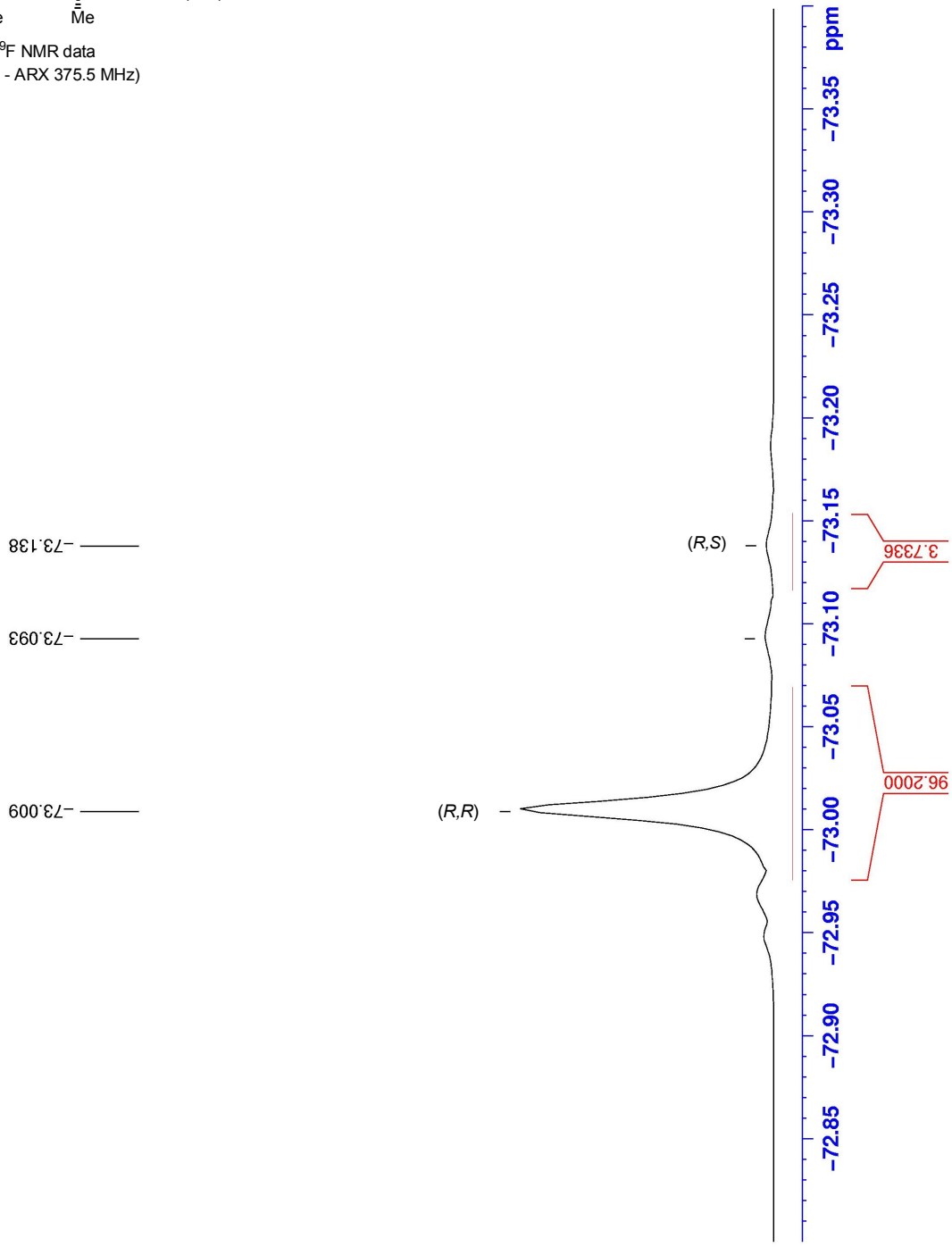
^{19}F NMR data
($CDCl_3$ - ARX 375.5 MHz)

ppm
-72.85
-72.90
-72.95
-73.00
-73.05
-73.10
-73.15
-73.20
-73.25
-73.30
-73.35
50.0000
50.7050
(R,R)
(R,S)
-73.010
-73.095
-73.137

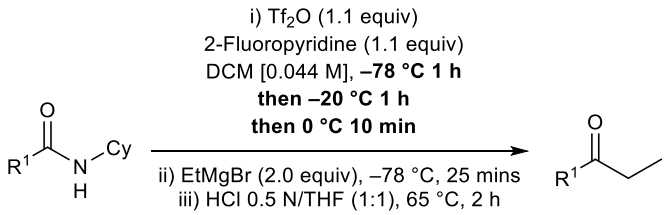


Enantioenriched
(*R*,*R*) isomer

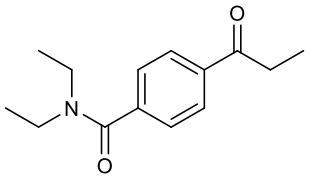
^{19}F NMR data
($CDCl_3$ - ARX 375.5 MHz)



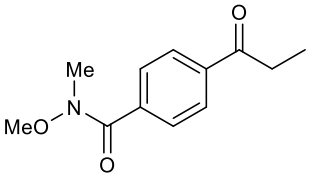
*Synthesis of ketones **3.3k**, **3.3l**, and **3.3p** by chemoselective and slow activation of amides **3.4k**, **3.4l**, and **3.4p** at –20 °C (Procedure D)*



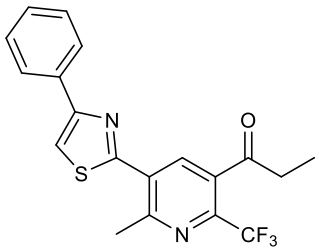
Procedure D: To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added the amide (1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 1 hour. The solution was slowly warmed to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred to –20 °C for 1 hour. Then, the solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. The reaction was then cooled to –78 °C again using an acetone/dry ice cooling bath and stirred for 2 min. A solution of EtMgBr in Et_2O (Aldrich Sure-Sealed (3.0 M) solution) (670 μL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at –78 °C and the reaction was stirred for 25 min at –78 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness.



***N*,*N*-Diethyl-4-propanoylbenzamide (3.3k) :** Following **procedure D**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 30% EtOAc/Hexanes to 100% EtOAc and fractions containing **3.3k** were concentrated to dryness. The product was isolated as a crystalline white solid (219.0 mg, 94% Yield). **mp**: 82-83 °C; $\mathbf{R_f}$: 0.10 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 3.56 (br q, *J* = 5.5 Hz, 2H), 3.22 (br q, *J* = 5.5 Hz, 2H), 3.01 (q, *J* = 7.0 Hz, 2H), 1.31-1.06 (m, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.6, 170.6, 141.9, 137.6, 128.6, 126.9, 43.6, 39.7, 32.3, 14.6, 13.3, 8.6; **FTIR** (cm^{-1}) (neat): 2972, 1681, 1622, 1405, 1345, 1283, 1223; **HRMS** (ESI, Pos): calc. for $C_{14}H_{20}O_2N$ $[M+H]^+$: 234.1494, found: 234.1488 *m/z*.

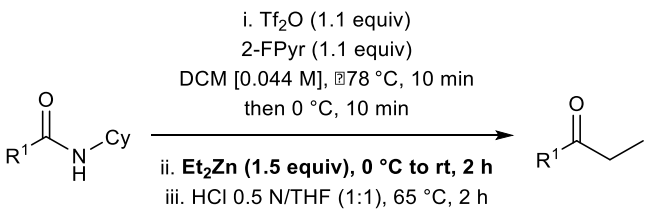


***N*-Methoxy-*N*-methyl-4-propanoylbenzamide (3.3l):** Following **procedure D**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 20% EtOAc/Hexanes to 100% EtOAc and fractions containing **3.3l** were concentrated to dryness. The product was isolated as a white powder (191.7 mg, 87% Yield). **mp**: 77-78 °C; $\mathbf{R_f}$: 0.15 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 3.56 (s, 3H), 3.40 (s, 3H), 3.05 (q, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.7, 169.4, 138.6, 128.7, 128.0, 61.6, 33.8, 32.4, 8.5; **FTIR** (cm^{-1}) (neat): 2975, 1686, 1653, 1362, 1216, 1110; **HRMS** (ESI, Pos): calc. for $C_{12}H_{16}O_3N$ $[M+H]^+$: 222.1130, found: 222.1125 *m/z*.

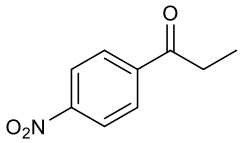


1-[6-methyl-5-(4-phenyl-1,3-thiazol-2-yl)-2-(trifluoromethyl)pyridin-3-yl]propan-1-one (3.3p): Following **procedure D**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 50% EtOAc/Hexanes and fractions containing **3.3p** were concentrated to dryness. The product was isolated as a white solid (368.9 mg, 99% Yield). **mp**: 127-128 °C; $\mathbf{R_f}$: 0.60 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 8.01-7.98 (m, 2H), 7.72 (s, 1H), 7.52-7.47 (m, 2H), 7.44-7.39 (m, 1H), 3.04 (s, 3H), 2.94 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.2, 162.9, 157.8, 157.2, 142.9 (q, J = 35.1 Hz, $J_{C\text{-}F}$), 136.5, 134.5, 134.1, 131.4, 129.3, 129.2, 121.6 (q, J = 274.1 Hz, $J_{C\text{-}F}$), 115.4, 37.4, 25.3, 8.2; **^{19}F NMR** ($CDCl_3$, 375.5 MHz): d –63.8; **FTIR** (cm^{-1}) (neat): 3109, 2987, 1701, 1681, 1650, 1523, 1440, 1386, 1316, 1262, 1223, 1177; **HRMS** (ESI, Pos): calc. for $C_{19}H_{16}F_3ON_2S$ $[M+H]^+$: 377.0935, found: 377.0942 *m/z*.

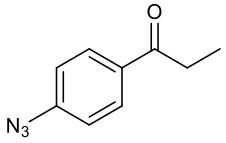
*Synthesis of ketones **3.3d**, **3.3e**, **3.3i**, **3.3j**, and **3.3o** according to **procedure E**:*



Procedure E: To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added the amide (1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. Neat Et_2Zn (AkzoNobel) (185.3 mg, 154 µL, 1.5 mmol, 1.5 equiv) was added in one portion to the reaction at 0 °C using a gaz tight syringe. The reaction was warmed to room temperature and the reaction was stirred for 2 hours at room temperature. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. ***Note***: *Caution: Manipulation of neat Et_2Zn should be performed with careful attention and exclusion of moisture and air in flasks, syringes and needles. Neat Et_2Zn is extremely pyrophoric under air and moisture.*

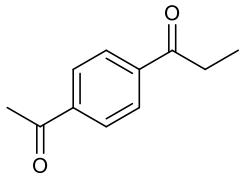


1-(4-Nitrophenyl)propan-1-one (3.3d):[74] Following **procedure E**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3d** were concentrated to dryness. The product was isolated as an off-white solid (111.0 mg, 62% Yield). **mp**: 81-82 °C, litt:[74] 86 °C; R_f: 0.60 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.35-8.30 (m, 2H), 8.15-8.10 (m, 2H), 3.07 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 198.9, 151.1, 142.2, 129.8, 124.7, 33.3, 8.7; **FTIR** (cm^{-1}) (neat): 2918, 2855, 1685, 1600, 1518, 1339, 1318, 1209; **HRMS** (ESI, Pos): calc. for $C_9H_{10}O_3N$ $[M+H]^+$: 180.0661, found: 180.0662 *m/z*.

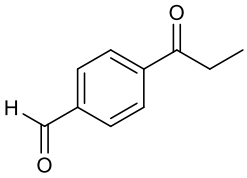


1-(4-Azidophenyl)propan-1-one (3.3e): Following **procedure E**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3e** were concentrated to dryness. The product was isolated as a gummy orange solid (139.8 mg, 80% Yield). **Note**: *See procedure C for characterization data of compound **3.3e**.*

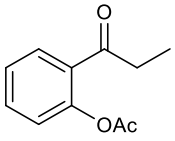
74. For literature characterization data, see: Jean, M., Renault, J., Uriac, P., Capet, M. & van de Weghe, P. Unexpected formation of aryl ketones by palladium-catalyzed coupling of aryl bromides with vinlic acetates. *Org. Lett.* **9**, 3623-3625 (2007).



1-(4-Acetylphenyl)propan-1-one (3.3i):[68] Following **procedure E**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3i** were concentrated to dryness. The product was isolated as a white solid (140.1 mg, 79% Yield). **Note**: *See procedure C for characterization data of compound **3.3i***

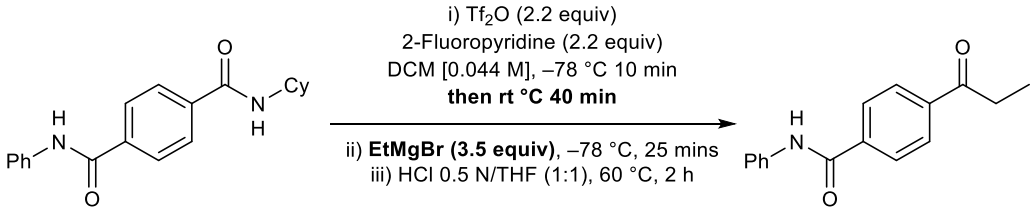


4-Propanoylbenzaldehyde (3.3j): Following **procedure E**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 24g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3j** were concentrated to dryness. The product was isolated as a yellow solid (130.0 mg, 80% Yield). **Note**: *See procedure C for characterization data of compound **3.3j***.



2-Propanoylphenyl acetate (3.3o):[70] Following **procedure E**, the crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 50% EtOAc/Hexanes and fractions containing **3.3o** were concentrated to dryness. The product was isolated as translucid oil (144.9 mg, 75% Yield). **Note**: *See procedure C for characterization data of compound **3.3o***.

*Synthesis of ketone **3.3m** by double activation of amide **3.4m** and addition of 3.5 equivalents of EtMgBr*

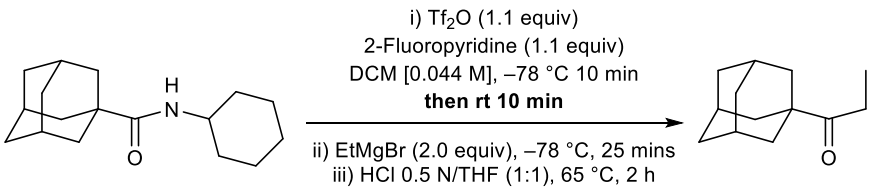


(Table 1, entry 13)

***N*-Phenyl-4-propanoylbenzamide (3.3m) :** To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added *N*-Cyclohexyl-*N'*-phenylterephtalamide (**3.4m**) (322.4 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (213.5 mg, 190 µL, 2.2 mmol, 2.2 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (620.2 mg, 370 µL, 2.2 mmol, 2.2 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to rt and the reaction was stirred for 40 min. The reaction was then cooled to –78 °C again using an acetone/dry ice cooling bath and stirred for 2 min. A solution of EtMgBr in Et_2O (Aldrich Sure-Sealed (3.0 M) solution) (1.17 mL, 3.5 mmol, 3.5 equiv) was added in one portion to the reaction at –78 °C and the reaction was stirred for 25 min at –78 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone **3.3m**. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 90% EtOAc/Hexanes and fractions containing **3.3m** were concentrated to dryness. The product was isolated as a yellow solid (153.0 mg, 60% Yield). **mp**: 166-168 °C; $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.12-8.08 (m, 2H), 8.00-7.97 (m, 2H),

7.83 (s, 1H), 7.67 (d, J = 7.5 Hz, 2H), 7.45-7.40 (m, 2H), 7.21 (tt, J = 1.0, 7.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.5, 165.2, 139.7, 139.1, 138.0, 129.6, 128.8, 127.8, 125.3, 120.7, 32.6, 8.5; **FTIR** (cm^{-1}) (neat): 3340, 2935, 1681, 1650, 1599, 1523, 1438, 1354, 1321, 1309, 1251; **HRMS** (ESI, Pos): calc. for $C_{16}H_{15}O_2N$ $[M+H]^+$: 254.1181, found: 254.1180 *m/z*.

*Synthesis of ketones **3.3w** from amide **3.4w** with Tf_2O activation at a higher temperature:*



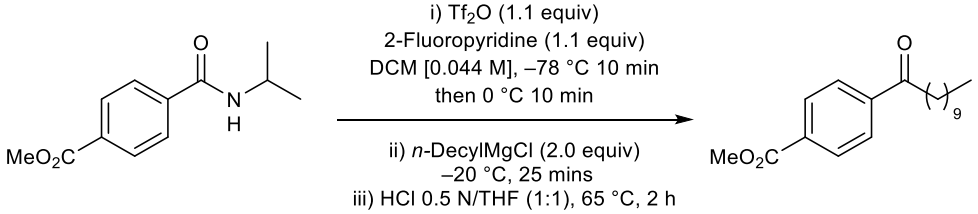
1-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)propan-1-one (3.3w):[(75)] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added **3.4w** (261.2 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to room temperature and the reaction was stirred for 10 min. The reaction was then cooled to –78 °C again using an acetone/dry ice cooling bath and stirred for 2 min. A solution of EtMgBr in Et_2O (Aldrich Sure-Sealed (3.0 M) solution) (670 μL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at –78 °C and the reaction was stirred for 25 min at –78 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by

75. For literature characterization data, see: Qin, X.-r.; Ishizuka, Y.; Lomas, J. S.; Tezuka, T.; Nakanishi, H. ^{17}O, ^{13}C, and ^{1}H NMR and IR spectral study of crowded ketones: possible intramolecular C–H···O interactions. *Magn. Reson. Chem.* **40**, 595-598 (2002).

flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 20% EtOAc/Hexanes and fractions containing **3.3w** were concentrated to dryness. The product was isolated as a translucid liquid (143.2 g, 75% Yield). $\mathbf{R_f}$: 0.90 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.46 (q, *J* = 7.0 Hz, 2H), 2.06-2.00 (m, 3H), 1.83-1.65 (m, 12H), 0.99 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 215.9, 46.6, 38.7, 37.0, 29.5, 28.4, 8.3; **FTIR** (cm^{-1}) (neat): 2903, 2850, 1701, 1452, 1378, 1346, 1169; **HRMS** (ESI, Pos): calc. for $C_{13}H_{21}O$ $[M+H]^+$: 193.1592, found: 193.1582 *m/z*.

Ketone synthesis (Table #3, entries 1-15, **3.3x-3.3al**):

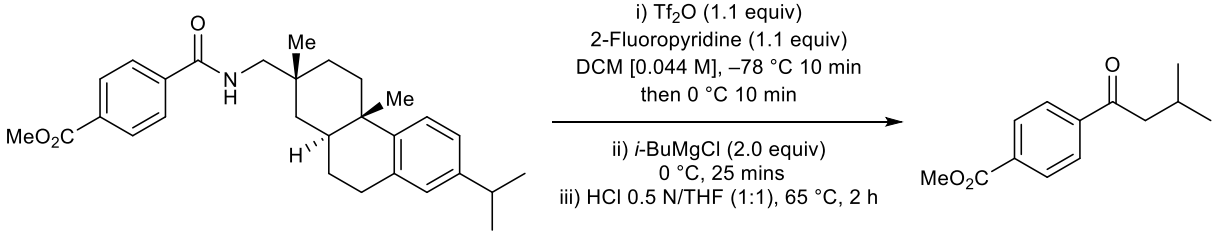
*Synthesis of methyl 4-undecanoylbenzoate (**3.4x**) by addition of n-decylmagnesium bromide solution to activated methyl 4-[(isopropylamino)carbonyl]benzoate (**3.3x**)*



Methyl 4-undecanoylbenzoate (3.3x): To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added methyl 4-[(isopropylamino)carbonyl]benzoate (**3.4x**) (221.1mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. The reaction was then cooled to –20 °C using *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred for 2 min. A solution of *n*-DecylMgCl in Et_2O (solution titrated at 0.80 M) (2.5 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at –20 °C and the reaction was stirred for 25 min at –20 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was warmed to 50 °C for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 60% EtOAc/Hexanes and fractions containing **3.3x** were concentrated to dryness. The product was isolated as a white solid (261.0 mg, 86% Yield). **mp**: 93-94 °C; $\mathbf{R_f}$: 0.65 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.15-8.12 (m, 2H), 8.03-8.00 (m, 2H), 3.97

(s, 3H), 3.00 (t, J = 7.5 Hz, 2H), 1.76 (qn, J = 7.5 Hz, 2H), 1.42-1.21 (m, 14H), 0.90 (t, J = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.5, 166.7, 140.7, 134.7, 134.1, 130.2., 128.3, 52.8, 39.4, 32.3, 30.0, 29.9 (2), 29.7 (2), 24.6, 23.1, 14.5; **FTIR** (cm^{-1}) (neat): 2916, 2847, 1721, 1679, 1463, 1281, 1111; **HRMS** (ESI, Pos): calc. for $C_{19}H_{29}O_3$ $[M+H]^+$: 305.2119, found: 305.2113 *m/z*.

*Synthesis of methyl 4-(3-methylbutanoyl)benzoate (**3.3y**) by addition of isobutylmagnesium chloride solution to activated methyl 4-[({[(2R,4aS,10aS)-7-isopropyl-2,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2 yl]methyl}amino) carbonyl]benzoate (**3.4y**)*

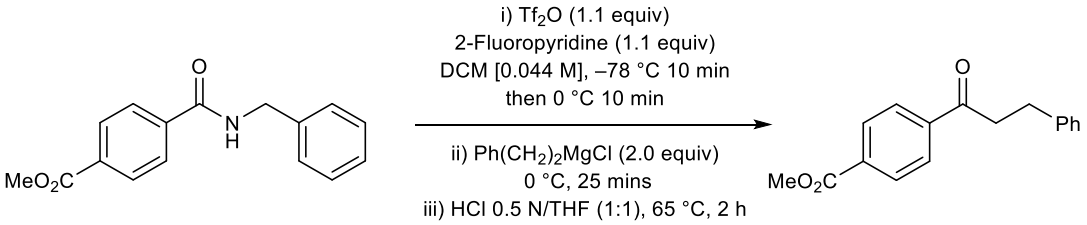


Methyl 4-(3-methylbutanoyl)benzoate (3.3y):[76] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4y** (447.3 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of *i*-BuMgCl in Et_2O (solution titrated at 2.31M) (866 μL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture

76. For literature characterization data, see: Sumida, Y., Takada, Y., Hayashi, S., Hirano, K., Yorimitsu, H. & Oshima, K. Rhodium-catalyzed allylation of aldehydes with homoallylic alcohols by retroallylation and isomerization to saturated ketones with conventional of microwave heating. *Chem. Asian J.* **3**, 119-125 (2008).

was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3y** were concentrated to dryness. The product was isolated as a off-white crystalline solid (205.5 mg, 94% Yield). **mp**: 37-38 °C; $\mathbf{R_f}$: 0.60 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.15-8.11 (m, 2H), 8.03-7.99 (m, 2H), 3.97 (s, 3H), 2.87 (d, *J* = 7.0 Hz, 2H), 2.32 (app h, *J* = 7.0 Hz, 1H), 1.02 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.1, 166.7, 141.0, 134.1, 130.2, 128.4, 52.8, 48.2, 25.4, 23.1; **FTIR** (cm^{-1}) (neat): 2954, 1721, 1682, 1465, 1406, 1364, 1274, 1209, 1106; **HRMS** (ESI, Pos): calc. for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1178, found: 221.1171 *m/z*.

*Synthesis of methyl 4-(3-phenylpropanoyl)benzoate (**3.3z**) by addition of phenethylmagnesium bromide solution to activated methyl 4-[(benzylamino)carbonyl]benzoate (**3.3z**)*

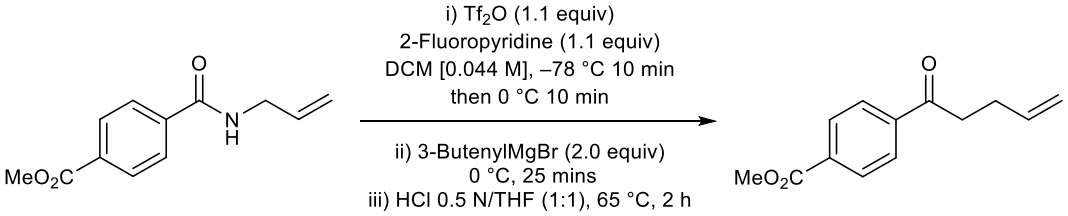


Methyl 4-(3-phenylpropanoyl)benzoate (3.3z):[77] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4z** (269.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution

77. For literature characterization data, see: Tatamidani, H., Yokota, K., Kakiuchi, F. & Chatani, N. Catalytic cross-coupling reaction of esters with organoboron compounds and decarbonylative reduction of esters $HCOONH_4$: A new route to acyl transition metal complexes through the cleavage of acyl-oxygen bonds in esters. *J. Org. Chem.* **69**, 5615-5621 (2004).

of $Ph(CH_2)_2MgCl$ in Et_2O (solution titrated at 1.57M)[78,79] (1.27 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 60% EtOAc/Hexanes and fractions containing **3.3z** were concentrated to dryness. The product was isolated as off-white to yellow solid (240.1 mg, 90% Yield). **mp**: 79-81 °C; $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.14-8.11 (m, 2H), 8.02-8.00 (m, 2H), 7.34-7.21 (m, 5H), 3.96 (s, 3H), 3.35 (t, *J* = 7.0 Hz, 2H), 3.10 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 199.1, 166.6, 141.4, 140.4, 134.3, 130.3, 130.0, 129.0, 128.8, 128.4, 126.7, 52.9, 41.2, 30.4; **FTIR** (cm^{-1}) (neat): 2957, 1719, 1673, 1570, 1434, 1406, 1277, 1108; **HRMS** (ESI, Pos): calc. for $C_{17}H_{17}O_3$ $[M+H]^+$: 269.1178, found: 269.1175 *m/z*.

*Synthesis of methyl 4-(pent-4-enoyl)benzoate (**3.3aa**) by addition of 3-butenylmagnesium bromide solution to activated methyl 4-[(allylamino)carbonyl]benzoate (**4.3aa**)*



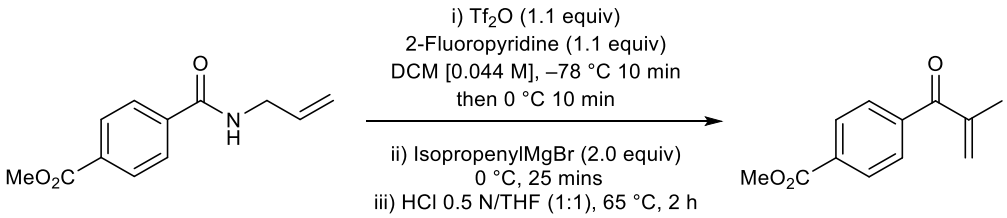
Methyl 4-(pent-4-enoyl)benzoate (3.3aa): To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **4.3aa** (219.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-

78. $Ph(CH_2)_2MgCl$ was made according to literature procedures with $Ph(CH_2)_2Cl$ and $Mg^{(0)}$ in Et_2O: Shibata, K. & Mitsunobu, O. Preparation of 1,4-dienefrom 2-(2-hydroxyalkylseleno)benzothiazoles by the reaction involving Se → O Azaaromatic ring rearrangement. *Bull. Chem. Soc. Jpn.* **65**, 3163-3173 (1992).

79. The reaction performed with commercially available $Ph(CH_2)_2MgCl$ 1M solution in THF (Aldrich) gave much lower conversion to the desired ketone **3z** (~50% by crude ^{1}H NMR) than freshly prepared Grignard reagent.

fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of 3-ButenylMgBr in THF (solution titrated at 0.3 M) (6.67 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 50% EtOAc/Hexanes and fractions containing **3.3aa** were concentrated to dryness. The product was isolated as a white solid (195.8 mg, 90% Yield). **mp**: 73-74 °C; **R_f**: 0.45 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.13-8.10 (m, 2H), 8.02-7.99 (m, 2H), 5.95-5.85 (m, 1H), 5.12-5.00 (m, 2H), 3.94 (s, 3H), 3.10 (t, J = 7.0 Hz, 2H), 2.53-2.48 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 199.3, 166.6, 140.5, 137.4, 134.2, 130.2, 128.3, 115.9, 52.8, 38.5, 28.4; **FTIR** (cm^{-1}) (neat): 2959, 1719, 1675, 1642, 1503, 1278, 1193, 1108; **HRMS** (ESI, Pos): calc. for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1021, found: 219.1016 *m/z*.

*Synthesis of methyl 4-(2-methylacryloyl)benzoate (**3.3ab**) by addition of isopropenylmagnesium bromide solution to activated methyl 4-[(allylamino)carbonyl]benzoate (**4.3aa**)*

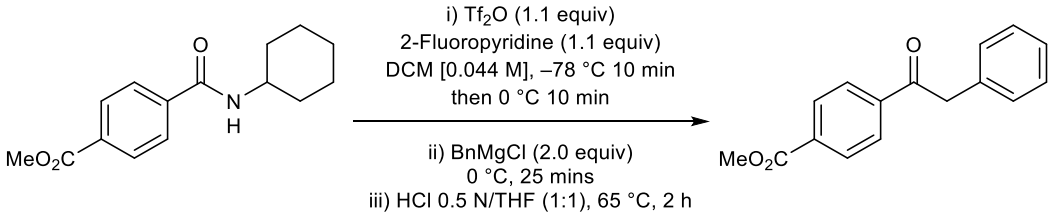


Methyl 4-(2-methylacryloyl)benzoate (3.3ab):[80] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4aa** (219.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of IsopropenylMgBr in THF (solution titrated at 0.39M) (5.12 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 50% EtOAc/Hexanes and fractions containing **3.3ab** were concentrated to dryness. The product was isolated as a white solid (177.9 mg, 87% Yield). **mp**: 51-52 °C, litt:[80] 44.5-50 °C; $\mathbf{R_f}$: 0.45

[80]. For literature characterization data, see: Takeuchi, Y., Guillet, J. E., Sugita, K., Ueno, N., Harada, K. & Suzuki, Y. Photolysis of unsubstituted and *p*-methoxycarbonyl substituted 2-methyl-1-phenylprop-2-en-1-one copolymers in solution. *J. Polym. Sci, Part A: Polym. Chem.* **34**, 789-799 (1996).

(20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 5.95 (d, *J* = 5.0 Hz, 1H), 5.60 (d, *J* = 3.0 Hz, 1H), 3.91 (s, 3H), 2.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 197.9, 166.7, 144.0, 142.0, 133.2, 129.7, 129.5, 128.8, 52.7, 18.7; **FTIR** (cm^{-1}) (neat): 2957, 1720, 1641, 1433, 1276, 1192, 1106; **HRMS** (ESI, Pos): calc. for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0865, found: 205.0858 *m/z*.

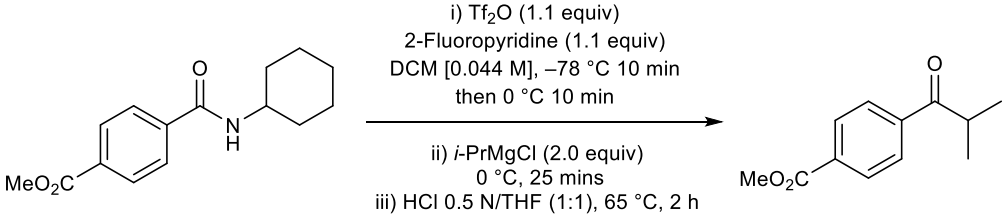
*Synthesis of methyl 4-(phenylacetyl)benzoate (**3.3ac**) by addition of benzylmagnesium chloride solution to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*



Methyl 4-(phenylacetyl)benzoate (3.3ac): To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added *N*-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**) (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of BnMgCl in Et_2O (solution titrated at 0.83 M) (2.4 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous

sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% to 80% EtOAc/Hexanes and fractions containing **3.3ac** were concentrated to dryness. The product was isolated as a white solid (232.4 mg, 92% Yield). **mp**: 109-110 °C; $\mathbf{R_f}$: 0.60 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.16-8.05 (m, 4H), 7.38-7.26 (m, 5H), 4.33 (s, 2H), 3.96 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 197.5, 166.6, 140.2, 134.4, 134.3, 130.3, 129.8, 129.2, 128.9, 127.5, 52.9, 46.3; **FTIR** (cm^{-1}) (neat): 2950, 1716, 1686, 1440, 1404, 1277, 1033; **HRMS** (ESI, Pos): calc. for $C_{16}H_{15}O_3$ $[M+H]^+$: 255.1021, found: 255.1015 *m/z*.

*Synthesis of methyl 4-(2-methylpropanoyl)benzoate (**3.3ad**) by addition of isopropylmagnesium bromide solution to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*

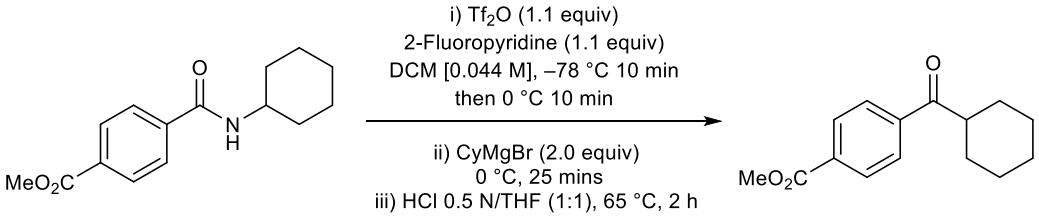


Methyl 4-(2-methylpropanoyl)benzoate (3.3ad):[81] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution

81. For literature characterization data, see: Jean, M., Renault, J., van de Weghe, P. Palladium-catalyzed arylation of vinylic acetates. Phosphine ligand influenced regioselectivity. *Tetrahedron Lett.* **50**, 6546-6548 (2009).

of *i*PrMgCl in THF (solution titrated at 1.90M) (1.05 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 20g) using a gradient of 0% EtOAc/Hexanes to 70% EtOAc/Hexanes and fractions containing **3.3ad** were concentrated to dryness. The product was isolated as a translucid oil (189.0 mg, 92% Yield). $\mathbf{R_f}$: 0.55 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.11-8.09 (m, 2H), 7.99-7.96 (m, 2H), 3.93 (s, 3H), 3.54 (h, *J* = 7.0 Hz, 1H), 1.20 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 204.3, 166.6, 140.0, 134.0, 130.2, 128.6, 52.8, 36.2, 19.3; **FTIR** (cm^{-1}) (neat): 2972, 1722, 1685, 1436, 1406, 1384, 1273, 1218, 1105, 1018; **HRMS** (ESI, Pos): calc. for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.1021, found: 207.1006 *m/z*.

*Synthesis of methyl 4-(cyclohexylcarbonyl)benzoate (**3.3ae**) by addition of isopropylmagnesium bromide solution to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*



Methyl 4-(cyclohexylcarbonyl)benzoate (3.3ae): To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The

solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 10 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 2 min. A solution of CyMgBr in Et_2O (solution titrated at 2.00M)[82,83] (1.00 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 20g) using a gradient of 0% EtOAc/Hexanes to 70% EtOAc/Hexanes and fractions containing **3.3ae** were concentrated to dryness. The product was isolated as a yellow powder (184.2 mg, 75% Yield). **mp**: 84-85 °C; **R_f**: 0.60 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.12 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 3.96 (s, 3H), 3.27 (tt, *J* = 3.0, 11.5 Hz, 1H), 1.94-1.83 (m, 4H), 1.79-1.73 (m, 1H), 1.56-1.23 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 203.8, 166.7, 140.1, 133.9, 130.2, 128.5, 52.8, 46.4, 29.7, 26.3, 26.2; **FTIR** (cm^{-1}) (neat): 2923, 2857, 1720, 1673, 1572, 1439, 1409, 1280, 1252, 1198, 1105; **HRMS** (ESI, Pos): calc. for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1334, found: 247.1324 *m/z*.

*Synthesis of methyl 4-(4-methylbenzoyl)benzoate (**3.3af**) by addition of p-tolylmagnesium bromide solution to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*

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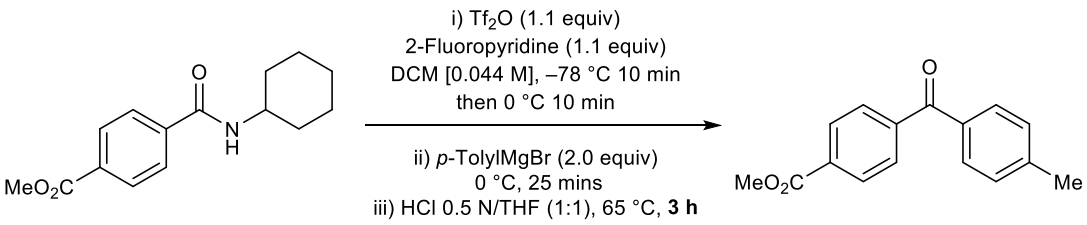
82. CyMgBr was made according to literature procedures with Cyclohexylbromide, I_2 (cat.), and $Mg^{(0)}$ in Et_2O: Conejo-García, A. *et al.* Homodimeric bis-quaternary heterocyclic ammonium salts as potent acetyl and butyrylcholinesterase inhibitors: a systematic investigation of the influence of linker and cationic heads over affinity and selectivity. *J. Med. Chem.* **2011**, *54*, 2627-2645.

83. The reaction performed with commercially available CyMgCl 2.0M solution in Et_2O (Aldrich) gave comparable conversion to the desired ketone **3.3ae –Not sure if it was supposed to put the ''3''** than freshly prepared Grignard reagent.

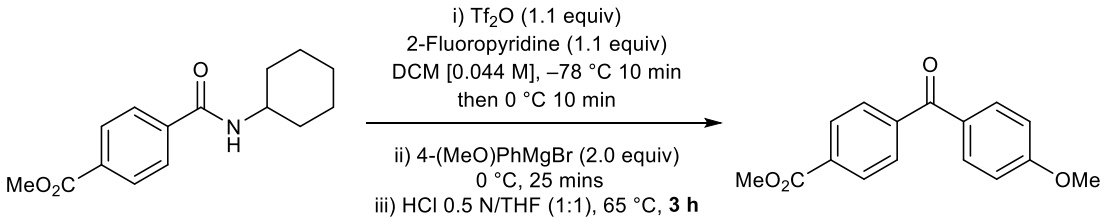


Methyl 4-(4-methylbenzoyl)benzoate (3.3af):[84] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of *p*-TolylMgBr in Et_2O (solution titrated at 0.60M) (3.33 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for **3 hours** to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 90% EtOAc/Hexanes and fractions containing **3.3af** were concentrated to dryness. The product was isolated as a white powder (225.5 mg, 89% Yield). **mp**: 120-121 °C, litt:[84] 125-126 °C; $\mathbf{R_f}$: 0.50 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.15 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.98 (s, 3H), 2.46 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 196.1, 166.8, 144.3, 142.1, 134.7, 133.4, 130.7, 130.0, 129.9,

84. For literature characterization data, see: Cai, M., Peng, J., Hao, W. & Ding, G. A phosphine-free carbonylative cross-coupling reaction of aryliodides with arylboronic acids by immobilization of palladium in MCM-41. *Green Chem.* **13**, 190-196 (2011).

129.8, 129.6, 52.8, 22.1; **FTIR** (cm^{-1}) (neat): 2957, 1719, 1645, 1605, 1434, 1405, 1278, 1184, 1106; **HRMS** (ESI, Pos): calc. for $C_{16}H_{15}O_3$ $[M+H]^+$: 255.1021, found: 255.1018 *m/z*.

*Synthesis of methyl 4-(4-methoxybenzoyl)benzoate (**3.3ag**) by addition of 4-methoxyphenylmagnesium bromide solution to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*



Methyl 4-(4-methoxybenzoyl)benzoate (3.3ag):[85] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of 4-(MeO)PhMgBr in THF/Et_2O (solution titrated at 0.91M)[86,87] (2.19 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for **3 hours** to ensure complete hydrolysis to the ketone. The

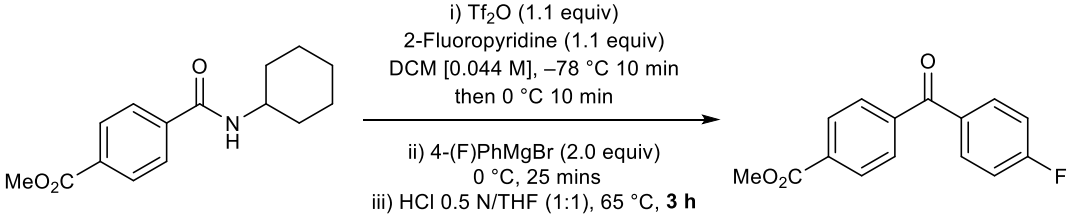
85. For literature characterization data, see: Salem, O. I. A. *et al.* Novel 5α-reductase inhibitors: synthesis, structure-activity studies, and pharmacokinetic profile of phenoxybenzoylphenyl acetic acids. *J. Med. Chem.* **49**, 748-759 (2006).

86. 4-(MeO)PhMgBr was made according to literature procedures with 4-bromoanisole, I_2 (cat.), and $Mg^{(0)}$ in Et_2O/THF: Organ, M. G. *et al.* Bisaryl made easy: PEPPSI and the Kumada-Tamao-Corriu reaction. *Chem. Eur. J.* **13**, 150-157 (2007).

87. The reaction performed with commercially available 4-(MeO)PhMgBr 0.5M solution in THF (Aldrich) and homemade 4-(MeO)PhMgBr in THF/Et_2O gave similar conversion but considerable amount of biphenyl side-product was obtained in the crude mixture of both reactions. Careful purification of the mixture by flash chromatography is needed in order to have pure **3ag**.

biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 90% EtOAc/Hexanes and fractions containing **3.3ag** were concentrated to dryness. The product was isolated as a crystalline white solid (220.2 mg, 82% Yield). **mp**: 163-164 °C, litt:[85] 161-162 °C; $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.18-8.14 (m, 2H), 7.86-7.79 (m, 4H), 7.01-6.98 (m, 2H), 3.99 (s, 3H), 3.92 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 195.2, 166.8, 164.0, 142.6, 133.2, 133.0, 130.0, 129.9 (2), 114.2, 56.0, 52.8; **FTIR** (cm^{-1}) (neat): 2937, 1712, 1682, 1638, 1599, 1568, 1498, 1304, 1278, 1174, 1146; **HRMS** (ESI, Pos): calc. for $C_{16}H_{15}O_4$ $[M+H]^+$: 271.0970, found: 271.0968 *m/z*.

*Synthesis of methyl 4-(4-fluorobenzoyl)benzoate (**3.3ah**) by addition of 4-fluorophenylmagnesium bromide solution to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*

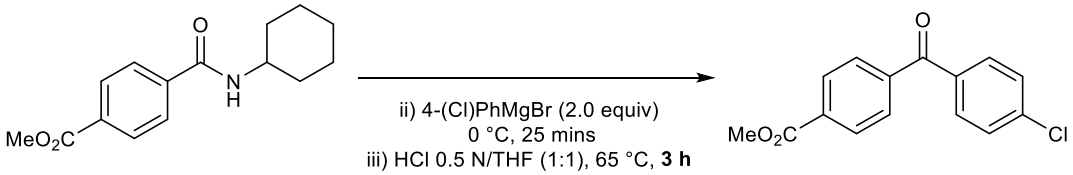


Methyl 4-(4-fluorobenzoyl)benzoate (3.3ah):[88] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution

88. For literature characterization data, see: Ishiyama, T., Kizaki, H., Hayashi, T., Suzuki, A., Miyaura, N. Palladium-catalyzed carbonylative cross-coupling of arylboronic acids with aryl electrophiles: synthesis of biaryl ketones. *J. Org. Chem.* **63**, 4726-4731 (1998).

of 4-(F)PhMgBr in THF (solution titrated at 0.89M) (2.25 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for **3 hours** to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 90% EtOAc/Hexanes and fractions containing **3.3ah** were concentrated to dryness. The product was isolated as a crystalline white solid (257.2 mg, 100% Yield). **mp**: 144-145 °C; $\mathbf{R_f}$: 0.45 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.19-8.16 (m, 2H), 7.89-7.81 (m, 4H), 7.22-7.17 (m, 2H), 3.99 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.9, 166.7, 166.1 (d, J = 254.1 Hz, $J_{C\text{-}F}$), 141.6, 133.7, 133.6 (d, J = 3.0 Hz, $J_{C\text{-}F}$), 133.2 (d, J = 9.0 Hz, $J_{C\text{-}F}$), 130.0 (2), 116.1 (d, J = 22.0 Hz, $J_{C\text{-}F}$), 52.9; **^{19}F NMR** ($CDCl_3$, 375.5 MHz): d –105.3; **FTIR** (cm^{-1}) (neat): 2959, 1715, 1646, 1597, 1499, 1406, 1278, 1191, 1155, 1104; **HRMS** (ESI, Pos): calc. for $C_{15}H_{12}O_3F$ $[M+H]^+$: 259.0770, found: 259.0768 *m/z*.

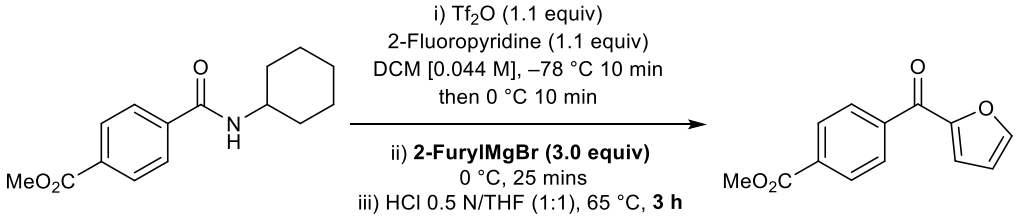
*Synthesis of methyl 4-(4-chlorobenzoyl)benzoate (**3.3ai**) by addition of 4-chlorophenylmagnesium bromide solution to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*



Methyl 4-(4-chlorobenzoyl)benzoate (3.3ai):[89] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of 4-(Cl)PhMgBr in THF (solution titrated at 1.10M) (1.81 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for **3 hours** to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% to 90% EtOAc/Hexanes and fractions containing **3.3ai** were concentrated to dryness. The product was isolated as a white powder (267.9 mg, 98% Yield). **mp**: 159-160 °C, litt:[89] 168-169 °C; $\mathbf{R_f}$: 0.55 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.17 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 3.99 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 195.2, 166.6, 141.3, 139.9, 135.6, 133.8, 131.9, 130.1, 130.0, 129.3, 52.9; **FTIR** (cm^{-1}) (neat): 2938, 1728, 1650, 1586, 1527, 1440, 1400, 1260; **HRMS** (ESI, Pos): calc. for $C_{15}H_{12}O_3F$ $[M+H]^+$: 275.0475, found: 275.0470 *m/z*.

89. For literature characterization data, see: Cai, M., Zheng, G., Zha, L. & Peng, J. Carbonylative Suzuki-Miyaura coupling of arylboronic acids with aryliodides catalyzed by the MCM-41-supported bidentate phosphane palladium(II) complexes. *Eur. J. Org. Chem.* 1585-1591 (2009).

*Synthesis of methyl 4-(furan-2-ylcarbonyl)benzoate (**3.3aj**) by addition of 2-furylmagnesium bromide solution to activated methyl 4-[(isopropylamino)carbonyl]benzoate (**3.4a**)*



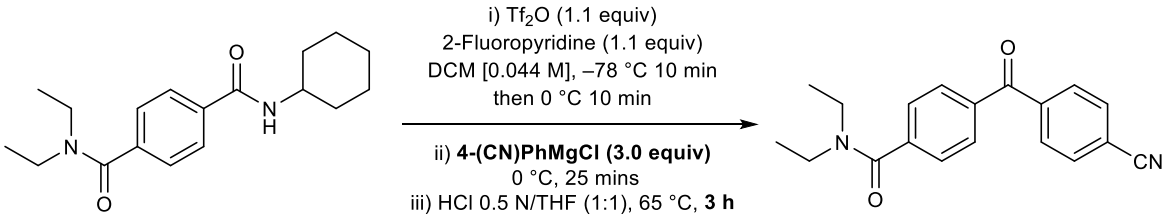
Methyl 4-(furan-2-ylcarbonyl)benzoate (3.3aj):[(90)] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of 2-FurylMgBr 0.70M in THF/Hexanes[(91)] (4.30 mL, 3.0 mmol, 3.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for **3 hours** to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 5% EtOAc/Hexanes to 100% EtOAc and fractions containing **3.3aj** were concentrated to dryness. The product was isolated

90. For literature characterization data, see: Li, H., Yang, M., Qi, Y. & Xue, J. Ligand-free Pd-catalyzed carbonylative cross-coupling reactions under atmospheric pressure of carbon monoxide: synthesis of aryl ketones and heteroaromatic ketones. *Eur. J. Org. Chem.* 2662-2667 (2011).

91. 2-FurylMgBr was made according to literature procedures with furan (the Grignard reagent was prepared in THF with commercially available *n*-BuLi in Hexanes and $MgBr_2 \cdot OEt_2$): Charette, A. B., Grenon, M., Lemire, A., Pourashraf, M. & Martel, J. Practical and highly regio- and stereoselective synthesis of 2-substituted dihydropyridines and piperidines: application to the synthesis of (–)-coniine. *J. Am. Chem. Soc.* **123**, 11829-11830 (2001).

as a yellow powder (156.4 mg, 68% Yield). **mp**: 96-97 °C; $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.20-8.17 (m, 2H), 8.06-8.03 (m, 2H), 7.55 (dd, *J* = 1.0, 2.0 Hz, 1H), 7.29 (dd, *J* = 1.0, 3.5 Hz, 1H), 6.44 (dd, *J* = 2.0, 3.5 Hz, 1H), 3.99 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 182.1, 166.7, 152.5, 147.9, 141.2, 133.8, 130.0, 129.6, 121.4, 112.9, 52.9; **FTIR** (cm^{-1}) (neat): 2953, 1726, 1681, 1645, 1503, 1392, 1263; **HRMS** (ESI, Pos): calc. for $C_{13}H_{11}O_4$ $[M+H]^+$: 231.0657, found: 231.0654 *m/z*.

*Synthesis of 4-(4-cyanobenzoyl)-N,N-diethylbenzamide (**3.3ak**) by addition of 4-benzonitrilemagnesium bromide lithium chloride complex solution to activated N'-cyclohexyl-N,N-diethylterephtalamide (**3.4k**)*

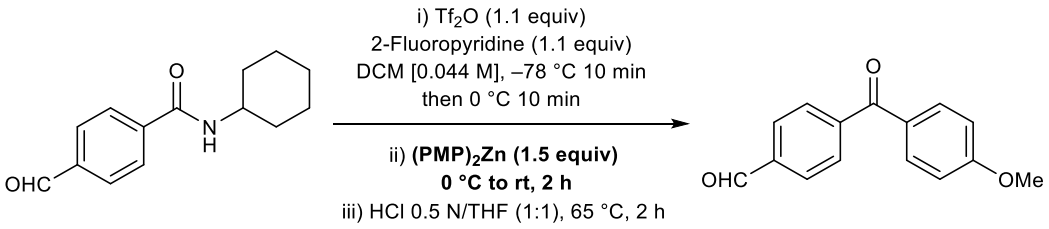


4-(4-Cyanobenzoyl)-*N,N*-diethylbenzamide (3.3ak): To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4k** (302.2 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 1 hour. The solution was slowly warmed to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred at –20 °C for 1 hour. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of 4-(CN)PhMgCl•LiCl 0.75M in THF prepared by using Knochel's procedure[92] (4.00 mL, 3.0 mmol, 3.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for **3**

92. 4-(CN)PhMgCl·LiCl was made according to literature procedures with 4-bromobenzonitrile (the Grignard reagent was prepared in THF with commercially available 1.3 M solution of *i*-PrMgCl·LiCl in THF): Knochel, P. & Krasovskiy, A. A LiCl-mediated Br/Mg exchange reaction for the preparation of functionalized aryl- and heteroarylmagnesium compounds from organic bromides *Angew. Chem., Int. Ed.* **43**, 3333-3336 (2004).

hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 15% EtOAc/Hexanes to 100% EtOAc and fractions containing **3.3ak** were concentrated to dryness. The product was isolated as a white powder (212.9 mg, 70% Yield). **mp**: 130-132 °C; $\mathbf{R_f}$: 0.30 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.92-7.89 (m, 2H), 7.86-7.82 (m, 4H), 7.55-7.52 (m, 2H), 3.60 (br q, *J* = 7.5 Hz, 2H), 3.28 (br q, *J* = 7.5 Hz, 2H), 1.30 (br t, *J* = 7.5 Hz, 3H), 1.15 (br t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.8, 170.3, 142.4, 141.2, 137.2, 132.7, 130.7, 130.6, 127.0, 118.3, 116.4, 43.7, 39.8, 14.7, 13.3; **FTIR** (cm^{-1}) (neat): 2989, 2231, 1682, 1651, 1623, 1600, 1524, 1438, 1314, 1289, 1106; **HRMS** (ESI, Pos): calc. for $C_{19}H_{19}O_3N_2$ $[M+H]^+$: 307.1447, found: 307.1450 *m/z*.

*Synthesis of methyl 4-(cyclohexylcarbonyl)benzoate (**3.4j**) by addition of di[(4-methoxy)phenyl]zinc to activated N-cyclohexyl-4-formylbenzamide (**3.3al**)*



4-(4-Methoxybenxoyl)benzaldehyde (3.3al):[(93)] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4j** (231.2 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution

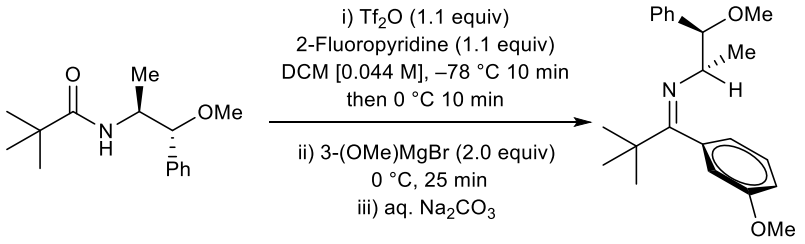
93. For literature characterization data, see: Ito, H., Tamashima, H., Iwasawa, N. & Kusama, H. Photochemically promoted transition metal-free cross-coupling of acylsilanes with organoboronic esters. *J. Am. Chem. Soc.* **2011**, *133*, 3716-3719.

was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. Neat $(PMP)_2Zn$[94] (419.5 mg, 1.5 mmol, 1.5 equiv) was added in one portion to the reaction at 0 °C and the reaction was slowly warmed to room temperature over 2 hours. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% EtOAc/Hexanes to 90% EtOAc/Hexanes and fractions containing **3.3al** were concentrated to dryness. The product was isolated as a white powder (192.3 mg, 80% Yield). **mp**: 104-106 °C; $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 10.13 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 194.9, 192.1, 164.2, 143.8, 138.5, 133.0, 130.4, 129.9, 129.8, 114.2, 56.0; **FTIR** (cm^{-1}) (neat): 2845, 1698, 1643, 1592, 1509, 1386, 1317, 1258, 1204, 1177, 1143, 1118; **HRMS** (ESI, Pos): calc. for $C_{15}H_{13}O_3$ $[M+H]^+$: 241.0865, found: 241.0861 *m/z*.

94. Neat $(PMP)_2Zn$ was synthesized according to literature procedures and was stored in a dry glovebox before use: Lee, K.-S., Brown, M. K., Hird, A. W. & Hoveyda, A. H. A practical method for enantioselective synthesis of all-carbon quarternary stereogenic centers through NHC-Cu-catalyzed conjugate additions of alkyl- and arylzinc reagents to β-substituted cyclic enones. *J. Am. Chem. Soc.* **128**, 7182-7184 (2006).

Imine synthesis (Table #4, entries 1-3, **3.6a-3.6c**):

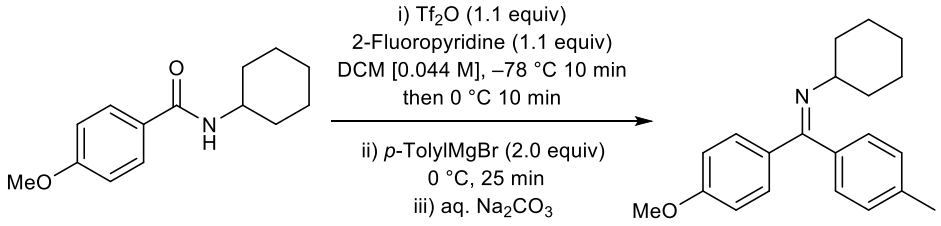
*Synthesis of (*1*R*,2*S*)-1-methoxy-*N*-[1-(3-methoxyphenyl)-2,2-dimethylpropylidene]1-phenylpro pan-2-amine ***(3.6a)*** *by addition of 3-methoxyphenylmagnesium bromide to activated N-[(1R,2S)-1-methoxy-1-phenylpropan-2-yl]-2,2-dimethylpropanamide* ***(3.4ab)***



(1*R*,2*S*)-1-Methoxy-*N*-[1-(3-methoxyphenyl)-2,2-dimethylpropylidene]1-phenylpro pan-2-amine (3.6a): To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added the amide **3.4ab** (249.2 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 μL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 μL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. Then, 3-(MeO)PhMgBr solution in THF (solution was titrated at 0.9M) (2.22 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of a saturated solution of Na_2CO_3 and transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude imine was purified by flash chromatography over basic alumina (Merck Type E (60 PF_{254}, pH at 10-11)) using a gradient of 0% EtOAc/Hexanes to 15% EtOAc/Hexanes and fractions containing **6a** were concentrated to dryness. The imine was isolated as a yellow oil (277 mg, 82% Yield). $\mathbf{[\alpha]_D^{20}}$: -106.7 (*c* 1.13, $CHCl_3$), $\mathbf{R_f}$: 0.80 (10% EtOAc/Hexanes); **^{1}H NMR** (CD_3OD, 400 MHz): (Mixture of rotamers) δ 7.37-7.29 (m, 3H),

7.26-7.21 and 7.14-7.10 (t, J = 8.0 Hz, 1H), 7.20-7.14 (m, 2H), 6.87-6.83 (m, 1H), 6.45 and 5.50 (d, J = 7.0 Hz, 1H), 6.38 and 5.53 (s, 1H), 4.16 and 4.13 (d, J = 5.0 Hz, 1H), 3.78 and 3.73 (s, 3H), 3.19 (s, 3H), 3.14-3.05 (m, 1H), 1.15 and 1.13 (d, J = 7.5 Hz, 3H), 0.93 (s, 9H); **^{13}C NMR** (CD_3OD, 100 MHz): δ 177.9 and 177.8, 159.5, 141.0 and 140.9, 138.8, 128.9 and 128.7, 128.3 and 128.2, 127.9 and 127.8, 127.6, 119.7 and 119.3, 113.1 and 112.9, 113.0 and 112.4, 88.2 and 88.2, 63.0, 56.2, 54.8 and 54.7, 39.5, 27.9, 18.5; **FTIR** (cm^{-1}) (neat): 2965, 1643, 1576, 1478, 1454, 1287, 1239, 1162, 1113; **HRMS** (ESI, Pos): calc. for $C_{22}H_{30}NO_2$ $[M+H]^+$: 340.2277, found: 340.2278 *m/z*.

*Synthesis of N-[(1E)-(4-methoxyphenyl)(4-methylphenyl)methylene]cyclohexanamide (**3.6b**) by addition of p-tolylmagnesium bromide to activated N-cyclohexyl-4-methoxybenzamide (**3.4ac**)*



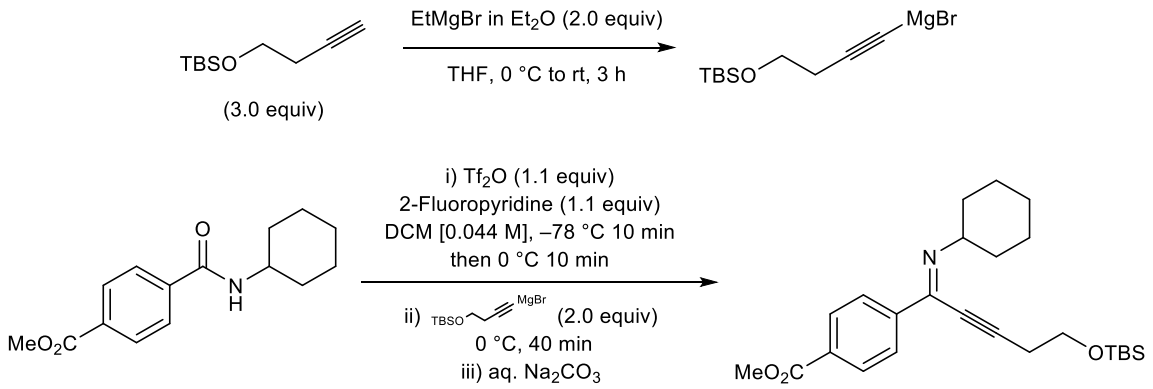
***N*-[(1*E*)-(4-Methoxyphenyl)(4-methylphenyl)methylene]cyclohexanamide (3.6b):** To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4ac** (233.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. Then, *p*-TolylMgBr solution in Et_2O (solution was titrated at 0.6M) (3.33 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of 8 mL of a saturated solution of Na_2CO_3 and transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4),

filtered over a sintered funnel and evaporated to dryness. The crude imine was purified by flash chromatography over basic alumina (Merck Type E (60 PF_{254}, pH at 10-11)) using a gradient of 0% EtOAc/Hexanes to 20% EtOAc/Hexanes and fractions containing **3.6b** were concentrated to dryness. The imine was isolated as a yellow oil consisting of a inseparable mixture of isomers for the imine (18:1, *E*:*Z* ratio relative to the *p*-OMe substituent)[95] (260 mg, 84% Yield). *For the major isomer*: $\mathbf{R_f}$: 0.75 (20% EtOAc/Hexanes); **^{1}H NMR** (CD_2Cl_2, 400 MHz): δ 7.60-7.56 (m, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 7.5 Hz, 2H), 6.89-6.86 (m, 2H), 3.84 (s, 3H), 3.30-3.22 (m, 1H), 2.48 (s, 3H), 1.83-1.77 (m, 2H), 1.69-1.57 (m, 5H), 1.38-1.16 (m, 3H); **^{13}C NMR** (CD_2Cl_2, 100 MHz): δ 164.2, 160.5, 137.4, 134.2, 133.1, 129.3, 128.6, 127.2, 112.7, 60.7, 54.9, 33.8, 25.5, 24.1, 20.7; **FTIR** (cm^{-1}) (neat): 2925, 2852, 1600, 1573, 1506, 1447, 1304, 1245, 1174, 1156, 1067, 837, 820; **HRMS** (ESI, Pos): calc. for $C_{21}H_{26}NO$ $[M+H]^+$: 308.2014, found: 308.2020 *m/z*.

Note: Attempts to purify the crude imine **3.6b** with basic alumina (Aldrich), neutral alumina (Aldrich) or neutralized silica gel with Et_3N/Hexanes resulted in isolation of a mixture of isomers (4:1, *E*:*Z* ratio) of the imine. When the crude imine **3.6b** is purified on silica gel without a pre-treatment with Et_3N/Hexanes a mixture of isomers (4:1, *E*:*Z* ratio) for the imine **3.6b** (60% yield) and a significant amount of the corresponding ketone (21% yield) is recuperated after the purification suggesting a partial hydrolysis of the imine **3.6b** on the column with these conditions.

*Synthesis of methyl 4-[(1Z)-5-{[tert-butyl(dimethyl)silyl]oxy}-N-cyclohexylpent-2-ynimidoyl] benzoate (**3.4a**) by addition of 4-{[tert-butyl(dimethyl)silyl]oxy}but-1-yn-1-ylmagnesium bromide to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.6c**)*

95. For an experimental study on equilibrium distribution of *E* and *Z* ketimine isomers, see: Bjørgo, J., Boyd, D. R., Watson, C. G. & Jennings, B. W. Equilibrium distribution of *E*-*Z* ketimine isomers. *J. Chem Soc., Perkin Trans. 2* 757-762 (1974).



Methyl 4-[(1*Z*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-cyclohexylpent-2-ynimidoyl] benzoate (3.6c): To a flame-dried and argon-flushed 10 mL round-bottom flask equipped with a stir-bar and a septum was added 4-{[*tert*-butyl(dimethyl)silyl]oxy}but-1-yne[(96)] (552.4 mg, 3.0 mmol, 3.0 equiv). The alkyne was diluted with dry THF (3.0 mL, 1M) and the solution was cooled to 0 °C using a water/ice bath. Then, a solution of EtMgBr in Et_2O (Aldrich Sure-Sealed (3.0 M) solution) (670 µL, 2.0 mmol, 2.0 equiv) was added dropwise to the alkyne solution at 0 °C. The rection was slowly warmed to room temperature and stirred for 3 hours at room temperature ensuring complete formation of 4-{[*tert*-butyl(dimethyl)silyl]oxy}but-1-yn-1-ylmagnesium bromide.

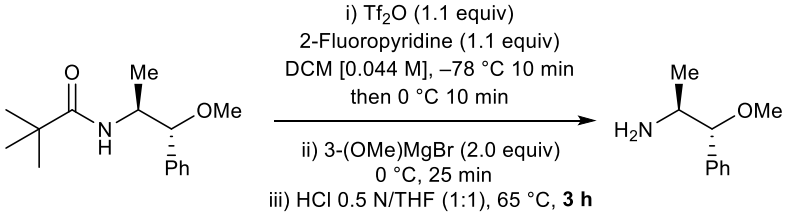
To a seperate flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. The solution of 4-{[*tert*-butyl(dimethyl)silyl]oxy}but-1-yn-1-ylmagnesium bromide in THF/Et_2O previously prepared (2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 40 min at 0 °C. The reaction was quenched by addition of 8 mL of a saturated solution of Na_2CO_3 and transferred to a 60 mL separation funnel using DCM and the layers

96. 4-{[*tert*-butyl(dimethyl)silyl]oxy}but-1-yne was made according to literature procedures: Smith, S. M., & Tackas, J. M. Amide-directed catalytic asymmetric hydroboration of trisubstituted alkenes. *J. Am. Chem. Soc.* **132**, 1740-1741 (2010).

were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude imine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% EtOAc/Hexanes to 30% EtOAc/Hexanes and fractions containing **3.6c** were concentrated to dryness. The product was isolated as a yellow oil consisting of a single isomer (375.0 mg, 88% Yield). $\mathbf{R_f}$: 0.30 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.10-8.03 (m, 4H), 3.96-3.89 (m, 1H), 3.94 (s, 3H), 3.86 (t, *J* = 7.0 Hz, 2H), 1.89-1.67 (m, 5H), 1.62-1.28 (m, 5H), 0.93 (s, 9H), 0.12 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.3, 148.0, 142.5, 131.5, 129.7, 127.9, 97.7, 74.8, 65.0, 61.8, 52.5, 33.8, 26.3, 26.2, 25.1, 24.3, 18.7, -4.9; **FTIR** (cm^{-1}) (neat): 2927, 2857, 1723, 1589, 1435, 1255, 1101; **HRMS** (ESI, Pos): calc. for $C_{25}H_{38}NO_3Si$ $[M+H]^+$: 428.2621, found: 428.2625 *m/z*.

Amine synthesis

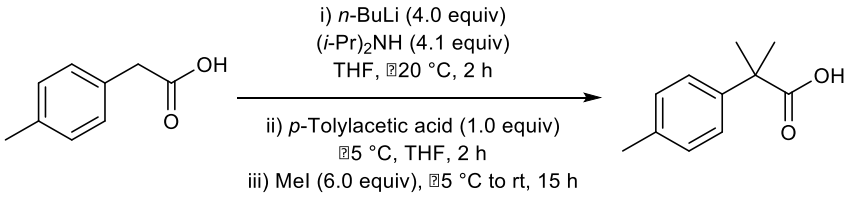
*Synthesis of (1R,2S)-1-methoxy-1-phenylpropan-2-amine from N-[(1R,2S)-1-Methoxy-1-phenylpropan-2-yl]2,2-dimethylpropanamide (**3.4ab**)*



(1*R*,2*S*)-1-Methoxy-1-phenylpropan-2-amine:[63] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added the amide **3.4ab** (249.2 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. Then, 3-(MeO)PhMgBr solution in THF (solution was titrated at 0.91 M) (2.22 mL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. The reaction was quenched by addition of of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The flask was kept opened to air and the biphasic mixture was warmed to a gentle reflux (65°C) for 3 hours to ensure complete hydrolysis (**Note:** It is important to evaporate the DCM in the process in order to transfer completely the HCl salt of the amine in the aqueous layer). The biphasic mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and transferred to a 250 mL extraction funnel. The amine was purified by acid/base extraction with 0.5 N HCl (4x). The aqueous layers were combined, washed with EtOAc (20 mL), and made basic by addition of an aqueous solution of NaOH 2N until pH~10-11 and then extracted with DCM (5x40 mL). The chlorinated organic layers were combined and dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The pure amine was isolated as yellow oil (140.1 mg, 85% Yield). **Note**: *See pages S31-S32 for characterization data of amine.*

Targretin (Bexarotene) analogue synthesis (Figure #2a-b):

Synthesis of 2-methyl-2-(4-methylphenyl)propanoic acid by double methylation of p-tolylacetic acid

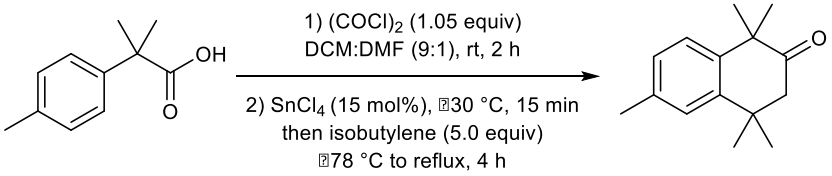


2-Methyl-2-(4-methylphenyl)propanoic acid :[97] To a flame-dried and argon-flushed 1L round-bottom flask equipped with a stir-bar and a septum was added diisopropylamine (21.89 g, 30.4 mL, 218 mmol, 4.1 equiv). The amine was dissolved with anhydrous THF (218 mL, [0.24 M]) and the reaction was cooled to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred for 5 min. A solution of *n*-BuLi in hexanes (solution titrated at 2.48 M) (85.4 mL, 212 mmol, 4.0 equiv) was added dropwise at –20 °C and the reaction was stirred for 2 hours at –20 °C. To a separate flame-dried 100 mL round-bottom flask, *p*-tolylacetic acid (8.00 g, 53 mmol, 1.0 equiv) was dissolved in anhydrous THF (53 mL, [1 M]). The *p*-tolylacetic acid solution was then added dropwise via canula in the LDA solution at –20 °C. The reaction was slowly warmed to –5 °C using a brine/ice cooling bath and stirred for 2 hours at –5 °C. Iodomethane (45.1 g, 19.8 mL, 318 mmol, 6.0 equiv) was then added dropwise at –5 °C and the reaction was gradually warmed up to room temperature and stirred for 15 hours at room temperature. The reaction is quenched by adding 100 mL of an aqueous solution of HCl 1N and diluted with Et_2O (200 mL). The biphasic mixture was then transferred to a 1 L separation funnel using Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude acid was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 80g) using a gradient of 5% EtOAc/Hexanes to 90% EtOAc/Hexanes and fractions containing the acid were concentrated to dryness. The product was isolated as a yellow oil

[97]. For literature characterization data, see: (a) Coteron, J. M. *et al.* Falcipain inhibitors: optimization studies of the 2-pyrimidinecarbonitrile lead series. *J. Med. Chem.* **53**, 6129-6152 (2010). (b) Buckle, D. R., Cantello, B. C. C., Smith, H., Smith, R. J. & Spicer, B. A. Synthesis and antiallergic activity of 2-hydroxy-3-nitro-1,4-naphthoquinones. *J. Med. Chem.* **20**, 1059-1064 (1977).

which solidified when stored in the freezer (8.51 g, 91% Yield). **mp**: 76-77 °C, litt:[97] 78-80 °C; $\mathbf{R_f}$: 0.20 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 11.83 (br s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.68 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 184.2, 141.4, 137.1, 129.6, 126.2, 46.4, 26.7, 21.4; **FTIR** (cm^{-1}) (neat): 2973, 1698, 1513, 1455, 1407, 1294, 1274, 1177, 1155; **HRMS** (ESI, Neg): calc. for $C_{11}H_{13}O_2$ $[M-H]^-$: 177.0916, found: 177.0920 *m/z*.

Synthesis of 1,1,4,4,6-pentamethyl-3,4-dihydronaphthalen-2(1H)-one by a Friedel-Crafts reaction on 2-methyl-2-(4-methylphenyl)propanoic acid



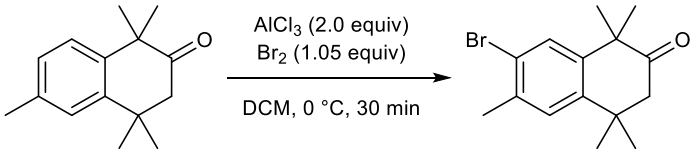
1,1,4,4,6-Pentamethyl-3,4-dihydronaphthalen-2(3.1*H*)-one:[98] To a flame-dried and argon-flushed 500 mL round-bottom flask equipped with a stir-bar and a septum was added 2-methyl-2-(4-methylphenyl)propanoic acid (7.1 g, 39 mmol, 1.0 equiv). The acid was dissolved in anhydrous DCM (118 mL, [0.33 M]) and anhydrous DMF (13 mL, [3 M]). Then, oxalyl chloride (5.21 g, 3.64 mL, 41.0 mmol, 1.05 equiv) was added dropwise to the acid solution and the reaction was stirred at room temperature for 2 hours. The solution was then cooled to –30 °C using a *i*-PrOH:H_2O (2:1)/dry ice cooling bath and stirred for 2 min at –30 °C. Catalytic amount of anhydrous neat $SnCl_4$ (1.523 g, 685 μL, 5.85 mmol, 0.15 equiv) was then added dropwise to the reaction *via* a syringe at –30 °C and the reaction was stirred for 15 min at –30 °C. The solution was cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min.

To a separate flame-dried and argon-flushed tared 3-neck flask equipped with a stir-bar, a cold-finger and a septum was added anhydrous THF (78 mL, [0.5 M]). The THF was cooled to –78 °C using an acetone/dry ice cooling bath and isobutylene (10.94 g, 18.61 mL, 195 mmol, 5.0 equiv) was condensed in the 3-neck flask. The isobutylene solution was canulated

98. For characterization data, see: Faul, M. A., Ratz, A. M., Sullivan, K. A., Trankle, W. G. & Winneroski, L. L. Synthesis of novel retinoid X receptors-selective retinoids. *J. Org. Chem.* **66**, 5772-5782 (2001).

dropwise into the 500 mL round-bottom flask at –78 °C and the reaction was slowly warmed to room temperature over 1.5 hours. A dry reflux condenser was installed on the 500 mL round-bottom flask in place of the septum and the reaction was heated to reflux (~70-80 °C) and stirred for 2.5 hours. The reaction was quenched by addition of water (100 mL) and the biphasic mixture was transferred into a 1 L separatory funnel and the layers were separated. The organic layer was washed with NaOH (2N) (1x), dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 80g) using a gradient of 5% EtOAc/Hexanes to 90% EtOAc/Hexanes and fractions containing the ketone were concentrated to dryness. The product was isolated as an orange solid (5.98 g, 71% Yield). **mp**: 68-69 °C; $\mathbf{R_f}$: 0.80 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.26 (d, J = 7.0 Hz, 1H), 7.21 (s, 1H), 7.11 (d, J = 8.0 Hz, 1H), 2.66 (s, 2H), 2.38 (s, 3H), 1.47 (s, 6H), 1.33 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 214.9, 143.9, 140.6, 136.5, 128.3, 127.6, 125.4, 52.0, 48.2, 38.3, 31.0, 28.9, 21.6; **FTIR** (cm^{-1}) (neat): 2966, 2868, 1709, 1457, 1380, 1366, 1312, 1236, 821; **HRMS** (ESI, Pos): calc. for $C_{15}H_2ONa$ $[M+Na]^+$: 239.1412, found: 239.1402 *m/z*.

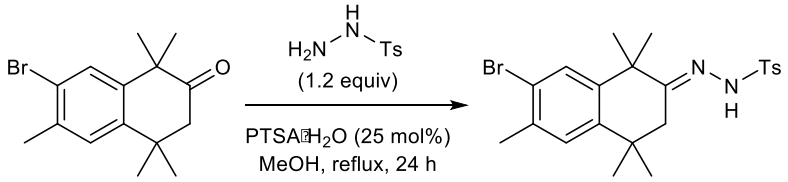
Synthesis of 4-[(3,5,5,8,8-pentamethyl-7-oxo-5,6,7-trihydronaphthyl)carbonyl]benzoate by an electrophilic bromination reaction on 1,1,4,4,6-pentamethyl-3,4-dihydronaphthalen-2(1H)-one



4-[(3,5,5,8,8-Pentamethyl-7-oxo-5,6,7-trihydronaphthyl)carbonyl]benzoate:[98] To a flame-dried and argon-flushed 250 mL round-bottom flask equipped with a stir-bar and a septum was added 1,1,4,4,6-pentamethyl-3,4-dihydronaphthalen-2(1*H*)-one (5.70 g, 26.4 mmol, 1.0 equiv). The ketone was dissolved in anhydrous DCM (39.4 mL, [0.67M]) and the solution was cooled to 0 °C. The ketone was treated with powdered anhydrous $AlCl_3$ (7.04 g, 52.8 mmol, 2.0 equiv) at 0 °C and the reaction was stirred at 0 °C for 5 min. In a separate flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added Br_2 (4.38 g, 1.41 mL, 27.7 mmol, 1.05 equiv). Bromine was then dissolved

in anhydrous DCM (19.7 mL, [1.34M]) and the solution was then canulated dropwise on the ketone solution at 0 °C and the reaction was stirred for 30 min at 0 °C. The reaction was carefully added into a 250 mL beaker containing crushed ice and was diluted with EtOAc (60 mL). The biphasic mixture was then transferred into a 250 mL separatory funnel and the layers were separated. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude aryl bromide was purified by recrystallization in MeOH. The product was isolated as a pale green solid (4.74 g, 61% Yield). **mp**: 100-102 °C; $\mathbf{R_f}$: 0.75 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.47 (s, 1H), 7.24 (s, 1H), 2.62 (s, 2H), 2.40 (s, 3H), 1.44 (s, 6H), 1.30 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 213.9, 143.3 (2), 136.4, 131.4, 127.3, 123.7, 51.7, 48.2, 38.0, 30.9, 28.9, 23.0; **FTIR** (cm^{-1}) (neat): 2957, 1710, 1481, 1419, 1383, 1307, 1293, 1235, 1079; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}OBr$ $[M+H]^+$: 295.0698 and 297.0677, found: 295.0695 and 297.0679 *m/z*.

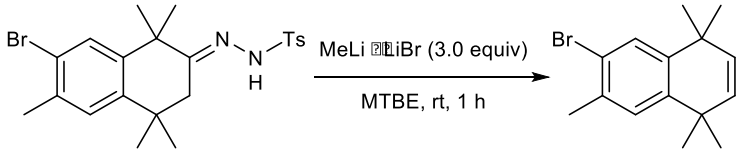
Synthesis of hydrazone by a condensation reaction with p-toluenesulfonylhydrazide on 4-[(3,5,5,8,8-pentamethyl-7-oxo-5,6,7-trihydronaphthyl)carbonyl]benzoate



[Aza(7-bromo-1,1,4,4,6-pentamethyl(2-1,3,4-trihydronaphthylidene))methyl][(4-methylphenyl)-sulfonyl]aniline:[98] To a flame-dried and argon-flushed 250 mL round-bottom flask equipped with a stir-bar, a reflux condenser, and a septum was added 4-[(3,5,5,8,8-pentamethyl-7-oxo-5,6,7-trihydronaphthyl)carbonyl]benzoate (4.70 g, 15.9 mmol, 1.0 equiv). The aryl bromide was dissolved in anhydrous MeOH (94.0 mL, [0.17M]). *p*-Toluenesulfonylhydrazide (3.55 g, 19.1 mmol, 1.2 equiv) and *p*-toluenesulfonic acid monohydrate (757 mg, 3.98 mmol, 0.25 equiv) were added to the aryl bromide solution and the reaction was warmed to reflux (~90 °C) for 24 hours. The reaction was then slowly cooled to room temperature and then the product was crystallized by cooling the flask to 0 °C using a water/ice cooling bath for 1 hour. The solid was then filtered on a Buchner filter and the solid was rinsed with cold MeOH (30 mL). The product was isolated as a white solid (5.65 g, 77%

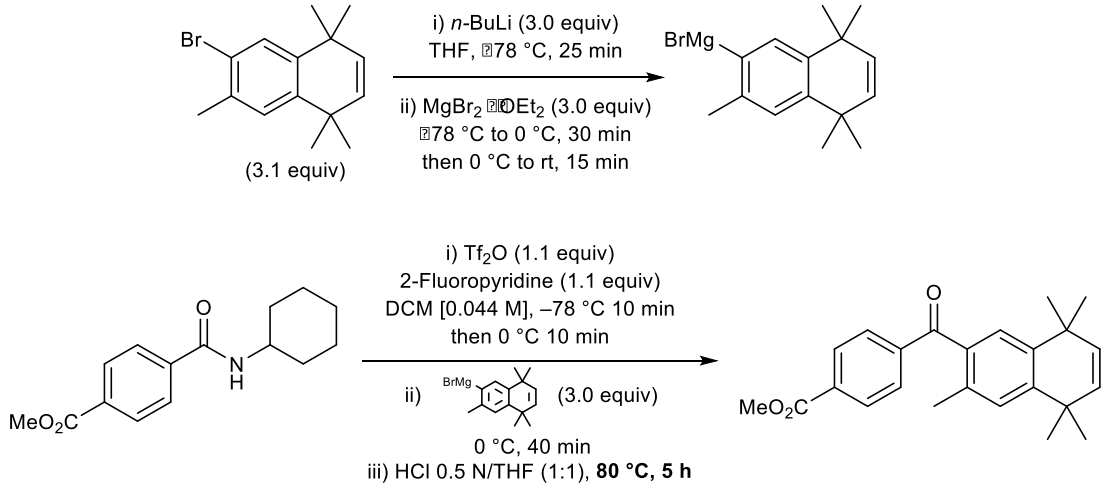
Yield). **mp**: 190-192 °C; $\mathbf{R_f}$: 0.35 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.32 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.45 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 2.49 (s, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 1.41 (s, 6H), 1.13 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 163.5, 144.4, 143.6, 143.4, 136.0, 135.6, 131.1, 129.8, 128.5, 127.4, 123.4, 43.3, 37.4, 36.7, 30.5, 30.2, 22.9, 22.0; **FTIR** (cm^{-1}) (neat): 2972, 1345, 1169, 1055, 1033, 1011; **HRMS** (ESI, Pos): calc. for $C_{22}H_{28}O_2N_2SBr$ $[M+H]^+$: 463.1055 and 465.1034, found: 463.1049 and 465.1038 *m/z*.

Synthesis of 6-bromo-1,1,4,4,7-pentamethyl-1,4-dihydronaphthalene by a Shapiro reaction on the hydrazone



6-Bromo-1,1,4,4,7-pentamethyl-1,4-dihydronaphthalene:[98] To a flame-dried and argon-flushed 250 mL round-bottom flask equipped with a stir-bar and a septum was added [aza(7-bromo-1,1,4,4,6-pentamethyl(2-1,3,4-trihydronaphthylidene))methyl][(4-methylphenyl)-sulfonyl]aniline (5.50 g, 11.9 mmol, 1.0 equiv). The hydrazone was diluted with MTBE (110 mL, [0.11M]) and the suspension was stirred at room temperature. A solution of MeLi•LiBr in Et_2O (solution titrated at 1.35M) (26.4 mL, 35.7 mmol, 3.0 equiv) was then added dropwise at room temperature on the hydrazone solution and the reaction was stirred for 1 hour at room temperature. The reaction was then quenched by addition of crushed ice in the reaction mixture and the biphasic mixture was then transferred into a 500 mL separatory funnel. The layers were separated and the aqueous layer was extracted with MTBE (2x). The organic layers were combined, dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The product was isolated as a white solid (3.31 g, 99% Yield). **mp**: 115-116 °C; $\mathbf{R_f}$: 0.80 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.52 (s, 1H), 7.24 (s, 1H), 5.52 (s, 2H), 2.41 (s, 3H), 1.35 (s, 12H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 142.8, 142.3, 135.4, 133.2, 133.1, 130.3, 129.0, 122.8, 35.5, 35.4, 33.0, 32.9, 23.0; **FTIR** (cm^{-1}) (neat): 2957, 2865, 1482, 1455, 1378, 1109; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}Br$ $[M+H]^+$: 279.0748 and 281.0728, found: 279.0743 and 281.0720 *m/z*.

*Synthesis of methyl 4-[(3,5,5,8,8-pentamethyl-2-5,8-dihydronaphthyl)carbonyl] benzoate (**10**) by addition of to activated N-cyclohexyl-4-(methoxycarbonyl)benzamide (**3.4a**)*



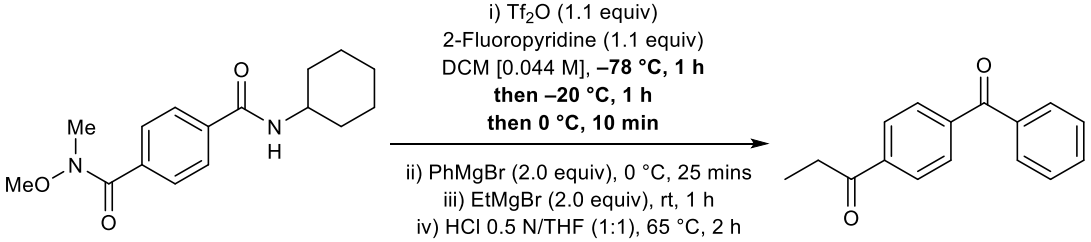
Methyl 4-[(3,5,5,8,8-pentamethyl-2-5,8-dihydronaphthyl)carbonyl] benzoate (3.14):[98] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added 6-bromo-1,1,4,4,7-pentamethyl-1,4-dihydronaphthalene (861.9 mg, 3.1 mmol, 3.1 equiv). The aryl bromide was diluted with anhydrous THF (12.5 mL, [0.25 M]) and the solution was cooled to to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. A solution of *n*-BuLi in hexanes (solution titrated at 2.58M) (1.16 mL, 3.0 mmol, 3.0 equiv) was added dropwise at –78 °C using a syringe. The reaction was then stirred at –78 °C for 30 min. Then, $MgBr_2 \cdot OEt_2$ (774.7 mg, 3.0 mmol, 3.0 equiv) was added to the reaction at –78 °C and the reaction was slowly warmed to 0 °C and stirred for 30 min. The reaction was then warmed to room temperature and stirred for 15 min to insure complete conversion to **3.13b** ($MgBr_2 \cdot OEt_2$ was completely dissolved).

To a seperate flame-dried and argon-flushed 100 mL round-bottom flask equipped with a stir-bar and a septum was added amide **3.4a** (261.1 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride

(Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 10 min. The solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. The preformed Grignard reagent **3.13b** (3.0 mmol, 3.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 40 min at 0 °C. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 16 mL of THF. The biphasic mixture was warmed to 80 °C for 5 hours to ensure complete hydrolysis to the ketone (**Note**: the imine intermediate is particularly stable to hydrolysis compared to other biaryl ketones synthesized in Table #2). The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude ketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40g) using a gradient of 0% EtOAc/Hexanes to 90% EtOAc/Hexanes and fractions containing **3.10** were concentrated to dryness. The product was isolated as a white powder (343.9 mg, 95% Yield). **mp**: 111-112 °C; **R_f**: 0.75 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.17-8.13 (m, 2H), 7.92-7.87 (m, 2H), 7.34 (s, 1H), 7.30 (s, 1H), 5.55 (s, 2H), 3.98 (s, 3H), 2.40 (s, 3H), 1.40 (s, 6H), 1.28 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 198.1, 166.8, 146.3, 142.3, 140.1, 135.6 125.3, 134.0, 133.2, 133.1, 130.4, 130.0, 129.5, 128.5, 52.9, 35.7, 35.3, 32.9, 32.8, 20.5; **FTIR** (cm^{-1}) (neat): 2957, 1715, 1670, 1498, 1458, 1437, 1363, 1189; **HRMS** (ESI, Pos): calc. for $C_{24}H_{27}O$ $[M+H]^+$: 363.1960, found: 363.1961 *m/z*.

Unsymmetrical diketone synthesis (Figure #2c):

*Synthesis of 1-(4-benzoylphenyl)propan-1-one (**3.14**) by chemoselective activation of N'-cyclohexyl-N-methoxy-N-methylterephtalamide (**3.4l**) –20 °C followed by successive addition of PhMgBr and EtMgBr.*

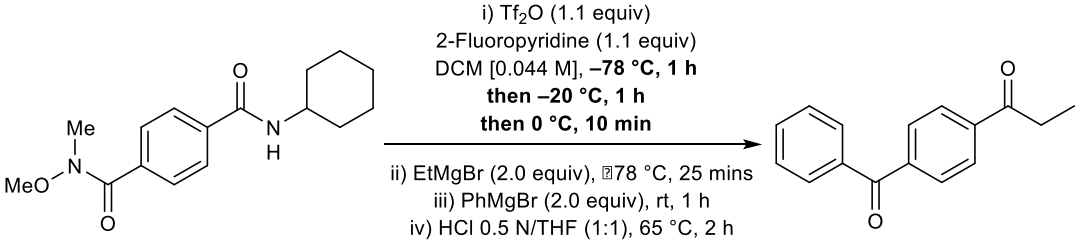


1-(4-Benzoylphenyl)propan-1-one (3.14):[99] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added *N'*-cyclohexyl-*N*-methoxy-*N*-methylterephtalamide (**3.4l**) (290.2 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 1 hour. The solution was slowly warmed to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred at –20 °C for 1 hour. Then, the solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. A solution of PhMgBr in Et_2O (solution titrated at 2.79M) (716 µL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was stirred for 25 min at 0 °C. Then, a solution of EtMgBr in Et_2O (Aldrich Sure-Sealed (3.0 M) solution) (670 µL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at 0 °C and the reaction was warmed to room temperature and stirred for 1 hour at room temperature. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL

[99]. For characterization data, see: Suhana, H. & Srinivasan, P. C. A facile synthesis of 1,4-diacylbenzenes *Synth. Commun.* **33**, 3097-3102 (2003).

separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude diketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 20g) using a gradient of 5% EtOAc/Hexanes to 90% EtOAc/Hexanes and fractions containing **3.14** were concentrated to dryness. The product was isolated as a white powder (230.1 mg, 97% Yield). **mp**: 80-81 °C, litt:[99] 86 °C; $\mathbf{R_f}$: 0.60 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.82-7.80 (m, 2H), 7.65-7.61 (m, 1H), 7.53-7.49 (m, 2H), 3.06 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.6, 196.4, 141.5, 139.9, 137.4, 133.5, 130.5, 130.4, 128.9, 128.2, 32.6, 8.5; **FTIR** (cm^{-1}) (neat): 2938, 1687, 1644, 1594, 1279, 1216; **HRMS** (ESI, Pos): calc. for $C_{16}H_{15}O_2$ $[M+H]^+$: 239.1072, found: 239.1068 *m/z*.

*Synthesis of 1-(4-benzoylphenyl)propan-1-one (**3.14**) by chemoselective activation of N'-cyclohexyl-N-methoxy-N-methylterephtalamide (**3.4l**) –20 °C followed by successive addition of EtMgBr and PhMgBr (inversed addition).*



1-(4-Benzoylphenyl)propan-1-one (3.14):[99] To a flame-dried and argon-flushed 50 mL round-bottom flask equipped with a stir-bar and a septum was added *N'*-cyclohexyl-*N*-methoxy-*N*-methylterephtalamide (**3.4l**) (290.2 mg, 1.0 mmol, 1.0 equiv). The amide was diluted with anhydrous DCM (22.5 mL, [0.044 M]) and 2-fluoropyridine (107.0 mg, 95 µL, 1.1 mmol, 1.1 equiv) was added to the solution. The solution was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 min. Trifluoromethanesulfonic anhydride (Tf_2O) (310.1 mg, 185 µL, 1.1 mmol, 1.1 equiv) was added dropwise *via* a syringe at –78 °C and the reaction was stirred for 1 hour. The solution was slowly warmed to –20 °C using an *i*-PrOH:H_2O (1:1)/dry ice cooling bath and stirred at –20 °C for 1 hour. Then, the solution was warmed to 0 °C using a water/ice bath and the reaction was stirred for 10 min. The solution

was then cooled to –78 °C using an acetone/dry ice cooling bath and stirred for 2 minutes. A solution of EtMgBr in Et_2O (solution titrated at 3.00 M) (670 µL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at –78 °C and the reaction was stirred for 25 min at –78 °C. Then, a solution of PhMgBr in Et_2O (solution titrated at 2.79M) (716 µL, 2.0 mmol, 2.0 equiv) was added in one portion to the reaction at –78 °C and the reaction was warmed to room temperature and stirred for 1 hour. The reaction was quenched by addition of 8 mL of an aqueous solution of HCl (0.5 N) and 8 mL of THF. The biphasic mixture was gently warmed to 65 °C (keeping the flask ventilated for DCM evaporation) for 2 hours to ensure complete hydrolysis to the ketone. The biphasic mixture was then transferred to a 60 mL separation funnel using DCM and the layers were separated. The aqueous layer was extracted with DCM (2x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude diketone was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 20g) using a gradient of 5% EtOAc/Hexanes to 90% EtOAc/Hexanes and fractions containing **3.14** were concentrated to dryness. The product was isolated as a white powder (226.0 mg, 95% Yield). **Note**: *See pages S76-S77 for characterization data of ketone **3.14**.*

Experimental section of Chapter 4

General Information

Unless otherwise stated, all glassware was stored in the oven and/or was flame-dried prior to use. All reactions were set up under an argon atmosphere[100] while adding reagents and were run with the exclusion of moisture. All reaction flasks were kept closed with a septum during the reaction times. Anhydrous solvents were obtained either by filtration through drying columns on a GlassContour system (Irvine, CA) such as THF, DCM, DMF, CH_3CN, CH_3OH or by distillation over calcium hydride system such as DCE. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV absorbance, aqueous potassium permanganate ($KMnO_4$), or ninhydrin. Flash column chromatography was performed on an automatic purification system Teledyne Isco Combiflash® Companion. Prepacked normal phase silica gel columns Redi*Sep*® Rf High Performance Gold (40 g, 80 g and 120 g) from Teledyne Isco were used for separation of products. Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}HNMR, ^{13}CNMR, ^{19}FNMR and ^{31}PNMR) were recorded on two Avance AV400 MHz and AV500 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform ($CDCl_3$) (δ = 7.27 ppm) as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (δ = 77.23 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Bruker Vertex Series FTIR (neat) and are reported in reciprocal centimeters (cm^{-1}). Analytical Supercritical Fluid

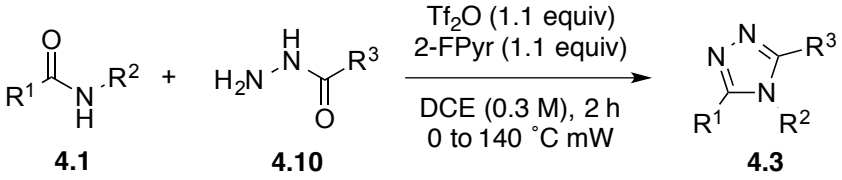
(100) Shriver, D. F. & Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*; 2nd Edition; Wiley: New York, 1986.

Chromatography (SFC) analysis were performed on a Aurora SFC Systems coupled to both Agilent 1260 HPLC and Agilent 6120 Simple Quadruple MS with a Multimode source. Analysed samples were dissolved in *i*-PrOH. Carbon dioxide was used as a carrier gas (150 psi). Data are reported as follows: column type, eluent, flow rate, temperature, backpressure, wavelength and retention times. Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (*c* in g/mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

Reagents

Unless otherwise stated, commercial reagents were used without purification. Triethylamine (Et_3N) was distilled over sodium and kept under argon before use. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over P_2O_5 (phosphorus pentoxide) and kept under argon before use.

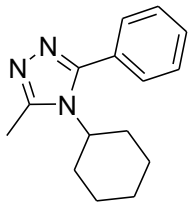
General conditions for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles



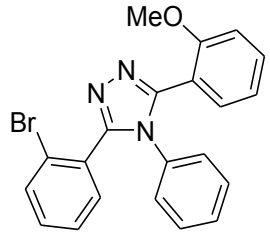
4.1 **4.10** **4.3**

To a flame-dried and argon-purged 5 mL glass microwave vial (Biotage ® 2-5 mL) equipped with a magnetic stir bar and a rubber septum was added the amide **4.1** (1.0 mmol, 1.0 equiv), dichloroethane (DCE) (3.33 mL, 0.3 M) and 2-fluoropyridine (2-FPyr) (98 μL, 1.1 mmol, 1.1 equiv). The solution was cooled to 0 °C using a water/ice cooling bath. Trifluoromethanesulfonic anhydride (Tf_2O) (185 μL, 1.1 mmol, 1.1 equiv) was added over 1 minute via syringe and the reaction was stirred at 0 °C for 10 minutes. The hydrazide **4.10** (1.1 mmol, 1.1 equiv) was added in one portion and the reaction was stirred at room temperature for 10 min. The rubber septum was removed and the microwave vial was quickly capped with a teflon microwave cap with aluminum o-ring using a crimper (Biotage ®). The reaction was heated for 2 h to 140 ˚C μW (very high absorption level) using a Biotage ® Initiator Classic. Once the reaction was cooled to room temperature, the cap was removed and the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (3 mL). The biphasic mixture was then transferred to a 60 mL separation funnel using DCM (10 mL) and an aqueous solution of saturated $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was washed with DCM (2 x 10 mL) and the organic layers were combined. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 40 g) or activated basic aluminium oxide (Al_2O_3) (column Redi*Sep*® Rf 40 g).

Characterization data of 1,2,4-triazoles

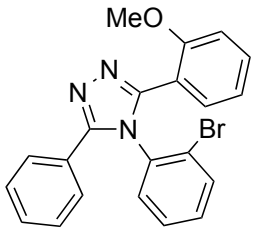


4-Cyclohexyl-3-methyl-5-phenyl-4*H*-1,2,4-triazole (4.3a): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3a** were concentrated to dryness. The product was isolated as a white solid (192.9 mg, 80% yield); **mp**: 121-123 ^{0}C, $\mathbf{R_f}$: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.51-7.47 (m, 5H), 4.05-3.97 (m, 1H), 2.63 (s, 3H), 1.93-1.80 (m, 6H), 1.74-1.66 (m, 1H), 1.32-1.21 (m, 2H), 1.20-1.10 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 155.2, 151.1, 129.8, 129.5, 128.7, 128.4, 56.4, 32.0, 25.9, 25.0, 13.5; **FTIR** (cm^{-1}) (neat) 2934, 2855, 1516, 1443, 1372, 995, 894, 768, 719, 699, 567, 491; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}N_3$ $[M+H]^+$: 242.1652, found: 242.1648 *m/z*.

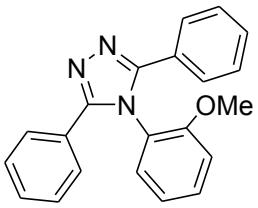


3-(2-Bromophenyl)-5-(2-methoxyphenyl)-4-phenyl-4*H*-1,2,4-triazole (4.3b): Following the general conditions for the synthesis of 1,2,4-triazoles, the reaction was performed in DCM instead of DCE. For the activation step, Tf_2O was added at −78 ˚C (instead of 0 ˚C) and the reaction was stirred at 0 ˚C for 10 min. For the cyclodehydration step, the reaction was heated for 4 h (instead of 2 h) to 140 ˚C μW. The crude 1,2,4-triazole was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3b** were concentrated to dryness. The product was isolated as a yellow solid (263.3 mg, 65% yield), **mp**: 140-142 ^{0}C; $\mathbf{R_f}$: 0.65 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.71-7 (dd,

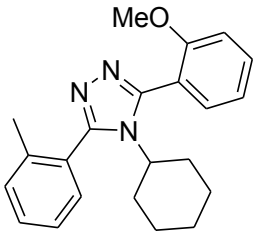
J=1.7 Hz, *J*=7.6 Hz, 1H); 7.54-7.50 (m, 2H), 7.42-7.37 (m, 1H), 7.35 (td, *J*=1.3 Hz, *J*=7.6 Hz, 1H), 7.27 (m, 1H), 7.16 (m, 3H), 7.21 (td, *J*=1.0 Hz, *J*=7.50 Hz, 1H), 6.95-6.92 (m, 2H), 6.74-6.74 (m, 1H), 3.30 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 156.7, 153.6, 153,0, 135.1, 132.9, 132.8, 132.3, 131.9, 131.5, 129.4, 128.6, 128.2, 127.2, 126.0, 124.4, 120.9, 116.4, 110.8, 54.7; **FTIR** (cm^{-1}) (neat): 2964, 2360, 2330, 1583, 1468, 1247, 972, 754, 644, 609; **HRMS** (ESI, Pos): calc. for $C_{21}H_{17}BrN_3O$ $[M+H]^+$: 406.0550 found: 406.0563 *m/z*.



4-(2-Bromophenyl)-3-(2-methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazole (4.3c): Following the general conditions for the synthesis of 1,2,4-triazoles, the reaction was performed in DCM instead of DCE. For the activation step, Tf_2O was added at −78 ˚C (instead of 0 ˚C) and the reaction was stirred at 0 ˚C for 10 min. For the cyclodehydration step, the reaction was heated for 4 h (instead of 2 h) to 140 ˚C μW. The crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 70% to 100% EtOAc/Hex, and the fractions containing **4.3c** were concentrated to dryness. The product was isolated as a pale yellow solid (162.0 mg, 40% yield), **mp**: 199-201 ^{0}C; **R_f**: 0.45 (100% EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.57 (dd, *J* = 1.7 Hz, *J* = 7.7 Hz, 1H), 7.54-7.51 (m, 1H), 7.48-7.44 (m, 2H), 7.37-7.33 (m, 2H), 7.31-7.26 (m, 4H), 7.25-7.19 (m, 1H), 6.98 (td, *J* = 1.0 Hz, *J* = 7.5 Hz, 1H), 6.75-6.72 (m, 1H), 3.54 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 157.1, 154.2, 153.6, 134.8, 133.5, 132.7, 131.9, 130.7, 129.9, 129.6, 128.4, 128.1, 127.8, 127.4, 122.5, 120.6, 116.2, 110.5, 54,8; **FTIR** (cm^{-1}) (neat): 2973, 1473, 1274, 1057, 1046, 1033, 800, 772, 705, 619; **HRMS** (ESI, Pos): calc. for $C_{21}H_{17}BrN_3O$ $[M+H]^+$: 406.0550 found: 406.0569 *m/z*.

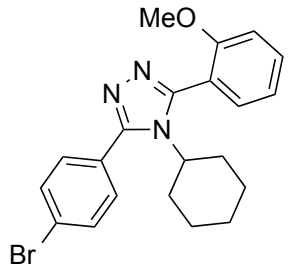


4-(2-Methoxyphenyl)-3,5-diphenyl-4*H*-1,2,4-triazole (4.3d): Following the general conditions for the synthesis of 1,2,4-triazoles, the reaction was performed in DCM instead of DCE. For the activation step, Tf_2O was added at −78 ˚C (instead of 0 ˚C) and the reaction was stirred at 0 ˚C for 10 min. For the cyclodehydration step, the reaction was heated for 4 h (instead of 2 h) to 140 ˚C μW. The crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3d** were concentrated to dryness. The product was isolated as a pale brown solid. (222.5 mg, 68% yield); **mp**: 151-153 ^{0}C, $\mathbf{R_f}$: 0.57 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.47-7.40 (m, 5H), 7.36-7.32 (m, 2H), 7.30-7.25 (m, 6H), 7.09 (dd, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H), 6.98-6.92 (m, 2H), 3.51 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 155.2, 154.8, 131.3, 129.4, 129.3, 128.3, 127.5, 124.2, 121.2, 112.5, 55.5; **FTIR** (cm^{-1}) (neat): 3066, 1599, 1502, 1468, 1278, 1248, 969, 779, 695, 573; **HRMS** (ESI, Pos): calc. for $C_{21}H_{17}N_3O$ $[M+H]^+$: 328.1444, found: 328.1446 *m/z*.

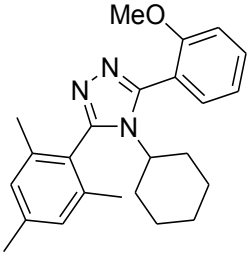


4-Cyclohexyl-3-(2-methoxyphenyl)-5-(2-methylphenyl)-4*H*-1,2,4-triazole (4.3e): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using 100% EtOAc and the fractions containing **4.3e** were concentrated to dryness. The product was isolated as a white solid (309.0 mg, 89% yield), **mp**: 153-155 ^{0}C; $\mathbf{R_f}$: 0.51 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.54-7.48 (m, 2H), 7.44-7.38 (m, 2H), 7.34-7.26 (m, 2H), 7.12- 7.08 (m. 1H), 7.03-7.00 (m, 1H), 3.82 (s, 3H), 3.70-3.64 (m, 1H), 2.24 (s, 3H), 1.88-1.75 (m, 2H), 1.67-1.59 (m, 2H), 1.48-1.34 (m, 3H), 1.03 (aqt, *J* = 3.5

Hz, *J* = 13.2 Hz, 2H), 0.74 (aqt, *J*=3.5 Hz, *J*=13.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 157.8, 153.6, 152.3, 138.9, 132.6, 131.8, 131.1, 130.2, 130.0, 128.9, 125.3, 120.8, 117.7, 110.9, 57.6, 55.4, 32.3, 26.0, 24.9, 20.0; **FTIR** (cm^{-1}) (neat): 2931, 2856, 1465, 1389, 1243, 1012, 769, 755, 725, 604.; **HRMS** (ESI, Pos): calc. for $C_{22}H_{26}N_3O$ $[M+H]^+$: 348.2070, found: 348.2074 *m/z.*

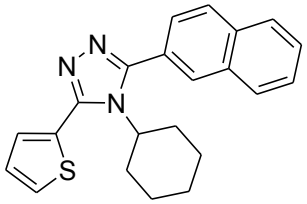


3-(4-Bromophenyl)-4-cyclohexyl-5-(2-methoxyphenyl)-4*H*-1,2,4-triazole (4.3f): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3f** were concentrated to dryness. The product was isolated as a pale yellow solid (349.4 mg, 85% yield), **mp**: 161-163 ^{0}C; **Rf**: 0.47 (1 % MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.67-7.63 (m, 2H), 7.53-7.43 (m, 4H), 7.11-7.06 (m, 1H), 7.02-6.99 (m, 1H), 3.87-3.79 (m, 4H), 1.90-1.76 (m, 2H), 1.71-1.63 (m, 2H), 1.54-1.39 (m, 3H), 1.08 (aqt, *J* = 3.5Hz, *J* = 13.3 Hz, 2H), 0.81 (aqt, *J*=3.0 Hz, *J*=13.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 157.9, 153.9, 152.7, 132.6, 132.0, 131.7 (2), 128.1, 124.4, 120.7, 117.7, 111.0, 57.8, 55.4, 32.8, 26.0, 24.9; **FTIR** (cm^{-1}) (neat): 2933, 2855, 1468, 1447, 1384, 1182, 1023, 1004, 837, 752; **HRMS** (ESI, Pos): calc. for $C_{21}H_{23}BrN_3O$ $[M+H]^+$: 412.1019, found: 412.1019 *m/z*.

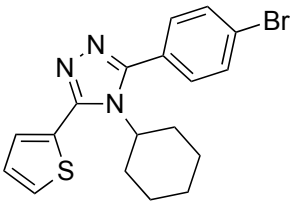


4-Cyclohexyl-3-(2,4,6-trimethylphenyl)-5-(2-methoxyphenyl)-4*H*-1,2,4-triazole (4.3g): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was

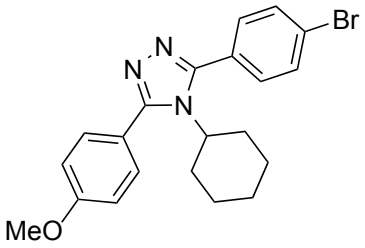
purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc, and the fractions containing **4.3g** were concentrated to dryness. The product was isolated as a white solid (251,4 mg, 67% yield), **mp**: 146-148 ^{0}C, $\mathbf{R_f}$: 0.30 (1% MeOH/EtOAc), 0.36 (1% MeOH/EtOAc, Silica Gold); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.55-7.50 (m, 2H), 7.12 (dd, *J* = 1.0 Hz, *J* = 7.5 Hz, 1H), 7.04-7.01 (m, 1H), 6.98-6.96 (m, 2H), 3.83 (s, 3H), 3.68 (tt, *J* = 3.2 Hz, *J* = 12.2 Hz, 1H), 2.37 (s, 3H), 2.13 (s, 6H), 1.89-1.79 (m, 2H), 1.70-1.60 (m, 2H), 1.50-1.33 (m, 3H), 1.06 (aqt, *J*= 3.2 Hz, *J* = 13.2 Hz, 2H), 0.77 (aqt, *J* = 3.7 Hz, *J* = 13.2 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 157.9, 153.0, 151.9, 139.5, 138.7, 132.5, 131.7, 128.3, 125.5, 120.7, 118.2, 110.9, 57.5, 55.5, 32.0, 26.0, 24.8, 21.3, 20.3; **FTIR** (cm^{-1}) (neat): 2934, 2858, 2361, 1736, 1506, 1258, 1164, 1010, 830, 698; **HRMS** (ESI, Pos): calc. for $C_{24}H_{31}N_3O$ $[M+H]^+$: 376.2383 found: 376.2387 *m/z*.



4-Cyclohexyl-3-(naphthalen-2-yl)-5-(thiophen-3-yl)-4*H*-1,2,4-triazole (4.3h): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc, and the fractions containing **4.3h** were concentrated to dryness. The product was isolated as a yellow solid (247.8 mg, 69 % yield), **mp**: 84-85 ^{0}C; $\mathbf{R_f}$: 0.63 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.10 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.95-7.92 (m, 2H), 7.65-7.55 (m, 4H), 7.44 (dd, *J* = 1.2 Hz, *J* = 3.7 Hz, 1H), 7.21 (dd, *J* = 3.7 Hz, *J* = 5.3 Hz, 1H), 4.26-4.20 (m, 1H), 1.98-1.91 (m, 2H), 1.78-1.68 (m, 4H), 1.57-1.51 (m, 1H), 1.25-1.13 (m, 2H), 0.90 (aqt, *J* = 3.2 Hz, *J* = 13.5 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 155.8, 149.7, 133.8, 132.8, 130.1, 129.9, 128.7, 128.6, 128.5, 128.3, 127.9, 127.4 (2), 127.0, 126.6, 126.1, 58.0, 33.2, 25.9, 24.7; **FTIR** (cm^{-1}) (neat): 3061, 2923, 2856, 2360, 1421, 1385, 830, 772, 749; **HRMS** (ESI, Pos): calc. for $C_{22}H_{22}N_3S$ $[M+H]^+$: 360.1529 found: 360.1538 *m/z*.

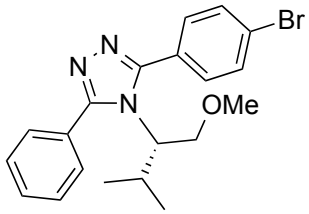


3-(4-Bromophenyl)-4-cyclohexyl-5-(thiophen-2-yl)-4*H*-1,2,4-triazole (4.3i): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc, and the fractions containing **4.3i** were concentrated to dryness. The product was isolated as a pale grey solid (272.3 mg, 70 % yield), **mp**: 160 ^{0}C; $\mathbf{R_f}$: 0.69 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.68-7.65(m, 2H), 7.57 (dd, *J* = 1.2, Hz, *J* = 5.2 Hz, 1H), 7.47-7.43 (m, 3H), 7.21-7.19 (m, 1H), 4.27 (tt, *J* = 3.5 Hz, *J* = 12.5 Hz, 1H), 1.93-1.86 (m, 2H), 1.81-1.74 (m, 2H), 1.71-157 (m, 3H), 1.22 (aqt, *J* = 3.5 Hz, *J* = 13.2 Hz, 2H), 0.95 (aqt, *J* = 3.7 Hz, *J* = 13.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 154.5, 149.8, 132.0, 131.5, 130.3, 129.0, 127.8, 127.6, 127.5, 124.9, 58.2, 33.2, 25.9, 24.7; **FTIR** (cm^{-1}) (neat): 3062, 2925, 2856, 2361, 1449, 1425, 1007, 851, 839, 743; **HRMS** (ESI, Pos): calc. for $C_{18}H_{19}BrN_3S$ $[M+H]^+$: 390.0458 found: 390.0469 *m/z*.

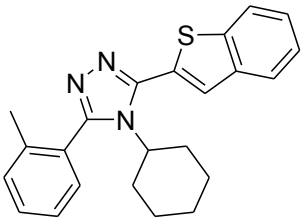


3-(4-Bromophenyl)-4-cyclohexyl-5-(4-methoxyphenyl)-4*H*-1,2,4-triazole (4.3j): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3j** were concentrated to dryness. The product was isolated as a white solid (324.8 mg, 79% yield); **mp**: 151-153 ^{0}C; $\mathbf{R_f}$: 0.35 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.67-7.64 (m, 2H), 7.51-7.48 (m, 2H) 7.47-7.44 (m, 2H), 7.04-7.01 (m, 2H), 4.00-3.94 (m, 1H), 3.89 (s, 3H), 1,87-1.81 (m, 2H), 1.74-1.68 (m, 2H), 1.60-1.50 (m, 4H), 1.14 (aqt, *J* = 3.2 Hz, *J* = 13.5, Hz,

2H), 1.09 (aqt, *J*=4.0 Hz, *J*=13.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 160.9, 155.5, 154.2, 131.9, 131.5, 131.3, 128.0, 124.5, 120.7, 114.1, 57.8, 55.4, 33.4, 25.9, 24.8; **FTIR** (cm^{-1}) (neat): 2931, 2855, 1612, 1472, 1248, 1033, 1008, 832, 587, 539; **HRMS** (ESI, Pos): calc. for $C_{21}H_{23}BrN_3O$ $[M+H]^+$: 412.1019, found: 412.1028 *m/z*.

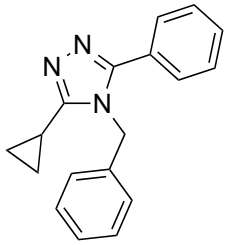


3-(4-Phenyl)-4-(1-methoxy-3-methylbutan-2-yl)-5-bromophenyl-4*H*-1,2,4-triazole (4.3k): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3k** were concentrated to dryness. The product was isolated as a white solid (287.4 mg, 72% yield), **mp**: 49-50 ^{0}C, **R_f**: 0.46 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.66-7.62 (m, 2H), 7.62-7.56 (m, 2H), 7.55-7.46 (m, 5H), 4.00 (td, *J* = 5 Hz, *J* = 10.7 Hz, 1H), 3.55-3.50 (m, 1H), 3.34 (t, *J* = 10.2 Hz, 1H), 3.34 (s, 3H), 1.72-1.60 (m, 1H), 0.73 (d, *J* = 6.5 Hz, 3H) 0.53 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 131.8 (4), 130.2 (2), 130.1, 128.5 (2), 124.6, 72.0, 63.5, 58.9, 30.3, 20.1, 19.5; **FTIR** (cm^{-1}) (neat): 2934, 2854, 2361, 1476, 1454, 918, 757, 681, 567, 491; **HRMS** (ESI, Pos): calc. for $C_{20}H_{22}N_3BrO$ $[M+H]^+$: 400.1019, found: 400.1023 *m/z*.

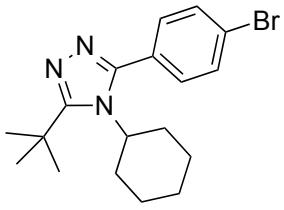


3-(2-Methylphenyl)-4-cyclohexyl-5-(1-benzothiophen-2-yl)-4*H*-1,2,4-triazole (4.3l): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3l** were concentrated to dryness. The product was isolated as a white solid (220.2 mg, 59%

yield), **mp**: 140-142 ˚C, $\mathbf{R_f}$: 0.62 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.95-7.88 (m, 2H), 7.67 (s, 1H), 7.47-7.41 (m, 3H), 7.38-7.28 (m, 3H), 4.22 (att, *J* = 3.5 Hz, *J* = 12.0 Hz, 1H), 2.26 (s, 3H), 1.96-1.90 (m, 2H), 1.77-1.70 (m, 2H), 1.67-1.51 (m, 3H), 1.19 (aqt, *J* = 3.5 Hz, *J* = 13.2 Hz, 2H), 0.86 (aqt, *J* = 3.5 Hz, *J* = 13.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 154.6, 149.4, 140.7, 139.2, 138.8, 130.9, 130.5, 130.3, 128.7, 128.6, 126.4, 125.6, 125.5, 124.9, 124.5, 122.3, 57.8, 32.6, 25.9, 24.7, 20.2; **FTIR** (cm^{-1}) (neat): 2939, 2853, 1448, 1423, 866, 770, 747, 728, 602, 560; **HRMS** (ESI, Pos): calc. for $C_{23}H_{24}N_3S$ $[M+H]^+$: 374.1685, found: 374.1691 *m/z*.

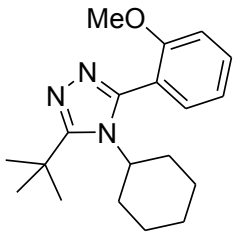


4-Benzyl-3-cyclopropyl-5-phenyl-4*H*-1,2,4-triazole (4.3m): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3m** were concentrated to dryness. The product was isolated as a white solid (187.1 mg, 68% yield), **mp**: 111-112 ˚C; $\mathbf{R_f}$: 0.73 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.54-7.50 (m, 2H), 7.46-7.30 (m, 6H), 7.06-7.03 (m, 2H), 5.28 (s, 2H), 1.64-1.58 (m, 1H), 1.19-1.15 (m, 2H), 0.96-0.91 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 157.3, 155.1, 135.5, 130.1, 129.2, 128.9, 128.8, 128.2, 127.0, 125.8, 47.3, 7.2, 5.8; **FTIR** (cm^{-1}) (neat): 3008, 2961, 2920, 1495, 1471, 823, 780, 767, 731, 715; **HRMS** (ESI, Pos): calc. for $C_{18}H_{18}N_3$ $[M+H]^+$: 276.1495 found: 276.1508 *m/z*.

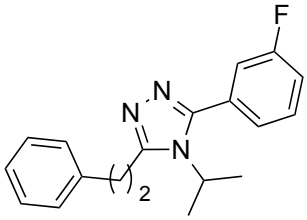


3-(4-Bromophenyl)-5-tert-butyl-4-cyclohexyl-4*H*-1,2,4-triazole (4.3n): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash

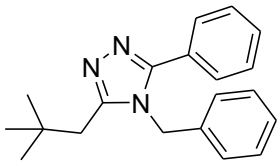
chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3n** were concentrated to dryness. The product was isolated as a white solid (274.5 mg, 76% yield), **mp**: 178-180 ^{0}C; **R_f**: 0.70 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.60-7.56 (m, 2H), 7.34-7.30 (m, 2H), 4.38 (tt, *J* = 3.5 Hz, *J* = 12.5 Hz, 1H), 1.86-1.73 (m, 4H), 1.43-1.30 (m, 11H), 1.25 (aqt, *J* = 3.5 Hz, *J* = 13.2 Hz, 2H), 0.83 (aqt, *J* = 3.5 Hz, *J* = 13,2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 160.7, 154.4, 132.6, 131.3, 129.8, 124.3, 57.4, 33.1, 32.6, 29.4, 26.4, 24.8; **FTIR** (cm^{-1}) (neat): 2973, 2933, 2846, 2359, 1598, 1461, 1364, 1007, 837, 835; **HRMS** (ESI, Pos): calc. for $C_{18}H_{24}BrN_3$ $[M+H]^+$: 362.1232 found: 362.1245 *m/z*.



3-Tert-butyl-4-cyclohexyl-5-(2-methoxyphenyl)-4*H*-1,2,4-triazole (4.3o): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3o** were concentrated to dryness. The product was isolated as a pale yellow oil (244.3 mg, 78% yield). **R_f**: 0.66 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.47-7.42 (m, 1H), 7.28 (dd, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H), 7.35 (td, *J* = 1.0 Hz, *J* = 7.5 Hz, 1H), 6.93 (dd, *J* = 0.5 Hz, *J* = 8.5 Hz, 1H), 4.23 (tt, *J* = 3.5 Hz, *J* = 12.2 Hz, 1H), 3.74 (s, 3H), 1.96-1.68 (m, 5H), 1.60-1.46 (m, 11H), 1.43-1.30 (m, 1H), 1.22 (aqt, *J* = 3.5 Hz, *J* = 13.0 Hz, 2H), 0.76 (aqt, *J* = 4.0 Hz, *J* = 13.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 160.2, 158.5, 152.1, 132.9, 131.6, 120.0, 119.7, 111.1, 57.2, 55.3, 32.5, 29.4 (2), 26.4, 25.0; **FTIR** (cm^{-1}) (neat): 2971, 2934, 2856, 1608, 1476, 1256, 1007, 725; **HRMS** (ESI, Pos): calc. for $C_{19}H_{278}N_3O$ $[M+H]^+$: 314.2227 found: 314.2241 *m/z*.

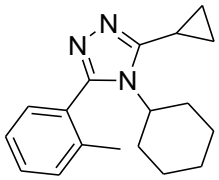


3-(2-Phenylethyl)-5-(3-fluorophenyl)-)-4-(propan-2-yl)-4*H*-1,2,4-triazole (4.3p): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3p** were concentrated to dryness. The product was isolated as a white solid (209.6 mg, 71% yield), **mp**: 94-95 ^{0}C; **R_f**: 0.75 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.49-7.44 (m, 1H), 7.35-7.18 (m, 9H), 4.42 (sep, J = 7.0 Hz, 1H), 3.34-3.28 (m, 2H), 3.17-3.13 (m, 2H), 1.38 (d, J = 7.0 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 162.5 (d, J = 246.7 Hz, $J_{C\text{-}F}$), 154.3, 153.5 (d, J = 2.4 Hz, $J_{C\text{-}F}$), 140.9, 130.5 (d, J = 8.3 Hz, $J_{C\text{-}F}$), 130.4 (d, J = 8.3 Hz, $J_{C\text{-}F}$), 128.7, 128.5, 126.5, 125.5 (d, J = 3.0 Hz, $J_{C\text{-}F}$), 117.0 (d, J = 20.8 Hz, $J_{C\text{-}F}$), 116.9 (d, J = 26.3 Hz, $J_{C\text{-}F}$), 48.1, 33.9, 29.1, 22.2; **FTIR** (cm^{-1}) (neat): 2971, 1584, 1499, 1456, 1129, 870, 795, 734, 700, 497; **HRMS** (ESI, Pos): calc. for $C_{18}H_{19}FN_3$ $[M+H]^+$: 296.1558, found: 296.1549 *m/z*.

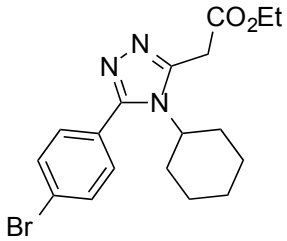


4-Benzyl-3-(2,2-dimethylpropyl)-5-phenyl-4*H*-1,2,4-triazole (4.3q): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3q** were concentrated to dryness. The product was isolated as a white solid (198.4 mg, 65% yield), **mp**: 139-141 ^{0}C; **R_f**: 0.57 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.52-7.48 (m, 2H), 7.45-7.37 (m, 3H), 7.35-7.27 (m, 3H), 6.92-6.89 (m, 2H), 5.19 (s, 2H), 2.57 (s, 2H), 1.07 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 154.7, 154.1, 135.6, 129.9, 129.2, 128.9, 128.8, 128.1, 127.7, 125.7, 47.2, 38.2, 32.4, 29.7; **FTIR** (cm^{-1}) (neat): 2951, 2867, 1512, 1473, 1452, 1362,

773, 718, 7001, 692; **HRMS** (ESI, Pos): calc. for $C_{20}H_{24}N_3$ $[M+H]^+$: 306.1965 found: 306.1979 *m/z*.

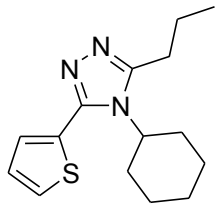


3-(2-Methylphenyl)-4-cyclohexyl-3-cyclopropyl-4*H*-1,2,4-triazole (4.3r): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g column) using a gradient of 0% to 1% MeOH/EtOAc and the fractions containing **4.3r** were concentrated to dryness. The product was isolated as a white solid (188.4 mg, 67% yield), **mp**: 96-98 ^{0}C; $\mathbf{R_f}$: 0.78 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.40-7.35 (m, 1H), 7.31-7.20 (m, 3H), 3.84-3.76 (m, 1H), 2.17 (s, 3H), 1.97-1.77 (m, 7H), 1.66-1.59 (m, 1H), 1.29-1.14 (m, 4H), 1.12-1.01 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 155.4, 154.1, 138.7, 130.5, 130.4, 130.0, 128.3, 125.6, 56.5, 32.1 (2), 25.9 (2), 25.0, 19.9; **FTIR** (cm^{-1}) (neat): 3013, 2933, 2854, 1708, 1450, 1425, 895, 765, 726; **HRMS** (ESI, Pos): calc. for $C_{17}H_{24}N_3$ $[M+H]^+$: 282.1965, found: 282.1966 *m/z*.

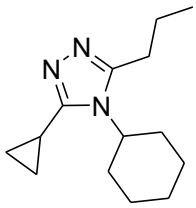


Ethyl [5-(4-bromophenyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]acetate (4.3s): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g column) using a gradient of 0% to 1% MeOH/acetone and the fractions containing **4.3s** were concentrated to dryness. The product was isolated as a yellow oil (256.4 mg, 68 % yield), $\mathbf{R_f}$: 0.48 (1% MeOH/Acetone); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.67-7.64 (m, 2H), 7.41-7.38 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 3.54 (tt, *J* = 3.5 Hz, *J* = 12.5 Hz, 1H), 1.95-1.82 (m, 4H), 1.72-1.60 (m, 3H), 1.34-1.22

(m, 5H), 1.08 (aqt, *J* = 3.5 Hz, *J* = 13 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 155.44, 154.06, 138.65, 130.53, 130.38, 130.03, 128.3, 125.64, 56.48, 32.48, 32.14, 25.93, 25.02, 19.91; **FTIR** (cm^{-1}) (neat): 3479, 3388, 2934, 2854, 2361, 1467, 1449, 781, 723, 542; **HRMS** (ESI, Pos): calc. for $C_{17}H_{21}N_3O_2$ $[M+H]^+$: 378.0812 found: 378.0810 *m/z*

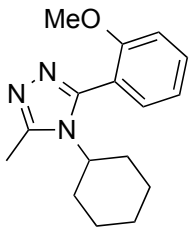


4-cyclohexyl-3-phenyl-5-thiophen-2-yl-4*H*-1,2,4-triazole (4.3t): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1% MeOH/EtOAc, and the fractions containing **4.3t** were concentrated to dryness. The product was isolated as a white solid (192.6 mg, 70% yield), **mp**: 68-70 ^{0}C; **R_f**: 0.74 (1% MeOH/EtOAc); **^{1}H NMR** (500 MHz, CDCl3) δ 7.50 (dd, *J* = 1.0 Hz, *J* = 5.0 Hz, 1H), 7.29 (dd, *J* = 1.2 Hz, *J* = 3.7 Hz 1H), 7.15 (dd, *J* = 3.5 Hz, *J* = 5 Hz, 1H), 4.20-4.11 (m, 1H), 2.83 (t, *J* = 7.7 Hz, 2H), 1.99-1.81 (m, 8H), 1.76-1.68 (m, 1H), 1.38-1.25 (m, 2H), 1.17 (aqt, *J*=3.5 Hz, *J*= 13.0 Hz, 1H), 1.09 (t, aqt, *J*=7.5 Hz, 3H); **^{13}C NMR** (CDCl3, 125 MHz): δ 155.3, 148.9, 129.6, 128.6, 128.4, 127.4, 56.7, 32.3, 29.0, 26.0, 25.0, 21.3, 14.2; **FTIR** (cm^{-1}) (neat): 2934, 2852, 2363, 1511, 1420, 1032, 850, 730, 718, 608; **HRMS** (ESI, Pos): calc. for $C_{18}H_{19}FN_3$ $[M+H]^+$: 276.1529 found: 276.1541 *m/z*.



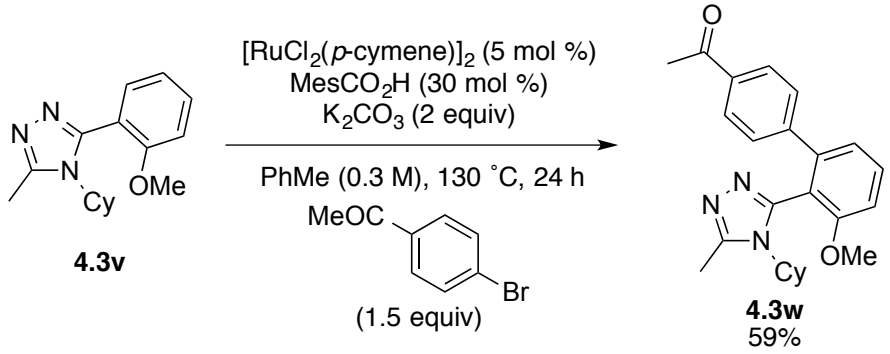
4-cyclohexyl-3-cyclopropyl-5-propyl-4*H*-1,2,4-triazole (4.3u): Following general conditions for 1,2,4- triazole, the crude mixture was purified by flash chromatography over activated basic aluminium oxide (Al_2O_3) (Redi*Sep*® Rf 40 g column) using a gradient of 0% to 1%

MeOH/EtOAc, and the fractions containing **4.3u** were concentrated to dryness. The product was isolated as a yellow solid (125.9 mg, 54% yield), **mp**: 84-85 ^{0}C; $\mathbf{R_f}$: 0.60 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 4.01 (tt, *J* = 3.7 Hz, *J* = 12.2 Hz, 1H), 2.69 (t, *J* = 7.7 Hz, 2H), 2.03 (qd, *J* = 3.5 Hz, *J* = 12.6 Hz, 2H), 1.98-1.86 (m, 4H), 1.85-1.73 (m, 4H), 1.40 (aqt, *J* = 3.5 Hz, *J* = 13.0 Hz, 2H), 1.24 (aqt, *J* = 3.2 Hz, *J* = 13.2 Hz, 1H), 1.17-1.12 (m, 2H), 1.04-0.97 (m, 5H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 155.3, 154.5, 55.9, 32.1, 28.2, 26.2, 25.2, 21.4, 14.0, 7.3 (2); **FTIR** (cm^{-1}) (neat): 2932, 2855, 1660, 1521, 1446, 1343, 1093, 1055, 1031, 894; **HRMS** (ESI, Pos): calc. for $C_{14}H_{23}N_3$ $[M+H]^+$: 234.1965 found: 234.1958 *m/z*.



4-cyclohexyl-3-(2-methoxyphenyl)-5-methyl-4*H*-1,2,4-triazole (4.3v): Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g column) using a gradient of 0% to 1% MeOH/acetone and the fractions containing **4.3v** were concentrated to dryness. The product was isolated as a white solid (228.6.9 mg, 84% yield); **mp**: 177-179 ^{0}C, $\mathbf{R_f}$: 0.40 (1% MeOH/Acetone); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.51-7.46 (m, 1H), 7.44-7.40 (m, 1H), 7.09-7.04 (m, 1H), 7.00-6.98 (m, 1H), 3.79 (s, 3H), 3.77-3.69 (m, 1H), 2.63 (s, 3H), 2.05-1.61 (m, 7H), 1.28-1.07 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 157.5, 152.9, 150.8, 132.6, 131.7, 120.9, 117.5, 110.8, 56.8, 55.3, 31.6, 26.0, 25.2, 13.4; **FTIR** (cm^{-1}) (neat): 2946, 1453, 1249, 1046, 1019, 999, 774; **HRMS** (ESI, Pos): calc. for $C_{16}H_{22}N_3O$ $[M+H]^+$: 272.1757, found: 272.1770 *m/z*.

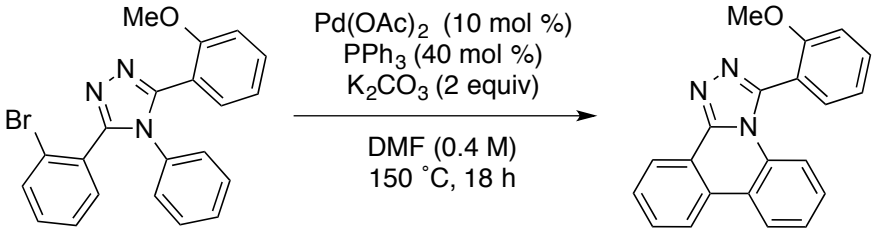
Experimental procedure for the Ru-catalyzed C-H arylation



1-(2'-(4-cyclohexyl-5-methyl-4H-1,2,4-triazol-3-yl)-3'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-one (4.3w): To a flame-dried and argon-purged 5 mL glass microwave vial (Biotage ® 2-5 mL) equipped with a magnetic stir bar and a rubber septum was added triazole **4.3v** (136.0 mg, 0.5 mmol, 1.0 equiv), 2,4,6-trimethylbenzoic acid (24.6 mg, 0.15 mmol, 30 mol %) and the aryl bromide (149.3 mg, 0.75 mmol, 1.5 equiv). The vial was then purged for 10 minutes (2x) with argon and transferred in a glovebox. $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol, 5 mol %) and K_2CO_3 (138.2 mg, 1.0 mmol, 2.0 equiv) were added to the vial under argon. The vial (with the rubber septum) was removed from the glovebox and the solids were dissolved with anhydrous toluene (2.5 mL, 0.3 M). The vial was quickly capped with a Teflon microwave cap (Biotage ® with aluminum o-ring). The reaction was heated to 130 °C using an oil bath and the reaction was stirred for 24 hours. The reaction was slowly cooled to rt and decapped. The reaction mixture was filtered over a pad of celite, rinsed using EtOAc (20 mL) and transferred to a 60 mL extraction funnel using EtOAc (10 mL), a saturated aqueous solution of $NaHCO_3$ (15 mL) and water (10 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 x 10 mL) and the organic layers were combined. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 40 g). using a gradient of 0% to 0.5% MeOH/EtOAc, and the fractions containing **4.3w** were concentrated to dryness. The product was isolated as a white solid (126.4 mg, 54% yield), **mp**: 182-184 ^{0}C; $\mathbf{R_f}$: 0.53 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.89-7.85 (m, 2H), 7.59 (t, J = 8 Hz, 1H), 7.44-7.40 (m, 2H), 7.13-7.11

(m, 1H), 7.09-7.050 (, 1H), 3.82 (s, 3H), 3.45-3.39 (m, 1H), 2.59 (s, 3H), 2.53 (s, 3H), 1.80-1.74 (m, 1H), 1.71-1.44 (m, 6H), 1.16-0.98 (m, 3H), 0.90-0.84 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 197.8, 159.2, 150.1, 150.0, 144.5, 143.4, 135.8, 131.8, 129.5, 128.2, 122.1, 110.7, 56.6, 55.9, 31.6, 30.9, 26.7, 25.9, 25.8, 25.0, 13.1; **FTIR** (cm^{-1}) (neat): 2939, 1677, 1267, 1057, 1010, 798, 759, 601, 585; **HRMS** (ESI, Pos): calc. for $C_{24}H_{28}N_3O_2$ $[M+H]^+$: 390.2176 found: 390.2189 *m/z*.

Experimental procedure for the Pd-catalyzed intramolecular C–H activation

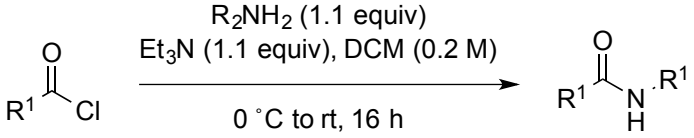


4.3b **4.3x**

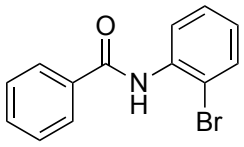
3-(2-methxyphenyl)-[1,2,4]triazolo[4,3-*f*]phenanthridine (4.3x): To a flame-dried and argon-purged 5 mL glass microwave vial (Biotage ® 2-5 mL) equipped with a magnetic stir bar and a rubber septum was added triazole **4.3b** (or **4.3c**) (406.3 mg, 1.0 mmol, 1.0 equiv). The vial was then purged for 10 minutes (2x) with argon and transferred in a glovebox. $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 10 mol%), PPh_3 (104.5 mg, 0.4 mmol, 40 mol%), and K_2CO_3 (276.4 mg, 2.0 mmol, 2.0 equiv) were added to the vial under argon. The vial (with the rubber septum) was removed from the glovebox and the solids were dissolved with anhydrous DMF (2.5 mL, 0.4 M). The vial was quickly capped with a Teflon microwave cap (Biotage ® with aluminum o-ring). The reaction was heated to 150 °C using an oil bath and the reaction was stirred for 18 hours. The reaction was slowly cooled to rt and decapped. The crude mixture was transferred to a 60 mL extraction funnel using DCM (10 mL). The reaction was quenched by addition of a saturated aqueous solution of brine (25 mL). The layers were separated and the aqueous layer was washed with DCM (2 x 10 mL) and the organic layers were combined. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash

chromatography over silica gel (column Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 1% MeOH/EtOAc, and the fractions containing **4.2x** were concentrated to dryness. The product was isolated as a white solid (146.4 mg, 45% yield from **4.3b**; 91.1 mg, 28% yield from **4.3c**), **mp**: 243-245 ^{0}C; $\mathbf{R_f}$: 0.40 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.87 (dd, *J* = 1.3 Hz, *J* = 7.7 Hz, 1H), 8.43 (dd, *J*=1.5 Hz, *J*=8.5 Hz, 1H), 8.40-8.36 (m, 1H), 7.77-7.67 (m, 3H), 7.64-7.60 (m, 1H), 7.52-7.46 (m, 2H), 7.32-7.28 (m, 1H), 7.21 (td, *J* = 1.0 Hz, *J* = 7.5 Hz, 1H), 7.08-7.05(m, 1H), 3.62 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 158.1, 148.8, 147.7, 132.4, 132.1, 131.5, 130.3, 129.0, 128.6, 128.5, 126.1, 125.0, 124.0, 122.7, 122.4, 121.5, 121.3, 119.2, 117.0, 111.2, 55.5; **FTIR** (cm^{-1}) (neat): 2954, 1654, 1449, 1325, 1119, 1023, 984, 762; **HRMS** (ESI, Pos): calc. for $C_{14}H_{23}N_3$ $[M+H]^+$: 326.1288 found: 326.1298 *m/z*.

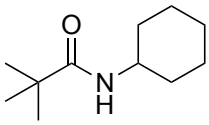
Experimental procedures for the synthesis of amides



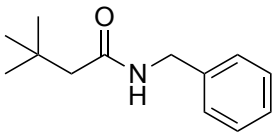
To a flame-dried round-bottom flask equipped with a septum and under argon was added the amine (1.1 equiv). It was solubilized in dichloromethane (0.20 M) and cooled to 0 °C. Triethylamine (1.1 equiv) was added to the reaction flask. Then, the acyl chloride (1.0 equiv) was slowly added *via* a syringe dropwise (or portionwise if solid). Then, the reaction was slowly warmed up to room temperature and stirred for 16 h. The reaction was quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11 and then diluted with dichloromethane. The biphasic mixture was transferred to a separation funnel. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was washed with 1N HCl and dried over anhydrous sodium sulphate (Na_2SO_4). The organic layer was then filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 120 g).



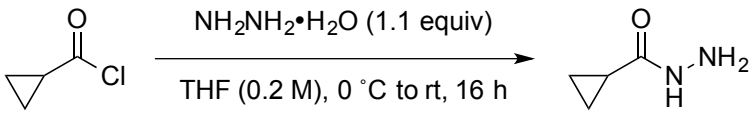
N-(2-Bromophenyl)benzamide (4.1c): Following the general conditions for the synthesis of amides, the crude mixture was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 120 g) using a gradient of 10% to 100% EtOAc/Hexanes and the fractions containing **4.1c** were concentrated to dryness. The product was isolated as a white solid 968 mg, 82% yield); **mp**: 112-114 ^{0}C; **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.58-8.56 (m, 1H), 8.47 (s, 1H), 7.96-7.92 (m, 2H), 7.61-7.57 (m, 2H), 7.55-7.51 (m, 2H), 7.41-7.36 (m, 1H), 7.05-7.00 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 165.3, 135.8, 134.6, 132.3, 132.2, 129.0, 128.6, 127.1, 125.3, 121.7, 113.7; **HRMS** (ESI, Pos): calc. for $C_{15}H_{20}N_3$ $[M+H]^+$: 274.9946, found: 274.9886*m/z*.



***N*-Cyclohexylpivalamide (4.1n):** Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 120 g) using a gradient of 10% to 100% EtOAc/Hexanes and the fractions containing **4.1n** were concentrated to dryness. The product was isolated as a white solid (1.23 g, 85% yield); **mp**: 118-120 ^{0}C, **R_f**: 0.73 (50% Hexane/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 5.43 (s, 1H), 3.78-3.69 (m, 1H), 1.92-1.85 (m, 2H), 1.72-1.65 (m, 2H), 1.63-1.56 (m, 1H), 1.41-1.31 (m, 2H), 1.20-1.03 (m, 12H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 177.4, 47.9, 38.5, 33.2, 27.6, 25.6, 24.9; **FTIR** (cm^{-1}) (neat): 3339, 2930, 2852, 1629, 1530, 1205, 639; **HRMS** (ESI, Pos): calc. for $C_{12}H_{24}NO$ $[M+H]^+$: 198.1852, found: 198.1851 *m/z*.



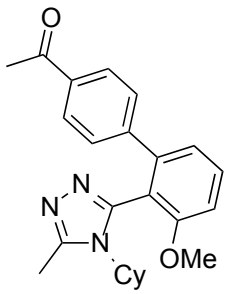
***N*-Benzyl-3,3-dimethylbutanamide (4.1q):** Following the general conditions for the synthesis of 1,2,4-triazoles, the crude mixture was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 120 g) using a gradient of 10% to 100% EtOAc/Hexanes and the fractions containing **4.1q** were concentrated to dryness. The product was isolated as a white solid (1.45 g, 87% yield); **mp**: 66-67 ^{0}C, $\mathbf{R_f}$: 0.53 (50% Hexane/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.36-7.26 (m, 5H), 5.62 (s, 1H), 4.44 (d, J = 5.5 Hz, 2H), 2.09 (s, 2H), 1.05 (s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 171.5, 138.5, 128.7, 128.0, 127.5, 50.7, 43.6, 31.0, 29.9; **FTIR** (cm^{-1}) (neat): 3282, 2953, 1634, 1544, 1462, 738, 693, 613, 580, 503; **HRMS** (ESI, Pos): calc. for $C_{13}H_{26}N_1O$ $[M+H]^+$: 212.2009, found: 212.2009 *m/z*.

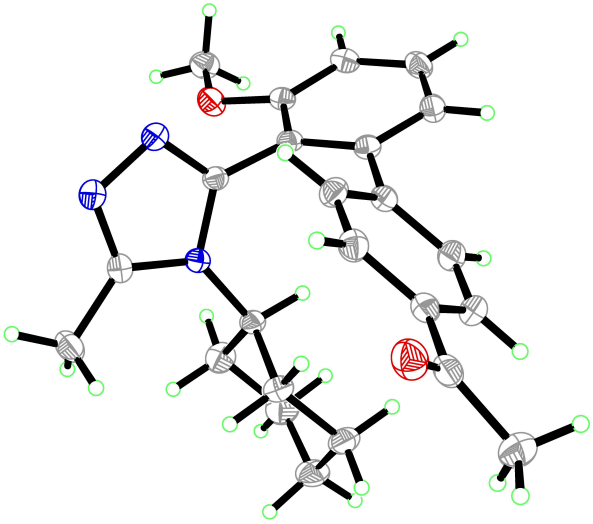


4.10r

4-cyclohexyl-3-(2-methoxyphenyl)-5-methyl-4*H*-1,2,4-triazole (4.10r): To a flame-dried round-bottom flask equipped with a septum and under argon was added cyclopropanecarboxylic acid chloride (2.27 mL, 25 mmol). It was solubilized in THF (125 mL, 0.20 M) and cooled to 0 °C. Hydrazine hydrate (4.85 mL, 0.15 mol, 4 equiv) was added to the reaction flask. Then, the reaction was slowly warmed up to room temperature and stirred for 16 h. The reaction was quenched by addition of a saturated aqueous Na_2CO_3 solution until pH~10-11 and then diluted with dichloromethane. The biphasic mixture was transferred to a separation funnel. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with dichloromethane (4x) and the organic layers were combined. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The product was isolated as a white solid (1.77 g, 71% yield); **mp**: 99-100 ^{0}C; **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.09 (s, 1H), 3.94 (s, 2H), 1.39-1.33 (m, 1H), 1.03-0.99 (m, 2H), 0.83-0.78 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 174.8, 12.9, 7.1; **FTIR** (cm^{-1}) (neat): 3191, 1590, 1495, 1463, 1438, 1210, 934, 821, 669, 508; **HRMS** (ESI, Pos): calc. for $C_4H_9N_2O$ $[M+H]^+$: 101.0709, found: 101.0708 *m/z*.

X-Ray data of compounds 4.3w





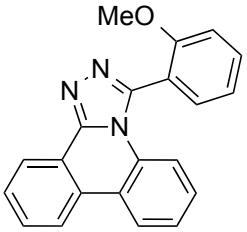
Crystal data and structure refinement for C24 H27 N3 O2

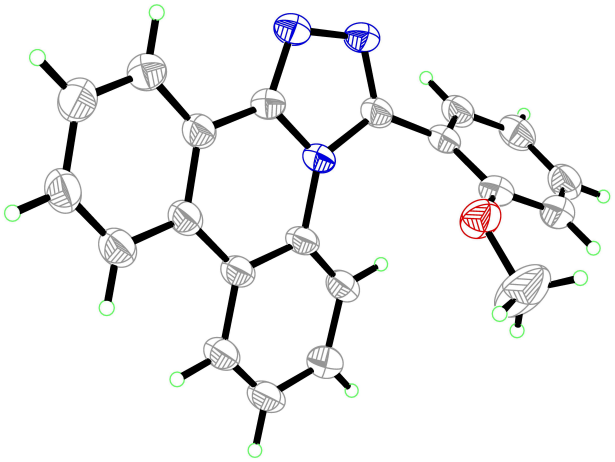
Performed on a …..

Identification code	SYLV15
Empirical formula	$C_{24}H_{27}N_3O_2$
Formula weight	389.48
Temperature/K	130
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	17.5333(8)
b/Å	9.2450(4)
c/Å	13.3467(6)
α/°	90
β/°	107.946(2)
γ/°	90
Volume/Å^3	2058.18(16)
Z	4
ρ_{calc}g/cm^3	1.257

μ/mm^{-1}	0.413
F(000)	832.0
Crystal size/mm^3	0.2 × 0.12 × 0.04
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	4.608 to 121.28
Index ranges	$-21 \leq h \leq 22$, $-11 \leq k \leq 12$, $-17 \leq l \leq 16$
Reflections collected	33023
Independent reflections	4716 [R_{int} = 0.0251, R_{sigma} = 0.0168]
Data/restraints/parameters	4716/0/265
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0360, wR_2 = 0.0925
Final R indexes [all data]	R_1 = 0.0386, wR_2 = 0.0947
Largest diff. peak/hole / e $Å^{-3}$	0.40/-0.16

X-Ray data of compounds 4.3x





Crystal data and structure refinement for C21 H1

Performed on a …..

Identification code	SYLVA7
Empirical formula	$C_{21}H_{15}N_3O$
Formula weight	325.36
Temperature/K	150
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.5706(11)
b/Å	17.3802(16)
c/Å	10.1316(10)
α/°	90
β/°	96.996(7)
γ/°	90
Volume/Å^3	1847.5(3)
Z	4
ρ_{calc}mg/mm^3	1.170
m/mm^{-1}	0.378
F(000)	680.0

Crystal size/mm^3	0.25 × 0.1 × 0.02
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection	8.564 to 125.58°
Index ranges	$-13 \leq h \leq 13$, $-22 \leq k \leq 22$, $-10 \leq l \leq 13$
Reflections collected	27948
Independent reflections	4273 [R_{int} = 0.1361, R_{sigma} = 0.0860]
Data/restraints/parameters	4273/0/227
Goodness-of-fit on F^2	0.985
Final R indexes [I>=2σ (I)]	R_1 = 0.0595, wR_2 = 0.1454
Final R indexes [all data]	R_1 = 0.1117, wR_2 = 0.1626
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.29

Experimental section of Chapter 5

General Information

Common substrates and reagents were obtained from commercial suppliers and used without further purification. Unless otherwise stated, reactions were run under an argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[101] All glassware was flame-dried prior to use. DCM, toluene, THF, MeOH, and DMF were obtained by filtration through drying columns on a filtration system. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV and aqueous potassium permanganate ($KMnO_4$). Flash column chromatography was performed using an automatic purification system (Teledyne Isco Combiflash® Rf or Sq16x). Prepacked normal phase silica gel column was used for separation of products using Teledyne Isco Redi*Sep*® Rf High Performance Gold or Silicycle Silia*Sep*TM High Performance columns (12 g, 24 g, 40 g, or 80 g). Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on an Avance AV400 MHz, Avance AV 300 MHZ, DRX400 MHz, or Avance 700 MHz (^{1}H, ^{13}C, ^{19}F, DEPT 135, COSY) spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard $CDCl_3$ (δ = 7.27 ppm), DMSO-*d*$_6$ (δ = 2.50 ppm), CD_2Cl_2 (δ = 5.32 ppm), or CD_3OD (δ = 3.31 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (δ = 77.23 ppm), DMSO-*d6* (δ = 39.52 ppm), CD3OD (δ = 49.00 ppm), or CD_2Cl_2 (δ = 53.13 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Bruker Vertex Series FTIR (neat) and are reported in

[101] Shriver, D. F. & Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*; 2nd Edition; Wiley: New York, 1986.

reciprocal centimeters (cm-1). High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

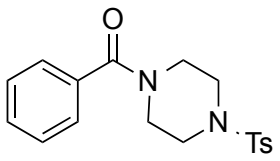
Experimental procedures and characterization data for the synthesis of 3-aminoindazoles

Hydrazonamides formation

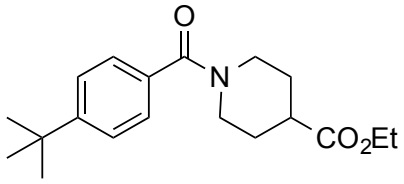
General procedure

Example of the synthesis of (E)-*N*,*N*-Diethyl-*N'*-tosylbenzohydrazonamide

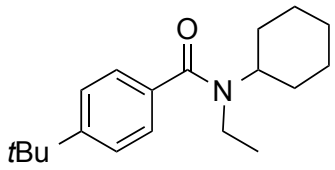
To a flame dried round bottom flask was added diethylbenzamide (0.564 mmol) in 2.8 mL [0.2 M] of anhydrous DCM followed by 2-methoxypyridine (0.73 mmol, 1.3 equiv.) under argon. The solution was cooled to 0 °C and stirred for 2 min. Then, triflic anhydride (103 µL, 0.621 mmol, 1.1 equiv.) was added dropwise *via* a syringe at 0 °C and the reaction was stirred for 10 min at this temperature. Then, 4-methylbenzenesulfonyl hydrazide (158 mg, 0.846 mmol, 1.5 equiv.) was added in one portion and the solution was stirred 10 min at 0 °C. The ice bath was removed to let the reaction mixture warmed up to room temperature. The reaction was stirred at room temperature for 3 h. Saturated $NaHCO_3$ (40 mL) and DCM (20 mL) were added, the mixture was transferred to an extraction funnel and the organic phase was extracted. The aqueous phase was further extracted two times with DCM (20 mL). The organic layers were combined, dried over anh. Na_2SO_4, filtered and evaporated to dryness using a rotary evaporator. The crude mixture was purified by automatic chromatography using a 12 g gold column and a 20% EtOAc/Hex gradient to afford 175 mg of a white solid as the desired product.



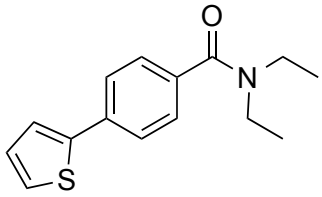
Phenyl(4-tosylpiperazin-1-yl)methanone (5.1d): General conditions; white solid, **mp**: 159-161 ^{0}C, **R_f**: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.65-7.61 (m, 2H), 7.44-7.30 (m, 7H), 4.01-3.33 (m, 4H), 3.21-2.75 (m, 4H), 2.46 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 170.4, 144.2, 134.8, 132.3, 130.2, 129.9, 128.6, 127.8, 127.1, 46.1, 21.6; **FTIR** (cm^{-1}) (neat) 2860, 1628, 1173, 943, 715, 545, 496; **HRMS** (ESI, Pos): calc. for $C_{18}H_{21}N_2O_3S$ $[M+H]^+$: 345.1267 *m/z*, found: 345.1278 *m/z*.



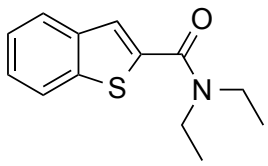
Ethyl 1-(4-*tert*-butyl)benzoyl)piperidine-4-carboxylate (5.1e): General conditions; yellow solid; **mp**: 82-83 ^{0}C, **R_f**: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.43-7.41 (m, 2H), 7.35-7.33 (m, 2H), 4.76-4.3 (m, 1H), 4.17 (q, *J* = 7.5 Hz, 2H), 4.07-3.53 (m, 1H), 3.18-2.91 (m, 2H), 2.61-2.55 (m, 1H), 2.18-1.57 (m, 4H), 1.34 (s, 9H), 1.27 (t, *J* = 7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 174.2, 170.6, 152.9, 133.1, 126.7, 125.4, 60.6, 47.1, 41.6, 41.2, 34.8, 31.2, 28.3, 14.2; **FTIR** (cm^{-1}) (neat) 2966, 2865, 1729, 1632, 1430, 1316, 1180, 1148, 1055, 1014; **HRMS** (ESI, Pos): calc. for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064 *m/z*, found: 318.2069 *m/z*.



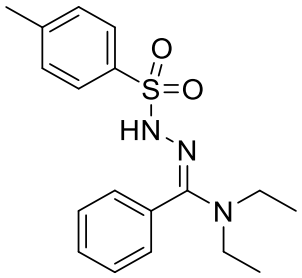
4-(*tert*-butyl)-*N*-cyclohexyl-*N*-ethylbenzamide (5.1f): General conditions; white solid; **mp**: 97-98 ^{0}C, $\mathbf{R_f}$: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.42-7.39 (m, 2H), 7.30-7.28 (m, 2H), 4.38-3.11 (m, 3H), 1.95-1.30 (m, 7H), 1.32-0.89 (m, 15H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 171.4, 152.0, 134.7, 125.9, 125.3, 58.7, 54.3, 39.8, 36.5, 34.7, 31.8, 31.3, 25.7, 25.3, 15.0; **FTIR** (cm^{-1}) (neat) 2930, 2857, 1628, 1419, 1312, 835; **HRMS** (ESI, Pos): calc. for $C_{19}H_{30}NO$ $[M+H]^+$: 288.2322 *m/z*, found: 288.2321 *m/z*.



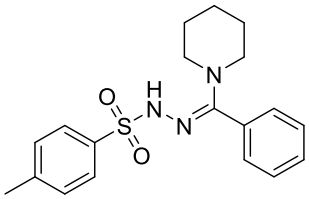
***N*,*N*-diethyl-4-(thiophen-2-yl)benzamide (5.1l):** General conditions; white solid; **mp**: 59-60 ^{0}C, $\mathbf{R_f}$: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.65-7.61 (m, 2H), 7.41-7.38 (m, 2H), 7.36-7.34 (m, 1H), 7.32-7.30 (m, 1H), 7.11-7.08 (m, 1H), 3.66-3.21 (m, 4H), 1.36-1.03 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 170.87, 143.50, 136.13, 135.22, 128.17, 127.09, 125.79, 125.42, 123.65, 43.31, 39.37, 14.27, 12.96; **FTIR** (cm^{-1}) (neat) 2976, 2935, 1617, 1425, 1290, 1097, 851, 825, 736, 713, 567; **HRMS** (ESI, Pos): calc. for $C_{15}H_{18}NOS$ $[M+H]^+$: 260.1104 *m/z*, found: 260.1115 *m/z*.



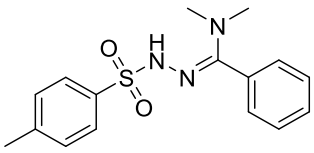
***N*,*N*-diethylbenzo[b]thiophene-2-carboxamide (5.1o):** General conditions; colourless oil; **R_f**: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.89-7.77 (m, 2H), 7.50-7.48 (m, 1H), 7.42-7.35 (m, 2H), 3.57 (q, *J* = 12 Hz, 4H), 1.28 (t, *J* = 12 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 164.3, 140.1, 138.8, 137.9, 125.6, 124.7, 124.5, 124.2, 122.3, 43.3, 40.9, 14.1, 13.3; **FTIR** (cm^{-1}) (neat) 2973, 1611, 1522, 1458, 1419, 1277, 1216, 820, 752, 725; **HRMS** (ESI, Pos): calc. for $C_{13}H_{16}NOS$ $[M+H]^+$: 234.0947 *m/z*, found: 234.0951 *m/z*.



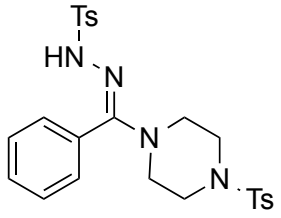
(E)-*N*,*N*-Diethyl-*N′*-tosylbenzohydrazonamide (5.2a): General conditions; white solid; **mp**: 117-118 °C; **R_f:** 0.30 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.75 (dt, 2H, *J* = 8.2, 1.7 Hz), 7.44-7.41 (m, 3H), 7.30 (d, 2H, *J* = 7.9 Hz), 7.01-6.98 (m, 2H), 6.04 (s, 1H), 3.09 (q, 4H, *J* = 7.0 Hz), 2.44 (s, 3H), 0.97 (t, 6H, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.5, 143.5, 135.7, 130.8, 129.9, 129.5, 129.3, 128.4, 128.0, 42.2, 21.8, 13.3; **FTIR** (cm^{-1}) (neat): 3113, 2980, 2937, 1541, 1330, 1159, 1087; **HRMS** (ESI, Pos): calc. for $C_{18}H_{23}N_3O_2S$ $[M+H]^+$: 346.15979 *m/z*, found: 346.15837 *m/z*.



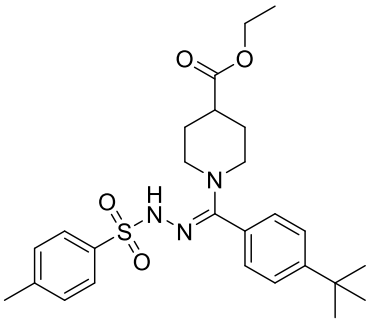
4-methyl-N'-(phenyl(piperidin-1-yl)methylene)benzenesulfonohydrazide (5.2b): General conditions; pale yellow solid; **mp**: 142-144 °C; **R_f:** 0.33 (30% acetone/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 7.74 - 7.80 (m, 2 H), 7.40 - 7.46 (m, 3 H), 7.31 (m, 2 H), 7.01 - 7.07 (m, 2 H), 6.22 (s, 1 H), 3.04 - 3.12 (m, 4 H), 2.46 (s, 3 H), 1.57 (m, 3 H), 1.42 - 1.51 (m, 3 H); **^{13}C NMR** ($CDCl_3$,126MHz): δ 159.7, 143.4, 135.4, 130.3, 130.0, 129.5, 129.2, 128.2, 128.1, 47.2, 25.4, 24.6, 21.6; **FTIR** (cm^{-1}) (neat) : 3067, 2944, 2852, 1332, 1160, 745, 654, 565, 543; **HRMS** (ESI, Pos): calc. for $C_{19}H_{23}N_3O_2S$ $[M+H]^+$: 358.15837 *m/z*, found: 358,15945 *m/z*.



N,N-dimethyl-N'-tosylbenzohydrazonamide (5.2c): General conditions; white solid; **mp**: 176-178 °C; **R_f** : 0.22 (30% Acetone/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 7.77 (d, J=8.4 Hz, 2 H), 7.40 - 7.47 (m, 3 H), 7.28 - 7.34 (m, 2 H), 6.99 - 7.08 (m, 2 H), 6.19 (br. s., 1 H), 2.71 (s, 6 H), 2.45 (s, 3 H); **^{13}C NMR** ($CDCl_3$,126MHz): δ 160.8, 143.4, 135.2, 130.2, 130.0, 129.4, 129.2, 128.2, 128.0, 38.5, 21.6; **FTIR** (cm^{-1}) (neat) : 3107, 2935, 1548, 1331, 1159, 740, 651, 557, 544; **HRMS** (ESI, Pos): calc. for $C_{16}H_{19}N_3O_2S$ $[M+H]^+$: 318.12707 *m/z*, found: 318.12793 *m/z*.

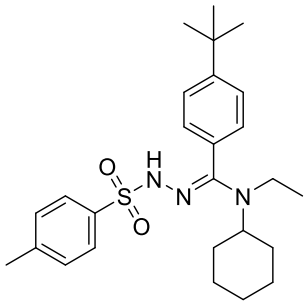


(*Z*)-4-methyl-*N*'-(phenyl(4-tosylpiperazin-1-yl)methylene)benzenesulfonohydrazide (5.2d): General conditions; yellow solid; **mp**: 77-78 ^{0}C, $\mathbf{R_f}$: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.73-7.69 (m, 2H), 7.63-7.59 (m, 2H), 7.47-7.40 (m, 3H), 7.36-7.32 (m, 2H), 7.29-7.26 (m, 2H), 7.01-6.97 (m, 2H), 6.37 (s, 1H), 3.24-3.11 (m, 4H), 2.98-2.91 (m, 4H), 2.46 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 144.0, 143.8, 135.0, 132.6, 130.7, 129.9, 129.8, 129.4, 128.7, 128.1, 127.8, 45.7, 45.4, 21.6, 21.6; **FTIR** (cm^{-1}) (neat) 2966, 2937, 1327, 1158, 1056, 1017, 724, 578, 546; **HRMS** (ESI, Pos): calc. for $C_{25}H_{29}N_4O_4S_2$ $[M+H]^+$: 513.1625 *m/z*, found: 513.1636 *m/z*.

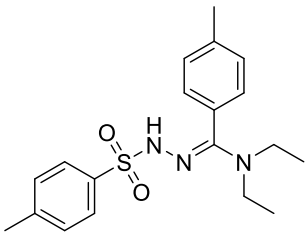


Ethyl 1-((4-(tert-butyl)phenyl)(2-tosylhydrazono)methyl)piperidine-4-carboxylate (5.2e): General conditions; white solid**; mp**: 118-120 °C; $\mathbf{R_f}$**:** 0.33 (30% Acetone/Hex); **^{1}H NMR** ($CDCl_3$,500MHz): δ 7.76 (d, J=8.3 Hz, 2 H), 7.44 (d, J=8.4 Hz, 2 H), 7.31 (d, J=8.1 Hz, 2 H), 6.98 (d, J=8.1 Hz, 2 H), 6.41 (br. s., 1 H), 4.14 (q, J=7.0 Hz, 2 H), 3.42 - 3.61 (m, 2 H), 2.71 (t, J=11.4 Hz, 2 H), 2.36 - 2.51 (m, 4 H), 1.73 - 1.89 (m, 2 H), 1.53 - 1.67 (m, 2 H), 1.35 (s, 9 H), 1.26 (t, J=7.2 Hz, 3 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 174.5, 153.6, 143.5, 135.3, 129.2, 128.1, 127.8, 126.5, 126.4, 65.8, 60.5, 45.7, 41.2, 34.9, 31.2, 27.6, 21.6, 14.2; **FTIR** (cm^{-1}) (neat): 3082, 2953, 2853, 1724, 1317, 1157, 741, 727, 562; **HRMS** (ESI, Pos): calc. for

$C_{26}H_{35}N_3O_4S$ $[M+H]^+$: 486,2421 *m/z*, found: 486,24398 *m/z*.

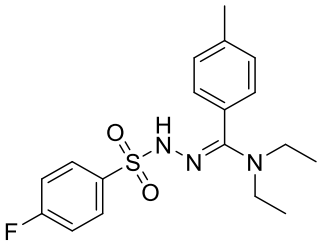


4-(tert-butyl)-N-cyclohexyl-N-ethyl-N'-tosylbenzohydrazonamide (5.2f): General conditions; white solid; **mp**: 130-132 °C; $\mathbf{R_f}$: 0.44 (30% Acetone/Hex); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.72 - 7.81 (m, 2 H), 7.39 - 7.48 (m, 2 H), 7.28 - 7.34 (m, 2 H), 6.86 - 6.98 (m, 2 H), 6.11 (s, 1 H), 3.14 (q, J=6.7 Hz, 2 H), 2.45 (s, 3 H), 1.48 - 1.79 (m, 5 H), 1.22 - 1.45 (m, 13 H), 0.97 - 1.10 (m, 2 H), 0.93 (t, J=7.0 Hz, 3 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 155.4, 152.6, 144.5, 144.1, 133.8, 129.0, 127.7, 121.7, 121.5, 118.5, 111.3, 58.3, 38.7, 35.2, 31.4, 30.8, 26.0, 25.7, 21.5, 15.5 ppm; **FTIR** (cm^{-1}) (neat) : 3197, 2928, 2856, 1325, 1160, 1090, 685, 566, 543; **HRMS** (ESI, Pos): calc. for $C_{26}H_{37}N_3O_2S$ $[M+H]^+$: 456.26792 *m/z*, found: 456.26935 *m/z*.

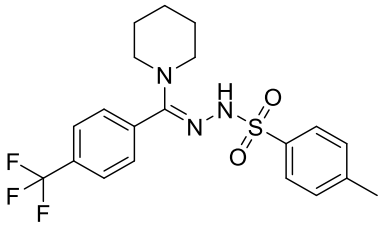


N,N-diethyl-4-methyl-N'-tosylbenzohydrazonamide (5.2g): General conditions; white solid; **mp**: 98-100 °C; $\mathbf{R_f}$**:** 0.33 (30% Acetone/Hex); **^{1}H NMR** (CHLOROFORM-d ,300MHz): δ

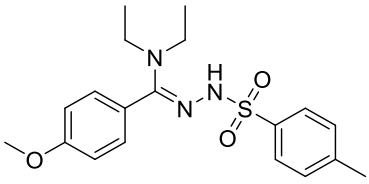
7.70 - 7.81 (m, 2 H), 7.30 (d, J=7.8 Hz, 2 H), 7.23 (d, J=7.8 Hz, 2 H), 6.87 (d, J=8.1 Hz, 2 H), 6.09 (s, 1 H), 3.10 (q, J=6.8 Hz, 4 H), 2.45 (s, 3 H), 2.40 (s, 3 H), 0.97 (t, J=7.1 Hz, 6 H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 159.8, 143.3, 140.0, 135.4, 130.0, 129.1, 128.9, 128.5, 128.2, 127.7, 126.3, 126.0, 42.3, 21.6, 21.3, 13.1; **FTIR** (cm^{-1}) (neat) : 3195, 2973, 2931, 2870, 1321, 1158, 813, 708, 554; **HRMS** (ESI, Pos): calc. for $C_{19}H_{25}N_3O_2S$ $[M+H]^+$: 360,17402 *m/z*, found: 360,1751 *m/z*.



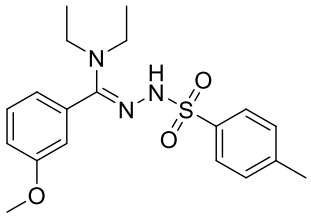
N,N-diethyl-N'-((4-fluorophenyl)sulfonyl)-4-methylbenzohydrazonamide (5.2h): General conditions; white solid; **mp**: 106-108 °C; **R_f:** 0.30 (30% Acetone/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.06 (dd, J=9.2, 0.6 Hz, 1 H), 7.65 - 7.71 (m, 2 H), 7.13 - 7.17 (m, 2 H), 7.11 (dd, J=9.2, 2.4 Hz, 1 H), 6.96 (d, J=2.2 Hz, 1 H), 3.83 (s, 3 H), 3.33 - 3.44 (m, 4 H), 2.33 (s, 3 H), 1.59 - 1.78 (m, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 164.2, 162.2, 143.5, 135.4, 130.0, 129.2, 128.3, 126.7, 116.6, 42.3, 21.6, 13.1; **FTIR** (cm^{-1}) (neat) : 3204, 2976, 2935, 2871, 1327, 1160, 710, 551, 542; **HRMS** (ESI, Pos): calc. for $C_{18}H_{22}FN_3O_2S$ $[M+H]^+$: 364.14895 *m/z*, found: 364.15005 *m/z*.



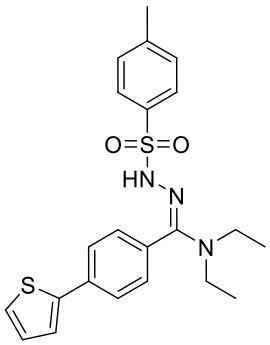
4-methyl-N'-(piperidin-1-yl(4-(trifluoromethyl)phenyl)methylene)benzenesulfonohydrazide (5.2i): General conditions; white solid; **mp**: 142-144 °C; $\mathbf{R_f}$: 0,31 (30% Acetone/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 7.77 (d, J=8.3 Hz, 2 H), 7.72 (d, J=7.9 Hz, 2 H), 7.28 - 7.35 (m, 4 H), 3.15 (br. s., 4 H), 2.46 (s, 3 H), 1.47 - 1.67 (m, 6 H); **^{13}C NMR** ; **FTIR** (cm^{-1}) (neat): 3181, 2934, 2855, 1318, 1158, 1129, 704, 589, 545; **HRMS** (ESI, Pos): calc. for $C_{20}H_{22}F_3N_3O_2S$ $[M+H]^+$: 426.14576 *m/z*, found: 426.14662 *m/z*.



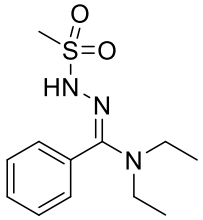
N,N-diethyl-4-methoxy-N'-tosylbenzohydrazonamide (5.2j): General conditions; yellow oil; $\mathbf{R_f}$: 0.26 (40% Acetone/Hex); **^{1}HNMR**; **^{13}C NMR** ($CDCl_3$, 126MHz): δ 155.8, 144.0, 130.0, 129.5, 129.2, 128.3, 128.1, 114.8, 113.6, 55.4, 25.3, 21.6, 16.7; **FTIR** (cm^{-1}) (neat): 3220, 2971, 2933, 1250, 1162, 812, 666, 583, 555; **HRMS** (ESI, Pos): calc. for $C_{19}H_{25}N_3O_3S$ $[M+H]^+$: 376.16894 *m/z*, found: 376.17196 *m/z*.



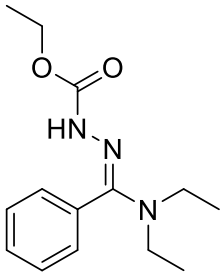
(*Z*)-*N*,*N*-diethyl-3-methoxy-*N*'-tosylbenzohydrazonamide (5.2k): General conditions; pale yellow solid; **mp**: 140-142 °C; $\mathbf{R_f}$: 0.26 (30% Acetone/Hex); **^{1}HNMR**; **^{13}CNMR**; **FTIR** (cm^{-1}) (neat): 3187, 2933, 2858, 1328, 1289, 1163, 698, 554, 543; **HRMS** (ESI, Pos).



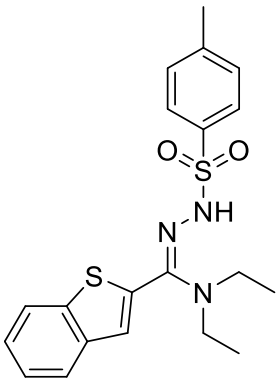
N,N-diethyl-4-(thiophen-2-yl)-N'-tosylbenzohydrazonamide (5.2l): General conditions; white solid, **mp**: 144-146 °C; $\mathbf{R_f}$: 0,24 (30% Acetone/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 7.77 (d, J=8.3 Hz, 2 H), 7.67 (d, J=8.6 Hz, 2 H), 7.37 (ddd, J=11.8, 4.3, 1.1 Hz, 2 H), 7.31 (d, J=7.9 Hz, 2 H), 7.13 (dd, J=5.0, 3.6 Hz, 1 H), 7.07 (d, J=7.7 Hz, 2 H), 6.17 (br. s., 1 H), 3.17 (br. s., 4 H), 2.46 (s, 3 H), 1.03 (t, J=6.7 Hz, 6 H); **^{13}C NMR**; **FTIR** (cm^{-1}) (neat): 3180, 3095, 2969, 2929, 1315, 1158, 704, 557, 544; **HRMS** (ESI, Pos): calc. for $C_{22}H_{25}N_3O_2S_2$ $[M+H]^+$: 428.14609 *m/z*, found: 428.14739 *m/z*.



(E)-*N,N*-Diethyl-*N′*-(methylsulfonyl)benzohydrazonamide (**5.2m**): General conditions; beige solid; **mp**: 77-78 °C; **R_f:** 0.30 (30% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.48-7.42 (m, 3H), 7.23-7.20 (m, 2H), 5.89 (br s, 1H), 3.19 (q, 4H, *J* = 7.0 Hz), 3.00 (s, 3H), 1.08 (t, 6H, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 160.9, 131.1, 129.8, 129.4, 128.0, 42.4, 37.2, 13.3; **FTIR** (cm^{-1}) (neat): 3188, 3062, 2970, 2933, 1428, 1311, 1291, 1163; **HRMS** (ESI, Pos): calc. for $C_{12}H_{19}N_3O_2S$ $[M+H]^+$: 270.12707 *m/z*, found: 270.12793 *m/z.*



(E)-Ethyl 2-((diethylamino)(phenyl)methylene)hydrazinecarboxylate (**5.2n**): General conditions : pale yellow oil; **R_f:** 0.30 (40% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.52-7.45 (m, 3H), 7.25-7.22 (m, 2H), 6.64 (br s, 1H), 4.12, br s, 2H), 3.20 (q, 4H, *J* = 7.0 Hz), 1.20 (br s, 3H), 1.08 (t, 6H, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 156.4, 154.0, 131.1, 129.8, 129.6, 128.0, 60.9, 41.7, 14.7, 13.2; **FTIR** (cm^{-1}) (neat): 3372, 2974, 2932, 1736, 1499, 1217, 1039; **HRMS** (ESI, Pos): calc. for $C_{14}H_{21}N_3O_2$ $[M+H]^+$: 264.17065 *m/z*, found: 264.17186 *m/z*.



N,N-diethyl-N'-tosylbenzo[b]thiophene-2-carbohydrazonamide (5.2o): General conditions; pale yellow solid; **mp**: 150-154 °C; $\mathbf{R_f}$: 0.26 (30% Acetone/Hex); **^{1}HNMR**; **^{13}C NMR** ($CDCl_3$, 126MHz): δ 161.9, 144.1, 137.6, 137.1, 131.8, 130.0, 129.3, 129.2, 127.8, 125.4, 121.1, 72.3, 51.8, 43.1, 21.6, 13.1; **FTIR** (cm^{-1}) (neat): 3188, 2966, 2931, 2868, 1324, 1157, 712, 564, 540; **HRMS** (ESI, Pos): calc. for $C_{20}H_{23}N_3O_2S_2$ $[M+H]^+$: 402.13044 *m/z*, found: 402.13196 *m/z*.

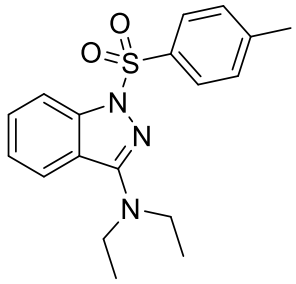
3.3 3-Aminoindazoles formation

General procedure

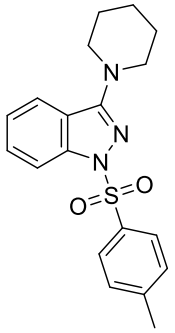
Example of the synthesis of *N,N*-Diethyl-1-tosyl-*1H*-indazol-3-amine

To a flame dried 25 mL round bottom flask charged with (E)-*N,N*-diethyl-*N'*-tosylbenzohydrazonamide (0.290 mmol) was added, in a glovebox under argon, CsOPiv (136 mg, 0.579 mmol, 2 equiv) and $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 0.1 equiv). Then, 2.9 mL [0.1 M] of anhydrous Toluene was added to the mixture under argon. Then, anhydrous air was bubbled in the solution for 2 minutes. A flame dried vigreux column was added and the system was purged under anhydrous air for 1 minute. An air balloon was added on the top of the vigreux column and the reaction mixture was stirred at 110 °C overnight using an oil bath. The reaction mixture was cooled down to room temperature and the solvent was evaporated using a rotary evaporator. The crude mixture was purified by automatic chromatography using

a 12 g gold column and a 10% EtOAc/Hex gradient to afford 65 mg of a pale yellow liquid-solid as the desired product.

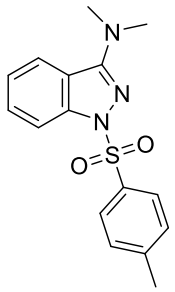


***N,N*-Diethyl-1-tosyl-*1H*-indazol-3-amine** (**5.3a**): General conditions; pale yellow liquid-solid; **R_f:** 0.30 (10% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.17 (d, 1H, *J* = 8.5 Hz), 7.70 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 1H, *J* = 8.2 Hz), 7.48-7.43 (m, 1H), 7.24-7.18 (m, 1H), 7.12 (d, 2H, *J* = 8.2 Hz), 3.54 (q, 4H, *J* = 7.1 Hz), 2.31 (s, 3H), 1.18 (t, 6H, *J* = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 155.6, 144.4, 143.9, 133.9, 129.3, 128.8, 127.8, 123.7, 122.1, 120.5, 114.9, 44.6, 21.7, 13.3; **FTIR** (cm-1) (neat): 3233, 3189, 3059, 2971, 2932, 1552, 1366, 1161; **HRMS** (ESI, Pos): calc. for $C_{18}H_{21}N_3O_2S$ $[M+H]^+$: 344.14272 *m/z*, found: 344.14400 *m/z*.

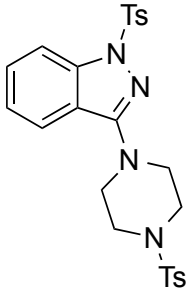


3-(piperidin-1-yl)-1-tosyl-1H-indazole (5.3b): General conditions; brown solid; **mp**: 116-118 °C; **R_f:** 0.41 (20% EtOAc/Hex); **^{1}H NMR** (CDCl3, 500MHz): δ 8.17 (dt, J=8.5, 0.9 Hz, 1 H), 7.70 - 7.76 (m, 2 H), 7.60 - 7.66 (m, 1 H), 7.48 (ddd, J=8.4, 7.2, 1.1 Hz, 1 H), 7.24 (ddd, J=8.1, 7.2, 0.9 Hz, 1 H), 7.16 (dd, J=8.6, 0.6 Hz, 2 H), 3.41 - 3.48 (m, 4 H), 2.33 (s, 3 H), 1.59

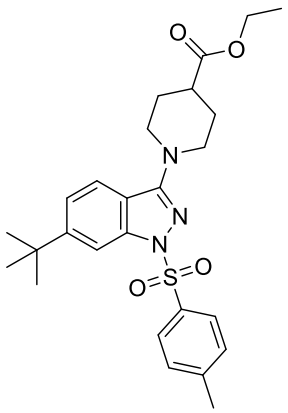
- 1.75 (m, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 157.9, 144.5, 143.4, 133.9, 129.3, 128.8, 127.5, 123.5, 121.6, 120.6, 114.5, 49.8, 25.3, 24.4, 21.5; **FTIR** (cm^{-1}) (neat): 2925, 2850, 2828, 1528, 1369, 1172, 751, 663, 538; **HRMS** (ESI, Pos): calc. for $C_{19}H_{21}N_3O_2S$ $[M+H]^+$: 356,14272 *m/z*, found: 356,14377 *m/z*.



N,N-dimethyl-1-tosyl-1H-indazol-3-amine (5.3c): General conditions; white solid; **mp**: 156-160 °C; **R_f**: 0.20 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.18 (dt, J=8.5, 0.8 Hz, 1 H), 7.68 - 7.77 (m, 3 H), 7.48 (m, 7.2, 1.0 Hz, 1 H), 7.23 (m, 7.2, 1.0 Hz, 1 H), 7.16 (d, J=8.1 Hz, 2 H), 3.15 (s, 6 H), 2.33 (s, 3 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 157.4, 144.3, 143.7, 133.8, 129.2, 128.8, 127.5, 123.5, 122.1, 120.4, 114.6, 40.6, 21.5; **FTIR** (cm^{-1}) (neat): 2923, 2853, 1360, 1169, 750, 672, 603, 567, 535; **HRMS** (ESI, Pos): calc. for $C_{16}H_{17}N_3O_2S$ $[M+H]^+$: 316.11142 *m/z*, found: 316.11198 *m/z*.

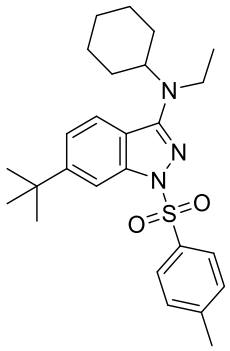


1-Tosyl-3-(4-tosylpiperazin-1-yl)-1*H*-indazole (5.3d): General conditions; white solid; **mp**: 212-214 ^{0}C, **R_f**: 0.19 (1% MeOH/EtOAc); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.17-8.12 (m, 1H), 7.71-7.63 (m, 4H), 7.52-7.45 (m, 2H), 7.37-7.32 (m, 2H), 7.24-7.19 (m, 1H), 7.15-7.10 (m, 2H), 3.60-3.51 (m, 4H), 3.21-3.13 (m, 4H), 2.44 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 156.2, 144.8, 144.0, 143.3, 133.8, 132.6, 129.8, 129.4, 129.3, 127.8, 127.4, 123.7, 120.9, 119.6, 114.6, 48.0, 45.4, 21.6; **FTIR** (cm^{-1}) (neat) 2921, 1349, 1162, 1054, 727, 673, 651, 564, 535; **HRMS** (ESI, Pos): calc. for $C_{25}H_{27}N_4O_4S_2$ $[M+H]^+$: 511.1468 *m/z*, found: 511.1479 *m/z*.

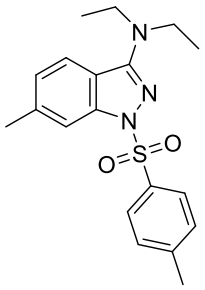


Ethyl 1-(6-(tert-butyl)-1-tosyl-1H-indazol-3-yl)piperidine-4-carboxylate (5.3e): General conditions; brown oil; **R_f:** 0.24 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.17 (d, J=1.1 Hz, 1 H), 7.68 - 7.75 (m, 2 H), 7.51 (d, J=8.4 Hz, 1 H), 7.31 (dd, J=8.4, 1.7 Hz, 1 H), 7.16 (d, J=8.1 Hz, 2 H), 4.17 (q, J=7.2 Hz, 2 H), 3.96 (dt, J=13.1, 3.3 Hz, 2 H), 2.99 - 3.10 (m,

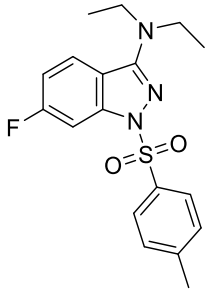
2 H), 2.51 (tt, J=11.1, 3.9 Hz, 1 H), 2.33 (s, 3 H), 2.01 (dd, J=13.6, 3.5 Hz, 2 H), 1.78 - 1.91 (m, 2 H), 1.41 (s, 9 H), 1.28 (t, J=7.2 Hz, 3 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 174.5, 157.2, 153.1, 144.4, 144.0, 133.8, 129.3, 127.5, 121.9, 120.8, 118.2, 111.0, 60.5, 48.2, 41.0, 35.4, 31.4, 27.5, 21.5, 14.2; **FTIR** (cm^{-1}) (neat): 2960, 2867, 1727, 1371, 1171, 1040, 667, 577, 544; **HRMS** (ESI, Pos): calc. for $C_{26}H_{33}N_3O_4S$ $[M+H]^+$: 484.22645 *m/z*, found: 484.2278 *m/z*.



6-(tert-butyl)-N-cyclohexyl-N-ethyl-1-tosyl-1H-indazol-3-amine (5.3f): General conditions; brown oil; **R_f**: 0.52 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.19 (d, J=1.3 Hz, 1 H), 7.66 - 7.74 (m, 2 H), 7.50 (d, J=8.6 Hz, 1 H), 7.29 (dd, J=8.6, 1.8 Hz, 1 H), 7.13 (d, J=8.1 Hz, 2 H), 4.03 (tt, J=11.5, 3.3 Hz, 1 H), 3.47 (q, J=7.0 Hz, 2 H), 2.32 (s, 3 H), 1.82 (t, J=15.7 Hz, 4 H), 1.70 (d, J=13.0 Hz, 1 H), 1.31 - 1.51 (m, 13 H), 1.08 - 1.19 (m, 4 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 155.4, 152.6, 144.5, 144.1, 133.8, 129.0, 127.7, 121.7, 121.5, 118.5, 111.3, 58.3, 38.7, 35.2, 31.4, 30.8, 26.0, 25.7, 21.5, 15.5; **FTIR** (cm^{-1}) (neat) : 2962, 2930, 2856, 1535, 1369, 1172, 669, 577, 544; **HRMS** (ESI, Pos): calc. for $C_{26}H_{35}N_3O_2S$ $[M+H]^+$: 454.25227 *m/z*, found: 454.2539 *m/z*.

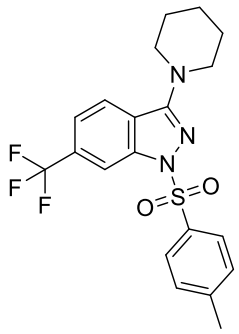


N,N-diethyl-6-methyl-1-tosyl-1H-indazol-3-amine (5.3g): General conditions; brown solid; **mp**: 84-86 °C; **R_f:** 0.34 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 7.98 (dt, J=1.5, 0.7 Hz, 1 H), 7.69 - 7.74 (m, 2 H), 7.46 (d, J=8.4 Hz, 1 H), 7.14 (dd, J=8.6, 0.6 Hz, 2 H), 7.01 - 7.06 (m, 1 H), 3.53 (q, J=7.0 Hz, 4 H), 2.50 (s, 3 H), 2.32 (s, 3 H), 1.17 (t, J=7.2 Hz, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 155.4, 144.4, 144.2, 139.3, 133.9, 129.1, 127.6, 125.3, 121.5, 118.3, 114.6, 44.4, 21.8, 21.5, 13.1; **FTIR** (cm^{-1}) (neat): 2968, 2928, 2865, 1555, 1366, 1173, 800, 575, 541; **HRMS** (ESI, Pos): calc. for $C_{19}H_{23}N_3O_2S$ $[M+H]^+$: 358,15837 *m/z*, found: 358,15926 *m/z*.

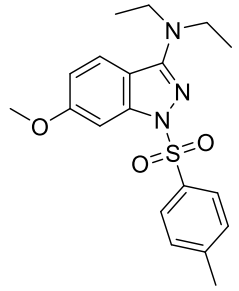


N,N-diethyl-6-fluoro-1-tosyl-1H-indazol-3-amine (5.3h): General conditions; white solid; **mp**: 136-138 °C; **R_f:** 0.34 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.86 (dd, J=9.5, 2.2 Hz, 1 H), 7.70 - 7.79 (m, 2 H), 7.54 (dd, J=8.9, 5.0 Hz, 1 H), 7.18 (d, J=7.8 Hz, 2 H), 6.96 (td, J=8.8, 2.4 Hz, 1 H), 3.52 (q, J=7.1 Hz, 4 H), 2.34 (s, 3 H), 1.11 - 1.25 (m, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 164.1, 162.1, 154.8, 144.6, 133.7, 129.3, 127.7, 123.3, 116.7, 112.4, 101.6, 44.5, 21.6, 13.1; **FTIR** (cm^{-1}) (neat) : 2971, 2932, 2874, 1367, 1172, 665, 606, 578,

544; **HRMS** (ESI, Pos): calc. for $C_{18}H_{20}FN_3O_2S$ $[M+H]^+$: 362,1333 *m/z*, found: 362,13434 *m/z*.

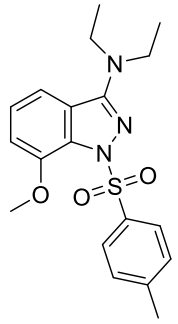


3-(piperidin-1-yl)-1-tosyl-6-(trifluoromethyl)-1*H*-indazole (5.3i): General conditions; pale yellow solid; **mp**: 132-134 °C; **R_f**: 0,47 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.46 (s, 1 H), 7.70 - 7.80 (m, 3 H), 7.46 (dd, J=8.4, 1.1 Hz, 1 H), 7.21 (d, J=8.1 Hz, 2 H), 3.40 - 3.51 (m, 4 H), 2.36 (s, 3 H), 1.61 - 1.78 (m, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 157.0, 145.0, 142.4, 133.8, 131.1, 130.8, 129.5, 127.6, 125.0, 122.8, 122.4, 120.0, 111.8, 49.9, 25.3, 24.2, 21.6; **FTIR** (cm^{-1}) (neat): 2939, 2855, 1329, 1170, 1123, 670, 602, 572, 549; **HRMS** (ESI, Pos): calc. for $C_{20}H_{20}F_3N_3O_2S$ $[M+H]^+$: 424.13011 *m/z*, found: 424.13076 *m/z*.

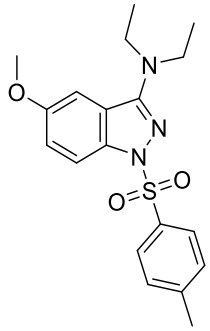


***N,N*-diethyl-6-methoxy-1-tosyl-1*H*-indazol-3-amine (5.3j):** General conditions; brown oil; **R_f**: 0,23 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 7.72 (d, J=8.4 Hz, 2 H), 7.64 (d, J=2.2 Hz, 1 H), 7.45 (d, J=8.8 Hz, 1 H), 7.16 (d, J=8.1 Hz, 2 H), 6.82 (dd, J=8.9, 2.3 Hz, 1 H), 3.93 (s, 3 H), 3.51 (q, J=7.1 Hz, 4 H), 2.34 (s, 3 H), 1.17 (t, J=7.1 Hz, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 160.7, 155.3, 145.7, 144.3, 133.8, 129.2, 127.6, 122.6, 114.1, 113.9, 97.2, 55.7,

44.4, 21.6, 13.1; **FTIR** (cm^{-1}) (neat): 2962, 2926, 2850, 1170, 1020, 790, 661, 576, 542; **HRMS** (ESI, Pos): calc. for $C_{19}H_{23}N_3O_3S$ $[M+H]^+$: 374.15329 *m/z*, found: 374.15378 *m/z*.

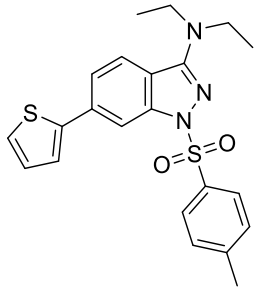


***N*,*N*-diethyl-7-methoxy-1-tosyl-1*H*-indazol-3-amine (5.3j'):** General conditions; brown oil; $\mathbf{R_f}$: 0.21 (20% EtOAc/Hex); **^{1}HNMR; ^{13}CNMR**; **FTIR** (cm^{-1}) (neat); **HRMS** (ESI, Pos): calc. for $C_{20}H_{23}N_3O_3S$ $[M+H]^+$: 386.15329 *m/z*, found: 386.15369 *m/z*;

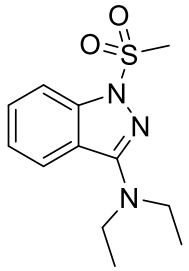


***N*,*N*-diethyl-5-methoxy-1-tosyl-1*H*-indazol-3-amine (5.3k):** General conditions; brown oil; $\mathbf{R_f}$: 0.25 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.06 (dd, J=9.2, 0.6 Hz, 1 H), 7.65

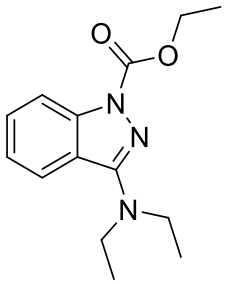
- 7.71 (m, 2 H), 7.13 - 7.17 (m, 2 H), 7.11 (dd, J=9.2, 2.4 Hz, 1 H), 6.96 (d, J=2.2 Hz, 1 H), 3.83 (s, 3 H), 3.33 - 3.44 (m, 4 H), 2.33 (s, 3 H), 1.59 - 1.78 ppm (m, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 156.4, 144.4, 138.5, 133.5, 129.2, 127.5, 121.6, 118.4, 115.6, 103.3, 55.8, 50.0, 25.3, 24.3, 21.5; **FTIR** (cm-1) (neat): 2923, 2857, 2823, 1365, 1171, 1033, 666, 577, 548; **HRMS** (ESI, Pos): calc. for $C_{20}H_{23}N_3O_3S$ $[M+H]^+$: 386.15329 *m/z*, found: 386.15399 *m/z*.



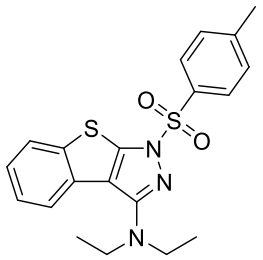
N,N-diethyl-6-(thiophen-2-yl)-1-tosyl-1H-indazol-3-amine (5.3l): General conditions; yellow solid; **mp**: 108-110 °C; **R_f**: 0,30 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.41 (dd, J=1.5, 0.6 Hz, 1 H), 7.75 (d, J=8.4 Hz, 2 H), 7.59 (d, J=8.1 Hz, 1 H), 7.47 - 7.52 (m, 2 H), 7.38 (dd, J=5.1, 1.1 Hz, 1 H), 7.12 - 7.20 (m, 3 H), 3.55 (q, J=7.2 Hz, 4 H), 2.33 (s, 3 H), 1.20 (t, J=7.2 Hz, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 155.0, 144.5, 144.4, 143.4, 135.1, 133.8, 129.3, 128.3, 127.7, 126.0, 124.5, 122.4, 122.1, 119.3, 111.2, 44.6, 21.6, 13.1; **FTIR** (cm^{-1}) (neat): 3075, 2971, 2929, 1170, 733, 668, 598, 570, 542; **HRMS** (ESI, Pos): calc. for $C_{22}H_{23}N_3O_2S_2$ $[M+H]^+$: 426.13044 *m/z*, found: 426.13162 *m/z*.



***N,N*-Diethyl-1-(methylsulfonyl)-*1H*-indazol-3-amine** (**5.3m**); General conditions; colorless oil; **R_f:** 0.30 (15% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.02 (dt, 1H, *J* = 8.5, 0.9 Hz), 7.74 (dt, 1H, *J* = 8.2, 0.9 Hz), 7.50-7.44 (m, 1H), 7.31-7.26 (m, 1H), 3.64 (q, 4H, *J* = 7.1 Hz), 2.97 (s, 3H), 1.29 (t, 6H, *J* = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 155.5, 143.7, 129.1, 123.8, 122.3, 120.0, 114.6, 44.6, 38.1, 13.5; **FTIR** (cm^{-1}) (neat): 2973, 2932, 1553, 1359, 1169, 983; **HRMS** (ESI, Pos): calc. for $C_{12}H_{17}N_3O_2S$ $[M+H]^+$: 268.11142 *m/z*, found: 268.11214 *m/z*.



Ethyl 3-(diethylamino)-1H-indazole-1-carboxylate (**5.3n)**: General conditions; colorless viscous oil; **R_f:** 0.30 (10% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.20 (d, 1H, *J* = 8.3 Hz), 7.74 (d, 1H, *J* = 8.2 Hz), 7.50-7.44 (m, 1H), 7.26-7.20 (m, 1H), 4.52 (q, 2H, *J* = 7.1 Hz), 3.64 (q, 4H, *J* = 7.1 Hz), 1.48 (t, 3H, *J* = 7.1 Hz), 1.28 (t, 6H, *J* = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 153.8, 151.2, 141.9, 128.9, 122.9, 122.0, 119.6, 115.3, 63.2, 44.3, 14.7, 13.4; **FTIR** (cm^{-1}) (neat): 2972, 2931, 1715, 1552, 1377, 1243, 1045; **HRMS** (ESI, Pos): calc. for $C_{14}H_{19}N_3O_2$ $[M+H]^+$: 262.15500 *m/z*, found: 262.15576 *m/z*.



N,N-diethyl-1-tosyl-1H-benzo[4,5]thieno[2,3-c]pyrazol-3-amine (5.3o): General conditions; brown oil; $\mathbf{R_f}$: 0.40 (20% EtOAc/Hex); **^{1}H NMR** ($CDCl_3$, 500MHz): δ 8.86 (dq, J=8.3, 0.7 Hz, 1 H), 7.88 - 8.08 (m, 1 H), 7.77 (dq, J=8.3, 0.6 Hz, 1 H), 7.65 - 7.71 (m, 2 H), 7.50 - 7.58 (m, 1 H), 7.42 - 7.49 (m, 1 H), 7.08 - 7.17 (m, 2 H), 3.44 (q, J=7.2 Hz, 4 H), 2.33 (s, 3 H), 1.16 (t, J=7.2 Hz, 6 H); **^{13}C NMR** ($CDCl_3$, 126MHz): δ 154.2, 146.1, 145.4, 144.5, 133.4, 129.2, 127.9, 126.3, 125.7, 125.5, 124.6, 123.8, 43.7, 30.9, 21.6, 13.4; **FTIR** (cm^{-1}) (neat): 2966, 2928, 2871, 1562, 1366, 727, 662, 588, 545; **HRMS** (ESI, Pos): calc. for $C_{20}H_{21}N_3O_2S_2$ $[M+H]^+$: 400.11479 *m/z*, found: 400.11531 *m/z*.

Experimental section of Chapter 6

General Information

Unless otherwise stated, all glassware was stored in the oven and/or was flame-dried prior to use. All reactions were set up under an argon atmosphere[102] while adding reagents and were run with the exclusion of moisture. All reaction flasks were kept closed with a septum during the reaction times. Anhydrous solvents were obtained either by filtration through drying columns on a GlassContour system (Irvine, CA) such as THF, DCM, DMF, CH_3CN, CH_3OH or by distillation over calcium hydride system such as DCE. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV absorbance, aqueous potassium permanganate ($KMnO_4$), or ninhydrin. Flash column chromatography was performed on an automatic purification system Teledyne Isco Combiflash® Companion. Prepacked normal phase silica gel columns Redi*Sep*® Rf High Performance Gold (40 g, 80 g and 120 g) from Teledyne Isco were used for separation of products. Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}HNMR, ^{13}CNMR, ^{19}FNMR and 31PNMR) were recorded on two Avance AV400 MHz and AV500 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform ($CDCl_3$) (δ = 7.27 ppm) as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (δ = 77.23 ppm) as the internal standard. All ^{13}C NMR spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Bruker Vertex Series FTIR (neat) and are reported in reciprocal centimeters (cm^{-1}). Analytical Supercritical Fluid

(102) Shriver, D. F. & Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*; 2nd Edition; Wiley: New York, 1986.

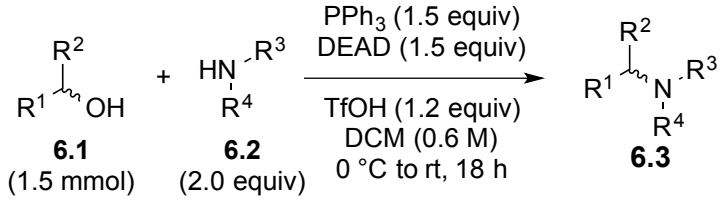
Chromatography (SFC) analysis were performed on a Aurora SFC Systems coupled to both Agilent 1260 HPLC and Agilent 6120 Simple Quadruple MS with a Multimode source. Analysed samples were dissolved in *i*-PrOH. Carbon dioxide was used as a carrier gas (150 psi). Data are reported as follows: column type, eluent, flow rate, temperature, backpressure, wavelength and retention times. Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 nm. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (*c* in g/mL), and solvent. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

Reagents

Unless otherwise stated, commercial reagents were used without purification. Triethylamine (Et_3N) was distilled over sodium and kept under argon before use. Trifluoromethanesulfonic acid (TfOH) was freshly used from newly opened commercial bottles and kept under argon before use. The purity of TfOH is vital to achieve the desired transformations with efficiency.

Experimental procedures

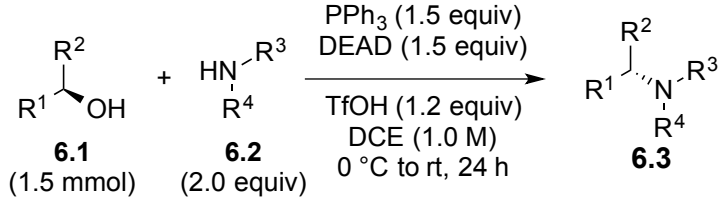
General conditions for the synthesis of di- and tri-substituted amines



To a flame-dried and argon-purged 10 mL round-bottom flask equipped with a stir-bar and a septum was added triphenyl phosphine (PPh_3) (590 mg, 2.25 mmol, 1.5 equiv) and anhydrous dichloromethane (DCM) (2.5 mL, 0.6 M). The solution was then cooled to 0 °C using a water/ice cooling bath and stirred for 3 min. Diethyl azodicarboxylate (DEAD) (354 µL, 2.25 mmol, 1.5 equiv) was added dropwise *via* a syringe and the reaction was stirred for 1 min.

Trifluoromethanesulfonic acid (TfOH) (354 µL, 2.25 mmol, 1.5 equiv) was added dropwise *via* a syringe and the reaction was stirred for 1 min. The alcohol (**1**) (1.5 mmol, 1.0 equiv) was added and the reaction was stirred for 1 min. The amine (**2**) (3.0 mmol, 2.0 equiv) was added and the reaction was stirred for another 5 min at 0 °C and for 18 h at room temperature. The reaction was quenched by addition of 5 mL of an aqueous solution of saturated $NaHCO_3$. The biphasic mixture was then transferred to a 60 mL separation funnel using 15 mL of DCM and the layers were separated. The aqueous layer was extracted with 15 mL DCM (2x) and the organic layers were combined. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 60% EtOAc/Hexanes depending on the product. ***Note:*** *For some secondary amines (as indicated), both EtOAc and hexanes used in the purification by flash chromatography contained 1% to 2% of Et3N. Unless otherwise stated, all flash chromatography were performed for 30 to 40 minutes and with a flow rate between 35 to 40 mL/min.*

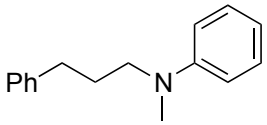
General conditions for the synthesis of α-chiral amines



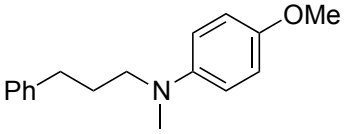
To a flame-dried and argon-purged 10 mL round-bottom flask equipped with a stir-bar and a septum was added triphenyl phosphine (PPh_3) (590 mg, 2.25 mmol, 1.5 equiv) and anhydrous dichloroethane (DCE) (1.7 mL, 1.0 M). The solution was then cooled to 0 °C using a water/ice

cooling bath and stirred for 3 min. Diethyl azodicarboxylate (DEAD) (354 µL, 2.25 mmol, 1.5 equiv) was added dropwise *via* a syringe and the reaction was stirred for 1 min. Trifluoromethanesulfonic acid (TfOH) (354 µL, 2.25 mmol, 1.5 equiv) was added dropwise *via* a syringe and the reaction was stirred for 1 min. The alcohol (**1**) (1.5 mmol, 1.0 equiv) was added and the reaction was stirred for 1 min. The amine (**2**) (3.0 mmol, 2.0 equiv) was added and the reaction was stirred for another 5 min at 0 °C and for 24 h at room temperature. The reaction was quenched by addition of 5 mL of an aqueous solution of saturated $NaHCO_3$. The biphasic mixture was then transferred to a 60 mL separation funnel using 15 mL of DCM and the layers were separated. The aqueous layer was extracted with 15 mL DCM (2x) and the organic layers were combined. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (column Redi*Sep*® Rf Gold 40 g) using a gradient from 0% to 60% EtOAc/Hexanes depending on the product. ***Note:*** *For some secondary amines (as indicated), both EtOAc and hexanes used in the purification by flash chromatography contained 1% to 2% of Et3N. Unless otherwise stated, all flash chromatography were performed for 30 to 40 minutes and with a flow rate between 35 to 40 mL/min.*

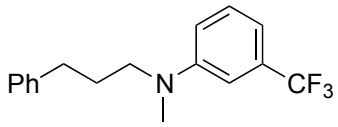
Characterization data compounds



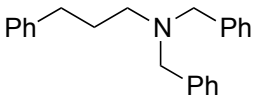
***N*-methyl-*N*-(3-phenylpropyl)aniline (6.3a):** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3a** were concentrated to dryness. The product was isolated as a pale yellow oil (270.4 mg, 80% yield). $\mathbf{R_f}$: 0.18 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.18 (m, 7H), 6.72-6.65 (m, 3H), 3.35 (t, *J* = 7.6 Hz, 2H), 2.93 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.97-1.89 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 149.3, 141.8, 129.2, 128.4 (2), 125.9, 116.1, 112.3, 52.3, 38.3, 33.4, 28.2; **FTIR** (cm^{-1}) (neat): 3025, 2938, 2862, 1679, 1597, 1504, 1365, 744, 690; **HRMS** (ESI, Pos): calc. for $C_{16}H_{20}N_1$ $[M+H]^+$: 226.1590 *m/z*, found: 226, 1588 *m/z*.



4-methoxy-*N*-methyl-*N*-(3-phenylpropyl)aniline (6.3b): Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3b** were concentrated to dryness. The product was isolated as a pale yellow oil (229.6 mg, 80% yield). $\mathbf{R_f}$: 0.16 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.31-7.26 (m, 2H), 7.22-7.17 (m, 3H), 6.86-6.80 (m, 2H), 6.74-6.67 (m, 2H), 3.77 (s, 3H), 3.26 (t, *J* = 7.6 Hz, 2H), 2.86 (s, 3H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.93-1.85 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 141.8, 128.4 (3), 125.9, 114.9 (2), 114.8, 55.8, 53.6, 39.3, 33.4, 28.0; **FTIR** (cm^{-1}) (neat): 2936, 2862, 1674, 1510, 1242, 1033, 814, 698; **HRMS** (ESI, Pos): calc. for $C_{17}H_{22}N_1O_1$ $[M+H]^+$: 256.1696 *m/z*, found: 256.1691 *m/z*.



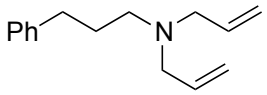
***N*-methyl-*N*-(3-phenylpropyl)-3-(trifluoromethyl)aniline (6.3c):** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3c** were concentrated to dryness. The product was isolated as a yellow oil (343.2 mg, 78% yield). **R_f**: 0.40 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33-7.25 (m, 3H), 7.24-7.18 (m, 3H), 6.92-6.89 (m, 1H), 6.82 (s, 1H), 6.79-6.75 (m, 1H), 3.37 (t, *J* = 7.6 Hz, 2H), 2.96 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.97-1.89 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 149.2, 141.4, 131.4 (q, *J* = 31.1 Hz), 129.5, 128.5, 128.3, 126.0, 124.6 (q, *J* = 270.6 Hz), 114.8, 112.2 (q, *J* = 3.8 Hz), 108.1 (q, *J* = 4.0 Hz), 51.9, 38.3, 33.2, 28.0; **^{19}F NMR** ($CDCl_3$, 376 MHz): δ −62.7; **FTIR** (cm^{-1}) (neat): 2939, 1609, 1319, 1161, 1115, 1072, 695; **HRMS** (ESI, Pos): calc. for $C_{17}H_{19}F_3N1$ $[M+H]^+$: 294,1464 found: 294.1467 *m/z*.



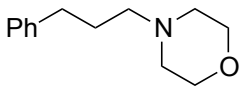
***N*,*N*-dibenzyl-3-phenylpropan-1-amine (6.3d)[103]:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 40% EtOAc/Hexanes and fractions containing **6.3d** were concentrated to dryness. The product was isolated as a colorless oil (402.2 mg, 85% yield). **R_f**: 0.84 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.39-7.35 (m, 4H), 7.34-7.29 (m, 4H), 7.27-

([103]) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9507.

7.21 (m, 4H), 7.18-7.13 (m, 1H), 7.11-7.08 (m, 2H), 3.57 (s, 4H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.83 (q, *J* = 7.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 142.6, 139.9, 128.8, 128.4, 128.3, 128.2, 126.8, 125.6, 58.4, 53.0, 33.6, 29.1; **FTIR** (cm^{-1}) (neat): 3025, 2939, 2794, 1493, 1452, 1028, 733, 695; **HRMS** (ESI, Pos): calc. for $C_{23}H_{26}N_1$ $[M+H]^+$: 316.20598, found: 316.2061 *m/z*.



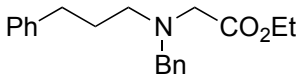
***N*-(3-phenylpropyl)-*N*-(prop-2-en-1-yl)prop-2-en-1-amine (6.3e):** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3e** were concentrated to dryness. The product was isolated as a colorless oil (271.3 mg, 84% yield). **R_f**: 0.17 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.31-7.25 (m, 2H), 7.21-7.15 (m, 3H), 5.92-5.80 (m, 2H), 5.20-5.09 (m, 4H), 3.10 (d, *J* = 6.8 Hz, 4H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H), 1.84-1.75 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 142.4, 135.8, 128.4, 128.3, 125.7, 117.3, 56.8, 52.9, 33.7, 28.7; **FTIR** (cm^{-1}) (neat): 2939, 2928, 2795, 994, 915, 747, 697; **HRMS** (ESI, Pos): calc. for $C_{15}H_{22}N_1$ $[M+H]^+$: 216.1747, found: 216.1749 *m/z*.



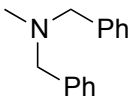
4-(3-phenylpropyl)morpholine (6.3f)[104]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3f** were concentrated to dryness. The product was isolated as a colorless oil (252.5 mg, 82% yield). **R_f**: 0.08 (40% EtOAc/Hexanes);

([104]) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *J. Org. Chem.* **2011**, *76*, 2328.

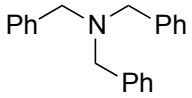
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.25 (m, 2H), 7.20-7.16 (m, 3H), 3.72 (t, *J* = 4.5 Hz, 4H), 2.65 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 4H), 2.37 (t, *J* = 8.0 Hz, 2H), 1.83 (qn, *J* = 7.5 Hz, *J* = 8.0 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 142.1, 128.4, 128.3, 125.8, 67.0, 58.4, 53.7, 33.6, 28.2; **FTIR** (cm^{-1}) (neat): 2941, 2853, 2806, 1495, 1453, 1116, 861, 746, 698; **HRMS** (ESI, Pos): calc. for $C_{15}H_{18}N_1$ $[M+H]^+$: 212.14338, found: 212.14268 *m/z*.



Ethyl [benzyl(3-phenylpropyl)amino]acetate (6.3g): Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 20% EtOAc/Hexanes and fractions containing **6.3g** were concentrated to dryness. The product was isolated as a colorless oil (378.4 mg, 81% yield). **R_f**: 0.46 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.37-7.23 (m, 7H), 7.19-7.14 (m, 3H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.80 (s, 2H), 3.31 (s, 2H), 2.70 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.87-1.79 (m, 2H), 1.26 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 171.5, 142.3, 139.0, 129.0, 128.4, 128.3 (2), 127.1, 125.7, 60.2, 58.1, 54.2, 53.4, 33.4, 29.4, 14.3; **FTIR** (cm^{-1}) (neat): 2981, 2938, 2857, 1731, 1453, 1182, 1027, 737, 697; **HRMS** (ESI, Pos): calc. for $C_{20}H_{26}N_1O_2$ $[M+H]^+$: 312.1958, found: 312.1956 *m/z*.

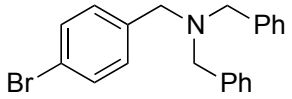


***N*-benzyl-*N*-methyl-1-phenylmethanamine (6.3h)**[105]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3h** were concentrated to dryness. The product was isolated as a colorless oil (291.6 mg, 92% yield). $\mathbf{R_f}$: 0.55 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.39-7.35 (m, 4H), 7.34-7.30 (m, 4H), 7.27-7.23 (m, 2H), 3.54 (s, 4H), 2.19 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 139.2, 129.0, 128.2, 127.0, 61.8, 42.2; **FTIR** (cm^{-1}) (neat): 3027, 2943, 2836, 2784, 1494, 1452, 1023, 733, 695, ; **HRMS** (ESI, Pos): calc. for $C_{15}H_{18}N_1$ $[M+H]^+$: 212.14338, found: 212.14252 *m/z*.

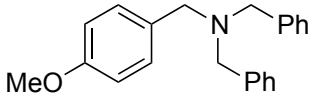


***N*,*N*-dibenzyl-1-phenylmethanamine (6.3i)**[103]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 40% EtOAc/Hexanes and fractions containing **6.3i** were concentrated to dryness. The product was isolated as a white solid (392.3 mg, 91% yield). $\mathbf{R_f}$: 0.84 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.43-7.39 (m, 6H), 7.34-7.29 (m, 6H), 7.25-7.21 (m, 3H), 3.56 (s, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 139.7, 128.8, 128.2, 126.9, 57.9; **FTIR** (cm^{-1}) (neat): 3025, 2923, 2798, 1492, 1028, 741, 695; **HRMS** (ESI, Pos): calc. for $C_{21}H_{22}N_1$ $[M+H]^+$: 288.17468, found: 288.17469 *m/z*.

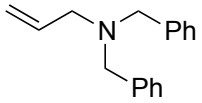
([105]) Zhao, Y. Foo, S. W.; Saito, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3006.



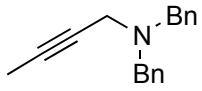
***N*,*N*-dibenzyl-1-(4-bromophenyl)methanamine (6.3j)**[103]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3j** were concentrated to dryness. The product was isolated as a colorless oil (516.5 mg, 94% yield). $\mathbf{R_f}$: 0.84 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.45-7.42 (m, 2H), 7.40-7.37 (m, 4H), 7.35-7.30 (m, 4H), 7.30-7.27 (m, 2H), 7.26-7.22 (m, 2H), 3.55 (s, 4H), 3.50 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 139.3, 138.8, 131.3, 130.4, 128.7, 128.3, 127.0, 120.6, 57.9, 57.2; **FTIR** (cm^{-1}) (neat): 3026, 2922, 2794, 1485, 1069, 1011, 795, 735, 695; **HRMS** (ESI, Pos): calc. for $C_{21}H_{20}Br_1N_1$ $[M+H]^+$: 366.08519, found: 366.08565 *m/z*.



***N*,*N*-dibenzyl-1-(4-methoxyphenyl)methanamine (6.3k)**[103]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3k** were concentrated to dryness. The product was isolated as a colorless oil (390.4 mg, 82% yield). $\mathbf{R_f}$: 0.79 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.43-7.39 (m, 4H), 7.34-7.30 (m, 6H), 7.25-7.21 (m, 2H), 6.89-6.85 (m, 2H), 3.80 (s, 3H), 3.55 (s, 4H), 3.50 (s, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 158.6, 139.8, 131.6, 129.9, 128.7, 128.2, 126.8, 113.6, 57.8, 57.2, 55.3; **FTIR** (cm^{-1}) (neat): 3027, 2930, 2792, 1509, 1245, 1033, 808, 736, 696; **HRMS** (ESI, Pos): calc. for $C_{22}H_{23}N_1O_1$ $[M+H]^+$: 318.18524, found: 318.18381 *m/z*.

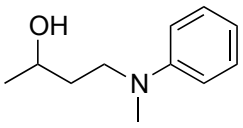


***N,N*-dibenzylprop-2-en-1-amine (6.3l)**[106]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes and fractions containing **6.3l** were concentrated to dryness. The product was isolated as a colorless oil (288.4 mg, 81% yield). $\mathbf{R_f}$: 0.84 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.40-7.36 (m, 4H), 7.34-7.29 (m, 4H), 7.26-7.21 (m, 2H), 5.97-5.88 (m, 1H), 5.25-5.19 (m, 1H), 5.18-5.14 (m, 1H), 3.58 (s, 4H), 3.07 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 139.7, 136.0, 128.8, 128.2, 126.8, 117.3, 57.8, 56.4; **FTIR** (cm^{-1}) (neat): 3062, 3027, 2922, 2792, 1494, 1453, 916, 734, 695; **HRMS** (ESI, Pos): calc. for $C_{17}H_{19}N_1$ $[M+H]^+$: 238.15903, found: 238.01584 *m/z*.

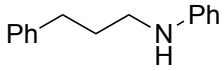


***N,N*-dibenzylbut-2-yn-1-amine (6.3m):** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 20% EtOAc/Hexanes and fractions containing **6.3m** were concentrated to dryness. The product was isolated as a colorless oil (329.1 mg, 88% yield). $\mathbf{R_f}$: 0.38 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.45-7.42 (m, 4H), 7.37-7.33 (m, 4H), 7.30-7.26 (m, 2H), 3.70 (s, 4H), 3.26-3.24 (d, *J* = 8.0 Hz, 2H), 1.95-1.93 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 139.2, 129.0, 128.2, 127.0, 80.9, 73.8, 57.5, 41.8, 3.6; **FTIR** (cm^{-1}) (neat): 3028, 2918, 2822, 2808, 1494, 1432, 1123, 948, 734, 695; **HRMS** (ESI, Pos): calc. for $C_{18}H_{20}N_1$ $[M+H]^+$: 250.1590, found: 250.1598 *m/z*.

([106]) Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166.

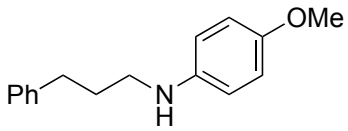


4-[methyl(phenyl)amino]butan-2-ol (6.3n): Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 40% EtOAc/Hexanes and fractions containing **6.3n** were concentrated to dryness. The product was isolated as a colorless oil (172.1 mg, 64% yield). $\mathbf{R_f}$: 0.34 (30% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.31-7.25 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.77 (t, *J* = 7.6 Hz, 2H), 4.00-3.91 (m, 1H), 3.54-3.39 (m, 2H), 2.95 (s, 3H), 2.26 (bs, 1H), 1.81-1.66 (m, 2H), 1.27-1.26 (d, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 149.7, 129.1, 117.0, 113.3, 66.9, 50.7, 38.5, 35.6, 24.0; **FTIR** (cm^{-1}) (neat): 3362, 2964, 2927, 2882, 1598, 1505, 1369, 1193, 1120, 746, 691; **HRMS** (ESI, Pos): calc. for $C_{11}H_{18}N_1O_1$ $[M+H]^+$: 180.1383, found: 180.1386 *m/z*.

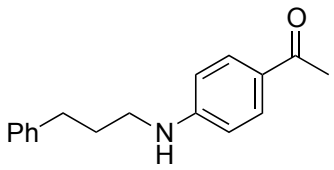


***N*-(3-phenylpropyl)aniline (6.3o)**[107]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 40% EtOAc/Hexanes and fractions containing **6.3o** were concentrated to dryness. The product was isolated as a yellow oil (237.7 mg, 75% yield). $\mathbf{R_f}$: 0.79 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.33-7.28 (m, 2H), 7.24-7.15 (m, 5H), 6.73-6.69 (m, 1H), 6.63-6.59 (m, 2H), 3.87 (bs, 1H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 2.01-1.93 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 148.1, 141.7, 129.3, 128.5, 128.4, 126.0, 117.5, 113.0, 43.6, 33.4, 31.0; **FTIR** (cm^{-1}) (neat): 3023, 2934, 2858, 1600, 1504, 1318, 1256, 744, 690; **HRMS** (ESI, Pos): calc. for $C_{15}H_{17}N_1$ $[M+H]^+$: 212.14338, found: 212.14323 *m/z*.

([107]) Liao, W.; Chen, Y.; Liu, Y.; Duan, H.; Petersena, J. L.; Shi, X. *Chem. Commun.* **2009**, 6436.

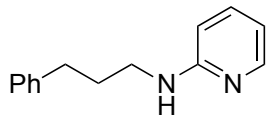


4-methoxy-*N*-(3-phenylpropyl)aniline (6.3p): Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 40% EtOAc/Hexanes (1% Et_3N) and fractions containing **6.3p** were concentrated to dryness. ***Note:*** *Both EtOAc and hexanes solvent used in the purification contain 1% of Et3N.* The product was isolated as a pale yellow oil (246.2 mg, 68% yield). **mp**: 85-86 °C; $\mathbf{R_f}$: 0.28 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.27 (m, 2H), 7.23-7.18 (m, 3H), 6.80-6.76 (m, 2H), 6.60-6.55 (m, 2H), 3.75 (s, 3H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 1.99-1.91 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 152.2, 142.4, 141.7, 128.4 (2), 125.9, 114.9, 114.3, 55.8, 44.6, 33.4, 31.1; **FTIR** (cm^{-1}) (neat): 3025, 2929, 2833, 1654, 1509, 1234, 1176, 1031, 818, 698; **HRMS** (ESI, Pos): calc. for $C_{16}H_{20}N_1O_1$ $[M+H]^+$: 242.1539, found: 242.1536 *m/z*.

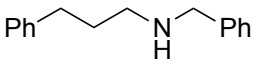


1-{4-[(3-phenylpropyl)amino]phenyl}ethanone (6.3q): Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 50% EtOAc/Hexanes and fractions containing **6.3q** were concentrated to dryness. ***Note:*** *The prepacked column of silica gel was treated with Et_3N prior to the purification.* The product was isolated as a white solid (190.0 mg, 50% yield). **mp**: 85-86 °C; $\mathbf{R_f}$: 0.16 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.82-7.80 (d, *J* = 7.2 Hz, 2H), 7.32-7.28 (m, 2H), 7.24-7.18 (m, 3H), 6.52-6.50 (d, *J* = 6.8 Hz, 2H), 4.16 (bs, 1H), 3.22 (q, *J* = 5.6 Hz, 2H), 2.74 (t, *J* = 5.6 Hz, 2H), 2.50 (s, 3H), 1.98 (qn, *J* = 5.6 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 196.3, 152.1, 141.2, 130.8, 128.5, 128.4, 126.7, 126.2, 111.3,

42.7, 33.3, 30.7, 26.0; **FTIR** (cm^{-1}) (neat): 3344, 2938, 2886, 1650, 1582, 1567, 1426, 1353, 1273, 1173, 744, 697; **HRMS** (ESI, Pos): calc. for $C_{17}H_{20}N_1O_1$ $[M+H]^+$: 254.1539, found: 254.1541 *m/z*.



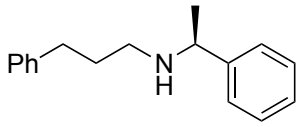
N*-(3-phenylpropyl)pyridin-2-amine (6.3r):** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 40% EtOAc/Hexanes (2% Et_3N) and fractions containing **6.3r** were concentrated to dryness. ***Note: *Both EtOAc and hexanes solvent used in the purification contain 2% of Et3N.* The product was isolated as a colorless oil (95.5 mg, 30% yield). $\mathbf{R_f}$: 0.28 (30% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.09-8.06 (m, 1H), 7.42-7.38 (m, 1H), 7.31-7.27 (m, 2H), 7.22-7.17 (m, 3H), 6.57-6.54 (m, 1H), 6.33 (d, *J* = 8.5 Hz, 1H), 4.47 (bs, 1H), 3.30 (q, *J* = 7.0 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 1.96 (qn, *J* = 7.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 158.8, 148.3, 141.6, 137.4, 128.4 (2), 126.0, 112.8, 106.4, 41.7, 33.3, 31.2; **FTIR** (cm^{-1}) (neat): 3258, 3024, 2931, 2857, 1702, 1598, 1495, 1444, 1287, 770, 734, 697; **HRMS** (ESI, Pos): calc. for $C_{14}H_{17}N_2$ $[M+H]^+$: 213.1386, found: 213.1396 *m/z*.



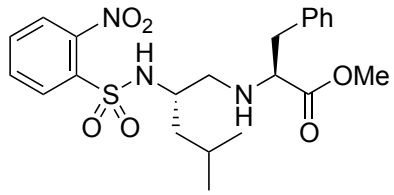
***N*-benzyl-3-phenylpropan-1-amine (6.3s)**[108]**:** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 40% EtOAc/Hexanes and fractions containing **6.3s** were concentrated to dryness. The product was isolated as a colorless oil (280.5 mg, 83% yield). $\mathbf{R_f}$: 0.66 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.35-7.23 (m, 7H), 7.21-7.16 (m, 3H), 3.79 (s, 2H), 2.68 (q, *J* = 7.0 Hz, 4H), 1.88-1.82 (m, 2H), 1.47 (bs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 142.2, 140.5, 128.4 (2), 128.3, 128.1, 126.9, 125.8, 54.0, 48.9, 33.7, 31.7; **FTIR** (cm^{-1}) (neat): 3025, 2925,

([108]) Das, S.; Addis, D.; Junge, K.; Beller, M. *Chem. Eur. J.* **2011**, *17*, 12186.

2857, 2814, 1494, 1452, 1118, 1029, 732, 695; **HRMS** (ESI, Pos): calc. for $C_{16}H_{19}N_1$ $[M+H]^+$: 226.15903, found: 226.15865 *m/z*.

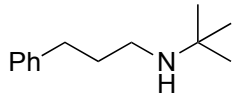


3-phenyl-*N*-[(1S)-1-phenylethyl]propan-1-amine (6.3t): Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 30% EtOAc/Hexanes (1% Et_3N) and fractions containing **6.3t** were concentrated to dryness. ***Note:*** *Both EtOAc and hexanes solvent used in the purification contain 1% of Et3N.* The product was isolated as a pale yellow oil (254.9 mg, 71% yield). $\mathbf{R_f}$: 0.32 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.38-7.24 (m, 7H), 7.22-7.16 (m, 3H), 3.77 (q, *J* = 6.8, 1H), 2.72-2.47 (m, 4H), 1.89-1.74 (m, 2H), 1.37 (d, *J* = 6.8, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 145.9, 142.2, 128.4 (2), 128.3, 126.8, 126.6, 125.7, 58.3, 47.4, 33.7, 31.9, 24.4; **FTIR** (cm^{-1}) (neat): 3025, 2959, 2925, 2857, 1494, 1451, 1180, 759, 748, 696, 552; **HRMS** (ESI, Pos): calc. for $C_{17}H_{22}N_1$ $[M+H]^+$: 240.1747, found: 240.1749 *m/z.*

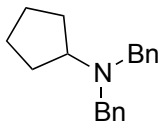


(S)-methyl 2-(((S)-4-methyl-2-(2-nitrophenylsulfonamido)pentyl)amino)-3-phenylpropanoate (6.3u): Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 10% to 40% EtOAc/Hexanes and fractions containing **6.3u** were concentrated to dryness. The product was isolated as a pale yellow oil (618.8 mg, 88% yield). $[\alpha]_D^{20}$: −48.3 (*c* 0.011, $CHCl_3$), $\mathbf{R_f}$: 0.22 (30% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.14-8.10 (m, 1H), 7.87-7.83 (m, 1H),

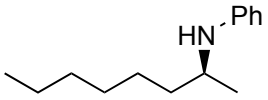
7.74-7.68 (m, 2H), 7.30-7.25 (m, 2H), 7.24-7.19 (m, 1H), 7.12-7.09 (m, 2H), 5.59 (d, 1H), 3.62 (s, 3H), 3.46-3.39 (m, 1H), 3.34 (t, J = 6.5 Hz, 1H), 2.85 (dd, J = 13.0 Hz, J = 6.0 Hz, 1H), 2.75 (dd, J = 13.5 Hz, J = 7.0 Hz, 1H), 2.67 (dd, J = 13.0 Hz, J = 5.0 Hz, 1H), 2.35 (dd, J = 12.5 Hz, J = 5.0 Hz, 1H), 1.55-1.45 (m, 1H), 1.32 -1.25 (m, 1H), 1.19-1.12 (m, 1H), 0.78 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 174.6, 147.8, 137.1, 135.2, 133.2, 132.7, 130.6, 129.2, 128.5, 126.8, 125.4, 63.5, 53.6, 51.7, 51.4, 42.4, 39.6, 24.3, 22.8, 22.0; **FTIR** (cm^{-1}) (neat): 3323, 2955, 1732, 1539, 1360, 1167, 729, 597; **HRMS** (ESI, Pos): calc. for $C_{22}H_{30}N_3O_6S_1$ $[M+H]^+$: 464.1850, found: 464.1857 *m/z.*



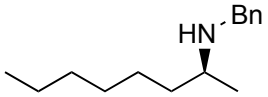
N*-tert-butyl-3-phenylpropan-1-amine (6.3v):** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 50% EtOAc/Hexanes (2% Et_3N) and fractions containing **6.3v** were concentrated to dryness. ***Note: *Both EtOAc and hexanes solvent used in the purification contain 2% of Et3N.* The product was isolated as a colorless oil (109.0 mg, 38% yield). **R_f**: 0.13 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 2.67 (t, J = 6.0 Hz, 2H), 2.59 (t, J = 6.0 Hz, 2H), 1.79 (qn, J = 6.0 Hz, 2H), 1.08 (s, 9H), 0.65 (bs, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 142.3, 128.4, 128.3, 125.7, 50.2, 42.2, 33.9, 32.7, 29.1; **FTIR** (cm^{-1}) (neat): 3026, 2963, 2934, 2860, 1453, 1360, 1231, 743, 696; **HRMS** (ESI, Pos): calc. for $C_{13}H_{22}N_1$ $[M+H]^+$: 192.1747, found: 192.1749 *m/z*.



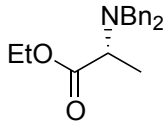
***N,N*-dibenzylcyclopentanamine (6.3w):** Following general conditions, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 5% EtOAc/Hexanes and fractions containing **6.3w** were concentrated to dryness. The product was isolated as a pale yellow oil (99.5 mg, 25% yield). $\mathbf{R_f}$: 0.65 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.39-7.35 (m, 4H), 7.31-7.27 (m, 4H), 7.23-7.18 (m, 2H), 3.61 (s, 4H), 3.18 (qn, *J* = 8.0 Hz, 1H), 1.79-1.71 (m, 2H), 1.65-1.43 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 140.7, 128.6, 128.1, 126.6, 62.1, 55.3, 28.1, 24.5; **FTIR** (cm^{-1}) (neat): 2950, 2866, 2796, 1493, 1452, 1123, 1071, 1028, 974, 741, 695; **HRMS** (ESI, Pos): calc. for $C_{19}H_{24}N_1$ $[M+H]^+$: 266.1903, found: 266.1904 *m/z*.



N*-[(2*S*)-octan-2-yl]aniline (6.3y):** Following general conditions for a-chiral amines, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 5% to 15% EtOAc/Hexanes and fractions containing **6.3y** were concentrated to dryness. ***Note: *The prepacked column of silica gel was treated with Et_3N prior to the purification.* The product was isolated as a yellow oil (184.8 mg, 60% yield). $\mathbf{[\alpha]_D^{20}}$: −6.3 (*c* 0.0096, $CHCl_3$), $\mathbf{R_f}$: 0.71 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.18-7.14 (m, 2H), 6.67-6.64 (m, 1H), 6.59-6.56 (m, 2H), 3.49-3.39 (m, 2H), 1.61-1.53 (m, 1H), 1.46-1.23 (m, 9H), 1.18-1.17 (d, *J* = 4.8 Hz, 3H), 0.89 (t, *J* = 5.6 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 147.7, 129.3, 116.7, 113.1, 48.5, 37.3, 31.9, 29.4, 26.1, 22.6, 20.8, 14.1; **FTIR** (cm^{-1}) (neat): 2957, 2925, 2855, 1601, 1504, 1317, 745, 691, 507; **HRMS** (ESI, Pos): calc. for $C_{14}H_{24}N_1$ $[M+H]^+$: 206.1903, found: 206.1902 *m/z*. The enantiomeric excess of compound **6.3y** could not be determined by SFC. A derivatization of **6.3y** was necessary. Please go to page S16.

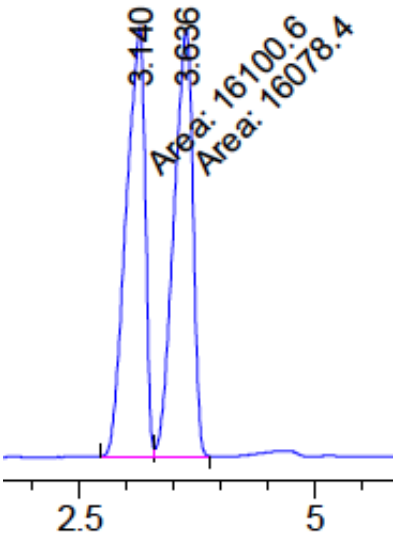


(2*S*)-*N*-benzyloctan-2-amine (6.3z): Following general conditions for α-chiral amines, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 5% to 60% EtOAc/Hexanes and fractions containing **6.3z** were concentrated to dryness. ***Note:*** *The prepacked column of silica gel was treated with Et_3N prior to the purification.* The product was isolated as a pale yellow oil (243.5 mg, 74% yield). $[\alpha]_D^{20}$: +0.96 (*c* 0.011, $CHCl_3$), R_f: 0.64 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.36-7.30 (m, 4H), 7.27-7.22 (m, 1H), 3.83 (d, *J* = 10.4 Hz, 1H), 3.74 (d, *J* = 10.4 Hz, 1H), 2.71-2.65 (m, 1H), 1.83 (bs, 1H), 1.53-1.46 (m, 1H), 1.34-1.24 (m, 9H), 1.08 (d, *J* = 4.8 Hz, 3H), 0.90-0.86 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 128.4, 128.2, 126.9, 52.5, 51.3, 37.0, 31.9, 29.5, 26.0, 22.6, 20.2, 14.1; **FTIR** (cm^{-1}) (neat): 2956, 2925, 2855, 1721, 1453, 1373, 748, 728, 695; **HRMS** (ESI, Pos): calc. for $C_{15}H_{26}N_1$ $[M+H]^+$: 220.2060, found: 220.2061 *m/z*. Enantiomeric excess was determined by SFC analysis on chiral stationary phase : Chirobiotic T, 25cm, 5um, 12% MeOH, 2 mL/min, 35˚C, 150 bar, 210 nm, tr (major) 2.5 min, tr (minor) 2.9 min. The enantiomeric excess of compound **6.3z** could not be determined by SFC. A derivatization of **6.3z** was necessary. Please go to page S18.

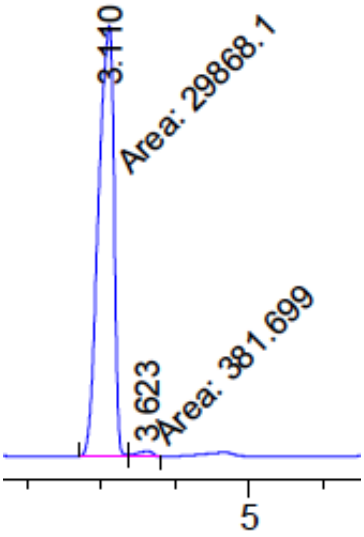


Ethyl (2*R*)-2-(dibenzylamino)propanoate (6.3aa): Following general conditions for a-chiral amines, the crude amine was purified by flash chromatography over silica gel ((Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 20% EtOAc/Hexanes and fractions containing **6.3aa** were concentrated to dryness. The product was isolated as a colorless oil (294.4 mg, 66% yield, 97% ee, 99% es). $[\alpha]_D^{20}$: +103.5 (*c* 0.012, $CHCl_3$), R_f: 0.64 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.43-7.40 (m, 4H), 7.35-7.31 (m, 4H), 7.28-7.24 (m, 2H), 4.30-4.17 (m, 2H), 3.87 (d, *J* = 11.2 Hz, 2H), 3.67 (d, *J* = 11.2 Hz, 2H), 3.52 (q, *J* = 5.6 Hz, 1H),

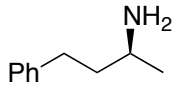
1.37-1.34 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 173.7, 140.0, 128.6, 128.2, 126.9, 60.1, 56.1, 54.4, 15.0, 14.5; **FTIR** (cm^{-1}) (neat): 3028, 2980, 2938, 2842, 1726, 1453, 1194, 1143, 731, 695; **HRMS** (ESI, Pos): calc. for $C_{19}H_{24}N_1O_2$ $[M+H]^+$: 298.1802, found: 298.1804 *m/z*. Enantiomeric excess was determined by SFC analysis on chiral stationary phase : OJ-H, 25cm, 5um, 4% *i*PrOH, 3 mL/min, 35˚C, 100 bar, 210.4 nm, tr (major) 3.1 min, tr (minor) 3.6 min.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.140	MF	0.2334	1.61006e4	1149.65771	50.0344
2	3.636	FM	0.2340	1.60784e4	1144.95801	49.9656

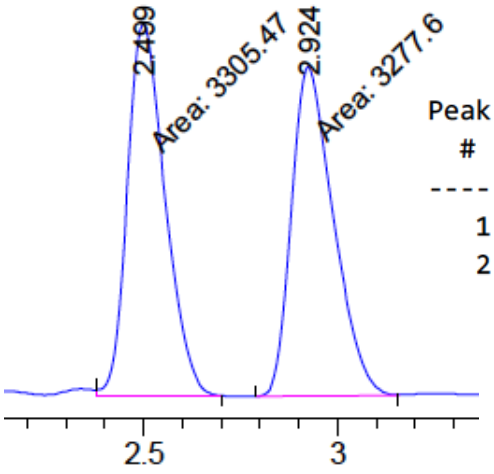


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.110	MF	0.2408	2.98681e4	2067.02637	98.7382
2	3.623	FM	0.2442	381.69910	26.05104	1.2618



(2*S*)-4-phenylbutan-2-amine (6.3ab): Following general conditions for a-chiral amines, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g)

using a gradient of 0% to 40% EtOAc/Hexanes and fractions containing **6.3ab** were concentrated to dryness. ***Note:*** *Both EtOAc and hexanes solvent used in the purification contain 2% of Et3N.* The product was isolated as a colorless oil (120.8 mg, 51% yield, 92% ee, 92% es). $[\alpha]_D^{20}$: −17.5 (*c* 0.010, $CHCl_3$), R_f: 0.24 (20% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.35-7.29 (m, 2H), 7.28-7.21 (m, 3H), 3.91-3.84 (m, 1H), 2.85-2.67 (m, 2H), 1.88-1.76 (m, 2H), 1.44 (bs, 1H), 1.28-1.27 (d, *J* = 4.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 142.1, 128.4, 125.8, 67.5, 40.9, 32.2, 23.7; **FTIR** (cm^{-1}) (neat): 3352, 3026, 2965, 2925, 2860, 1715, 1454, 1127, 1054, 744, 697; **HRMS** (ESI, Pos): calc. for $C_{10}H_{15}N$ $[M+H]^+$: 150.1277, found: 150.1278 *m/z*. Enantiomeric excess was determined by SFC analysis on chiral stationary phase : OD-H, 25cm, 5um, 12% MeOH, 3 mL/min, 35˚C, 150 bar, 210.4 nm, tr (major) 2.5 min, tr (minor) 2.9 min.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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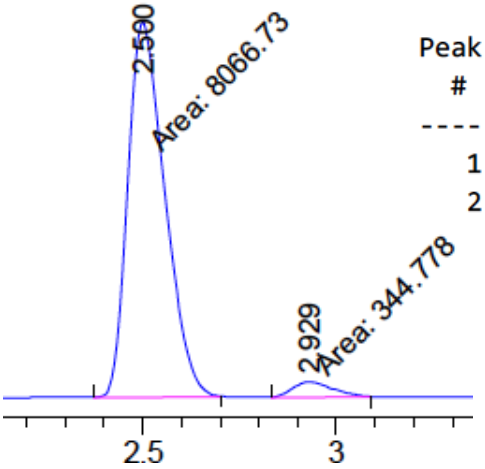
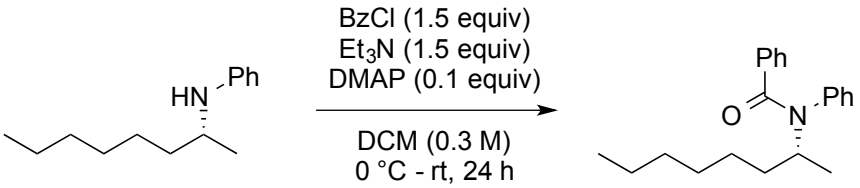
2	2.924	MM	0.1251	3277.59717	436.69635	49.7883



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.500	MM	0.1104	8066.72705	1217.50964	95.9011
2	2.929	MM	0.1161	344.77805	49.49785	4.0989

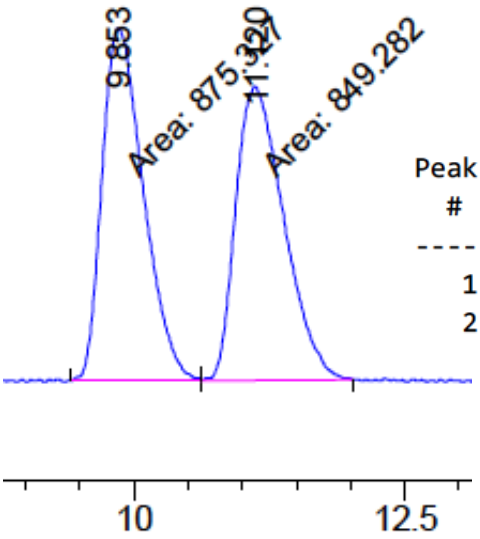
Determination of enantiomeric excess for amines 6.3y, 6.3z



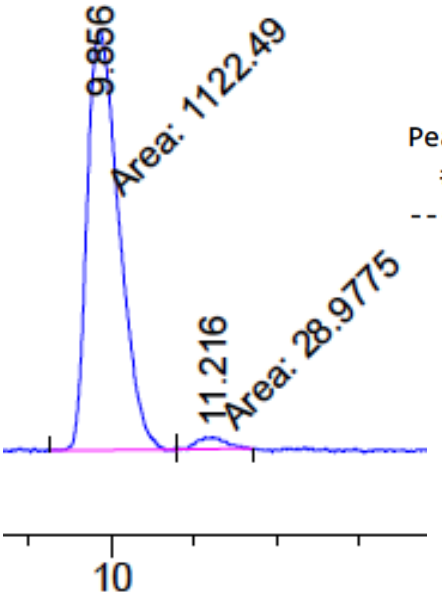
6.3y **6.4y**

***N*-[(2*S*)-octan-2-yl]-*N*-phenylbenzamide (6.4y):** To a flame-dried and argon-purged 25 mL round-bottom flask equipped with a septum and a stir-bar was added amine **6.3y** (180 mg, 0.876 mmol, 1.0 equiv) and anhydrous dichloromethane (DCM) (2.2 mL, 0.3 M). The solution was then cooled to 0 °C using a water/ice cooling bath and stirred for 3 min. Triethylamine (Et_3N) (0.19 mL, 1.315 mmol, 1.5 equiv), 4-(dimethylamino)pyridine (DMAP) (10.71 mg, 0.0876 mmol, 0.1 equiv) and benzoyl chloride (BzCl) (0.15 mL, 1.315 mmol, 1.5 equiv) were added successively. The reaction was warmed up to room temperature and stirred for 24 h. The reaction was quenched by addition of 5 mL of an aqueous solution of saturated $NaHCO_3$. The biphasic mixture was then transferred to a 30 mL separation funnel using 10 mL of DCM and the layers were separated. The aqueous layer was extracted with 10 mL DCM (2x) and the organic layers were combined. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient

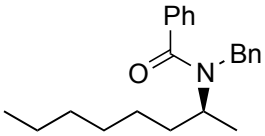
of 0% to 20% EtOAc/Hexanes and fractions containing **6.4y** were concentrated to dryness. The product was isolated as a colorless oil (239 mg, 88% yield, 95% ee, 96% es). **$[\alpha]_D^{20}$**: +64.4 (*c* 0.0092, $CHCl_3$), **R_f**: 0.31 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.27-7.08 (m, 8H), 7.03-6.98 (m, 2H), 4.93 (bs, 1H), 1.73-1.64 (m, 1H), 1.51-1.25 (m, 9H), 1.18 (d, *J* = 5.6 Hz, 3H), 0.88 (t, *J* = 5.6 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 170.9, 140.2, 137.5, 130.3, 128.9, 128.6, 128.2, 127.6, 127.2, 52.4, 35.3, 31.8, 29.3, 26.9, 22.6, 19.2, 14.1; **FTIR** (cm^{-1}) (neat): 2956, 2926, 2856, 1640, 1594, 1493, 1334, 697, 654; **HRMS** (ESI, Pos): calc. for $C_{21}H_{28}N_1O_1$ $[M+H]^+$: 310.2165, found: 310.2181 *m/z*. Enantiomeric excess was determined by SFC analysis on chiral stationary phase : OD-H, 25cm, 5um, 4% *i*PrOH, 3 mL/min, 35˚C, 150 bar, 254.4 nm, tr (major) 9.9 min, tr (minor) 11.2 min.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.853	MF	0.4416	875.32666	33.03312	50.7551
2	11.120	FM	0.5146	849.28174	27.50654	49.2449

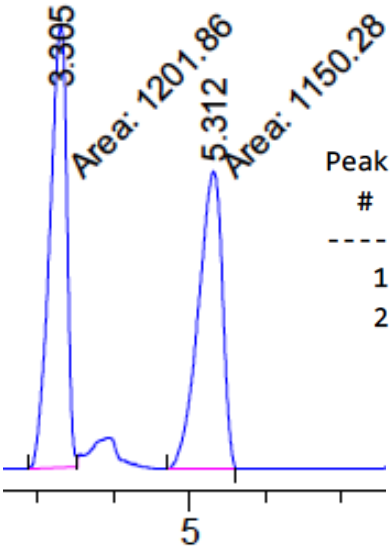


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.856	MF T	0.4452	1122.48596	42.02257	97.4834
2	11.216	FM T	0.4152	28.97752	1.16330	2.5166

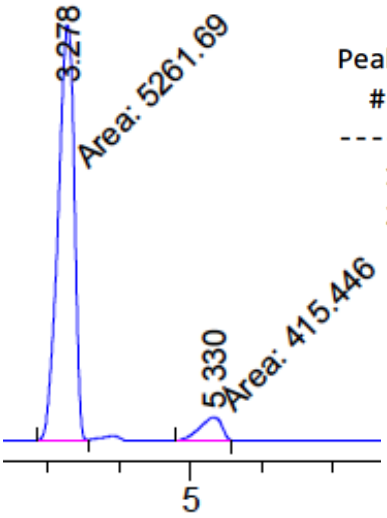


***N*-benzyl-*N*-[(2S)-heptan-2-yl]benzamide (6.4z):** Following general conditions for a-chiral amines, the crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 40 g) using a gradient of 0% to 20% EtOAc/Hexanes and fractions containing **6.4z** were concentrated to dryness. The product was isolated as a colorless oil (287 mg, 85% yield, 85% ee, 87% es). $[\alpha]_D^{20}$: −8.6 (*c* 0.010, $CHCl_3$), R_f: 0.26 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$,

500 MHz): δ 7.49-7.23 (m, 10H), 4.89 (d, J = 12.4 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 3.98-3.90 (m, 1H), 1.64-1.53 (m, 1H), 1.39-1.01 (m, 12H), 0.94-0.83 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 172.8, 139.4, 137.4, 129.2, 128.5, 128.4, 127.5, 126.8, 126.5, 55.3, 43.6, 35.2, 31.6, 29.0, 26.3, 22.6, 20.2, 14.1; **FTIR** (cm^{-1}) (neat): 2955, 2926, 2856, 1630, 1445, 1432, 1342, 728, 697; **HRMS** (ESI, Pos): calc. for $C_{22}H_{30}N_1O_1$ $[M+H]^+$: 324.2322, found: 324.2337 *m/z*. Enantiomeric excess was determined by SFC analysis on chiral stationary phase : OJ-H, 25cm, 5um, 5% *i*PrOH, 3 mL/min, 35˚C, 150 bar, 254.4 nm, tr (major) 3.3 min, tr (minor) 5.3 min.

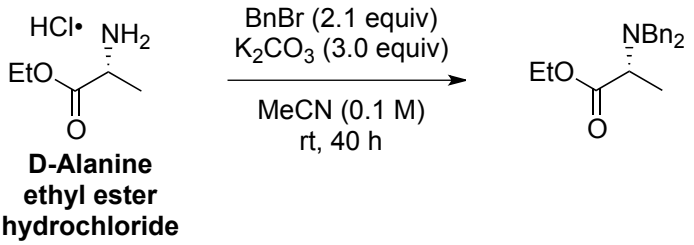


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.305	MF	0.2590	1201.85681	77.35059	51.0964
2	5.312	MM	0.3679	1150.27930	52.11043	48.9036



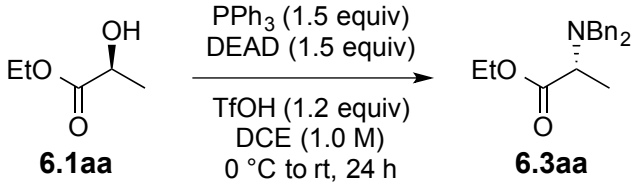
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.278	MF	0.2647	5261.68945	331.29004	92.6821
2	5.330	MM	0.3707	415.44571	18.67785	7.3179

Determination of the enantiomer for amine 6.3aa



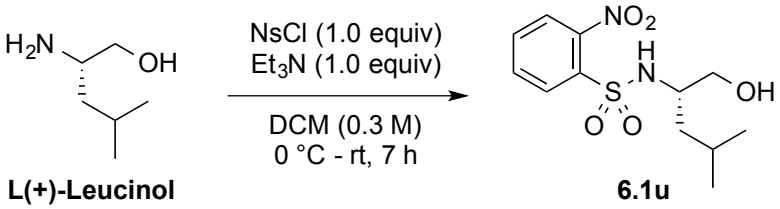
D-Alanine ethyl ester hydrochloride

Ethyl (2*R*)-2-(dibenzylamino)propanoate : To a flame-dried and argon-purged 250 mL round-bottom flask equipped with a septum and a stir-bar was added D-Alanine ethyl ester hydrochloride (1.83 g, 11.9 mmol, 1.0 equiv) and acetonitrile (120 mL, 0.10 M). Benzyl bromide (3.0 mL, 25.0 mmol, 2.1 equiv) was added drop wise via syringe and the reaction was stirred at rt for 40 h. Solvent was removed under reduced pressure. The resulting white solid was dissolved in 150 mL of EtOAc and 100 mL of water. The biphasic mixture was then transferred to a 500 mL separation funnel using 20 mL of EtOAc and the layers were separated. The aqueous layer was extracted with 80 mL EtOAc (2x) and the organic layers were combined. The organic solution was washed with 50 mL of an aqueous solution of saturated $NaHCO_3$ and 50 mL of an aqueous solution of saturated NaCl. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 120 g) using a gradient of 0% to 20% EtOAc/Hexanes and fractions containing the desired were concentrated to dryness. The product was isolated as a colourless oil (3.48 g, 98% yield). $[\alpha]_D^{20}$: +107.8 (*c* 0.012, $CHCl_3$). R_f: 0.64 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.43-7.40 (m, 4H), 7.35-7.31 (m, 4H), 7.28-7.24 (m, 2H), 4.30-4.17 (m, 2H), 3.87 (d, *J* = 11.2n Hz, 2H), 3.67 (d, *J* = 11.2 Hz, 2H), 3.52 (q, *J* = 5.6 Hz, 1H), 1.37-1.34 (m, 6H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 173.7, 140.0, 128.6, 128.2, 126.9, 60.1, 56.1, 54.4, 15.0, 14.5; **FTIR** (cm^{-1}) (neat): 3028, 2980, 2938, 2842, 1726, 1453, 1194, 1143, 731, 695; **HRMS** (ESI, Pos): calc. for $C_{19}H_{23}N_1O_2$ $[M+H]^+$: 298.1802, found: 298.1804 *m/z*.



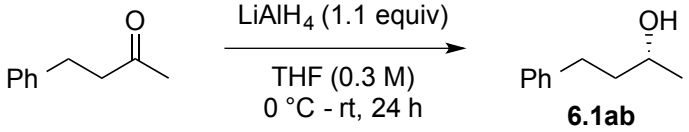
3aa (Table 4, entry 3), $[\alpha]_D^{20}$: +103.5 (*c* 0.012, $CHCl_3$)

Experimental procedures for the synthesis of starting materials



The reaction was cooled to 0 ˚C and NsCl (2.84 g, 12.80 mmol, 1.0 equiv) was added. The reaction was stirred at 0 ˚C for 10 min and at room temperature for 7 h. The reaction was quenched by addition of 50 mL of an aqueous solution of saturated $NaHCO_3$. The biphasic mixture was then transferred to a 250 mL separation funnel using 10 mL of DCM and the layers were separated. The aqueous layer was extracted with 40 mL DCM (2x) and the organic layers were combined. The organic solution was dried over anhydrous sodium sulphate (Na_2SO_4), filtered over a sintered funnel and evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 120 g) using a gradient of 10% to 60% EtOAc/Hexanes and fractions containing **6.1u** were concentrated to dryness. The product was isolated as a white solid (2.79 g, 72% yield). $[\alpha]_D^{20}$: +53.2 (*c* 0.011, $CHCl_3$); $\mathbf{R_f}$:

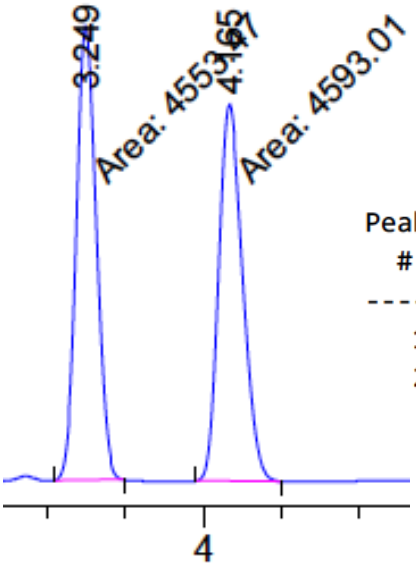
0.08 (40% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.22-8.18 (m, 1H), 7.93-7.89 (m, 1H), 7.80-7.74 (m, 2H), 5.40 (d, *J* = 7.5 Hz, 1H), 3.66-3.52 (m, 3H), 1.77 (t, *J* = 6.0 Hz, 1H), 1.65-1.56 (m, 1H), 1.45-1.32 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 147.8, 134.9, 133.5, 132.9, 130.7, 125.4, 65.4, 55.1, 41.0, 24.3, 22.9, 21.7; **FTIR** (cm^{-1}) (neat): 3540, 3342, 2957, 2871, 1537, 1359, 1337, 1163 ; **HRMS** (ESI, Pos): calc. for $C_{12}H_{19}N_2O_5S_1$ $[M+H]^+$: 303.1009, found: 303.1021 *m/z*.



6.1ab

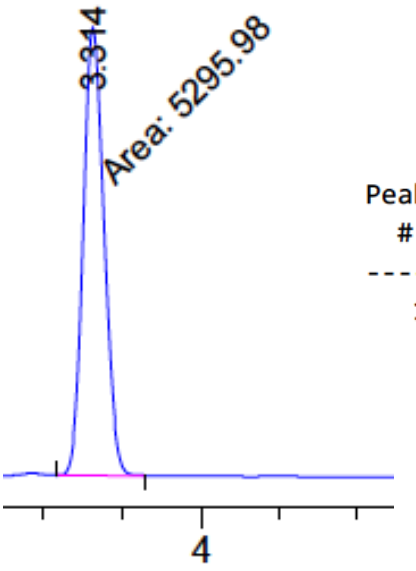
(*R*)-4-phenylbutan-2-ol (6.1ab): To a flame-dried and argon-purged 250 mL round-bottom flask equipped with a septum and a stir-bar was added 4-phenyl-2-butanone (5.0 mL, 33.4 mmol, 1.0 equiv) and THF (100 mL, 0.3 M) under argon. The solution was cooled to 0 °C and $LiAlH_4$ (1.49 g, 39.3 mmol, 1.18 equiv) was slowly added. The reaction was allowed to warm to room temperature and was stirred for 24 h. The reaction mixture was transferred to a 500 mL Erlenmeyer and was quenched with the addition of sodium sulfate decahydrate and THF (100 mL) and stirred for 10 minutes until all precipitate turned completely white. The mixture was filtered over a sintered funnel and the organic solution was evaporated to dryness. The crude amine was purified by flash chromatography over silica gel (Redi*Sep*® Rf Gold 80 g) using a gradient of 5% to 50% EtOAc/Hexanes and fractions containing **6.1ab** were concentrated to dryness. The product was isolated as a colorless oil (4.89 g, 98% yield). The

racemic sample (1.4 g) was further purified by SFC Prep 70 from Thar Technologies in multiple injections using a column Chiralpak OD-H, 250 mm, 21 mm ID, 5 mic, 7% MeOH, 6 min of run time, 60 g/min, 35 ˚C, 150 bar. The product was isolated as a colorless oil (630 mg, 90% yield, 100% ee). **$[\alpha]_D^{20}$**: −18.0 (*c* 0.010, $CHCl_3$), **literature[109] $[\alpha]_D$**: −17.32 (*c* 1.6, $CHCl_3$). **R_f**: 0.17 (10% EtOAc/Hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.31-7.27 (m, 2H), 7.23-7.17 (m, 3H), 3.88-3.80 (m, 1H), 2.80-2.73 (m, 1H), 2.72-2.64 (m, 1H), 1.84-1.72 (m, 2H), 1.38 (s, 1H), 1.24-1.23 (d, *J* = 5.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 142.1, 128.4, 125.8, 67.5, 40.9, 32.2, 23.7; **FTIR** (cm^{-1}) (neat): 3346, 3026, 2965, 2926, 1495, 1454, 1127, 1054, 744, 697; **HRMS** (ESI, Pos): calc. for $C_{10}H_{14}NaO$ $[M+Na]^+$: 173.0937, found: 173.0930 *m/z*; calc. for $C_{10}H_{18}N_1O_1$ $[M+NH_4]^+$: 168.1383, found: 168.1379 *m/z*. Enantiomeric excess was determined by SFC analysis on chiral stationary phase : OD-H, 25cm, 5um, 8% MeOH, 3 mL/min, 35˚C, 150 bar, 210.4 nm, tr (major) 3.3 min, tr (minor) 4.2 min.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.249	MM	0.1461	4553.47021	519.58881	49.7839
2	4.165	MM	0.1779	4593.00781	430.36026	50.2161

([109]) Sokeirik, Y. S.; Mori, H.; Omote, M.; Sato, K.; Tarui, A.; Kumadaki, I.; Ando, A. *Org. Lett.* **2007**, *9*, 1927.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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