

Université de Montréal  
Département de chimie, Faculté des arts et des sciences

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*Cette thèse intitulée*

**Développement de réactions photochimiques pour la synthèse d'hétérocycles azotés en chimie en flux continu**

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# **Développement de réactions photochimiques pour la synthèse d'hétérocycles azotés en chimie en flux continu**

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## Résumé

Cette thèse portera sur le développement de nouvelles méthodologies photochimiques utilisant la chimie en flux continu. Les travaux présentés au chapitre 2 décrivent l'utilisation d'un photocatalyseur à base de fer(II) pour la synthèse de carbazoles substitués. La cyclisation de diaryles et triarylamines a été effectuée en utilisant le système catalytique  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2/\text{O}_2$  avec des rendements variants entre 63 et 91 %. La technologie de chimie en flux continu a permis d'entreprendre l'étude de l'agrandissement d'échelle de cette réaction photochimique. La technique de « numbering-up » a permis de diminuer de moitié le temps du procédé pour former un gramme du produit final.

Le chapitre 3 porte sur le développement d'un nouveau réacteur photochimique composé de DELs mauves. Ce photoréacteur permet d'effectuer la décomposition d'azotures aromatiques pour fournir des hétérocycles azotés de type carbazoles, indoles et pyrroles. Plus de 21 exemples ont été synthétisés avec des rendements entre 33 à 95 %. De plus, des carbazoles comportant un lien carbone-halogène ont été synthétisés sans bris de lien ce qui peut être utilisé comme levier synthétique dans un processus multi-étapes.

Finalement, le chapitre 4 présente les travaux incorporant la réaction de photodécomposition d'azotures développée au chapitre 3 dans un processus multi-étapes en flux continu (post-fonctionnalisation). La synthèse de dérivés de la Clausine C a été étudiée en utilisant la photodécomposition d'azotures fournissant un dérivé bromé qui peut être par la suite transformé via un couplage croisé de Suzuki. Ce type de processus multi-étapes a permis d'élaborer une librairie de huit dérivés de la Clausine C avec des rendements globaux allant de 36 à 74 % (sur 2 étapes). De plus, le premier processus multi-étapes incorporant deux transformations photochimiques subséquentes a été étudié en utilisant un couplage métallophotorédox permettant la formation de lien  $\text{Csp}^2\text{-Csp}^3$ . Le dérivé benzylique de la Clausine C a été synthétisé avec un rendement total de 39 % (sur 2 étapes).

**Mots-clés :** flux continu, photochimie, photocatalyse, hétérocycles, fer, azotures

## Abstract

This thesis will focus on the development of new photochemical methodologies using continuous flow chemistry. The work presented in Chapter 2 describes the use of an iron(II) photocatalyst for the synthesis of substituted carbazoles. The cyclization of diaryls and triarylaminines was carried out using the  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2/\text{O}_2$  catalyst system with yields varying between 63 and 91 %. Continuous flow chemistry technology has made it possible to undertake the study of the scale-up of this photochemical reaction. The numbering-up technique reduced by half the process time to form one gram of final product.

Chapter 3 deals with the development of a new photochemical reactor composed of purple LEDs. This photoreactor makes it possible to carry out the decomposition of aromatic azide to provide heterocycles like carbazoles, indoles and pyrroles. More than 21 examples were synthesized with yields from 33 to 95 %. In addition, carbazoles having a carbon-halogen bond have been synthesized without bond breakage which can be used as a synthetic handle in a multi-step process.

Finally, Chapter 4 presents the work incorporating the azide photodecomposition reaction developed in Chapter 3 into a multi-step continuous flow process (post-functionalization). Clausine C derivatives synthesis was investigated using the azide photodecomposition providing a brominated derivative that can be subsequently transformed upon Suzuki cross-coupling. This type of multi-step process has made it possible to develop a library of eight Clausine C derivatives with overall yields ranging from 36 to 74 % (over 2 steps). In addition, the first multi-step process incorporating two subsequent photochemical transformations was studied using a metallophotoredox coupling to form a  $\text{Csp}^2\text{-Csp}^3$  bond. The synthesis of the benzyl derivative of Clausine C was obtained with a total yield of 39 % (over 2 steps).

**Keywords :** continuous flow, photochemistry, photocatalysis, heterocycles, iron, azides

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## Liste des abréviations

4CzIPN	1,2,3,5-tétrakis(carbazol-9-yl)-4,6-dicyanobenzène
Ac	acétate
anh	anhydre
ATP	adénosine triphosphate
BFTC	3-(dibenzo[b,d]furan-4-yl)-9-(4,6-diphenyl-1,3,5-triazin-2-yl)-9 <i>H</i> -carbazole
bpy	2,2'-bipyridyle (2,2'-bipyridyl)
BTTC	3-(dibenzo[b,d]thiophen-4-yl)-9-(4,6-diphenyl-1,3,5-triazin-2-yl)-9 <i>H</i> -carbazole
br	broad
CB2	cannabinoid receptor 2
CFL	ampoule fluocompactes
CI	conversion interne
CIS	conversion intersystème
COD	1,5-cyclooctadiene
cp*	1,2,3,4,5-pentaméthylecyclopentadiényle
cy	cyclohexyle
CzSi	9-(4- <i>tert</i> -butylphenyl)-3,6-bis(triphenylsilyl)-9 <i>H</i> -carbazole
°	degré
d	doublet
δ	déplacement chimique
DCM	dichlorométhane
dba	dibenzylideneacetone
DEL	diode électroluminescente
DMA	<i>N,N</i> -diméthylacétamide
dme	diméthoxyéthane
dmbpy	4,4'-diméthoxy-2,2'-bipyridyle (4,4'-diméthoxy-2,2'-bipyridyl)
DMF	<i>N,N</i> -diméthylformamide
DMSO	diméthylsulfoxyde
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyle (4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl)
<i>ee</i>	excès énantiomérique

équiv.	équivalent
ESI	electrospray ionization
Et	éthyle
Fppy	2-(2,4-difluorophényl)pyridyle
g	gramme
GF	groupement fonctionnels
h	heure
Het	heterocycle
h $\nu$	lumière
HRMS	high resolution mass spectroscopy
HTM	transporteur de trou électronique
Hz	hertz
Imes	1,3-dimésitylimidazol-2ylidène
<i>i</i> Pr	<i>isopropyle</i>
IR	infra-rouge
<i>J</i>	couplings constants
KSP	kenesin spindle protein
LDA	lithium <i>diisopropylamide</i>
LED	<i>light-emitting diode</i>
M	molarité
m	multiplet
<i>m</i>	meta
Me	méthyle
Mes	mésityle
MFC	régulateur de débit massique (masse flow controler)
mg	milligramme
MHz	mégahertz
min	minute
mL	millilitre
MLTC	transfert de charge du métal au ligand
mmol	millimole



mol %	pourcentage molaire
$\mu$ W	microonde
NBS	N-bromosuccinimide
neo	2,9-dimethyl-1,10-phenantroline
nm	nanomètre
NMP	<i>N</i> -méthyle-2-pyrrolidone
ns	nanoseconde
<i>o</i>	ortho
<i>o</i> -DCB	1,2-dichlorobenzène
OLED	diode électroluminescente organique
<i>p</i>	para
PC	photocatalyseur
PFA	perfluoroalcoxyalcane
Ph	phényle
phen	1,10-phénantroline
pin	pinacole
Piv	pivaloyle
ppm	partie par million
ppy	2-phénylpyridyle
psi	livre-force par pouce carré
<i>q</i>	quadruplet
R <sub>f</sub>	rapport frontal
RMN	résonance magnétique nucléaire
<i>s</i>	singulet
SCE	électrode au calomel saturée en KCl
SET	transfert d'électron simple
<i>t</i>	triplet
<i>t</i>	<i>tert</i>
t.a.	température ambiante
TBA	tetrabutylammonium
terpy	2,2':6',2''-terpyridyle (2,2':6',2''-terpyridyl)

TETT	transfert d'énergie triplet-triplet
Tf	triflate
TFA	acide trifluoroacétique
THF	tétrahydrofurane
TLC	thin-layer chromatography
TM	tamis moléculaire
tMCzPN	2,4-diphenyl-6-(4-(1,3,6,8-tetramethyl-carbazol-9-yl)phenyl)nicotinonitrile
TMEDA	tétraméthyléthylènediamine
TMS	tetramethylsilane
$t_R$	temps de résidence
UV	ultraviolette
V	volt
$V_r$	volume réactionnel
$V_s$	versus
W	watts
xPhos	2-dicyclohexylphosphino-2',4',6'-trisisopropylbiphenyl

*À toutes ma famille*

*The gin and tonic has saved more Englishmen's lives and mind than all the doctors in the Empire*

- Sir Winston Churchill

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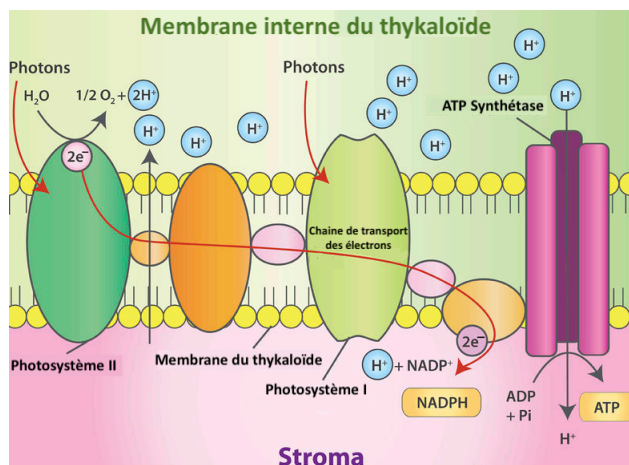
J'aimerai aussi remercier mes amis du bac pour leur support lors de ces dernières années : Véro, Félix, Joanie, Thierry, Roxanne, Louis, Geneviève, Trévor, Martin et Audrey. Véro, nos soirées de jeux de société et de bouffe indienne m'ont toujours fait sourire. Félix et Joanie, que ce soit les soirées à essayer de me faire boire de la bière, l'essai du crossfit ou le petit GH, vous me manquez énormément en ce moment. Je vous souhaite beaucoup de plaisir et de succès en Allemagne. Thierry et Roxanne même si vous êtes déménagés à Longueuil, j'aime toujours aller visiter votre petite famille (Romy et Adèle), même si on ne joue pas à des jeux de société. De plus, vous essayez de me faire découvrir des aliments que je n'ai jamais goûté, comme si j'étais votre troisième enfant. Louis, avec nos longues soirées d'étude pour nos cours gradués et a joué à certains jeux de société, on peut toujours finir par se revoir autour d'un bon verre. Audrey, nous avons partagé nos histoires de laboratoire de recherche durant ces cinq années et on a finalement survécu!

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# 1. Introduction

## 1.1 Principe de la photochimie

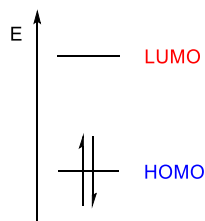
La photochimie est l'étude des transformations chimiques provoquées ou accélérées par la lumière.<sup>1</sup> Le rayonnement solaire est la source de la vie sur Terre, due à la présence des organismes photosynthétiques tels que les plantes. Ces organismes peuvent transformer l'énergie lumineuse en énergie chimique grâce à la photosynthèse (Figure 1.1). Ce processus implique deux photosystèmes contenus dans la membrane des chloroplastes. Ce dernier est un organe photosensible des cellules végétales. Le photosystème II absorbe un photon lumineux pour fournir de l'énergie à un électron. Cet électron activera le complexe de cytochromes pour produire la première source d'énergie sous forme d'adénosine triphosphate (ATP) suite à une dissipation d'énergie sous forme de chaleur. Un second quanta de lumière est absorbé par le photosystème I excitant un deuxième électron. Un transfert d'électron a lieu dans l'enzyme NADP<sup>+</sup> réductase pour réduire NADP<sup>+</sup> en NADPH, une autre source d'énergie cellulaire.<sup>2</sup>



**Figure 1.1** Schématisation des photosystèmes impliqués dans la photosynthèse. *Reproduit avec la permission de la réf. 2. Copyright 2012 EPRI.*

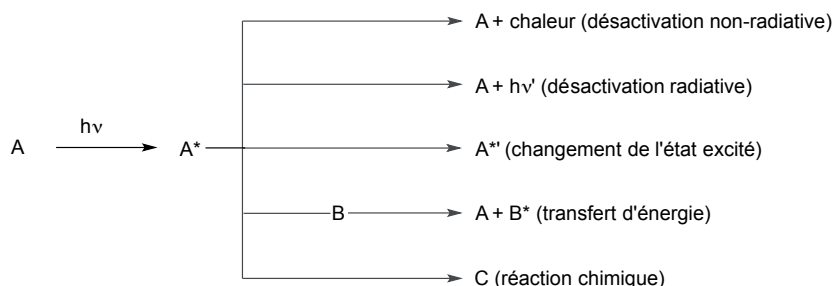
C'est au début des années 1910 que des chimistes organiciens, tels que Ciamician et Silber, commencent à s'intéresser à la photochimie dans le cadre de la synthèse organique.<sup>3</sup> Toute molécule organique possède un état électronique fondamental à obscurité et à température constante. Ce niveau énergétique fondamentalement stable ( $S_0$ ) est généralement de multiplicité de

spin unitaire (singulet) et est décrit par différentes orbitales moléculaires liantes et anti-liantes.<sup>4</sup> À l'état électronique  $S_0$  (Figure 1.2), l'orbitale moléculaire de plus haute énergie qui est occupée est appelée HOMO (*Highest Occupied Molecular Orbital*). L'orbitale inoccupée de plus basse énergie est appelée LUMO (*Lowest Unoccupied Molecular Orbital*).



**Figure 1.2** Diagramme des orbitales moléculaires d'une molécule à l'état fondamental  $S_0$ .

Lors d'une réaction photochimique, la première étape est l'absorption d'un photon par une molécule à son niveau fondamental  $S_0$ ; ceci permet l'obtention de son état excité par la promotion d'un électron à un niveau énergétique plus élevé et moins stable. Une fois à ce niveau énergétique  $S_1$  moins stable, la molécule peut atteindre soit le niveau  $T_1$  ou retourner au niveau  $S_0$ , par cinq processus différents de désactivation (Figure 1.3). Le premier processus consiste en la perte non-radiative de l'énergie, par dissipation de chaleur. La deuxième désactivation a lieu de manière radiative par l'émission d'un photon de plus faible énergie. Le troisième processus se caractérise par le changement d'état excité de la molécule. Le quatrième comprend un transfert d'énergie à une molécule B selon l'équation réactionnel suivante :  $A^* + B \rightarrow A + B^*$ . Le dernier processus se caractérise par une réaction chimique menant à un produit C.

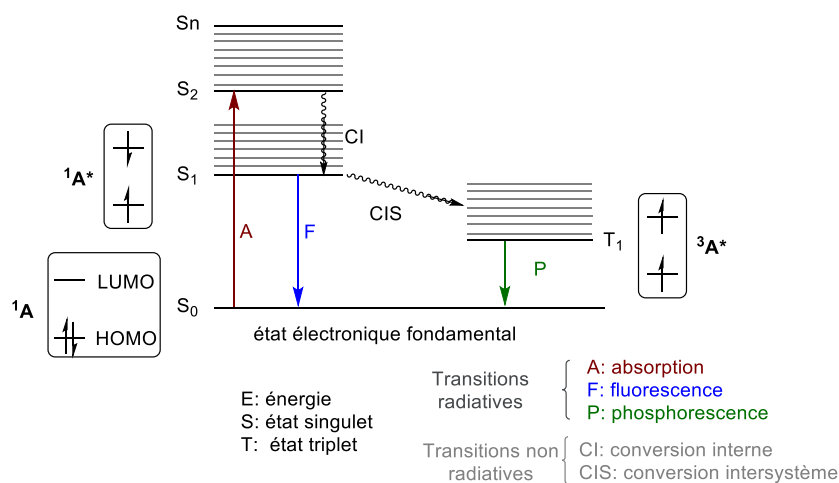


**Figure 1.3** Processus de désactivation de l'état excité  $A^*$ .

À l'aide du diagramme de Jablonski (Figure 1.4)<sup>5</sup>, il est possible d'illustrer au niveau électronique ces différents processus de désactivation. Ce diagramme représente la distribution des



niveaux électroniques d'une molécule et toutes les transitions possibles entre l'état fondamental et les états excités.

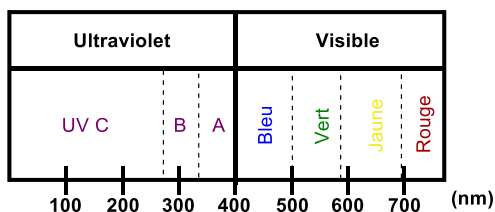


**Figure 1.4** Diagramme de Jablonski illustrant les différents processus de désactivation d'une molécule à l'état excité.

Une molécule  $^1A$  (état singlet) possédant un état électronique  $S_0$ , peut absorber un photon pour subir une excitation vers un niveau de plus haute énergie. Cette excitation s'explique par le déplacement d'un électron de l'état fondamental  $S_0$  à un état excité  $S_n$ . Par la suite, l'électron au niveau  $S_n$  perd de l'énergie par relaxation vibrationnelle pour atteindre le niveau excité singlet  $S_1$  (molécule  $^1A^*$ ). Ceci consiste en une conversion interne qui libère l'énergie sous forme de chaleur. D'une part, il existe deux transitions non radiatives, symbolisées par des flèches ondulées, soit la conversion interne (CI) et la conversion intersystème (CIS). La première consiste en une transition entre deux états électroniques de même multiplicité de spin (singlet à singlet). La seconde se traduit par un changement de spin permettant l'obtention de l'état triplet  $T_1$  (molécule  $^3A^*$ ). D'autre part, il y a deux types de transitions radiatives, symbolisées par des flèches droites. D'abord, la fluorescence correspond à une transition énergétique entre des niveaux électroniques de spin identiques (passage de  $S_1$  à  $S_0$ ), tandis que la phosphorescence est due à l'émission d'un photon lors d'une transition entre des niveaux électroniques de spin différents (passage de  $T_1$  à  $S_0$ ).

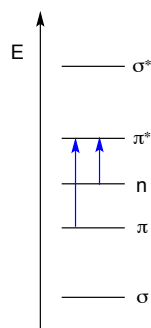
Une des conditions requises pour qu'une réaction soit considérée photochimique est qu'un des réactifs absorbe directement un photon de lumière ultraviolette (UV) ou visible. La partie visible du spectre électromagnétique, qui comprend les longueurs d'onde situées entre 390 nm (violet) et 750 nm (rouge), est distinguable par l'œil humain. En plus des longueurs d'onde du

visible, le rayonnement solaire est composé également de rayons UV dont la longueur d'onde est inférieure à 390 nm. Les radiations ultraviolettes se divisent en trois domaines : UV-A (390 nm-315 nm), UV-B (315 nm-280 nm) et UV-C (280 nm-100 nm) (Figure 1.5).



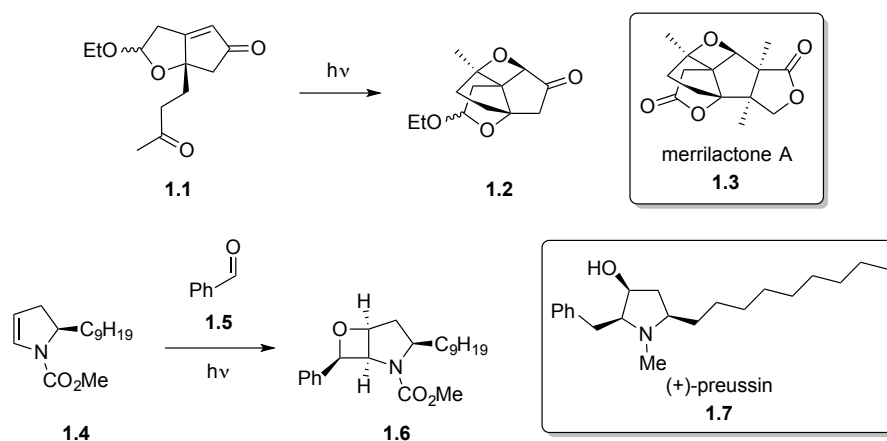
**Figure 1.5** Gamme de longueurs d'onde de l'ultraviolet au proche infrarouge.

L'absorption d'énergie sous forme de longueur d'onde permet d'atteindre l'état excité de la molécule. Ce niveau excité donne accès à une réactivité différente comparativement aux réactions thermiques.<sup>6</sup> À titre d'exemple, lors d'une réaction photochimique, la formation de produits thermodynamiquement défavorisés peut être observée. De plus, il est possible de franchir en peu de temps certaines barrières d'activation et ainsi accéder à des réactivités uniques. C'est pour ces raisons que la photochimie en synthèse organique a connu une popularité grandissante dans la décennie 1950-1959. La photochimie utilisant les longueurs d'onde UV s'est développée en premier, puisque la plupart des composés organiques sont incolores et donc absorbent normalement entre 200 à 400 nm. Les réactions photochimiques UV peuvent être classées selon le groupement fonctionnel réactif impliqué lors de l'excitation. Il existe principalement les réactions des alcènes, des composés aromatiques et celles des carbonyles.<sup>7</sup> La raison pour laquelle ces fonctionnalités sont susceptibles de réagir avec une longueur d'onde UV est par l'énergie requise pour promouvoir un électron d'un niveau à l'autre. Ceci s'explique par la différence d'énergie qui est moindre pour effectuer les transitions  $\pi \rightarrow \pi^*$  et  $n \rightarrow \pi^*$  que celle pour effectuer les transitions  $\sigma \rightarrow \sigma^*$ , d'où la réactivité des systèmes comportant une double liaison (Figure 1.6).



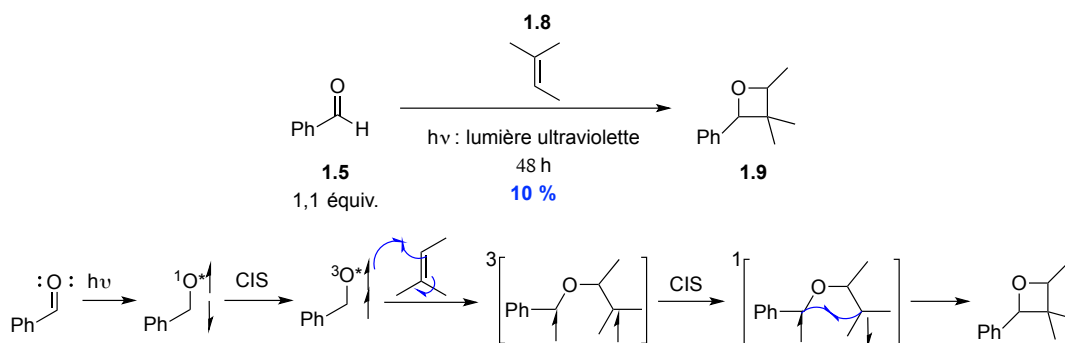
**Figure 1.6** Transitions énergétiques potentielles suite à une excitation photochimique UV.

Une réaction photochimique bien connue est la réaction de Paternò-Büchi qui fait réagir un groupement carbonyle et un alcène pour former un composé oxétane. Cette réaction a été utilisée dans les années 2000 pour effectuer la synthèse de produits naturels, tels que la merrilactone A **1.3**<sup>8</sup> et la (+)-preussin **1.7**<sup>9</sup> (Schéma 1.1).



**Schéma 1.1** Exemples de produits naturels synthétisés utilisant la réaction de Paternò-Büchi.

C'est en 1954, que le groupe de Büchi a revisité cette réaction pour en comprendre mieux son mécanisme et sa régiosélectivité. La réaction étudiée est celle entre le benzaldéhyde **1.5** et l'alcène trisubstitué **1.8** pour former l'oxétane **1.9** avec seulement 10 % de rendement après 48 heures de réaction (Schéma 1.2).<sup>10</sup>



**Schéma 1.2** Réaction photochimique de Paternò-Büchi pour former l'oxétane **1.9** et mécanisme proposé.

À la suite de la formation préférentielle d'un régioisomère, une proposition mécanistique a été élaborée faisant réagir l'état excité triplet du carbonyle. Dans un premier temps, un électron non liant de l'oxygène est promu dans l'orbitale  $\pi$  anti-liante de la double liaison C=O, ce qui donne un caractère électrophile à l'oxygène. Par la suite, une conversion intersystème a lieu pour fournir l'état triplet, qui réagit de façon radicalaire avec la double liaison de l'alcène pour former le radical tertiaire, plus stable. Suivant une seconde conversion intersystème pour obtenir l'état singulet de l'espèce biradicalaire, une étape de formation de lien C-C a lieu pour obtenir l'oxétane **1.9** désiré.

Une partie importante d'une réaction photochimique est la source d'énergie, soit la lumière. Il existe plusieurs moyens pour fournir cette lumière à un mélange réactionnel. La première source à laquelle les chimistes ont pensé est le rayonnement solaire. Cependant, elle varie selon la période d'ensoleillement de la journée, la température et la saison, ce qui la rend imprévisible et peu optimale pour l'utilisation en laboratoire.<sup>3b</sup> Une deuxième source possible sont les lasers monochromatiques de haute intensité; toutefois, ceux-ci ont une surface d'irradiation trop petite pour être utilisés de façon efficace en synthèse organique. La dernière option est l'emploi de lampe au mercure. Il existe trois types de lampe, soit à haute, moyenne ou basse pression.<sup>7a</sup> Ces sources lumineuses émettent différentes longueurs d'onde selon la pression. Les lampes à haute pression irradient entre 405 et 365 nm, celles à moyenne pression vers 315 nm et celles à basse pression jusqu'à 254 nm (Figure 1.7).



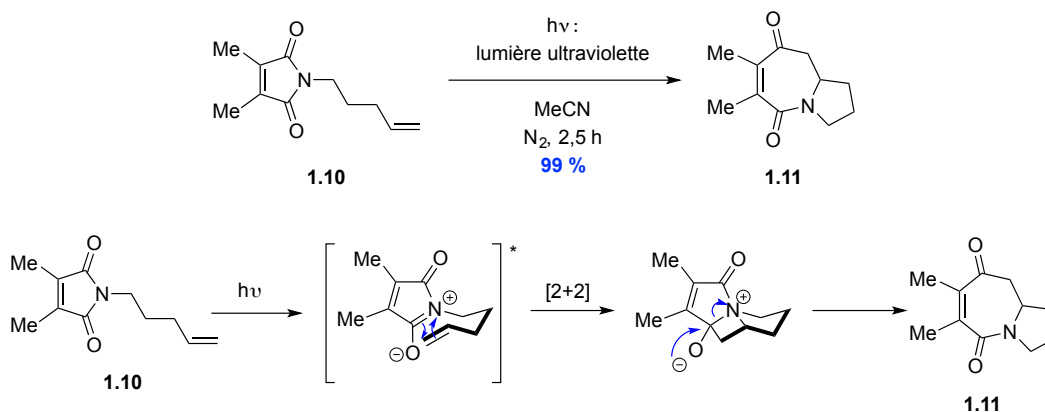
**Figure 1.7** Lampe au mercure utilisée pour la photochimie : a) à haute pression, b) à moyenne pression, c) à basse pression. *Reproduit avec la permission de la réf. 7a. Copyright 2009 Wiley-VCH.*

Malgré l'accès à plusieurs longueurs d'onde différentes, ces sources lumineuses peuvent dégager de la chaleur, donc un moyen de ventilation ou de réfrigération doit être employé pour minimiser l'effet de celle-ci sur la réaction photochimique voulue. De plus, la verrerie conventionnelle en Pyrex® normalement utilisée en laboratoire est problématique, car ce verre absorbe les radiations inférieures à 300 nm. Pour effectuer des réactions avec une source qui émet en dessous de 300 nm, il faut donc utiliser de la verrerie de quartz plus dispendieuse que la verrerie de Pyrex®. Le type de montage photochimique grandement utilisé en laboratoire de recherche académique comprend un puits d'immersion dans lequel une lampe au mercure a été insérée à l'intérieur (Figure 1.8).<sup>11</sup> Il est possible de faire circuler un liquide froid, comme l'eau, pour maintenir la température de la réaction près de la température ambiante. Ce type de montage est limité par la grosseur du puit et de la source lumineuse, ce qui rend difficile l'augmentation d'échelle pour l'utilisation industrielle.



**Figure 1.8** Lampe au mercure à pression moyenne dans un puits d'immersion. *Reproduit avec la permission de la réf. 7a. Copyright 2009 Wiley-VCH.*

Récemment, le groupe du professeur Kevin I. Booker-Milburn a développé une réaction de photocyclisation intramoléculaire pour la formation de perhydroazaazulène en utilisant ce type de montage réactionnel. Cette transformation fait réagir la forme de résonance de l'amide excité avec l'alcène terminal du maléimide **1.10** dans une cycloaddition [2+2] pour former une espèce tricyclique. Par la suite, une fragmentation d'un lien C-N de l'azétidine a lieu pour donner le bicyclic azaazulène **1.11** (Schéma 1.3).<sup>11</sup>



**Schéma 1.3** Photocyclisation intramoléculaire du maléimide **1.10** dans la synthèse du perhydroazaazulène **1.11** et le mécanisme associé.

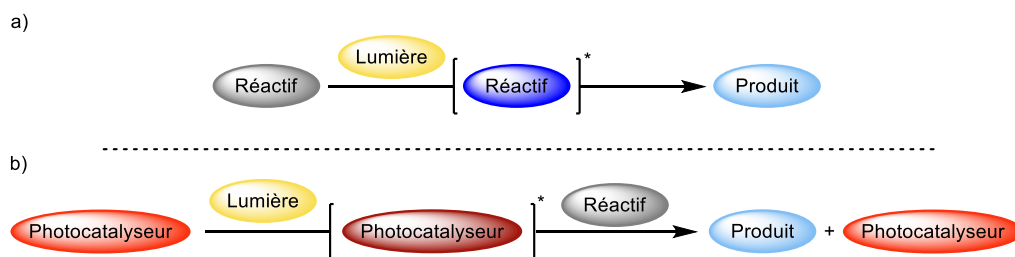
En résumé, une réaction photochimique fait réagir les niveaux électroniques d'une molécule organique qui a absorbé un photon lumineux d'une certaine énergie. Cette excitation, qui est différente de l'activation thermique, permet d'observer des réactivités nouvelles ou non favorisées normalement. Avec un nouvel intérêt pour cette branche de la chimie dans la décennie 1950-1959, une meilleure compréhension des mécanismes et des nouvelles réactivités est obtenue. Cependant, la nature des sources lumineuses, l'utilisation de la verrerie de quartz et l'utilisation de méthodes de refroidissement ont limité la transposition aux applications industrielles. C'est pour ces raisons qu'une nouvelle sous-catégorie de réactions photochimiques a été développée dans les années 2000, soit la photocatalyse.

## 1.2 Photocatalyse

### 1.2.1 Principe général

Dans une réaction photochimique traditionnelle, un réactif photoactif absorbe un photon de lumière pour atteindre son état excité. Cette espèce excitée peut réagir pour former le produit désiré

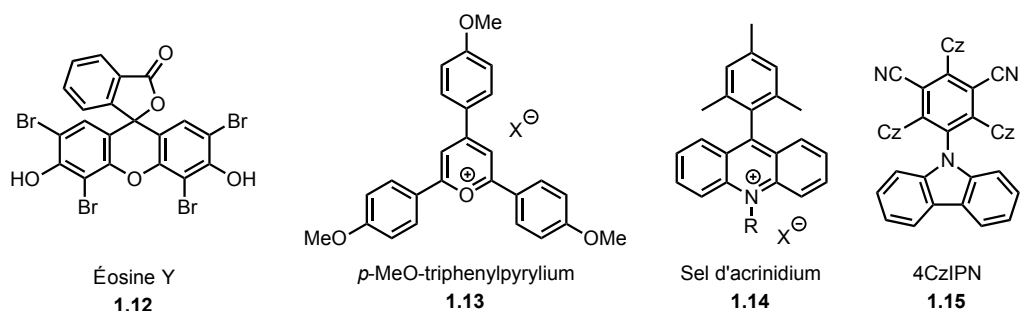
de la réaction (Figure 1.9a). En revanche, la photocatalyse est l'utilisation d'un catalyseur qui absorbe l'énergie sous forme de lumière pour accélérer une réaction chimique en favorisant un mécanisme différent. Les photocatalyseurs utilisés sont soit de nature inorganique, organique ou organométallique. Ils absorbent normalement dans la région visible du spectre électromagnétique, donc les réactifs organiques ne sont pas directement excités par le photon de lumière (énergie). Étant donné la nature colorée des catalyseurs, des sources lumineuses visibles moins énergétiques et plus abordables sont donc employées. L'utilisation d'ampoules fluocompactes (CFL) ou de diodes électroluminescentes (DEL) simplifie grandement les montages réactionnels. De plus, les longueurs d'ondes employées étant plus élevées que 300 nm, il est possible d'utiliser la verrerie en Pyrex®. Une réaction photocatalytique est caractérisée par l'utilisation d'une substance activée par la lumière. Le photocatalyseur est impliqué lors de la transformation chimique, sans pour autant être altéré structurellement à la fin de celle-ci (Figure 1.9b).<sup>12</sup> La photocatalyse accélère le processus de transformation soit par un transfert d'électron ou par un transfert d'énergie photo-induit.<sup>13</sup>



**Figure 1.9** Simplification de la comparaison entre a) une réaction photochimique et b) une réaction photocatalytique.

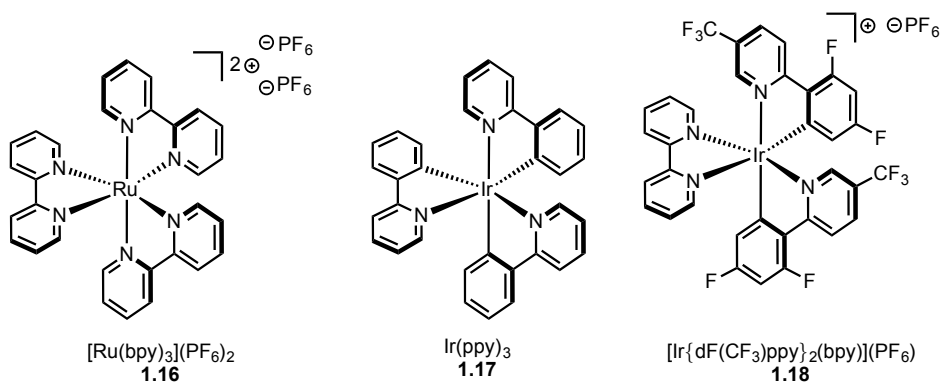
## 1.2.2 Photocatalyseurs

Il existe trois classes de catalyseurs photochimiques : les matériaux inorganiques, les composés organiques et les complexes métalliques. Les photocatalyseurs inorganiques comme  $\text{TiO}_2$ ,<sup>14</sup>  $\text{SnO}_2$ <sup>15</sup> et  $\text{ZrO}_2$ <sup>16</sup> ont été étudiés récemment pour leurs propriétés photophysiques. Au début des années 1970, Fujishima et Honda ont effectué le craquage de l'eau à l'aide d'un semi-conducteur de  $\text{TiO}_2$  pour former du dihydrogène et du dioxygène.<sup>17</sup> Les catalyseurs photochimiques organiques<sup>18</sup> de types éosine Y **1.12**<sup>19</sup>, le *p*-MeO-triphénylpyrylium **1.13**<sup>20</sup>, les sels d'acridinium **1.14**<sup>21</sup> et le 4CzIPN **1.15**<sup>22</sup> peuvent aussi être employés dans le domaine de la photocatalyse (Figure 1.10).



**Figure 1.10** Photocatalyseurs organiques.

Enfin, les complexes composés de métaux de transition peuvent servir de photocatalyseurs. Ces complexes sont basés généralement sur le ruthénium<sup>23</sup> ou l'iridium.<sup>24</sup> Plus récemment, l'efficacité de certains complexes à base de chrome,<sup>25</sup> de cuivre<sup>26</sup> ou de fer<sup>27</sup> a été démontrée. Parmi ces métaux de transitions, les photocatalyseurs tels que [Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> **1.16**, Ir(ppy)<sub>3</sub> **1.17**, ou bien [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(bpy)](PF<sub>6</sub>) **1.18** sont les plus utilisés (Figure 1.11).<sup>13b</sup> Ces derniers sont normalement complexés par des ligands de type polypyridyle et possèdent six sites de liaisons. Il existe des complexes de type homoleptiques comme [Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> **1.16** et Ir(ppy)<sub>3</sub> **1.17** qui possède le même ligand dans toutes ses sites de complexation. De plus, il existe aussi des complexes hétéroleptiques tels que [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(bpy)](PF<sub>6</sub>) **1.18** qui possèdent deux ligands différents, ou plus, autour du noyau métallique.



**Figure 1.11** Structure des photocatalyseurs à base de métaux de transition **1.16**, **1.17** et **1.18**.

### 1.2.3 Mécanismes de photocatalyse

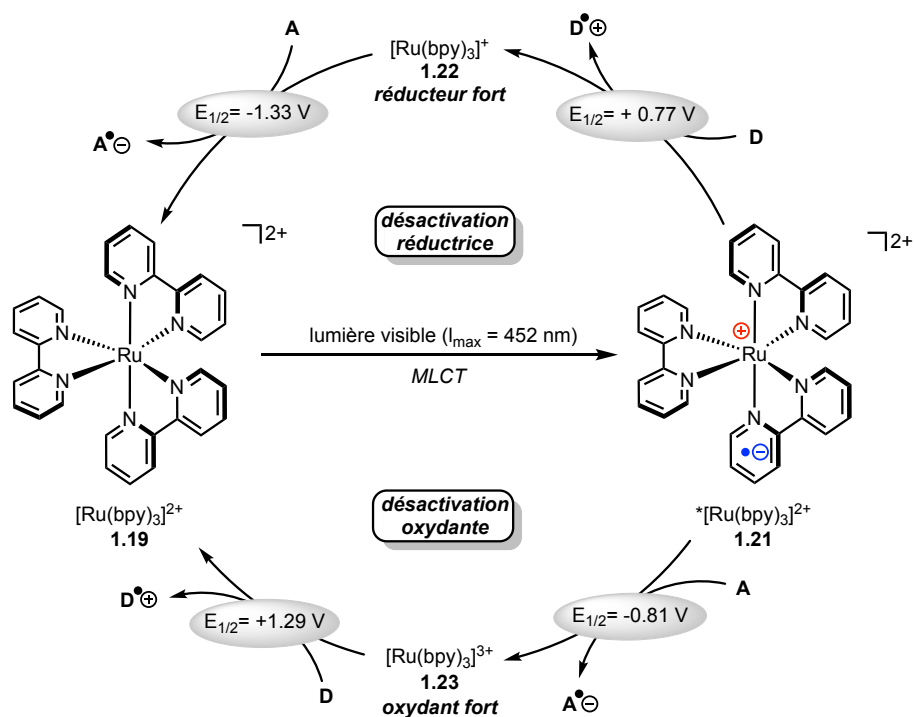
Ces complexes servant comme photocatalyseurs sont grandement utilisés pour leurs propriétés photochimiques et photophysiques. Comme ils sont faciles à synthétiser et qu'ils sont stables à température et atmosphère ambiantes, leur utilisation est pratique et avantageuse.



L'existence de plusieurs variantes de ces complexes permet d'avoir accès à plusieurs potentiel rédox et de réaliser plusieurs types de réactions. Par exemple, le complexe à base de ruthénium **1.19** peut absorber les longueurs d'ondes émises vers 452 nm (lumière visible) et possède un temps de demi-vie d'excitation de 1100 ns. En comparaison, le complexe d'iridium **1.20** absorbe aussi dans la région du faible visible, vers 380 nm, mais son temps de demi-vie est de 1900 ns.<sup>13b, 28</sup>

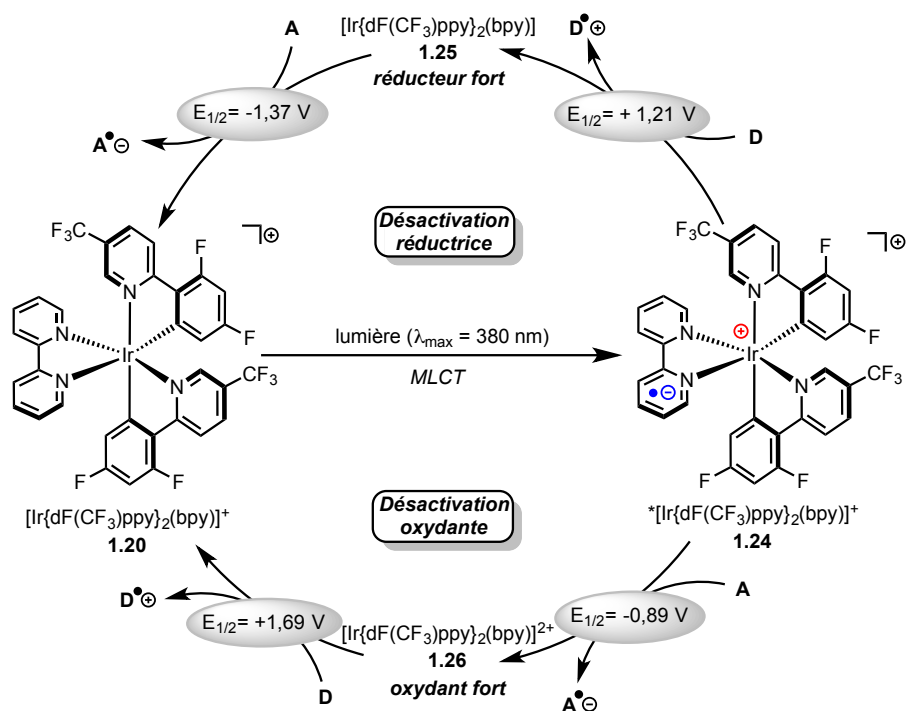
### 1.2.3.1 Photorédox

Lors de l'excitation de  $[\text{Ru}(\text{bpy})_3]^{2+}$  **1.19** par un photon, une transition électronique du centre métallique au ligand, appelée transfert de charge du métal au ligand (MLCT), a lieu pour fournir l'espèce  $^*[\text{Ru}(\text{bpy})_3]^{2+}$  **1.21**. Cette espèce excitée peut être désactivée selon deux mécanismes, soit de façon oxydante ou de façon réductrice, par un transfert d'électron singulet (SET) avec une autre molécule (Figure 1.12).<sup>13b, 29</sup> Lors d'une désactivation réductrice, le  $^*[\text{Ru}(\text{bpy})_3]^{2+}$  **1.21** accepte l'électron d'une espèce **D** (où **D** est un donneur d'électron) pour former l'espèce réduite  $[\text{Ru}(\text{bpy})_3]^+$  **1.22**. Le composé  $[\text{Ru}(\text{bpy})_3]^+$  **1.22** devient alors un réducteur fort qui peut maintenant donner un électron à une espèce **A** (où **A** est un accepteur d'électron) avec un potentiel de réduction  $E_{1/2} = -1,33 \text{ V}$  contre une électrode de calomel saturé (SCE). De façon analogue, lors d'une désactivation oxydante, le  $^*[\text{Ru}(\text{bpy})_3]^{2+}$  **1.21** donne un électron à l'espèce **A** pour former l'espèce oxydée  $[\text{Ru}(\text{bpy})_3]^{3+}$  **1.23**. L'intermédiaire  $[\text{Ru}(\text{bpy})_3]^{3+}$  **1.23** est fortement oxydant et peut facilement prendre un électron d'une espèce **D** avec un potentiel d'oxydation  $E_{1/2} = 1,29 \text{ V}$  contre SCE. Ce type de réaction, où le photocatalyseur absorbe le photon pour former une espèce excitée qui peut donner ou prendre un électron à une molécule organique, est appelé une réaction photorédox.



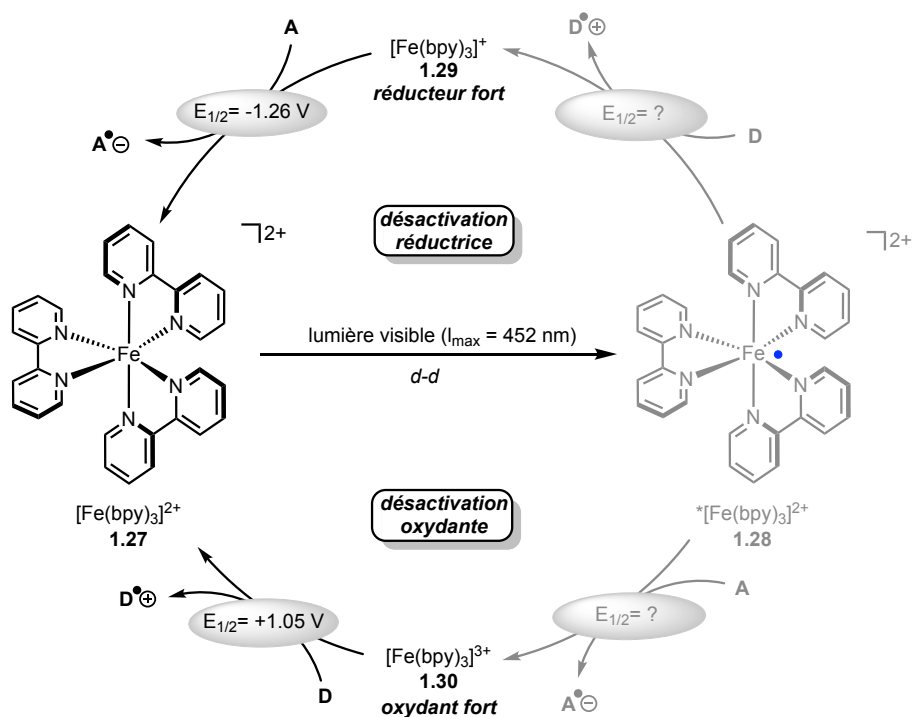
**Figure 1.12** Cycles généraux de désactivation du  $[Ru(bpy)_3]^{2+}$  1.21.

En comparant les cycles généraux de désactivation du ruthénium 1.19 et de l'iridium 1.20, on peut observer certaines différences. Dans un premier temps, les deux complexes subissent une transition électronique de type MLCT, mais le  $[Ru(bpy)_3]^{2+}$  1.19 absorbe à 452 nm et le  $[Ir\{dF(CF_3)ppy\}_2(bpy)](PF_6)$  1.18 absorbe à 380 nm. De plus, l'espèce oxydante  $[Ir\{dF(CF_3)ppy\}_2(bpy)]^{2+}$  1.26 est plus oxydante que  $[Ru(bpy)_3]^{3+}$  1.23, avec un potentiel  $E_{1/2} = +1,69$  V qui surpasse de 0,4 V celui du ruthénium. Donc, le complexe d'iridium 1.20 est un meilleur oxydant (Figure 1.13).



**Figure 1.13** Cycles généraux de désactivation du  $^*[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{bpy})]^+$  1.24.

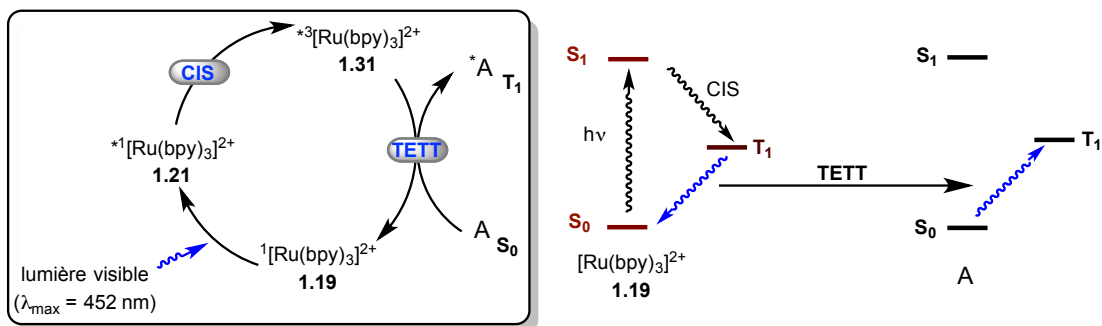
Les propriétés photophysiques des complexes polypyridyles à base de fer(II) diffèrent de ceux à base de ruthénium(II). Normalement, la transition électronique étudiée lors d'une réaction photochimique est le transfert de charge du métal au ligand (MLCT). Cependant, celle impliquée pour le fer est centrée sur le métal (d-d).<sup>30</sup> De plus, en comparant les temps de demi-vie d'excitation, on peut constater que celui du fer est très court, de seulement 0,81 ns.<sup>30-31</sup> Ayant un temps de demi-vie d'excitation si court, il est difficile de mesurer expérimentalement les potentiels de réduction et d'oxydation de l'état excité. De plus, les potentiels de réduction du fer(I) et d'oxydation du fer(III) sont plus faibles que ceux des complexes de ruthénium correspondants (Figure 1.14). Cependant, le prix et l'abondance terrestre du fer<sup>32</sup> fait de ces complexes des alternatives intéressantes aux complexes de métaux rares, comme le ruthénium et l'iridium.<sup>33</sup>



**Figure 1.14** Cycles généraux de désactivation du  $^*[\text{Fe}(\text{bpy})_3]^{2+}$  **1.28**.

### 1.2.3.2 Transfert d'énergie

Il existe un autre moyen de catalyser une réaction photochimique à partir de l'état excité; soit par transfert d'énergie.<sup>13b, 34</sup> L'irradiation de l'espèce  $[\text{Ru}(\text{bpy})_3]^{2+}$  **1.19** (Figure 1.15) excite le complexe de son état fondamental singulet ( $\text{S}_0$ ) vers son état excité singulet ( $\text{S}_1$ ). Un croisement intersystème peut avoir lieu pour fournir l'état excité triplet ( $\text{T}_1$ ) plus stable. Cet état ( $\text{T}_1$ ) peut effectuer un transfert d'énergie triplet-triplet (**TETT**) avec un accepteur. La relaxation de  $^*[\text{Ru}(\text{bpy})_3]^{2+}$  **1.31** de son état triplet ( $\text{T}_1$ ) à son état fondamental ( $\text{S}_0$ ) promeut un électron de la molécule **A** de l'état fondamental ( $\text{S}_0$ ) vers le plus faible état d'énergie triplet ( $\text{T}_1$ ). L'énergie contenue dans l'état triplet du complexe de ruthénium **1.19** est de 49,0 kcal/mol, tandis que l'énergie triplet du complexe d'iridium **1.20** est de 61,8 kcal/mol.<sup>34</sup> Cependant, les données de **TETT** pour les complexes polypyridines à base de fer n'ont pas encore été mesurées expérimentalement.



**Figure 1.15** Transfert d'énergie du  $^*[\text{Ru}(\text{bpy})_3]^{2+}$  **1.21** vers l'accepteur A par TETT.

## 1.2.4 Synthèse des photocatalyseurs

La plupart des photocatalyseurs à base de métaux de transition tels que le ruthénium ou l'iridium, sont disponibles commercialement. Cependant, la nature des ligands sur les complexes commerciaux est restreinte. C'est pour cela qu'il peut être intéressant de développer des synthèses pratiques permettant la variation des ligands.

### 1.2.4.1 Complexes de ruthénium

La synthèse du photocatalyseur de ruthénium  $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$  **1.16** (Schéma 1.4) débute par un déplacement de ligands. Trois équivalents de la bipyridine **1.32** complexent le ruthénium en déplaçant les ligands chlorures et les molécules d'eau. Ce déplacement s'effectue dans l'éthanol à reflux pendant 18 heures, et est possible en raison de la propriété bidentate des ligands bipyridines. Le centre métallique subit une réduction pour donner le ruthénium(II); ce processus s'effectue par l'oxydation de l'éthanol. Par la suite, l'addition d'un excès de sel d'hexafluorophosphate d'ammonium s'effectue à chaud et le mélange réactionnel est refroidi à température ambiante. Le produit désiré est obtenu par précipitation dans l'eau, sous forme de solide rougeâtre.<sup>35</sup> Ce composé est un exemple de complexe de ruthénium homoleptique. Les synthèses de complexes hétéroleptiques à base de ruthénium sont plus difficiles, car il faut passer par un complexe intermédiaire ou par un dimère métallique.

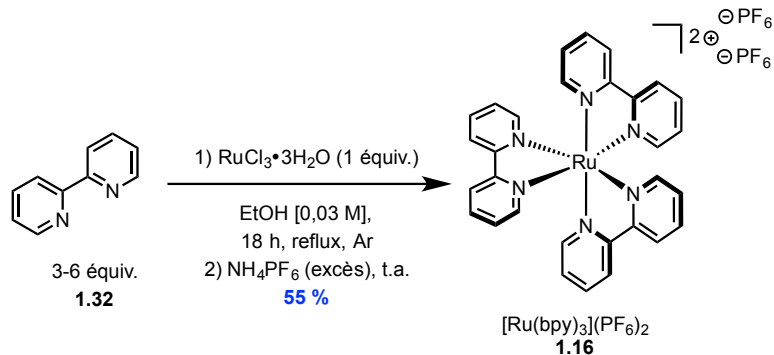


Schéma 1.4 Synthèse du  $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$  **1.16**.

### 1.2.4.2 Complexes d'iridium

Il est possible d'utiliser des complexes d'iridium(III) comme photocatalyseur. La synthèse des composés d'iridium hétéroleptiques s'effectue en 3 étapes avec une purification par chromatographie. Dans un premier temps, une insertion C-H de l'iridium doit avoir lieu avec le 2-phénylpyridine substitué **1.33** pour former le complexe bimétallique **1.34**. Cette réaction nécessite une température élevée pendant 18 heures sous atmosphère d'argon. Par la suite, un déplacement des ligands chlorures pontants chlorure est effectué par un ligand bidentate bipyridine **1.32**. Avant d'isoler le complexe, une colonne chromatographique et un échange anionique doivent être réalisés. Cette échange de contre-cation à lieu en ajoutant un excès d'hexafluorophosphate d'ammonium ce qui fait précipiter un solide jaune (Schéma 1.5).<sup>36</sup>

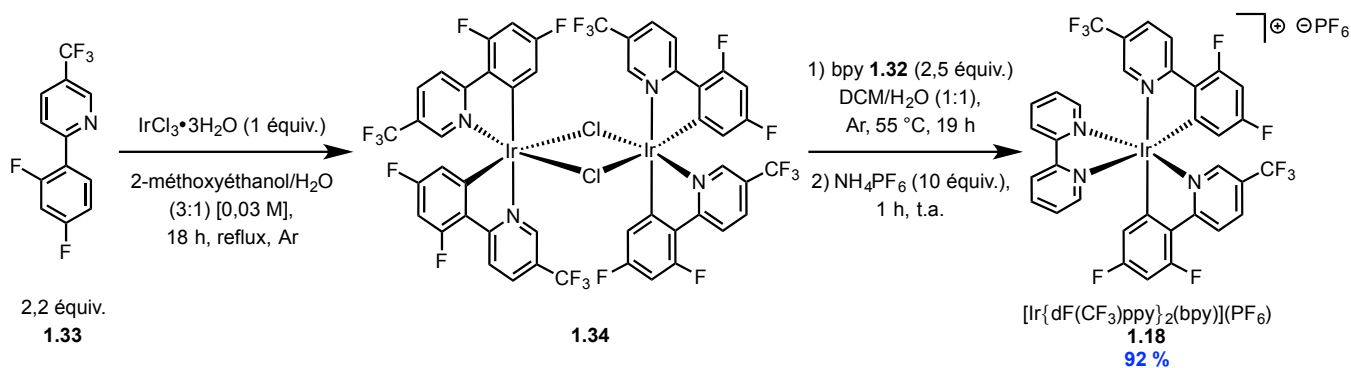


Schéma 1.5 Synthèse du  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{bpy})](\text{PF}_6)$  **1.18**.

### 1.2.4.3 Complexes de fer

Certains photocatalyseurs de fer(II) possèdent les mêmes ligands que ceux à base de Ru(II).<sup>37</sup> À titre d'exemple, le complexe  $[\text{Fe}(\text{bpy})_3](\text{PF}_6)_2$  **1.35**, analogue au complexe  $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$  **1.16**, est synthétisé à partir du chlorure de fer(II) tétrahydrate (Schéma 1.6). Dans un premier temps, le  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  est dissous dans l'eau à 60 °C pendant 20 minutes. Par la suite, 3,05 équivalents de bipyridine **1.32** sont ajoutés sous forme d'une solution d'éthanol, toujours à 60 °C, et le mélange est agité pendant 20 minutes. Comme pour la synthèse du  $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$  **1.16**, une complexation de ligands a lieu pour former le complexe polypyridyle de fer(II). Finalement, l'ajout d'un excès (3 équivalents) d'hexafluorophosphate de potassium permet d'effectuer l'échange de contre-ion afin d'obtenir le complexe désiré  $[\text{Fe}(\text{bpy})_3](\text{PF}_6)_2$  **1.35**. La précipitation d'un solide rouge a lieu lors du refroidissement à température ambiante; une filtration est effectuée pour isoler le complexe.<sup>38</sup>

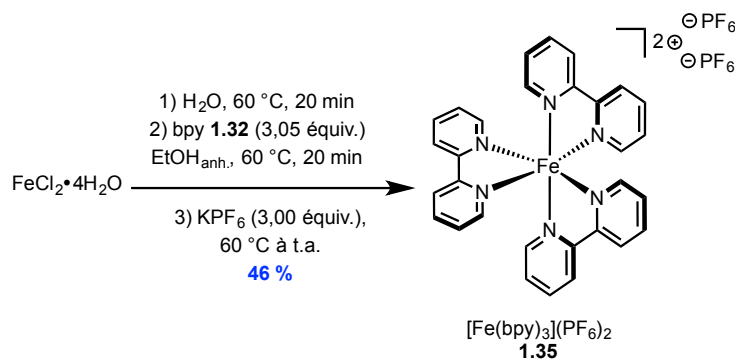


Schéma 1.6 Synthèse du  $[\text{Fe}(\text{bpy})_3](\text{PF}_6)_2$  **1.35**.

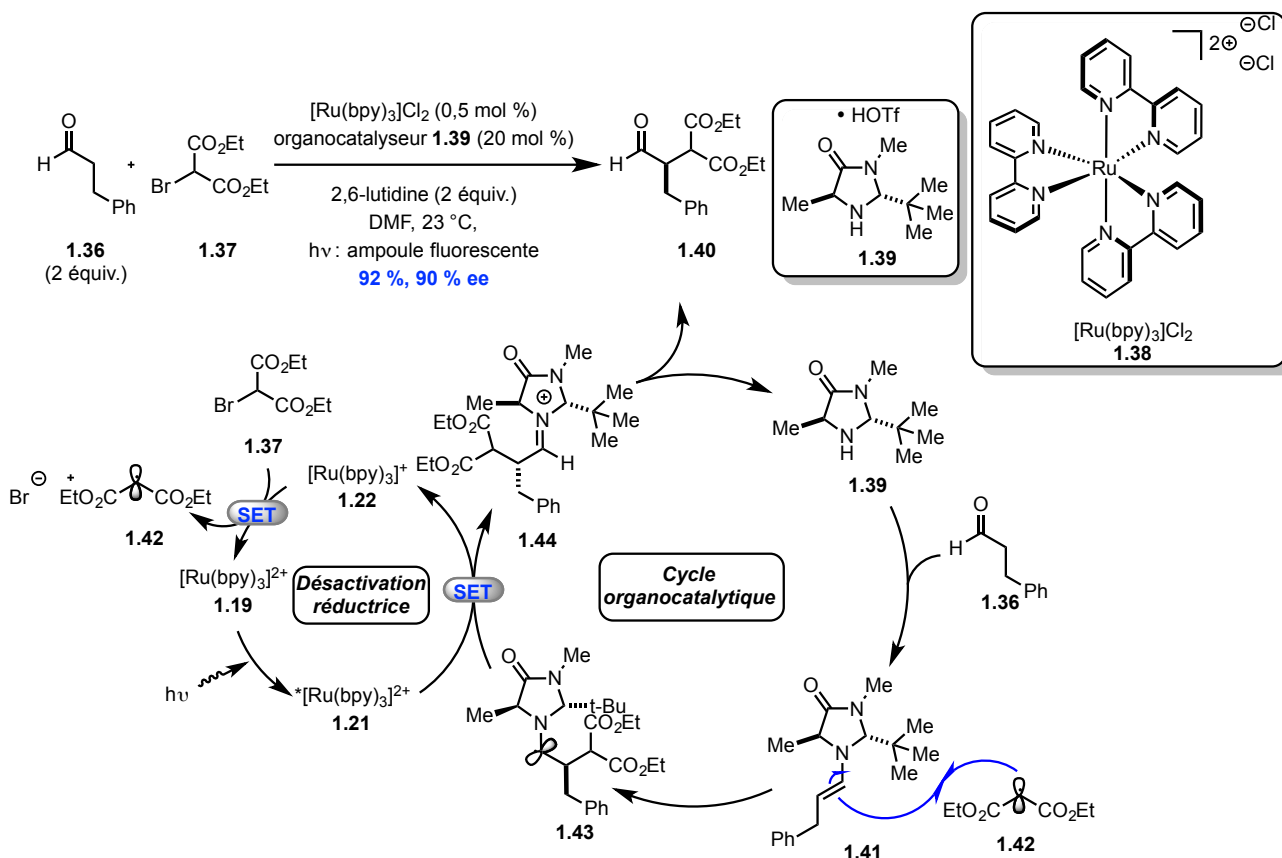
### 1.2.5 Réactions typiques de photocatalyse

Vers la fin de la première décennie du 21<sup>e</sup> siècle, les réactions de type photocatalyse ont pris de l'importance dans le domaine de la chimie organique de synthèse. Cet essor est dû au développement de photocatalyseurs à base de ruthénium et à base d'iridium possédant des propriétés photophysiques intéressantes.<sup>13b, 29</sup> Comme mentionné précédemment, il existe entre autres deux types de mécanismes, soit le transfert d'électron singulet (**SET**) ou le transfert d'énergie triplet-triplet (**TETT**).

### 1.2.5.1 Photorédox

En 2008, le groupe du professeur MacMillan a développé des conditions réactionnelles combinant la chimie photorédox et l'organocatalyse pour effectuer une alkylation stéréosélective d'aldéhydes (Schéma 1.7).<sup>23a</sup> À titre d'exemple, ce processus fait réagir le 3-phénylpropanal **1.36** avec le 2-bromomalonate d'éthyle **1.37** en présence du photocatalyseur de ruthénium **1.38** et de l'organocatalyseur **1.39** pour former le nouvel aldéhyde **1.40**. Du côté mécanistique, cette réaction combine deux cycles catalytiques distincts, soit un cycle d'organocatalyse et un cycle de photorédox. Le tout commence par une condensation entre l'organocatalyseur d'imidazolidinone **1.39** et le 3-phénylpropanal **1.36**, suivie d'une tautomérisation formant l'énamine **1.41**. Cette espèce **1.41** réagit avec le radical déficient en électron **1.42** (formé lors de la régénération du catalyseur photoactif **1.19**), pour mener à l'espèce radicalaire **1.43**. Celle-ci subit un transfert d'électron singulet (SET) avec l'espèce de  $^*[Ru(bpy)_3]^{2+}$  **1.21**, ce qui l'oxyde pour donner l'iminium **1.44** et le  $[Ru(bpy)_3]^+$  **1.22** fortement réducteur. Ce nouveau réducteur réagit avec le bromure d'alkyle **1.37** dans une réaction de SET pour fournir le radical correspondant **1.42** (qui a réagi précédemment avec l'énamine **1.41**). Le ruthénium est régénéré en l'espèce photoactive **1.19**, pour ainsi recommencer le cycle photorédox. Une hydrolyse de l'imine fournira le produit désiré **1.40** et régénérera l'organocatalyseur **1.39**. Cette réaction donne l'aldéhyde **1.40** avec un rendement de 92 % et un excès énantiomérique (ee) de 90 %.

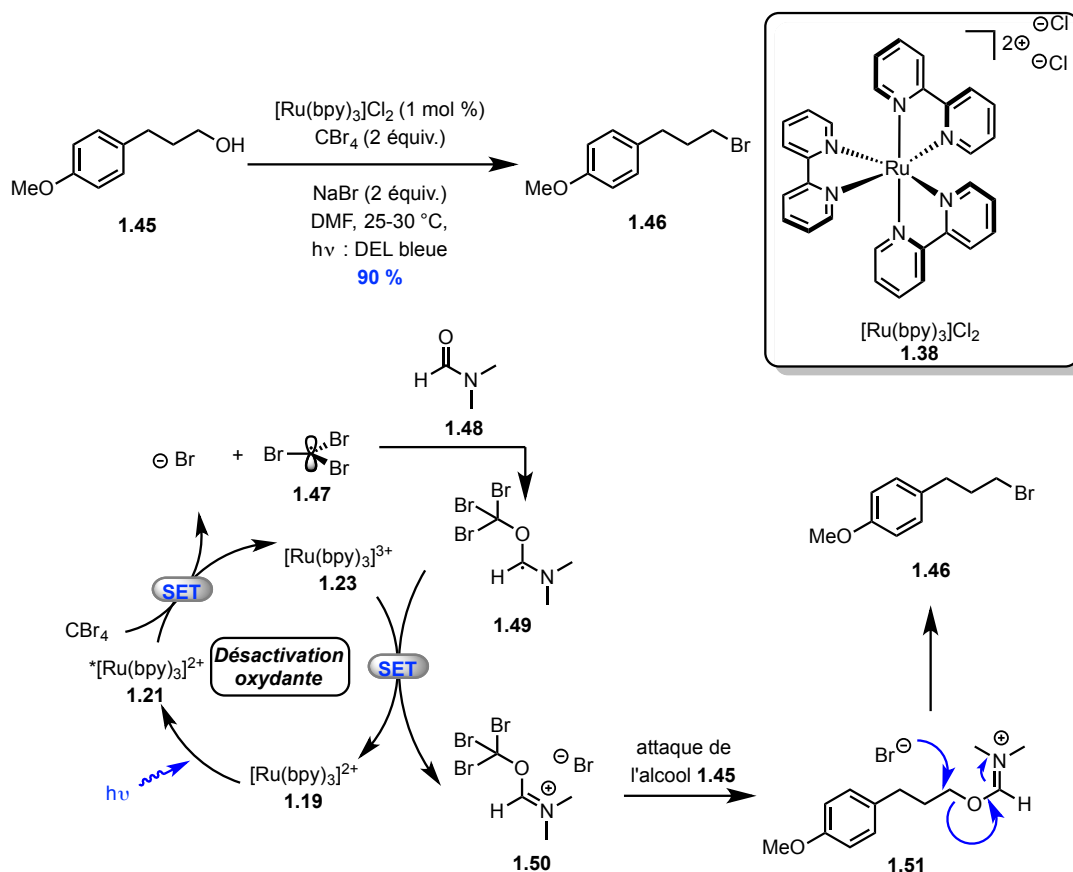




**Schéma 1.7** Réaction et mécanisme d'alkylation stéréosélective d'aldéhyde développée par MacMillan.

Stephenson a de son côté rapporté l'utilisation de la chimie photorédox pour effectuer la conversion d'alcools en leurs dérivés halogénés correspondants (Schéma 1.8).<sup>23b</sup> Cette réaction dérivée de la transformation d'Apple permet de diminuer les sous-produits stœchiométriques en utilisant le photocatalyseur à base de ruthénium **1.38**. Le 3-(4-méthoxyphényl)propan-1-ol **1.45** réagit en présence du [Ru(bpy)<sub>3</sub>]<sup>2+</sup> **1.19** et de tétrabromocarbène (CBr<sub>4</sub>) pour former le 1-(3-bromopropyl)-4-méthoxybenzène **1.46** avec un rendement de 90%. Le mécanisme commence avec l'activation photochimique du catalyseur de ruthénium **1.19** formant l'espèce <sup>\*</sup>[Ru(bpy)<sub>3</sub>]<sup>2+</sup> **1.21**. Par la suite, le tétrabromocarbène effectue un transfert d'électron singulet (SET) pour former le radical **1.47** et l'espèce fortement oxydante [Ru(bpy)<sub>3</sub>]<sup>3+</sup> **1.23**. Le radical **1.47** s'additionne sur le DMF fournissant un nouveau radical. Cette espèce radicalaire **1.49** subit une seconde réaction SET avec l'oxydant **1.23** pour régénérer le ruthénium **1.19** et donner l'iminium **1.50**. À la suite d'une réaction d'addition-élimination sur l'iminium **1.50** par l'alcool **1.45**, le nouvel iminium **1.51** est

produit. Celui-ci subit une substitution nucléophile de deuxième ordre par un ion bromure pour produire le dérivé bromé **1.46**.



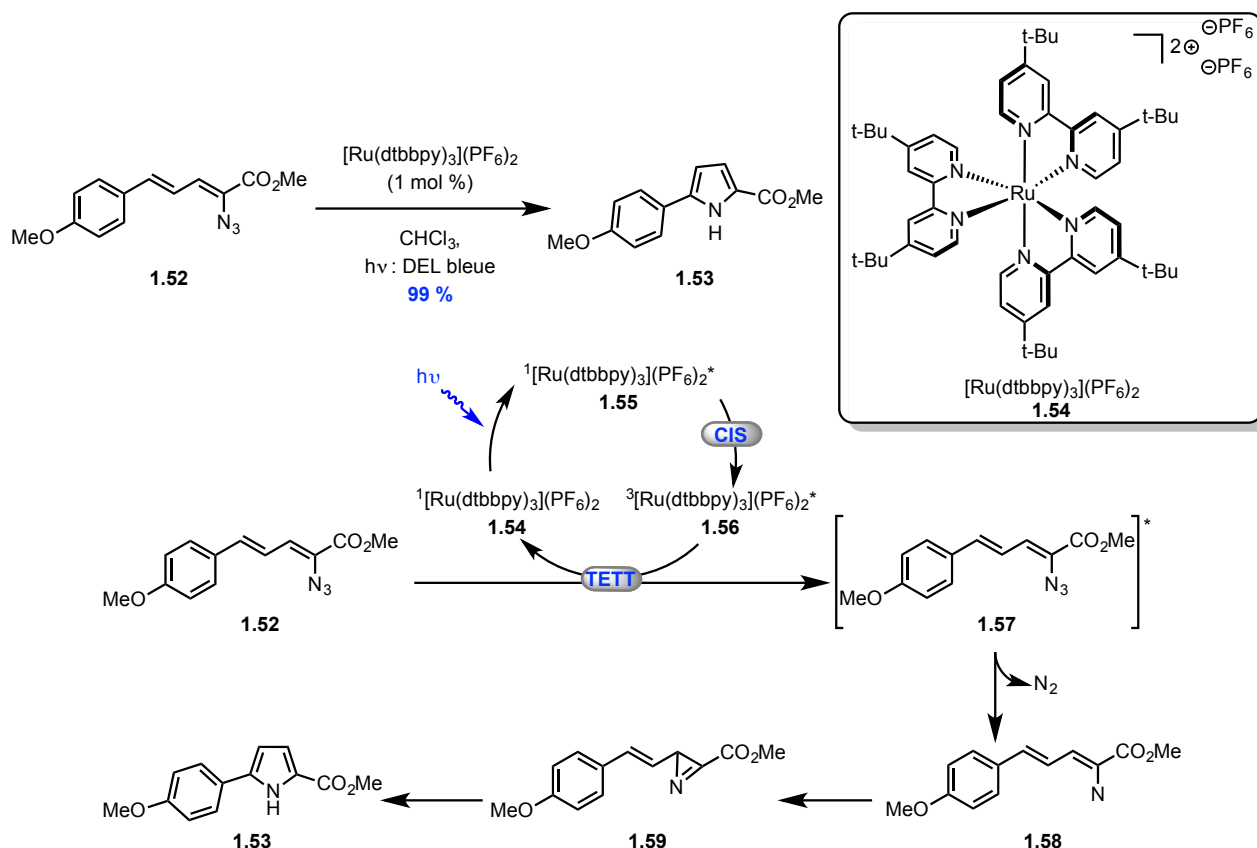
**Schéma 1.8** Réaction et mécanisme de la conversion d'alcools en dérivés halogénés présentés par Stephenson.

Les deux réactions présentées utilisent deux types de mécanismes potentiels lors d'une transformation photorédox, soit la désactivation réductrice dans l'exemple de MacMillan ou la désactivation oxydante dans l'exemple de Stephenson. Il existe aussi un autre mode de réactivité photochimique, le transfert d'énergie triplet-triplet.

### 1.2.5.2 Transfert d'énergie

En 2014, Yoon et ses collaborateurs ont développé la transformation de l'azoture vinylique **1.52** du pyrrole **1.53** grâce à l'utilisation du catalyseur de ruthénium **1.54** par un transfert d'énergie (Schéma 1.9).<sup>39</sup> Le  $^1[\text{Ru}(\text{dtbbpy})_3](\text{PF}_6)_2$  **1.54** est activé par l'absorption d'un photon. Une conversion intersystème a lieu pour passer de l'état singulet vers l'état triplet du catalyseur de

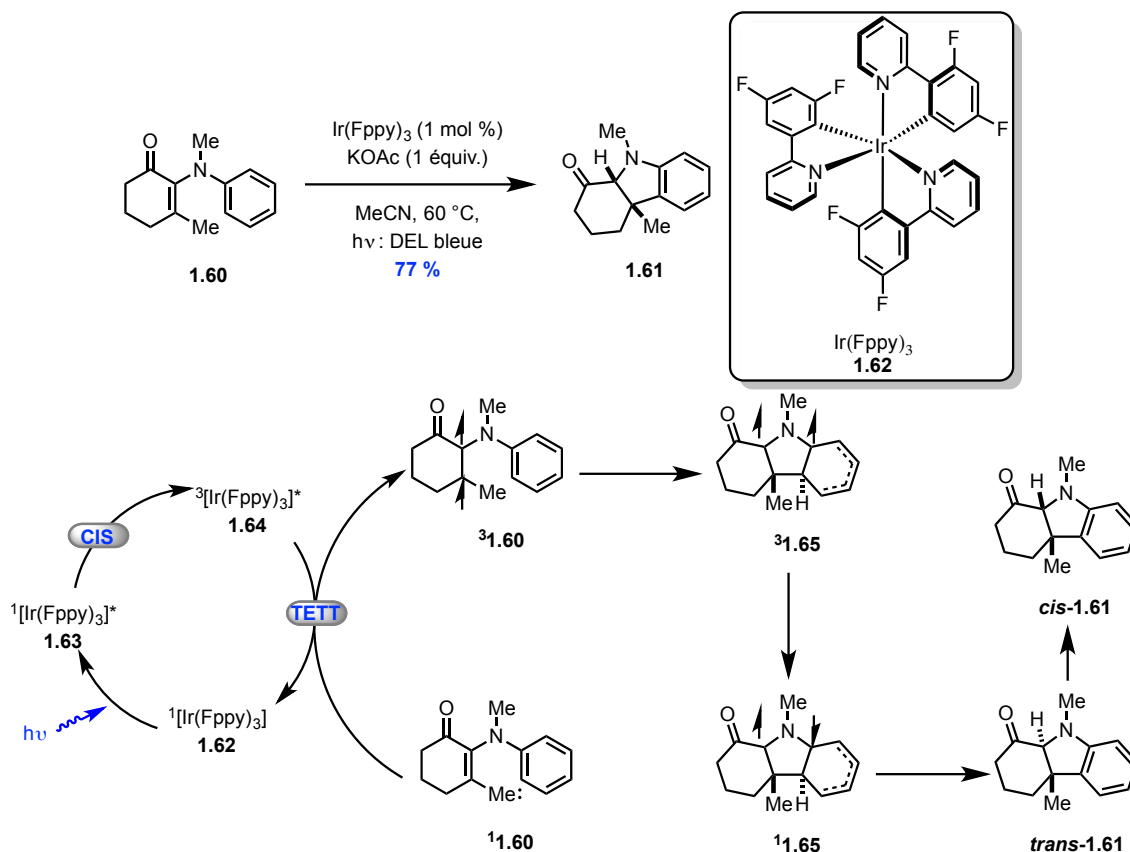
ruthénium excité. Une fois l'état triplet  $^3[\text{Ru}(\text{dtbbpy})_3](\text{PF}_6)_2^*$  **1.56** atteint, un transfert d'énergie triplet-triplet entre le ruthénium et l'azoture **1.52** donne l'état triplet de l'azoture **1.57** et régénère le catalyseur de ruthénium **1.54**. L'azoture **1.57** excité perd une molécule de diazote sous forme gazeuse pour former le nitrène **1.58**. Ce nitrène réagit avec une double liaison adjacente dans la molécule pour fournir l'azirine **1.59**. Celle-ci subit un réarrangement et un transfert de proton intramoléculaire pour former le pyrrole **1.53** avec un rendement de 99 %.



**Schéma 1.9** Réaction et mécanisme de la photodécomposition d'azoture proposé par Yoon.

En 2017, la collaboration entre les professeurs Paton et Smith a permis l'étude d'une réaction de photocyclisation  $6\pi$  catalysée par le complexe d'iridium **1.62** par transfert d'énergie (Schéma 1.10).<sup>40</sup> La réaction transforme l'amine tertiaire **1.60** en l'hétérocycle azoté **1.61** en présence d'une quantité stœchiométrique d'acétate de potassium avec un rendement de 77 %. Le  $^1[\text{Ir}(\text{Fppy})_3]$  **1.62** est excité par l'absorption d'un photon pour fournir le  $^1[\text{Ir}(\text{Fppy})_3]^*$  **1.63**. Par la suite, une conversion intersystème transforme l'état singulet excité en état triplet excité **1.64**. Cette

espèce d'iridium **1.64** réagit avec l'amine tertiaire **1.60** pour produire l'état triplet de **3.1.60**. C'est l'espèce **3.1.60** qui effectue la cyclisation pour donner le produit **3.1.65**. Ensuite, cet intermédiaire subit une seconde conversion intersystème pour fournir l'état singulet du composé *trans*-**1.61**. Finalement, un transfert de proton 1,4 et une épimérisation mènent au produit final *cis*-**1.61**.

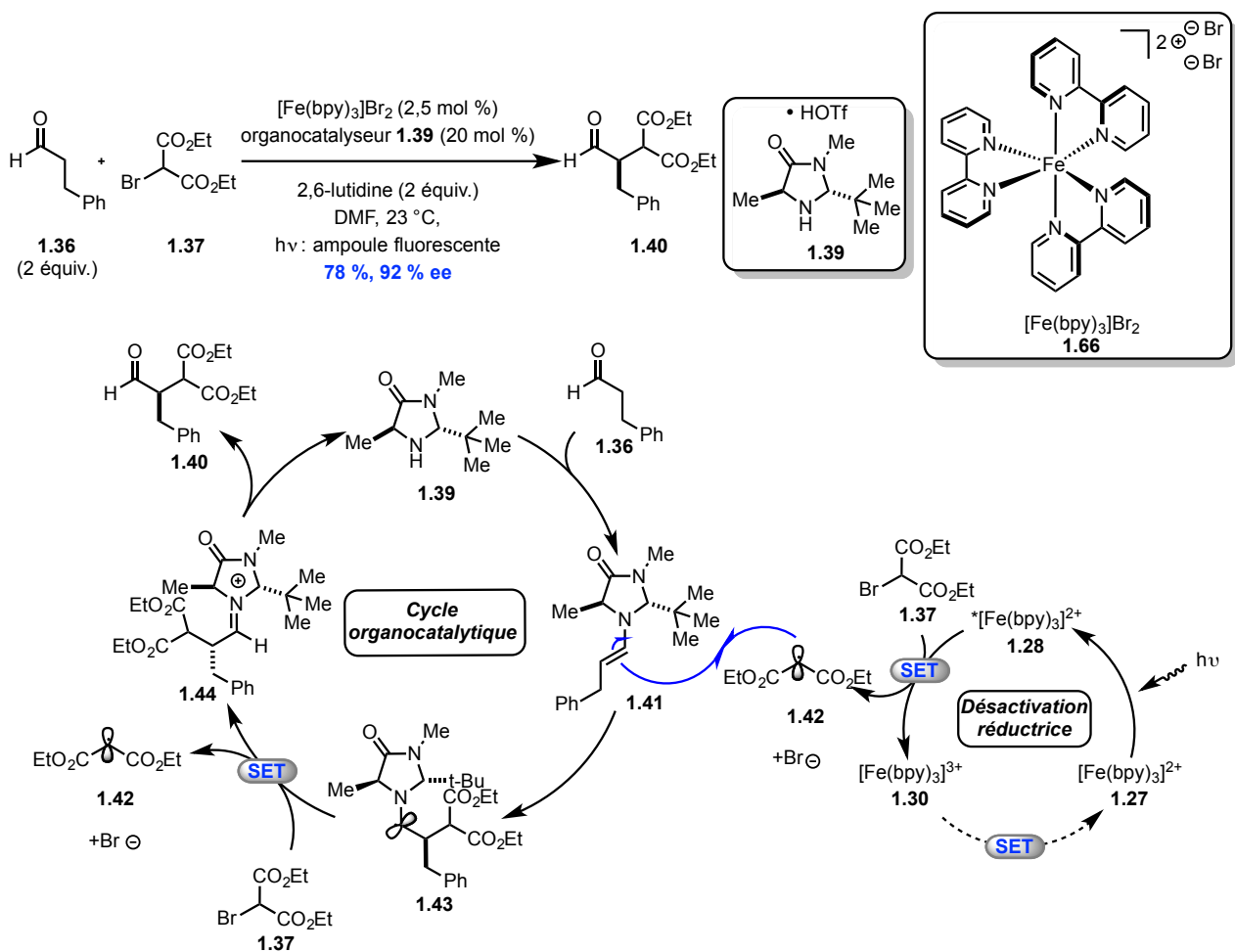


**Schéma 1.10** Réaction et mécanisme de la photocyclisation  $6\pi$  réalisée par Paton et Smith.

### 1.2.5.3 Photocatalyse à base de fer

En 2015, les groupes de Ceroni et de Cozzi ont revisité la réaction d'alkylation sétérosélective d'aldéhydes précédemment développée par MacMillan (discutée à la section **1.2.5.1**) en utilisant le photocatalyseur à base fer **1.66** au lieu du complexe de ruthénium **1.38** (Schéma 1.11).<sup>27</sup> Pour comparer les deux protocoles, le 3-phénylpropanal **1.36** réagit avec le 2-bromomalonate d'éthyle **1.37** en présence du  $[\text{Fe}(\text{bpy})_3]\text{Br}_2$  **1.66** et de l'organocatalyseur **1.39** pour former l'aldéhyde **1.40** avec un rendement un peu plus faible de 78 % avec un excès énantiomérique similaire de 92 %. Étant donné que les photopropriétés des complexes de fer sont difficiles à confirmer, les groupes de Ceroni et de Cozzi propose un mécanisme qui commence par la formation

du radical **1.42** par un transfert d'électron singlet avec l'espèce excitée de Fe(II) **1.28**. Ce composé radicalaire réagit similairement avec l'énamine **1.41**. L'autre différence majeure avec le mécanisme proposé par MacMillan est le transfert d'électron singlet de l'espèce radicalaire **1.43** pour former l'iminium **1.44**. Ces étapes s'effectuent selon un processus radicalaire en chaîne (propagation radicalaire) car il forme le radical **1.42** sans l'utilisation du photocatalyseur de fer **1.66**.

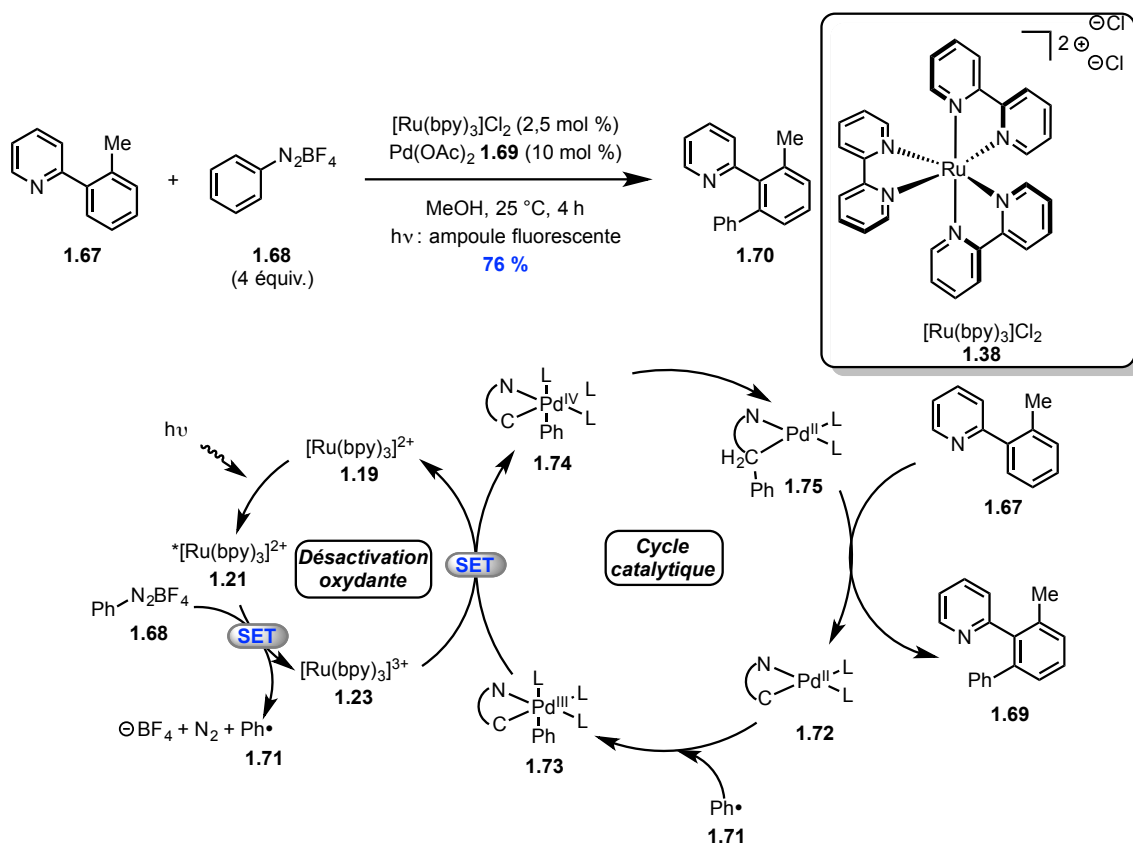


**Schéma 1.11** Réaction et mécanisme d'alkylation stéréosélective d'aldéhyde développé par Ceroni et Cozzi.

## 1.2.6 Metallophotorédox

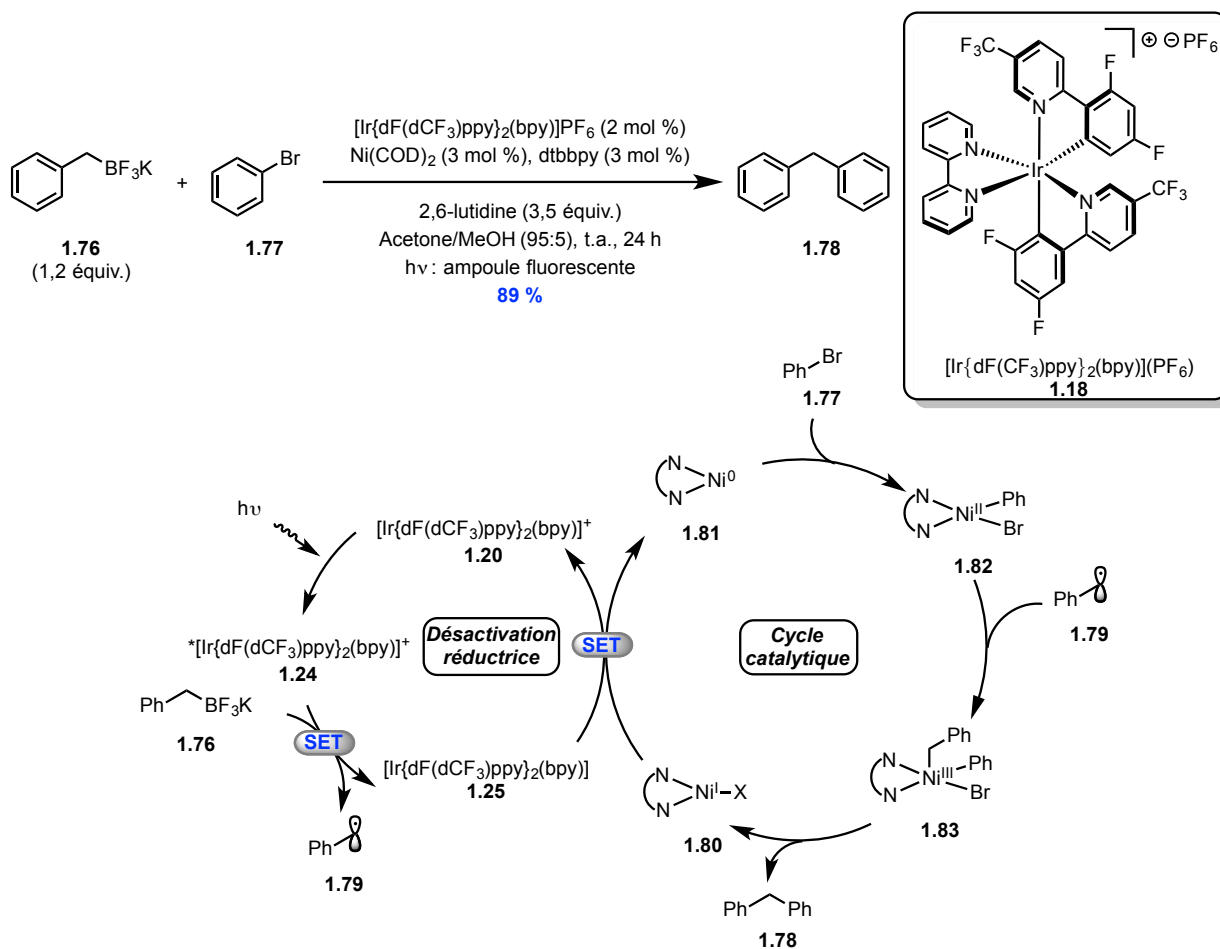
Une des sous-catégories de la chimie photorédox est la metallophotorédox, qui combine un cycle photorédox avec un cycle catalytique métallique.<sup>41</sup> Une des premières réactions développées dans ce domaine est une contribution du groupe de la professeure Sanford combinant un cycle photorédox avec un cycle catalytique au palladium (Schéma 1.12).<sup>42</sup> Cette réaction fait réagir le

phénylpyridine **1.67** avec le sel de phényldiazonium **1.68** pour former le biphenylpyridine **1.69**, en présence du photocatalyseur **1.38** et de l'acétate de palladium **1.69**. Le cycle catalytique métallique commence avec une insertion C-H du palladium **1.69** sur le produit de départ **1.67** pour former l'espèce catalytique **1.72**. Par la suite, le radical phényle **1.71** (formé de manière photochimique) réagit avec l'espèce palladium(II) pour fournir le palladium(III) **1.73**. Afin de favoriser l'élimination réductrice, une oxydation jusqu'au palladium(IV) **1.74** a lieu par un transfert d'électron singulet (SET) avec l'espèce oxydante  $[\text{Ru}(\text{bpy})_3]^{3+}$  **1.23**. Une fois le complexe de palladium(IV) formé, une élimination réductrice peut avoir lieu pour fournir le produit désiré **1.70**. En ce qui concerne le cycle photorédox, le  $[\text{Ru}(\text{bpy})_3]^{2+}$  **1.19** est excité par l'absorption d'un photon lumineux formant le  $^*[\text{Ru}(\text{bpy})_3]^{2+}$  **1.21**. Le complexe excité de ruthénium réagit dans une réaction SET avec le sel de diazonium **1.68**, ceci fournissant le radical phényle **1.71** (précédemment utilisé dans le cycle catalytique métallique).



**Schéma 1.12** Réaction et mécanisme pour le couplage croisé métallophtorédox développé par Sanford.

En 2014, le groupe du professeur Molander a effectué une avancée dans le domaine des couplages croisés en utilisant un nucléophile organoboré  $sp^3$  (Schéma 1.13).<sup>43</sup> Cet avancement a été permis en combinant la chimie photorédox du complexe d'iridium **1.18** et la réactivité catalytique du complexe de nickel **1.81**. Le composé trifluoroborate **1.76** réagit avec le bromobenzène **1.77** pour former le diphénylméthane **1.78** avec un rendement de 89 %. La partie photorédox du mécanisme commence par l'excitation de l'iridium **1.20** par un photon, pour obtenir le  $^*[\text{Ir}(\text{dF}(\text{dCF}_3)\text{ppy})_2(\text{bpy})]\text{PF}_6$  **1.24**. Cette espèce excitée réagit dans un transfert d'électron singulet (SET) avec l'organoborate **1.76** donnant lieu au radical benzylique **1.79** et au réducteur **1.25**. Le  $[\text{Ir}(\text{dF}(\text{dCF}_3)\text{ppy})_2(\text{bpy})]\text{PF}_6$  réagit ensuite dans un SET avec le nickel(I) **1.80** pour régénérer le nickel(0) **1.81** et l'iridium **1.20** photoactif. L'espèce nickel (0) subit une addition oxydante avec le bromobenzène ce qui génère le complexe de nickel(II) **1.82**. Ce complexe réagit avec le radical benzylique pour former le nickel(III) **1.83** et, à la suite d'une élimination réductrice, cette espèce nickel(III) produit le diphénylméthane **1.78** et le nickel(I).



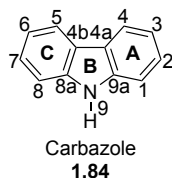
**Schéma 1.13** Réaction et mécanisme pour le couplage croisé métallophtorédox au nickel présenté par Molander.

Plusieurs groupes de recherche utilisent la métallophtorédox afin de découvrir de nouvelles réactivités ou bien de rendre des transformations déjà existantes plus attrayantes, par l'utilisation de conditions plus douces. Le plus intéressant dans ce domaine est la possibilité d'utiliser différents photocatalyseurs ou catalyseurs métalliques. Outre les photocatalyseurs à base de ruthénium<sup>42, 44</sup> ou d'iridium<sup>43, 45</sup>, certains catalyseurs organiques tels que le 4CzIPN<sup>22c, 46</sup> ont été utilisés avec succès dans des transformations chimiques. Grâce à la variété de catalyseurs disponibles (Pd<sup>42, 47</sup>, Ni<sup>22c, 43, 48</sup>, Au<sup>49</sup>, Cu<sup>44, 50</sup>, Co<sup>46, 51</sup>), il est possible de sélectionner un photocatalyseur et de l'agencer au potentiel (eV) d'une transformation chimique voulue.



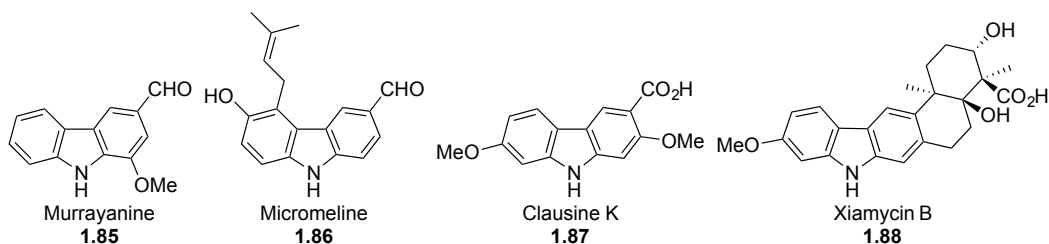
### 1.3 Synthèses des carbazoles

Les carbazoles font partie de la famille des composés aromatiques hétérocycliques. Ce sont des molécules tricycliques constituées de deux noyaux benzyliques (cycle à 6 chaînons conjugué) fusionnés à un cycle pyrrolidine (cycle à 5 chaînons comportant un azote). Le carbazole a été isolé pour la première fois en 1872 par Graebe et Glazer lors de la liquéfaction du charbon. Depuis, une variété de carbazoles a été rapportée en utilisant ce processus.<sup>52</sup> Dans la nomenclature du carbazole, les lettres A, B et C sont utilisées pour nommer chacun des cycles. La numérotation du corps tricycliques commence par le carbone du cycle A et compte chaque carbone portant un hydrogène ainsi que l'azote du cycle B. Les carbones effectuant une jonction entre les différents cycles possèdent le numéro du carbone précédent en plus d'une lettre pour pouvoir les différencier (Figure 1.16).<sup>53</sup>



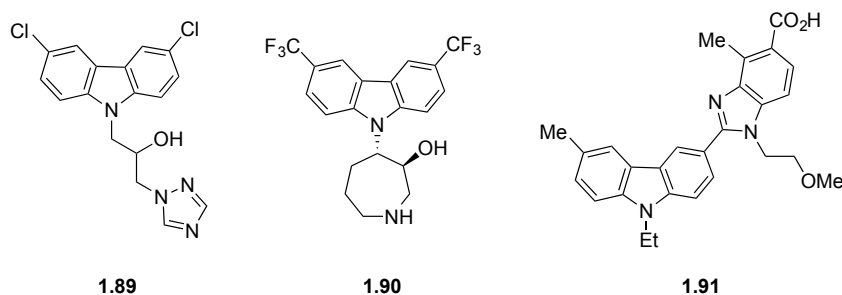
**Figure 1.16** Numérotation générale du carbazole **1.84**.

On retrouve une grande quantité de produits naturels comportant le motif carbazole. Le premier de ceux-ci est la Murrayanine **1.85** (Figure 1.17) qui a été isolée dans les années 1960<sup>54</sup> et possède des propriétés antifongiques et antibactériennes.<sup>55</sup> Depuis, le nombre d'alcaloïdes à base de carbazole possédant une activité biologique grandit chaque année.<sup>56</sup> Certaines de ces molécules peuvent avoir des effets antituberculeux, comme la Micromeline **1.86**, isolée en 2005.<sup>57</sup> D'autres sont des agents inhibiteurs du VIH, comme la Clausine K **1.87**, découverte en 1996.<sup>58</sup> De plus, plusieurs d'entre elles ont des effets antibactériens, dont la Xiamycin B **1.88** qui possède une activité contre des souches de bactéries résistantes à la Methicillin et la Vancomycin.<sup>59</sup>



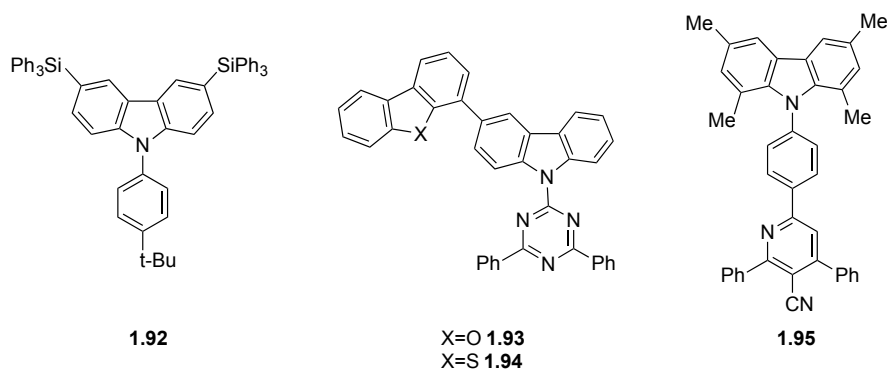
**Figure 1.17** Produits naturels contenant un motif carbazole.

Les nombreuses propriétés biologiques associées aux alcaloïdes possédant un motif carbazole, a poussé l'industrie pharmaceutique à introduire cet hétérocycle dans plusieurs composés actifs.<sup>60</sup> À titre d'exemple, l'alcool-carbazole **1.89** (Figure 1.18) a été développé pour son potentiel antimicrobien.<sup>61</sup> Un autre composé, l'azepanylcarbazole **1.90** possède une activité antiparasitaire<sup>62</sup>, tandis que le dérivé benzimidazole **1.91** agit comme antagoniste du récepteur hEP4-R dans le traitement de l'endométriose.<sup>63</sup>



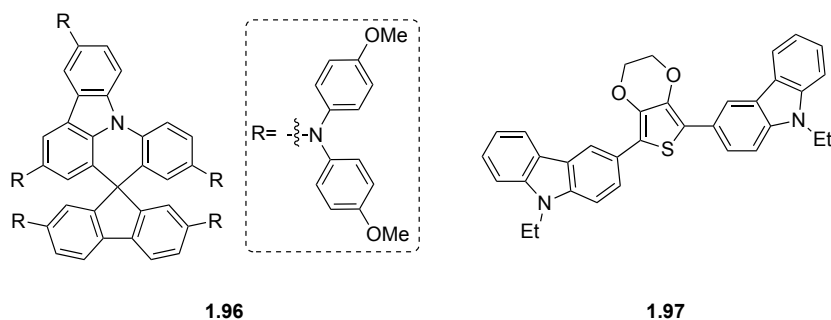
**Figure 1.18** Composés actifs comportant un motif carbazole.

On retrouve également le motif carbazole dans le domaine des matériaux. Grâce à leurs stabilités thermique et photochimique, ceux-ci sont utilisés dans les diodes électroluminescentes organiques (Organic Luminescent Electronic Diodes, *OLEDs*) et dans les cellules solaires.<sup>64</sup> Les carbazoles sont grandement utilisés dans les *OLEDs* en raison de leur modification structurale et de leur potentiel de conjugaison, ce qui permet d'obtenir différentes couleurs. Le composé commercial CzSi **1.92**<sup>65</sup> est utilisé dans certaines *OLEDs* bleues, tandis que les molécules BFTC **1.93** et BTTC **1.94** sont de couleur verte<sup>66</sup> et que le carbazole tMCzPN **1.95**<sup>67</sup> se retrouve dans les *OLEDs* rouges (Figure 1.19).



**Figure 1.19** Molécules contenant un motif carbazole utilisées dans la conception des *OLEDs*.

Dans les cellules solaires, les carbazoles sont utilisés pour leur capacité de donneur d'électron et leur potentiel comme transporteurs de trou électronique (*HTM*). Les composés **1.96**<sup>68</sup> et **1.97**<sup>69</sup> sont utilisés dans les cellules photovoltaïques à base de pérovskites comme matériel donneur d'électron (Figure 1.20).



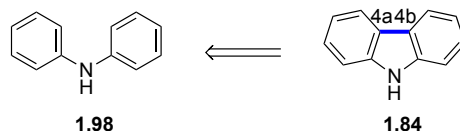
**Figure 1.20** Matériaux comportant un motif carbazole utilisés dans la fabrication de cellules solaires.

Étant donné leur large utilisation dans l'industrie, autant dans le domaine pharmaceutique pour leurs propriétés biologiques que dans le domaine des matériaux pour leurs propriétés physicochimiques, le développement constant de nouvelles méthodologies de synthèse pour former des carbazoles reste d'actualité.

### 1.3.1 Synthèse par la formation du lien C-C

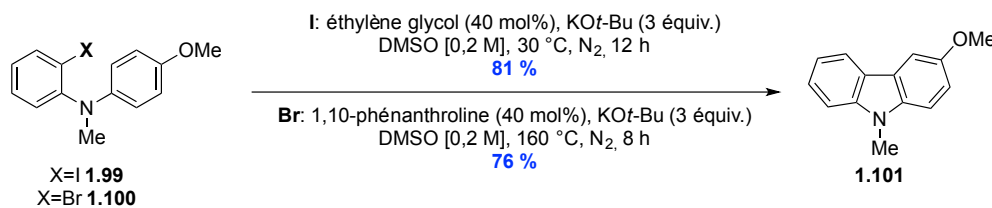
Une des stratégies de synthèse des carbazoles emploie formation du lien C<sub>4a</sub>-C<sub>4b</sub> pour former le cycle B (Figure 1.21). La réaction idéale de ce type s'effectuerait par le couplage de deux carbonnes sp<sup>2</sup> à partir de la diphenylamine **1.98**. Bien qu'il existe une cyclisation

déhydrohalogénative catalysée au palladium<sup>70</sup> depuis les années 1980, celle-ci demeure peu utilisée pour la synthèse des carbazoles.



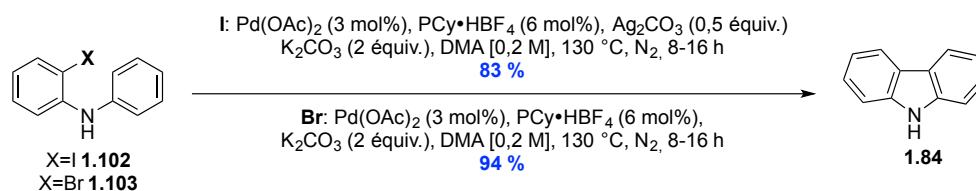
**Figure 1.21** Formation du lien C<sub>4a</sub>-C<sub>4b</sub>.

Tout récemment, le groupe de recherche de Wu a utilisé des motifs diphenylamines préfonctionnalisés par des halogènes pour produire des carbazoles (Schéma 1.14). La méthodologie utilise un excès de *tert*-butoxyde de potassium et 40 mol% d'un ligand bidentate pour former le carbazole alkyle correspondant. Lorsqu'ils utilisent l'iode comme halogène, l'éthylène glycol est employé comme ligand pour donner 81 % du carbazole **1.101**. Dans le cas où le brome est utilisé, il faut employer la 1,10-phénanthroline comme ligand pour obtenir 76 % du carbazole **1.101**.<sup>71</sup>



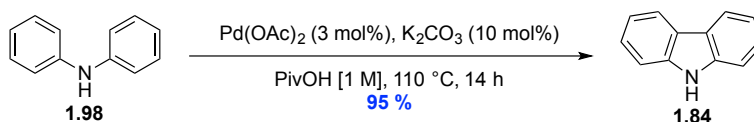
**Schéma 1.14** Synthèse du carbazole **1.101** par une cyclisation déhydrohalogénative.

Dans le début des années 2000, le groupe du professeur Fagnou a développé des méthodologies fournissant des composés carbazoles comportant un N-H libre (Schéma 1.15). Ces transformations utilisent une préfonctionnalisation sous forme d'halogène et une catalyse avec un complexe de palladium. En utilisant 3 mol% de palladium(II) acétate et 6 mol% d'un sel de tétrafluoroborate de tricyclohexylphosphine, le carbazole **1.84** est obtenu avec un rendement de 83 %. Lorsque l'halogène est un iode, il faut en plus ajouter 0,5 équivalent d'un sel de carbonate d'argent.<sup>72</sup> Dans le cas où le brome est utilisé, 94 % de rendement pour la formation du carbazole **1.84** est observé sans l'ajout de sel de carbonate d'argent.<sup>72b</sup> De plus, ils ont aussi étudié, la réactivité des chlorures en utilisant un NHC comme ligand.<sup>73</sup>



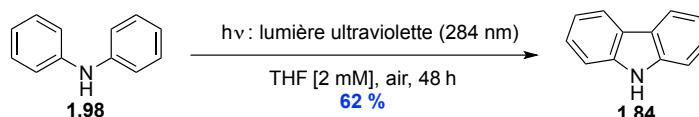
**Schéma 1.15** Synthèse du carbazole **1.84** par une cyclisation déhydrohalogénative catalysée par un complexe de palladium(II).

Vers la fin des années 2000, ce même groupe a effectué un couplage oxydatif catalysé par un complexe de palladium, se débarrassant ainsi de la préfonctionnalisation requise précédemment (Schéma 1.16).<sup>74</sup> Ce nouveau système catalytique permet l'obtention du carbazole **1.84** à 95 % à partir de la diphenylamine **1.98** en présence de 3 mol% d'acétate de palladium(II), d'acide pivalique et d'air.<sup>75</sup>



**Schéma 1.16** Synthèse du carbazole **1.84** par couplage oxydatif catalysé au palladium à partir de la diphenylamine **1.98**.

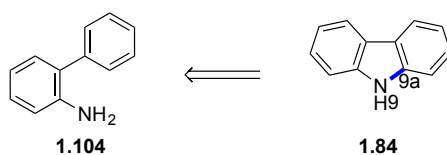
Il est également possible d'utiliser la photochimie pour réaliser la synthèse de carbazoles. Dans les années 1960, Clark et ses collègues ont étudié la photocyclisation de composés diarylamines, dont la diphenylamine **1.98** (Schéma 1.17). Celle-ci réagit sous irradiation lumineuse à 284 nm pendant 48 heures pour donner le carbazole **1.84** avec un rendement de 62 %.<sup>76</sup>



**Schéma 1.17** Synthèse du carbazole **1.84** par photocyclisation à partir de la diphenylamine **1.98**.

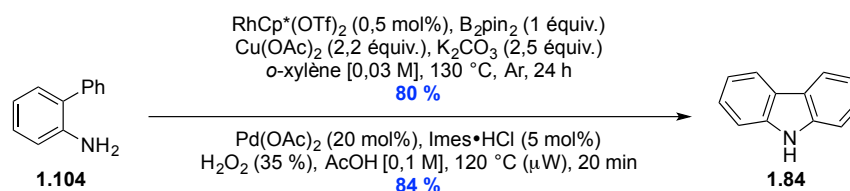
### 1.3.2 Synthèse par la formation du lien C-N

Une autre méthode de synthèse des carbazoles passe par la formation du lien C<sub>9a</sub>-N<sub>9</sub> du cycle B (Figure 1.22). L'idée derrière ce type de stratégie est de faire réagir le 2-aminobiphényle **1.104** pour créer le lien entre le carbone hybridé sp<sup>2</sup> et l'azote hybridé sp<sup>3</sup>. Une des méthodologies très utilisées pour synthétiser des carbazoles est la cyclisation de Cadogan, où le lien C-N provient de la réduction d'un groupement nitro en nitrene qui effectue une insertion dans le lien C-H.<sup>77</sup>



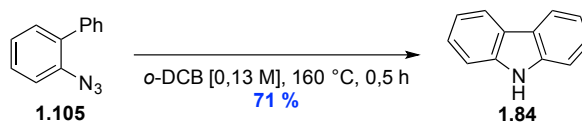
**Figure 1.22** Formation du lien C<sub>9a</sub>-N<sub>9</sub>.

En 2013, le groupe de recherche du professeur Yan a montré qu'il est possible d'utiliser le 2-aminobiphényle **1.104** pour former le carbazole **1.84**. Leur méthode emploie une quantité catalytique d'un complexe de rhodium et 1 équivalent de (bis)pinacole diborane pour préfonctionnaliser la molécule. Dans un second temps, 2,2 équivalents d'acétate de cuivre(II) sont utilisés pour former le lien C-N entre l'amine et le carbone lié au bore avec un rendement de 80 % (Schéma 1.18).<sup>78</sup> Quelques années plus tard, Elumalai et Bjørsvik ont développé une méthodologie pour transformer le 2-aminobiphényle **1.105** en carbazole **1.84**. Cette transformation s'effectue en présence de 20 mol% d'acétate de palladium(II) et 5 mol% d'un ligand de type NHC.<sup>79</sup>



**Schéma 1.18** Synthèse du carbazole **1.84** par méthode catalytique à partir du 2-aminobiphényle **1.104**.

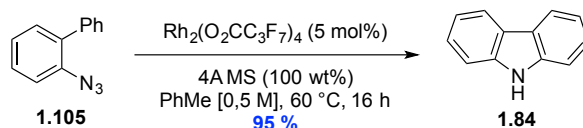
Vers la fin des années 2000, le groupe de Sapi a réutilisé la décomposition thermique d'azoture pour effectuer la formation du lien C-N formant ainsi des carbazoles (Schéma 1.19).<sup>80</sup> Dans cette réaction, le 2-azidobiphényle **1.105** est chauffé à 160 °C pour réaliser la décomposition en nitrène et une insertion C-H s'ensuit pour former le carbazole **1.84** à 71 %.<sup>81</sup>



**Schéma 1.19** Synthèse du carbazole **1.84** par décomposition thermique du 2-azidobiphényle **1.105**.

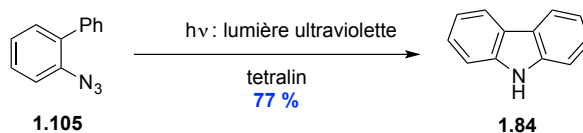
Toujours dans les années 2000, le professeur Driver et son équipe ont étudié le potentiel d'une réaction catalytique pour la décomposition d'azoture. L'utilisation d'un catalyseur de

rhodium permet de réduire la température d'activation à 60 °C pour donner le carbazole **1.84** avec 95 % de rendement (Schéma 1.20).<sup>82</sup> Par la suite, plusieurs méthodes catalytiques pour la décomposition d'azotures ont été développées. Ces méthodes utilisent des catalyseurs métalliques à base de rhodium,<sup>83</sup> d'iridium,<sup>84</sup> de fer<sup>85</sup> et de palladium.<sup>86</sup>



**Schéma 1.20** Synthèse du carbazole **1.84** par décomposition catalysée par un complexes de rhodium(II) du 2-azidobiphényle **1.105**.

Il existe également une décomposition photochimique d'azotures, étudiée dans les années 1950 par Smith et Brown. Ils ont utilisé la lumière ultraviolette pour former l'intermédiaire nitrène à partir du 2-azidobiphényle **1.105** formant le carbazole avec un rendement de 77 % (Schéma 1.21).<sup>87</sup> Plusieurs limitations ont été observées lors de cette étude, soit l'étendue de la réaction, la source lumineuse utilisée, le solvant et le temps de réaction. À la suite de cette découverte, seul le mécanisme a été analysé en détail.<sup>88</sup>



**Schéma 1.21** Synthèse du carbazole **1.84** par photodécomposition du 2-azidobiphényle **1.105**.

## 1.4 Chimie en flux continu

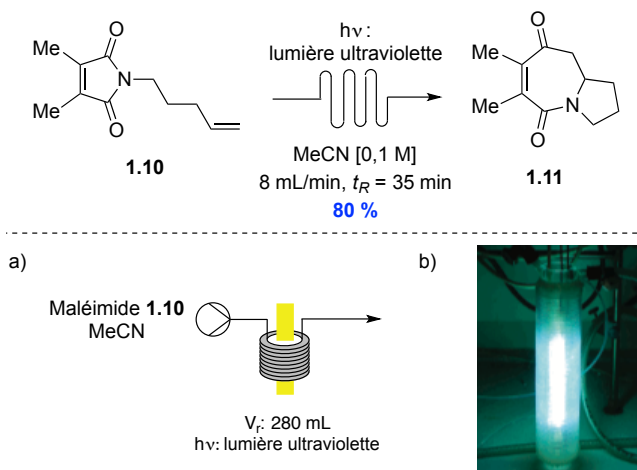
La chimie en flux continu consiste à pomper un mélange réactionnel à travers un tube de petit diamètre. Ce principe permet l'obtention d'un mélange réactionnel dynamique. Cette nouvelle technologie comporte plusieurs avantages qui lui confère un intérêt accru pour la synthèse de molécules d'intérêt. Celle-ci permet un contrôle précis des conditions réactionnelles comme le temps de réaction, la température et la pression. De plus, l'augmentation du transfert de masse dans le mélange réactionnel permet une accélération des réactions homogènes et biphasiques grâce au contrôle des différents régimes d'éluion ou l'utilisation de mélangeurs. En plus d'effectuer des réactions très rapides ou à très hautes températures et pressions, la chimie en flux continu permet de contrôler de façon sécuritaire la formation de produits dangereux et ainsi de minimiser les

risques qui sont liés à leur manipulation. Ce ne sont que quelques exemples des avantages qu'apporte cette technique qui en fait un outil important pour le chimiste de synthèse.<sup>89</sup>

#### 1.4.1 Photochimie en flux continu

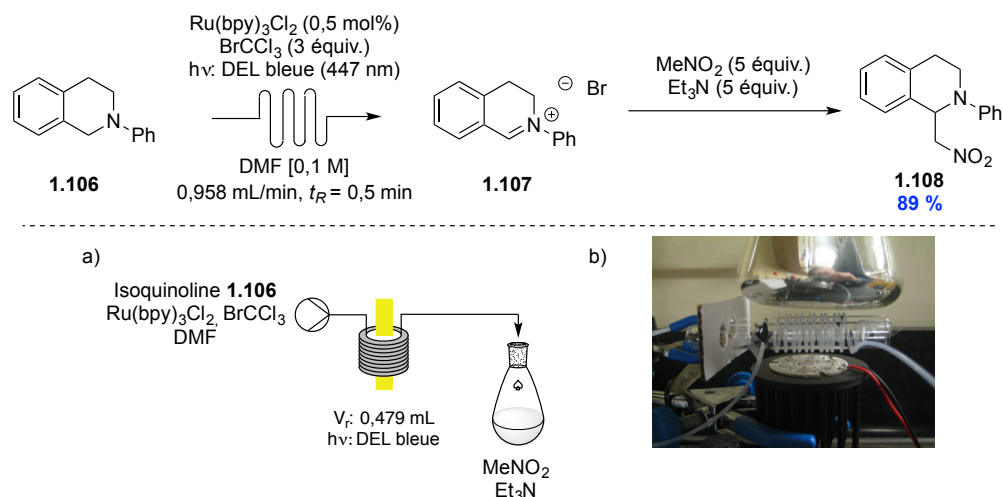
Effectuer une réaction photochimique en flux continu comporte plusieurs avantages tels qu'une meilleure irradiation du mélange réactionnel et la possibilité d'effectuer ce type de réactions sur une plus grande échelle.<sup>90</sup> L'amélioration de l'irradiation se traduit par une augmentation des photons absorbés et permet une diminution du temps réactionnel augmentant ainsi la capacité de production de la réaction. Ceci a été démontré en 2005 par le groupe du professeur Booker-Milburn en revisitant la photocyclisation intramoléculaire du maléimide **1.10** (Figure 1.23).<sup>91</sup> À l'aide de leur montage maison constitué d'une lampe au mercure à pression moyenne placée à l'intérieur d'un puits d'immersion entouré de tubes de fluoropolymère, ils ont fabriqué un réacteur photochimique de 280 mL. Avec celui-ci, la réaction s'effectue en seulement 35 minutes de temps de résidence pour obtenir 80 % du perhydroazaazulène **1.11**. En comparant ce processus photochimique en flux continu avec son équivalent en « batch », on observe une diminution du temps réactionnel d'un facteur 4. De plus, 178 g de produit peuvent être obtenus en 24 heures en flux continu, tandis que seulement 12 g peuvent être produits en « batch » en raison de la limite de l'échelle du montage.<sup>11</sup>





**Figure 1.23** Photocyclisation intramoléculaire du maléimide **1.10** dans la synthèse du perhydroazaazulène **1.11**: a) montage de flux continu b) photoréacteur en flux continu développé par Booker-Milburn. *Reproduit avec la permission de la réf. 91. Copyright 2005 American Chemical Society.*

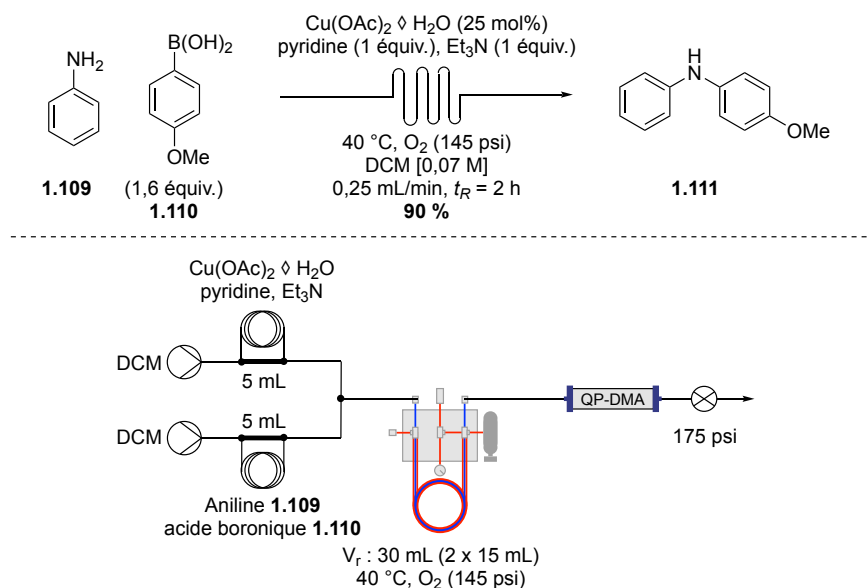
Les mêmes principes de chimie en flux continu peuvent être appliqués à la photocatalyse pour en améliorer la réactivité et la production. Les groupes de recherche de Stephenson et de Jamison ont collaboré pour développer l'utilisation de la chimie en flux continu dans le domaine de la photocatalyse, pour la formation de l'iminium **1.107** (Figure 1.24).<sup>92</sup> Leur montage consiste à enrouler un tube de fluoropolymère sur un tube de culture en borosilicate et d'irradier le tout avec une DEL bleue en utilisant un miroir d'aluminium pour réfléchir la lumière. Le volume du réacteur étant de 0,479 mL et le mélange d'isoquinoline **1.106**, Ru(bpy)<sub>3</sub>Cl<sub>2</sub> et BrCCl<sub>3</sub> dans le DMF étant pompé à 0,958 mL/min, un temps de résidence de 0,5 minutes est obtenu. Suivant l'élution, le tout est collecté dans un ballon contenant du nitrométhane (5 équiv.) et de la triéthylamine (5 équiv.) pour fournir 89 % du produit d'addition nucléophile **1.108**. Le temps nécessaire pour effectuer la formation de l'iminium **1.107** en « batch » est de 3 heures pour fournir 0,081 mmol/h,<sup>93</sup> tandis que le montage en flux continu permet de préparer 5,75 mmol/h de l'iminium **1.107** ce qui correspond à une augmentation de productivité de 7000 %.



**Figure 1.24** Formation oxydative de l'iminium **1.107** suivie d'une aza-Henry formant **1.108**: a) montage de flux continu b) photoréacteur en flux continu développé par Stephenson et Jamison. Reproduit avec la permission de la réf. 92. Copyright 2012 John Wiley and Sons.

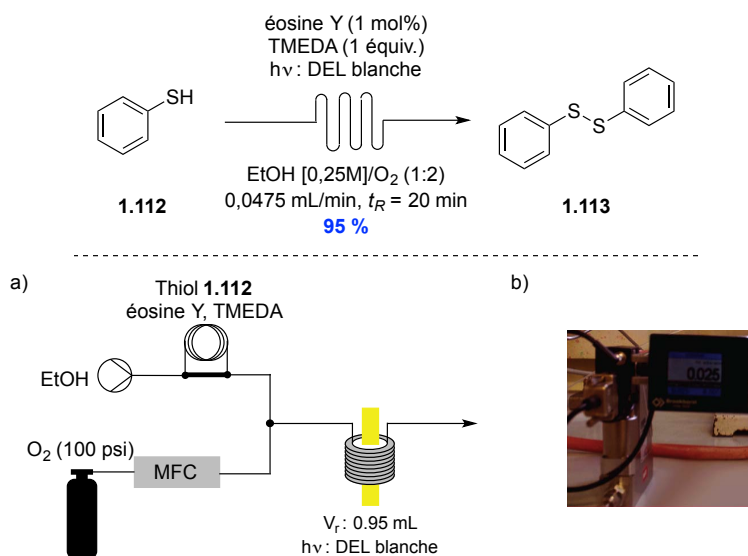
## 1.4.2 Utilisation de gaz en flux continu

Un autre avantage de la chimie en flux continu est l'utilisation contrôlée et sécuritaire de différents gaz. Ceux-ci sont incorporés à l'aide de différents types de montages réactionnels et permettent donc un contrôle précis du débit et de la pression.<sup>94</sup> L'emploi d'un réacteur de type « tube-in-tube » permet une saturation homogène du gaz dans la solution réactionnelle, ce qui procure un régime d'éluion laminaire.<sup>95</sup> Dans le cas où un régulateur de débit massique (en anglais MFC) est utilisé, il est possible d'obtenir un régime de type segmenté, ce qui se traduit par un mélange réactionnel biphasique (liquide/gaz).<sup>96</sup> En 2016, le groupe de recherche du professeur Baxendale a rapporté l'utilisation d'oxygène gazeux dans un réacteur « tube-in-tube » commercialisé par la compagnie Vapourtec (Figure 1.25).<sup>97</sup> Lors de l'application d'une pression positive du gaz, celui-ci traverse la membrane perméable de fluoropolymère pour saturer la solution réactionnelle. À l'aide de ce montage, ils ont étudié le couplage catalytique oxydatif de Chan-Lam en flux continu. Leur montage est constitué de deux réacteurs « tube-in-tube » chauffés à 40 °C où est élué le mélange réactionnel pour un temps de résidence total de 2 heures. Leur protocole permet de transformer l'aniline **1.109** en la diarylamine **1.111** avec 90 % de rendement.



**Figure 1.25** Couplage catalytique oxydatif de Chan-Lam de l'aniline **1.109** formant le diarylamine **1.11**.

L'utilisation d'un régulateur de débit massique avec l'oxygène gazeux a été étudié en 2015 à la suite d'une collaboration entre les professeurs Noël et Hessel qui ont développé une réaction photocatalytique d'oxydation de thiols en disulfures (Figure 1.26).<sup>19c</sup> Leur montage utilise un MFC avec un cylindre d'oxygène à une pression de 100 psi, qui est introduit à la solution réactionnelle via une jonction en T, pour que par la suite, celle-ci soit éluée pendant 20 minutes dans un microphotoréacteur de 0,95 mL, en utilisant des DEL blanches. Cette transformation fournit 99 % du disulfure **1.113** à partir du thiol **1.112** en présence du photocatalyseur organique éosine Y **1.12** et d'un équivalent de tétraméthyléthylènediamine (TMEDA). En comparant les conditions de réaction pour effectuer la même transformation en « batch », on constate un rendement similaire de 99 %, cependant la réaction prend 48 fois plus de temps (16 heures vs 20 minutes).

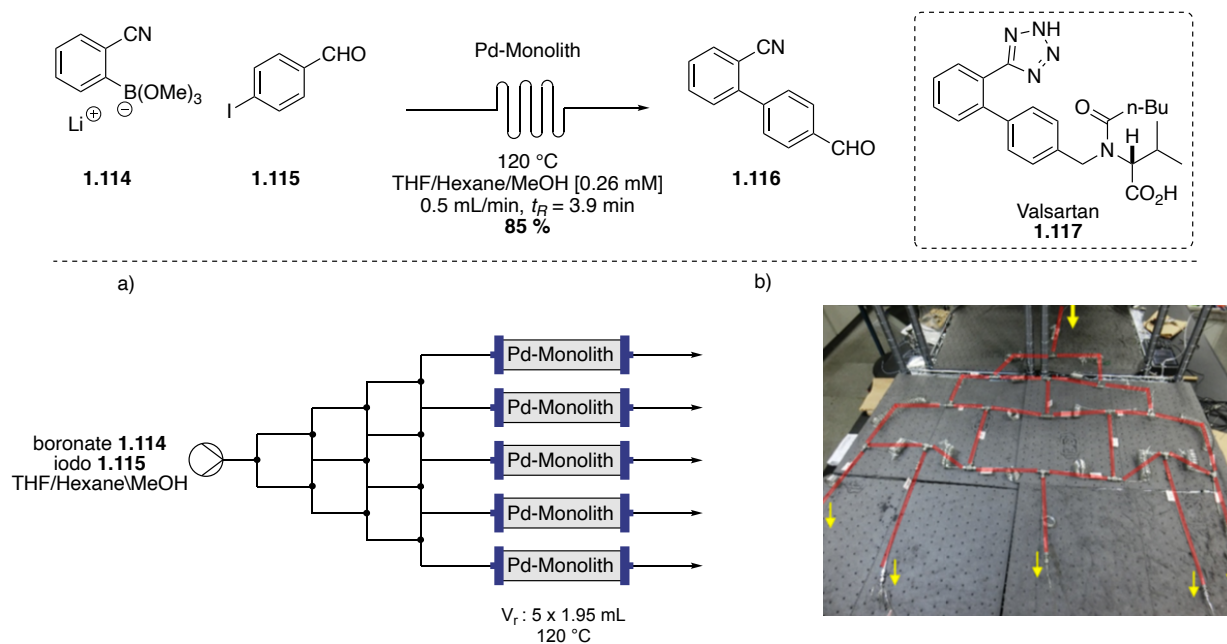


**Figure 1.26** Photocatalyse oxydative de thiol **1.112** formant le disulfure **1.113**: a) montage de flux continu b) régulateur de débit massique de Bronkhorst. *Reproduit avec la permission de la réf. 19c. Copyright 2015 Wiley-VCH.*

### 1.4.3 Agrandissement d'échelle en flux continu

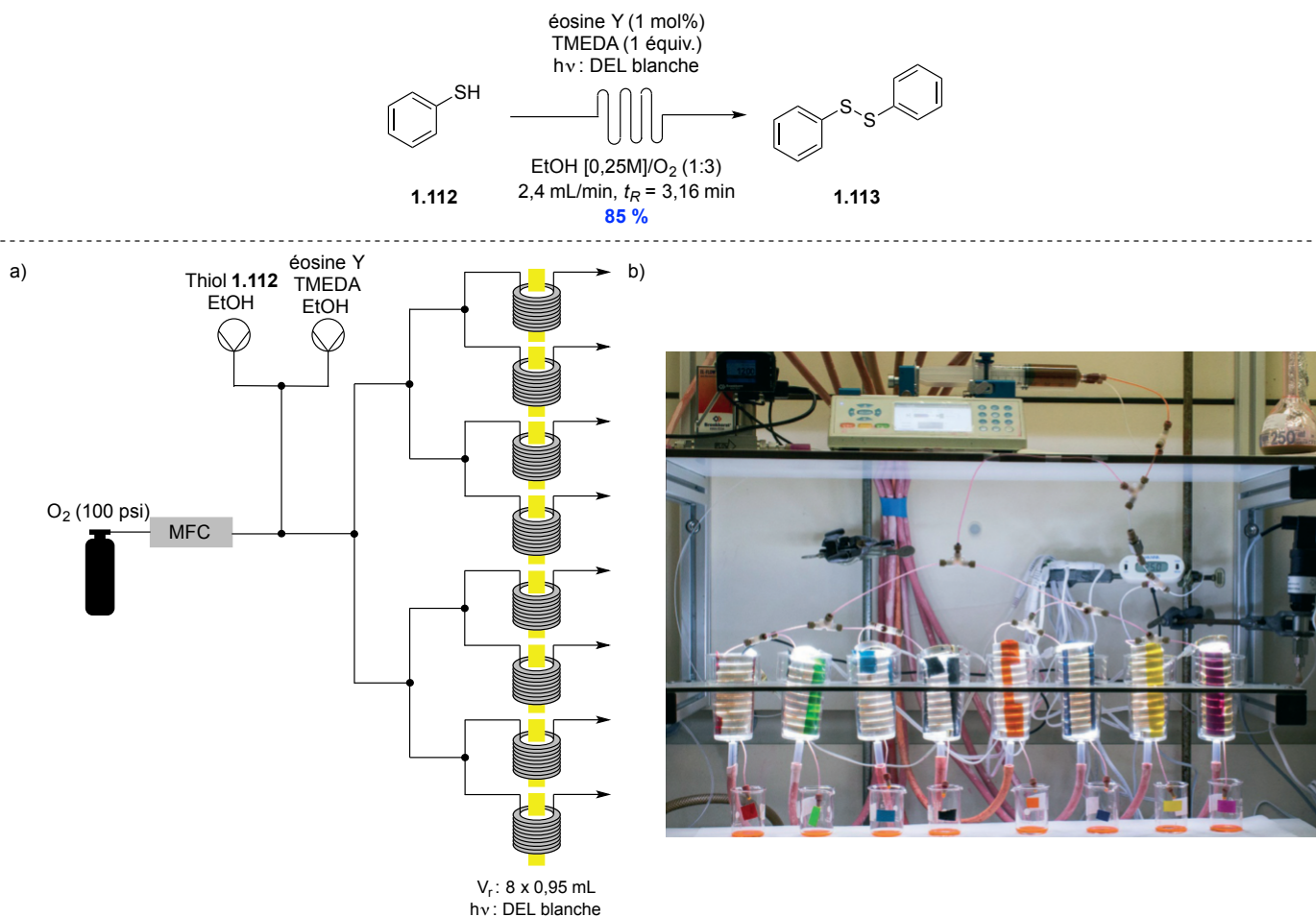
La chimie en flux continu permet d'effectuer des agrandissements d'échelle qui reproduisent de façon fiable les conditions à plus petites échelles. Il existe deux stratégies différentes pour arriver à augmenter la production d'un processus photochimique en flux continu. Une des méthodes repose sur la possibilité d'augmenter le volume du réacteur pour pouvoir transformer plus de matériel dans un temps de traitement plus court, ceci est le « numbering-out ».<sup>98</sup> L'autre stratégie, « numbering-up », consiste à augmenter le nombre de réacteurs utilisés en parallèle, toujours dans le but de convertir plus de réactifs en moins de temps. Cette dernière technique permet de conserver les paramètres réactionnels constants dans chaque réacteur tels que la pression, le mélange et le débit.<sup>99</sup> Certains agrandissements d'échelle auront une meilleure reproductibilité en utilisant le « numbering-up » comme les réactions utilisant un catalyseur supporté (hétérogène) ou les réactions photochimiques. Par exemple, le groupe du professeur Yoshida a effectué un couplage de Suzuki hétérogène catalysé par le palladium-monolithe en utilisant la stratégie de « numbering-up » (Figure 1.27).<sup>100</sup> Pour augmenter la production de l'intermédiaire biaryle **1.116** utilisé pour la synthèse du médicament Valsartan **1.117**, ils ont employé un montage contenant cinq réacteurs à lit fixe (*packed bed reactor*) contenant le catalyseur

de palladium-monolithe supporté. Celui-ci permet de transformer le boronate **1.114** en biaryle **1.116** avec un rendement de 85 % en seulement 3,9 minutes de temps de résidence.



**Figure 1.27** Couplage de Suzuki entre le boronate **1.114** et l'iodoaryle **1.115** catalysé par le palladium formant l'aryle **1.116**: a) montage de flux continu b) montage « numbering-up » développé par Yoshida. *Reproduit avec la permission de la réf. 100. Copyright 2016 American Chemical Society.*

Cette stratégie peut aussi être appliquée aux transformations photochimiques. Les groupes de recherche des professeurs Noël et Hessel ont notamment montré l'application de cet agrandissement d'échelle dans une oxydation photochimique du thiol **1.112** en disulfure **1.113** (Figure 1.28).<sup>101</sup> Leur montage comprend huit microphotoréacteurs de 0,95 mL de volume et ils éluent un mélange réactionnel de thiol **1.112**, d'éosine Y et d'oxygène (MFC), pour former le disulfure **1.113** avec un rendement de 85 % en seulement 3,16 minutes.



**Figure 1.28** Photocatalyse oxydative du thiol **1.112** formant le disulfure **1.113**: a) montage de flux continu b) montage « numbering-up » développé par Noël et Hessel. *Reproduit avec la permission de la réf. 101. Copyright 2016 The Royal Society of Chemistry.*

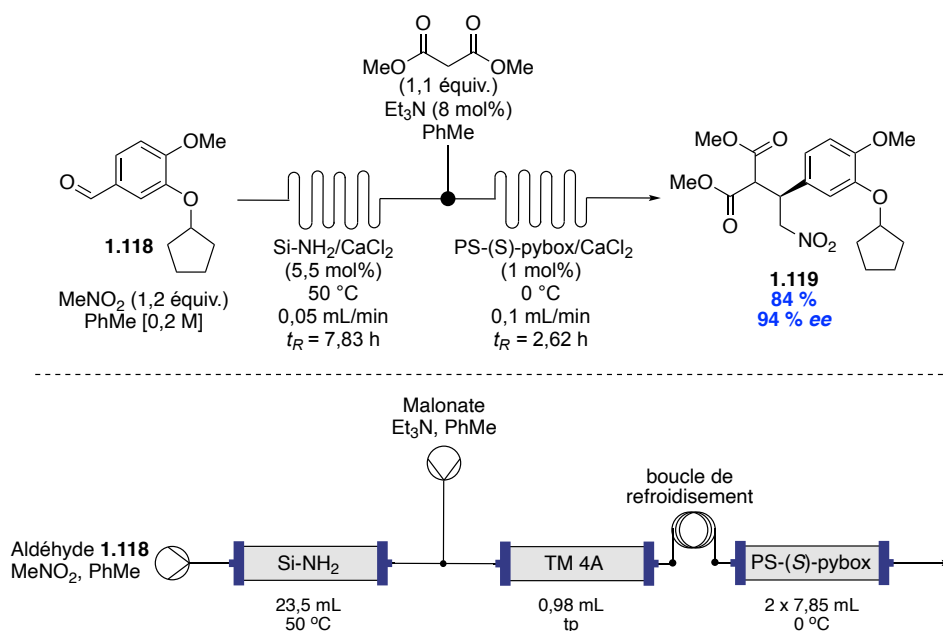
#### 1.4.4 Synthèse multi-étapes en flux continu

La synthèse multi-étapes séquentielle est un autre avantage de la chimie en flux continu. Ceci est possible grâce à l'ajout de nouveaux réactifs à la sortie d'un réacteur pour réaliser une seconde transformation chimique sans isoler l'intermédiaire formé dans la réaction précédente. Ce type de technique comporte certains défis pour assurer une réaction contrôlée. Ces défis sont la compatibilité des solvants, des réactifs et des catalyseurs, la minimisation des sous-produits et des réactifs excédentaires, et les concentrations réactionnelles. Certaines solutions ont été développées pour surmonter ces défis telles que l'utilisation de catalyseurs ou de réactifs supportés, ce qui diminue les complications au niveau de la compatibilité et des réactifs excédentaires. De plus, l'emploi de transformation nécessitant seulement une source énergétique pour effectuer la réaction

réduit la formation de sous-produits, la quantité de réactifs excédentaires et les catalyseurs. Ces sources d'énergie peuvent être thermique ou photochimique.<sup>102</sup>

#### 1.4.4.1 Utilisation de catalyseurs supportés

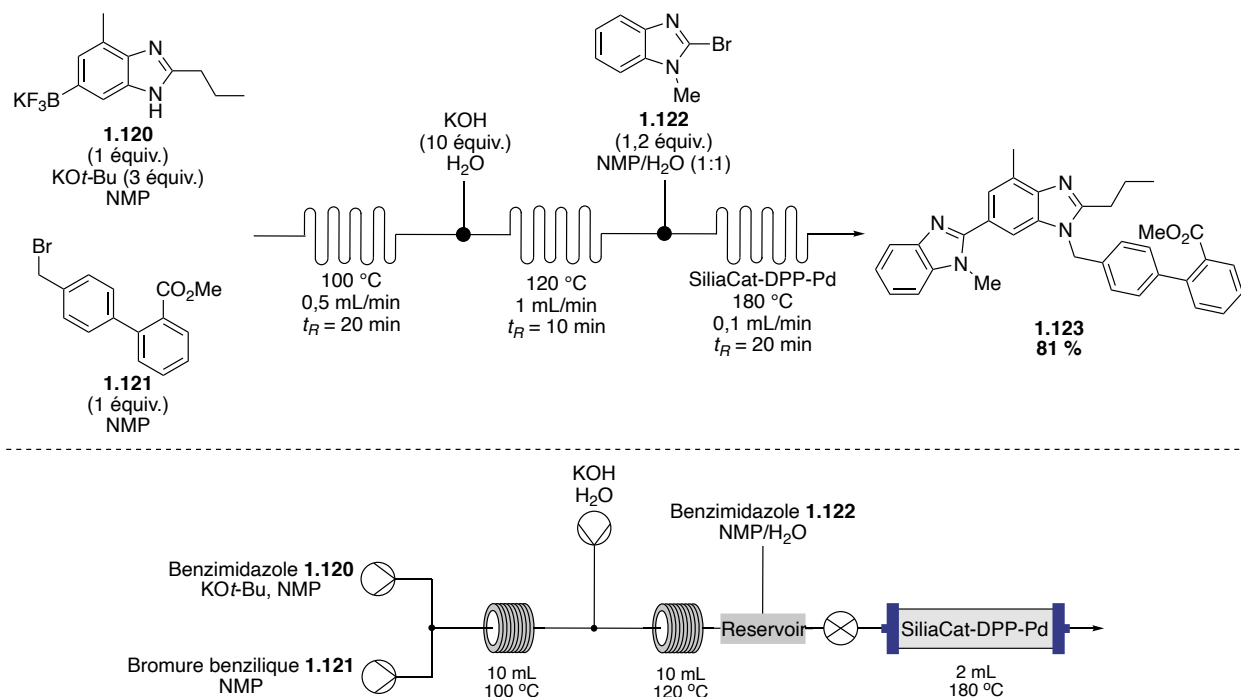
L'utilisation de catalyseurs supportés dans les réactions multi-étapes permet de minimiser l'incompatibilité des réactifs de différentes réactions, ce qui facilite l'addition de nouvelles transformations à la sortie d'un réacteur. Cette technique a été employée par le groupe de Kobayashi en 2015 pour effectuer les synthèses multi-étapes en flux continu de la (*R*)- et (*S*)-Rolipram (Figure 1.29).<sup>103</sup> Le montage réactionnel est constitué de deux séries de colonnes comportant un catalyseur supporté. La première transformation est catalysée par une base aminée supportée sur silice qui est diluée dans du chlorure de calcium pour obtenir un volume de 23,5 mL et le tout est chauffé à 50 °C pour former l'intermédiaire nitroalcène qui réagira dans la seconde réaction. Celle-ci requiert un catalyseur chiral de pyridine-bis(oxazoline) supporté sur des billes de polystyrène aussi dilué dans du chlorure de calcium. La deuxième transformation est effectuée dans deux colonnes fournissant un volume réactionnel total de 15,7 mL, refroidi à 0 °C. Cette méthodologie permet de transformer l'aldéhyde aromatique **1.118** en aryle **1.119** avec un rendement de 84 % et un excès énantiomérique de 94 % en deux étapes.



**Figure 1.29** Réaction multi-étapes utilisant des catalyseurs supportés transformant l'aldéhyde **1.118** en aryle **1.119**.

Il est aussi possible d'utiliser des catalyseurs à base de métaux supportés pour effectuer des couplages de Suzuki.<sup>104</sup> Ce type de transformation a été étudié par le groupe de recherche du professeur Gupton dans le but de synthétiser le médicament Telmisartan **1.123** en utilisant un montage multi-étapes en flux continu (Figure 1.30).<sup>105</sup> Comme dernière étape, ce montage comporte une colonne chargée de catalyseur SiliaCat-DPP-Pd pour effectuer le couplage de Suzuki à 180 °C pendant 20 minutes. Le processus global transforme le benzimidazole **1.120** lors d'une alkylation avec le bromure benzylique **1.122** dans un réacteur tubulaire à 100 °C pendant 20 minutes. Ceci est suivi par l'ajout d'hydroxyde de potassium pour effectuer la saponification de l'ester méthylique à 120 °C pendant 10 minutes. Finalement l'ajout du benzimidazole bromé **1.122** réagissant avec le catalyseur de palladium(II) fournit le produit final Telmisartan **1.123** avec un rendement de 81 % sur trois étapes.

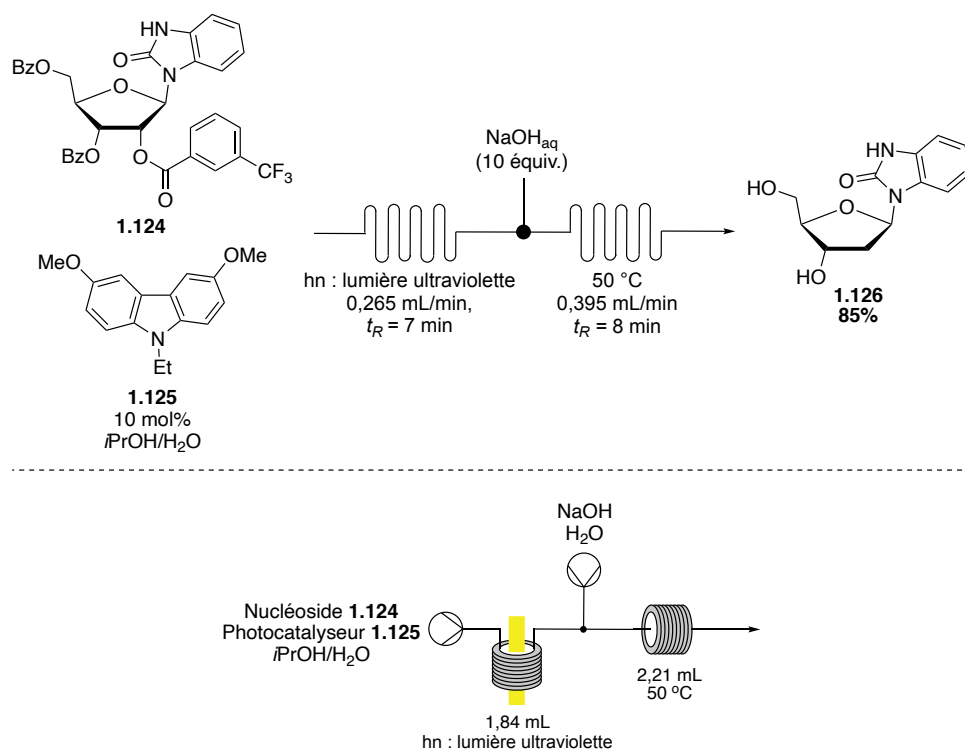




**Figure 1.30** Réaction multi-étapes utilisant des catalyseurs de palladium(II) supportés transformant le benzimidazole **1.120** en Telmisartan **1.123**.

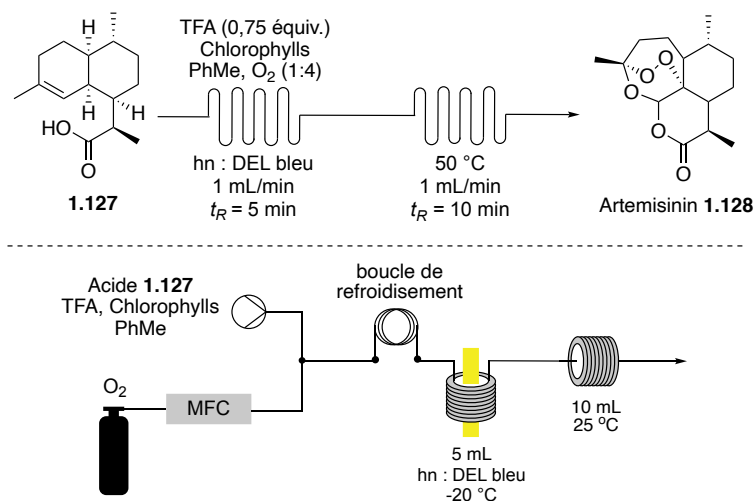
#### 1.4.4.2 Photochimie

La photochimie peut être utilisée comme source d'énergie pour minimiser l'ajout de réactif excédentaire lors de processus multi-étapes en flux continu. En 2012, le professeur Jamison a démontré l'utilisation de la photocatalyse UV pour effectuer la déshydratation de nucléosides en deux étapes (Figure 1.31).<sup>106</sup> Le photoréacteur employé ressemble au montage précédemment mentionné du professeur Booker-Milburn. Le nucléoside **1.124** et le photocatalyseur organique **1.125** sont élués et irradiés dans un réacteur de 1,84 mL pour une durée de 7 minutes. L'ajout d'hydroxyde de sodium permet d'effectuer la déprotection des groupements benzoates et ainsi fournir le nucléoside déshydraté **1.126** avec un rendement de 85 % sur deux étapes.



**Figure 1.31** Photodéshydratation du nucléoside **1.124** pour fournir le nucléoside **1.126**

Il est aussi possible d'utiliser la photocatalyse visible dans les processus multi-étapes, ce que le groupe de professeur Seeberger a montré à plusieurs reprises dans leur étude de la synthèse de l'Artémisinine **1.128**.<sup>107</sup> Dans leur toute dernière procédure, ils ont adopté une stratégie de synthèse multi-étapes en employant un extrait brut de la plante *Artemisia annua* comme mélange réactionnel (Figure 1.32).<sup>108</sup> La synthèse débute avec l'acide dihydroartermisinique **1.127** en présence de chlorophylle (photocatalyseur), d'acide trifluoroacétique (TFA) et d'oxygène. La photooxydation fournit un intermédiaire qui réagit à 50 °C avec le TFA pour former l'Artémisinine **1.128** avec 67 % de rendement sur deux étapes.



**Figure 1.32** Photooxydation de l'acide dihydroartémisinique **1.127** pour fournir l'Artémisinine **1.128** dans un processus multi-étapes en flux continu.

Toutes ces techniques et avantages démontrent clairement l'importance de la chimie en flux continu comme outil de synthèse d'appoint dans le domaine de la production de molécules d'intérêt. Celle-ci permet le développement de nouveaux processus chimiques autrefois difficiles à contrôler, à faire réagir ou à effectuer sur grande échelle et ce de manière fiable.

## 1.5 Buts de recherche

Étant donné l'intérêt accru pour la photocatalyse dans les dernières années, un grand nombre d'études sur de nouveaux catalyseurs métalliques ont été effectuées pour démontrer leur utilité synthétique (section 1.2). La plupart de ces complexes sont basés sur le ruthénium, l'iridium et, plus récemment, sur le cuivre. Cependant, les complexes de fer ont été peu étudiés comme remplacement durable des complexes de ruthénium. C'est avec cette optique de durabilité que mon premier projet a été réalisé, pour lequel mes objectifs étaient les suivants (chapitre 2) :

1. Développer de nouveaux photocatalyseurs de type polypyridyle à base de fer(II). Ces nouveaux complexes seront utilisés dans une réaction de photocyclisation de diaryles et triarylamines précédemment développée dans notre groupe.<sup>109</sup>
2. Utiliser l'oxygène comme oxydant. Afin de s'aligner avec les principes de la chimie verte, le remplacement de l'iode par l'oxygène dans cette réaction a été étudié.

3. Développer une stratégie d'agrandissement d'échelle en flux continu. Étant donné les avantages pour la photochimie en flux continu, le développement de ce processus a été effectué pour permettre une synthèse sur l'échelle du gramme (chapitre 2).

La chimie en flux continu devient un outil très utile dans le domaine de la synthèse, soit pour son contrôle des paramètres réactionnels, les agrandissements d'échelles facilités et la synthèse multi-étapes (section 1.4). Cette technologie jumelée à la photochimie ouvre de nouvelles portes au niveau réactionnel, ce qui a été grandement démontré dans les dernières années (section 1.4.1). Cependant, l'utilisation de processus photochimiques dans une synthèse multi-étapes en flux continu ce fait rare. Dans les cinq dernières années, une centaine d'articles sur des processus de synthèse multi-étapes ont été publiés, seulement cinq exemples utilisaient la photochimie comme étape initiale de la séquence de transformations (section 1.4.4.2). C'est pour cette raison que mon deuxième projet porte sur l'utilisation d'un processus photochimique dans une synthèse multi-étapes en flux continu, où pour atteindre ce but, les objectifs suivants ont été réalisés :

1. Développer un processus photochimique de décomposition d'azotures pour la formation d'hétérocycles azotés en flux continu. En utilisant seulement la lumière ultraviolette et un azoture aromatique, il serait possible de minimiser les sous-produits et réactifs excédentaires pour faciliter l'ajout d'une seconde réaction à la sortie (chapitre 3).
2. Étudier l'étendue de la réaction et la tolérance des groupements fonctionnels. Des groupements fonctionnels tels qu'un bromure ou un aldéhyde pourraient servir de point de post-fonctionnalisation lors d'une séquence multi-étapes (chapitre 3).
3. Tester la possibilité d'incorporer une réaction de couplage croisé de Suzuki suite à la photodécomposition d'azoture. L'utilisation d'un catalyseur de palladium(II) supporté sur silice pourrait faciliter l'ajout des autres réactifs (chapitre 4).
4. Tester la possibilité d'introduire une réaction de métallophotorédox pour effectuer un couplage croisé  $Csp^2-Csp^3$ . Ce type de processus multi-étapes serait le premier utilisant deux transformations photochimiques subséquentes (chapitre 4).

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## 2 Photochemical Synthesis of Carbazoles Using a [Fe(phen)<sub>3</sub>](NTf<sub>2</sub>)<sub>2</sub>/O<sub>2</sub> Catalyst System: Catalysis Towards Sustainability.

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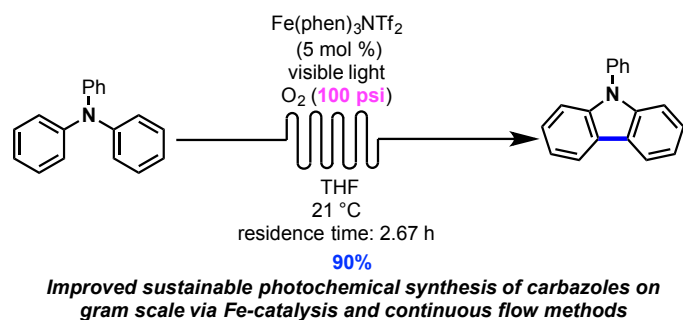
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### Contributions:

- Shawn Parisien-Collette participated in the design of the experiments, did all the experimental work in the optimization, the triaryl/diarylamine substrate scope and the scale up by numbering-up and contributed to the writing of the manuscript.
- Augusto C. Hernandez-Perez participated in the preliminary work and the evaluation of some photocatalyst activity.
- Shawn K. Collins participated in the design of the experiments and writing of the manuscript.

## 2.1 Abstract

An increasingly sustainable photochemical synthesis of carbazoles has been developed using a catalytic system of  $\text{Fe}(\text{phen})_3(\text{NTf}_2)_2/\text{O}_2$  under continuous flow conditions and demonstrated on gram-scale using a numbering-up strategy. Photocyclization of triaryl and diarylamines into the corresponding carbazoles occurs in general in higher yields than with previously developed photocatalysts.

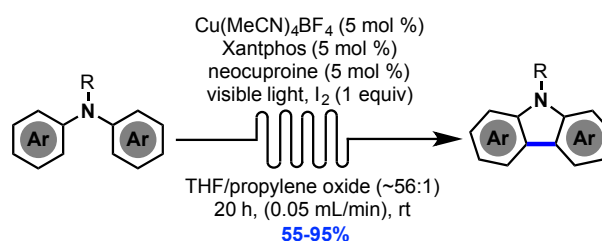


## 2.2 Introduction



Photocatalysis has experienced a resurgence in interest as a tool for organic synthesis, particularly as the use of light as an energy source is widely viewed as a green technology.<sup>1</sup> The harvesting of light by sensitizers and subsequent electron transfer to different molecules can promote a number of important organic transformations via catalysis. In parallel, continuous flow methods have complemented the development of new photochemical technologies, allowing faster reaction times and improved scale-up to synthetically relevant scales.<sup>2</sup> Among metal-based sensitizers for photoredox catalysis, Ru- and Ir-based complexes possessing polypyridine and associated ligands have demonstrated utility in a host of transformations.<sup>3</sup> However, questions of sustainability have led to the exploration of heterogeneous photocatalysis via sensitized  $\text{TiO}_2$ <sup>4</sup> or mesoporous carbon nitride polymers,<sup>5</sup> as well as homogeneous photocatalysis using organic dyes.<sup>6</sup>

The use of Cu-based sensitizers<sup>7</sup> has now attracted attention as a cheaper, and more abundant metal source for photocatalysis although they remain underexplored in comparison to their Ru and Ir-based counterparts. Our group has previously described the use of heteroleptic copper complexes for the synthesis of carbazole heterocycles (Scheme 2.1).<sup>8</sup> The complex

Cu(Xantphos)(neo)BF<sub>4</sub> formed in-situ promoted the oxidative cyclization of di- and tri-aryl amines to the corresponding carbazoles, using visible light irradiation and a continuous flow set-up. Despite the good yields and wide substrate scope, several key drawbacks were identified (Figure 2.1), especially when scale-up would be considered. Although copper remains a more abundant and cheaper metal than Ru or Ir, both metal and ligand costs would have to be revisited. A change from molecular iodine to molecular oxygen or air would permit a more benign oxidant system. Lastly, the copper-catalyzed reaction required relatively long residence times for a continuous flow process, and decreasing the residence time through either chemical reactivity or reaction engineering would be valued. Herein we report the synthetic utility of a soluble Fe-based sensitizer complex for a photocatalytic oxidative transformation under continuous flow conditions.



**Scheme 2.1** Photoredox synthesis of carbazoles using a Cu-based sensitizer/I<sub>2</sub> catalyst system.

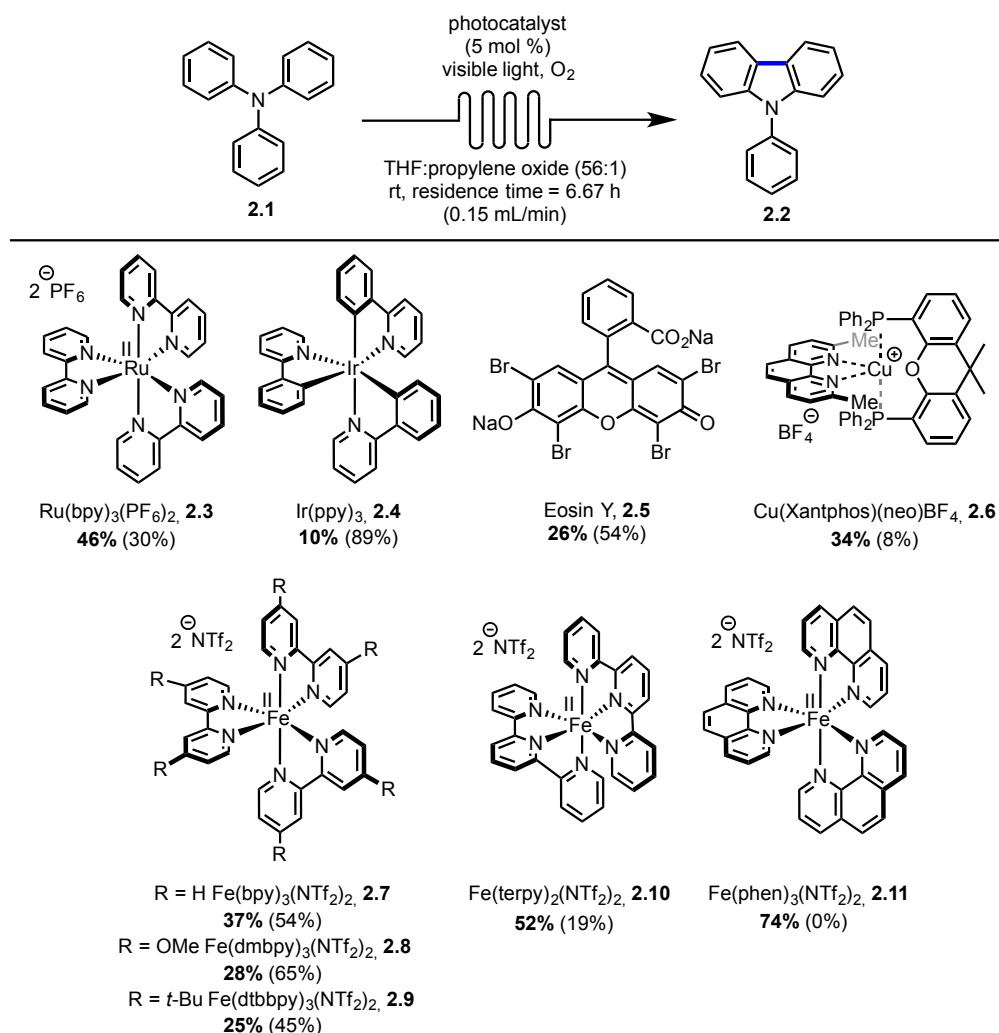
<p><b>Photocatalysis via Cu complexes (Past Work):</b></p> <ol style="list-style-type: none"> <li>1) Required toxic oxidant/solvent system (I<sub>2</sub>/THF)</li> <li>2) Utility demonstrated on small scales (&lt; 100 mg)</li> <li>3) Relatively long residence times for a continuous process (approx. 20 h)</li> </ol>	<p><b>Cu</b></p> 
<p><b>Photocatalysis via Fe complexes (This Work):</b></p> <ol style="list-style-type: none"> <li>1) Exploit molecular oxygen as a benign oxidant</li> <li>2) Demonstrate scalability in continuous flow synthesis</li> <li>3) Improved reactivity/residence times</li> </ol>	<p><b>Fe</b></p> 

**Figure 2.1** Limitations of the Cu-based sensitizer/I<sub>2</sub> catalyst system and targets for a new catalysts system.



## 2.3 Results and Discussion

The first goal was to survey photocatalysts that could efficiently form the carbazole nucleus using molecular oxygen as an oxidant. Molecular oxygen can accept an electron and act as a reagent to promote organic oxidative transformations.<sup>9</sup> As such, a variety of sensitizers were evaluated in an oxidative cyclization to form 9-phenylcarbazole employing molecular oxygen (Figure 2.2). All reactions were performed in continuous flow using household lightbulbs as the light source. To achieve the goal of using molecular oxygen as the stoichiometric oxidant,<sup>10</sup> a tube-in-tube reactor<sup>11</sup> was used to insure a high concentration of dissolved oxygen in THF.<sup>12</sup> For convenience, a flow rate of 0.15 mL/min (irradiation time: 6.67 h) was employed. First, the synthesis of carbazole **2.2** was performed in the dark and >90% of the starting material **2.1** was recovered. In addition, attempts to promote the reaction thermally also failed (heating in batch, 80% recovered **2.1**). The reaction also failed to afford significant yields of carbazole **2.2** (13% **2.2**, 86% recovered **2.1**) when performed in the absence of any photocatalyst. When a Ru- [Ru(bpy)<sub>3</sub>Cl<sub>2</sub>] and Ir-based sensitizer [Ir(ppy)<sub>3</sub>] were studied, each afforded modest to low yields of the desired carbazole (46 and 10% yield respectively). Next, a previously developed Cu-based sensitizer [Cu(Xantphos)(neo)BF<sub>4</sub>, 34% yield] and an organic sensitizer (eosin Y,<sup>13</sup> 26% yield) were also evaluated, but provided low yields as well. A Fe-based catalyst [Fe(bpy)<sub>3</sub>(NTf<sub>2</sub>)<sub>2</sub>]<sup>14</sup> afforded a 37% yield of carbazole **2.2**. The NTf<sub>2</sub><sup>-</sup> counterion was chosen specifically to augment the solubility of the Fe complex for its use in continuous flow. Other iron-based complexes were also investigated, and the phen-derived complex **2.11**<sup>15</sup> provided the desired carbazole in the highest yield (74%). Finally, further optimization via the removal of the propylene oxide additive, previously used to trap any acidic by-products, improved the isolated yield of **2.2** to 95%.

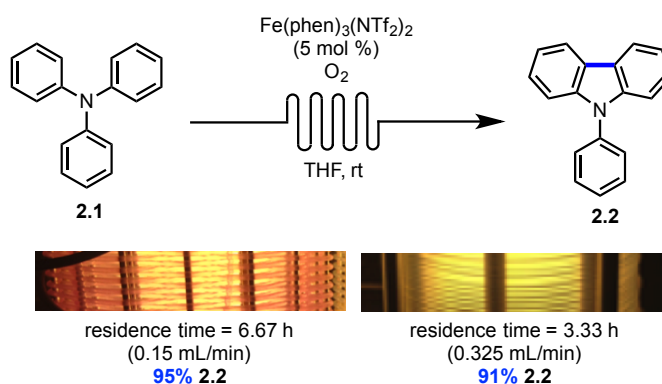


**Figure 2.2** Optimization Evaluation of Photocatalysts for the Synthesis of 9-Phenylcarbazole. Yields following flash chromatography. Recovered starting material **2.1** indicated in brackets.

It should be noted that the excited states of polypyridyl complexes of the type  $^*FeL_3^{2+}$  are short compared to analogous Ru-based analogs<sup>16,17</sup> and hence should not operate via the single electron transfer mechanisms common in photoredox catalysis. Given the abundance of literature data which supports that photoredox catalysis via metal-to-ligand charge transfer for Fe(II)-polypyridyl complexes is not possible in solution,<sup>18</sup> it is reasonable to assume that some other mechanism must be promoting the photochemical transformation. It may also be possible that catalysis is achieved through Fe(III)-based impurities. A control experiment was performed where commercially available Fe(II)Cl<sub>2</sub> was purified using a reported protocol to remove any Fe(III)-based impurities and the corresponding catalyst **2.11** was prepared. Once again, the transformation (**2.1**→**2.2**) occurred in high yield (~80% of **2.2**) and required visible light irradiation (in the absence

of light, 5% **2.2**, 94% recovered **2.1**). Given the necessity of the iron complex, light and oxygen for the reaction to occur, the oxidation of the amines to carbazoles could proceed mechanistically via formation of superoxide.<sup>19</sup> The improved mixing of O<sub>2</sub><sup>20</sup> made possible via the flow tube-in-tube system likely helps accelerate the reaction rate. In addition, when the transformation (**2.1**→**2.2**) was performed with Fe(III)(phen)<sub>3</sub>PF<sub>6</sub> in either catalytic or stoichiometric quantities, no productive formation of the desired carbazole **2.2** was observed.

A second goal to improve the synthesis of carbazoles was to decrease the reaction time. The use of continuous flow techniques is crucial to the success of the Fe(phen)<sub>3</sub>(NTf<sub>2</sub>)<sub>2</sub>/O<sub>2</sub> photocatalytic system. When the analogous carbazole synthesis (**2.1**→**2.2**) was performed in batch with a reaction time of 6.67 h, only traces of **2.2** could be isolated from the reaction mixtures. When a reaction time of 50 h was used, the desired carbazole could be isolated in 15% yield. In addition, in the absence of the tube-in-tube reactor, the yields of the carbazole **2.2** were ranging from 46-95% yield, highlighting the need for efficient dissolution of molecular oxygen in the reaction media. To decrease the residence time, modifications to the continuous flow reactor were made so that the tubing was no longer in an interwoven pattern. Consequently, improved irradiation allowed a decrease in the residence time to 3.33 h, while maintaining high yields of **2.2** (91%) (Scheme 2.2).



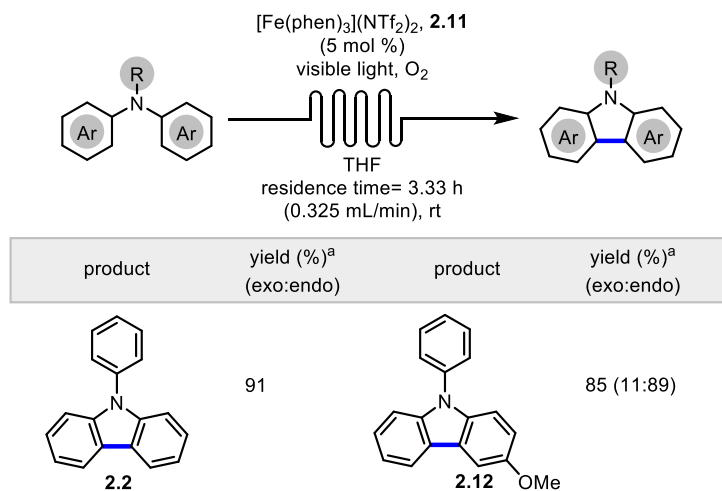
**Scheme 2.2** Control reactions highlighting the need for both the Fe complex and light and improved irradiation with reactor design.

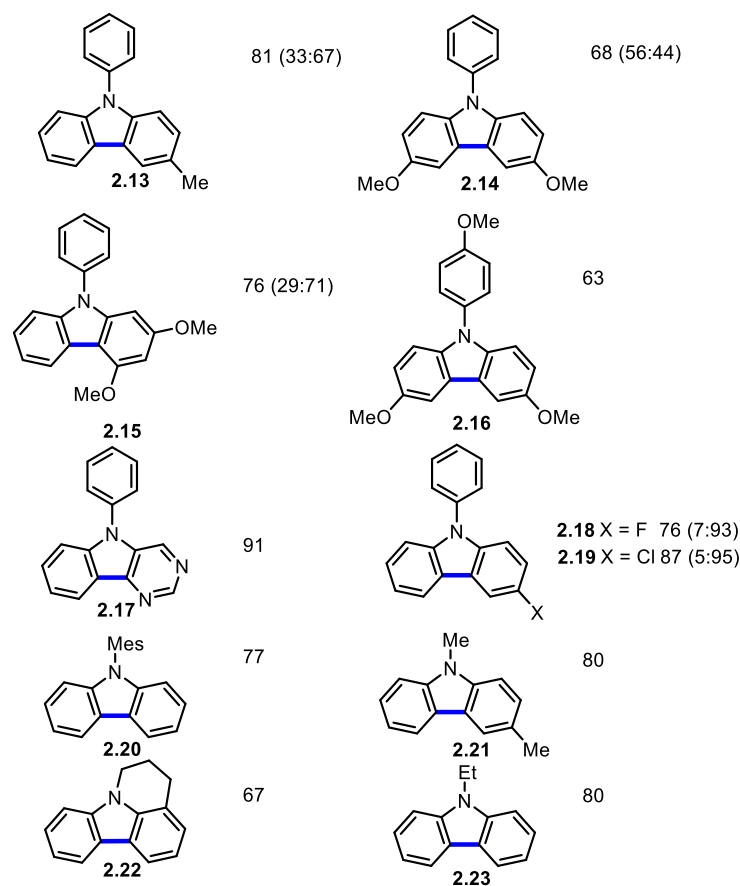
To probe the efficiency of the Fe(phen)<sub>3</sub>(NTf<sub>2</sub>)<sub>2</sub>/O<sub>2</sub> system a series of carbazoles were prepared from the corresponding diaryl- or triarylamines (Table 1). First, triarylamines bearing an electron-donating OMe or Me substituent were cyclized using the optimized conditions. The

carbazoles **2.12** and **2.13** were isolated in 85 and 81% yields respectively. The synthesis of carbazoles having an even greater number of electron-donating methoxy groups could also be prepared. The dimethoxy carbazoles **2.14** and **2.15** were prepared in 68 and 76% yields, and the trimethoxy derivative **2.16** was isolated in 63% yield. The synthesis of a pyrimidoindole was also possible as **2.17** was synthesized in 91% yield.

When we explored the scope of the synthesis of carbazoles, two halogenated substrates underwent productive cyclization to provide halogenated carbazoles **2.18** and **2.19** in good yields (76 and 87% respectively). Both the fluoro- and chlorocarbazoles were isolated as predominantly the endo isomers. A sterically encumbered mesityl group was also tolerated and afforded the carbazole **2.20** in 77% yield. Three different *N*-alkylated carbazoles were also evaluated and isolated in good yields: the *N*-Me carbazole **2.21** in 80% yield, the *N*-Et carbazole **2.22** in 80% yield and the tetracyclic heterocycle **2.23** in 67% yield. In addition, upon comparison with the previously developed catalyst system employing a Cu-based catalyst and I<sub>2</sub> as molecular oxidant,<sup>9</sup> the yields were all higher employing the Fe-based sensitizer/O<sub>2</sub> catalyst system and performed in a much shorter reaction time (residence times 3.33 vs 20 h for Fe- vs Cu-based catalyst systems).

**Table 2.1** Efficiency of the Fe(phen)<sub>3</sub>(NTf<sub>2</sub>)<sub>2</sub>/O<sub>2</sub> system for the synthesis of carbazoles.

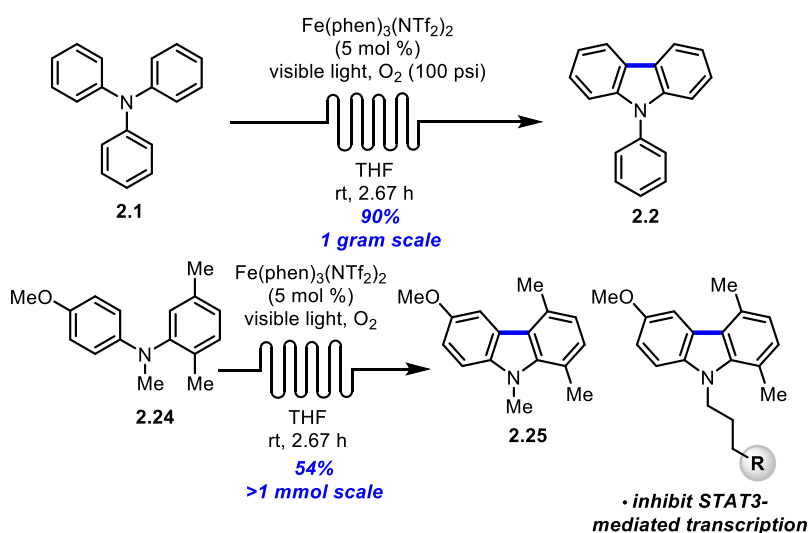




<sup>a</sup> Isolated yields following flash chromatography. Major product is shown. In the cyclization of substituted triarylamines, the incorporation of the substituted aryl group is defined as the *endo* product, while exclusion of the substituted aryl is defined as the *exo* substituent.

The improved protocol utilizing molecular oxygen and shorter residence times was explored on ~40 mg scales. It was decided to explore the scalability in the photochemical synthesis of carbazoles up to a gram scale. Using an experimental set-up which involved 5 tubing reactors in series, at ~40 mg scales, the desired carbazole **2.2** was obtained in 91%. When the scale of the reaction was increased to one gram, the reaction profile remained highly reproducible (88% of **2.2**). A drawback was the long overall process time required for the scale-up: the 1 gram transformation (**2.1**→**2.2**) required approximately 50 hours to complete. To demonstrate improved protocols for scale-up, proof-of-principle for the utility of a “numbering-up” strategy<sup>21</sup> was explored (Scheme 3). The reaction mixture was first pumped through a tube-in-tube reactor where the O<sub>2</sub> pressure was increased (40→100 psi) compared to smaller scales. Following elution from the gas/liquid reactor, the flow was “split” into the two reactor sequences with two 8 bar back pressure regulators

connected to the end of the flow system. As such, **2.2** was obtained in 90% yield and the overall process time had been reduced by more than 50 % (approximately ~1 g/day). The optimized photocatalytic synthesis of carbazoles was also applied to the synthesis of the carbazole core of recently reported inhibitors of STAT3,<sup>22</sup> an emerging biomarker in tumour therapy.<sup>23</sup> The photocyclization of the diarylamine **2.24** was performed on >1 mmol scale using the numbering-up reactor design. The highly substituted desired carbazole **2.25** was obtained in 54% yield.



**Scheme 2.3** Numbering up strategy for the gram-scale synthesis of carbazole **2.2**: synthesis of simple and complex carbazoles.

## 2.4 Conclusions

In summary, a new photochemical synthesis of carbazoles has been developed. Key improvements include: 1) a catalytic system of  $\text{Fe}(\text{phen})_3(\text{NTf}_2)_2$  allows the use of  $\text{O}_2$  as stoichiometric oxidant, 2) employing a tube-in-tube type reactor under continuous flow conditions improved the reaction time compared to previous methods and 3) the photochemical synthesis of carbazoles was demonstrated in scale-up via a numbering-up strategy. The  $\text{Fe}(\text{phen})_3(\text{NTf}_2)_2/\text{O}_2$  system could also promote photocyclization for the synthesis of carbazoles in higher yields than the first generation copper-based catalyst system. Further fundamental work is currently directed toward a better understanding of the mechanism via Fe-complexes and application in other photochemical syntheses.

### Supporting Information

Experimental procedures and characterization data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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### 3. Photochemical Intramolecular Amination for the Synthesis of Heterocycles

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#### Contributions:

-Shawn Parisien-Collette participated in the design of the experiments, did all the experimental work in the optimization, some of the azide substrate scope, the synthesis of Carprofen and the kinetic isotope effect study, and contributed to the writing of the manuscript.

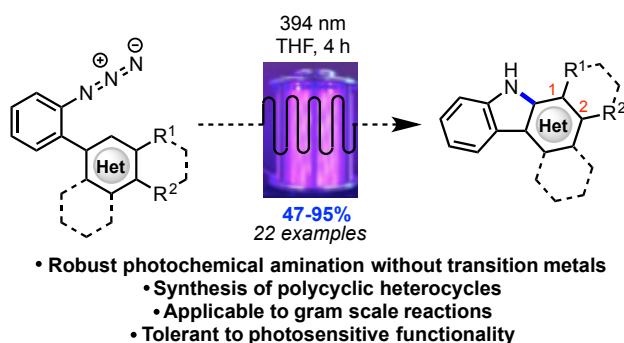
-Corentin Cruché participated in the azide substrate scope.

-Xavier Abel-Snape participated in the azide substrate scope

-Shawn K. Collins participated in the design of the experiments and writing of the manuscript.

### 3.1 Abstract

Polycyclic heterocycles can be formed in good to excellent yields via photochemical conversion of the corresponding substituted aryl azides under irradiation with purple LEDs in a continuous flow reactor. The experimental set-up is tolerant to UV-sensitive functional groups while affording diverse carbazoles, as well as an indole and pyrrole framework, in short reaction times. The photochemical method is presumed to progress through a mechanism differing from the other methods of azide activation involving transition metal catalysis.



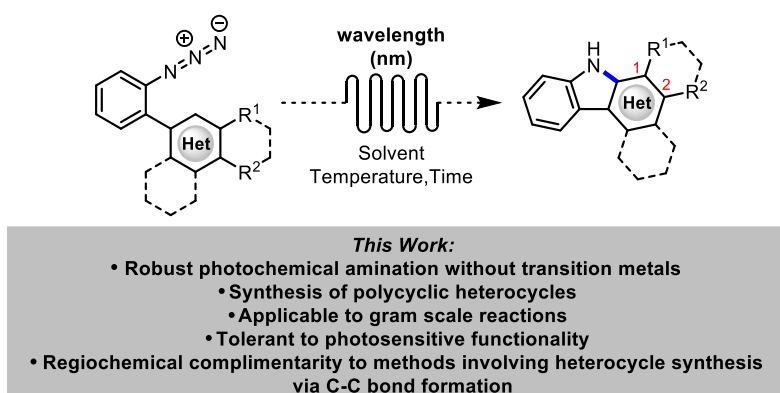
### 3.2 Introduction

The drive for ever more sustainable and environmentally friendly technologies for molecular synthesis has led to a resurgence in the interest of synthetic photochemistry.<sup>1</sup> Light is an attractive “reagent”, as it is traceless and can be accessed through wavelength selective, low-energy sources such as light emitting diode (LEDs). When synthetic photochemistry is exploited within a continuous flow manifold, issues of light penetration, over-irradiation and scalability are easily overcome. Consequently, it is not surprising that photochemical continuous flow processes are of increasing interest for the synthesis of high-value pharmaceuticals.<sup>2</sup>

Polycyclic nitrogen heterocycles are important structural motifs that are embedded into the core skeletons of natural products, pharmaceuticals<sup>3</sup> and compounds of interest in materials science.<sup>4</sup> Due to the structural complexity often encountered, chemists are faced with the challenge of developing synthetic methods that afford high levels of regiocontrol despite substitution patterns, and are tolerant to the density of heteroatoms present. Consequently, the synthesis of polycyclic heterocycles remains a challenging problem in organic synthesis. One of the more recent

developments in strategies to form nitrogen-based heterocycles concerns amination via azide activation.<sup>5</sup> Following the report of Rh-based catalysis for decomposition of azides and the synthesis of heterocycles by Driver and co-workers,<sup>6</sup> examples of Ir,<sup>7</sup> Ru<sup>8</sup> as well as Fe-based catalysis were reported.<sup>9</sup> The decomposition of azides via transition metals has led to a variety of methods for the synthesis of carbazoles, indoles, aziridines, pyrroles and pyrrolidines via either C<sub>sp</sub><sup>3</sup>-H or C<sub>sp</sub><sup>2</sup>-H amination.<sup>5-9</sup>

Despite the recent interest in C-H amination via transition metal catalysis, the photochemical activation of azides via, resulting in a formal C-H amination, initially reported over 60 years ago by Smith and Brown in 1951, could be exploited to form the same products without added reagents or transition metal catalysts.<sup>10</sup> Further investigation of the photochemical decomposition of azides for C-H amination has been relegated to studies of the mechanism,<sup>8,11</sup> and further development as a robust synthetic method to access both common and complex polycycles has been rare. The scarcity of new photochemical methods is all the more surprising given their complementarity with existing protocols.<sup>12</sup> Notably, our group has reported the photochemical oxidation of diaryl- and triarylaminines to form carbazoles,<sup>13</sup> but the existing methods fail to promote heterocycle formation when starting materials possess a free amine. In the current context of sustainable synthesis, the development of practical photochemical amination would be a welcome addition to the toolbox of synthetic chemists. Herein we describe a photochemical continuous flow synthesis<sup>14</sup> of unprotected, free N-H, carbazoles, indoles and pyrroles, in addition to complex polycyclic heterocycles, from their corresponding azido-aryl precursors (Figure 3.1).

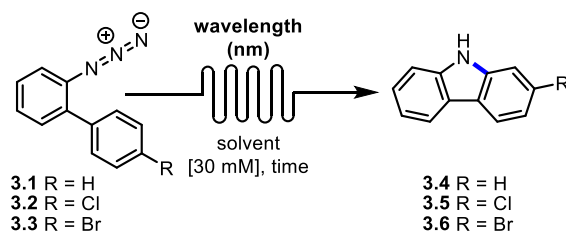


**Figure 3.1** Photochemical approach to polycyclic heterocycles,

### 3.3 Results and Discussion

The photochemical decomposition of azidobiaryl **3.1** was first studied at 254 nm using a previously reported UV-flow reactor.<sup>15</sup> At a concentration of 30 mM in THF, the corresponding carbazole **3.4** was obtained in 80% yield with a residence time of only 10 min (Table 3.1). With an eye on developing a photochemical method that would tolerate a variety of functionality, a chlorinated derivative **3.2** was also evaluated. Unfortunately, under the identical conditions, a lower yield of 61% was observed along with the formation of dechlorinated by-products. When an analogous brominated azide **3.3** underwent irradiation with light at 254 nm, the desired bromo-carbazole **3.6** was isolated in only 45%. After examining various wavelengths, it was found that the irradiation from purple LEDs (394 nm) overlapped with the tail end of the absorption of azidobiaryl **3.1** (Figure 3.2 and 3.3).

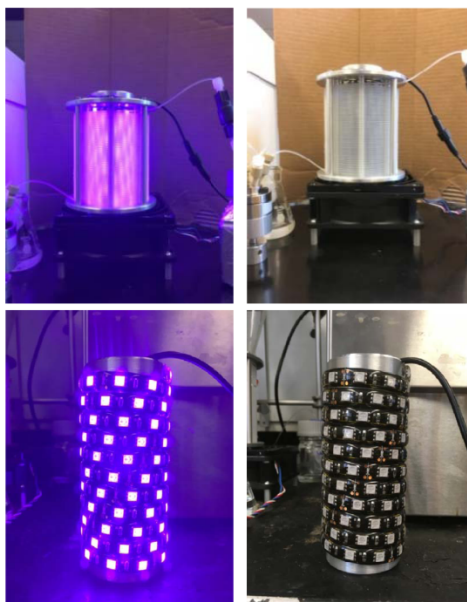
**Table 3.1** Survey of photochemical protocols.



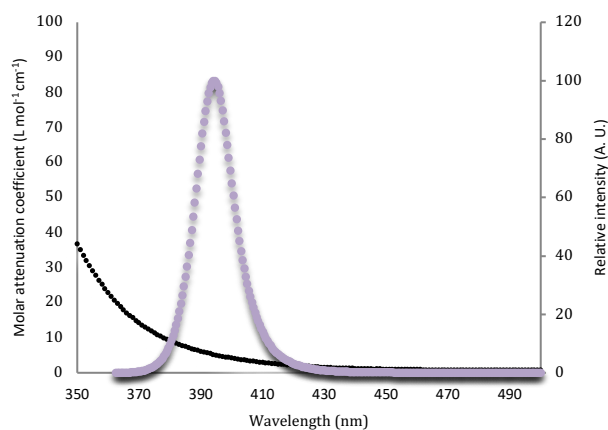
entry <sup>a</sup>		time	solvent	wavelength (nm)	yield (%)
<b>1</b>	<b>3.1</b>	10 min	THF	254	80 <sup>b</sup>
<b>2</b>	<b>3.1</b>	10 min	EtOAc	254	70
<b>3</b>	<b>3.2</b>	10 min	THF	254	61
<b>4</b>	<b>3.3</b>	10 min	THF	254	45
<b>5</b>	<b>3.1</b>	2 h	THF	394	80 <sup>c,d</sup>
<b>6</b>	<b>3.1</b>	2 h	EtOAc	394	80 <sup>d</sup>
<b>7</b>	<b>3.2</b>	2 h	EtOAc	394	62 <sup>d</sup>
<b>8</b>	<b>3.2</b>	4 h	THF	394	81 <sup>d</sup>
<b>9</b>	<b>3.3</b>	4 h	THF	394	80 <sup>d</sup>
<b>10</b>	<b>3.3</b>	4 h	EtOAc	394	69

<sup>a</sup>Yields following flash chromatography. <sup>b</sup>74% of **3.4** at 75 mM. <sup>c</sup>63% of **3.4** at 75mM.

<sup>d</sup>Mass balance is unreacted azide.



**Figure 3.2** Photochemical reactors for irradiation at 394 nm (purple LEDs) (on, left, off right). The temperature within purple LED reactor can increase over time (temperature reaches a maximum of 24.6 °C) A cooling fan was installed at the bottom of the reactor to maintain the temperature.



**Figure 3.3** Overlapping the absorption spectrum for 2-azido-1,1'-biphenyl (**3.1**, black) with the emission spectrum of the purple LED (purple) at the concentration used for the photochemical decomposition of the azide (30 mM in THF).

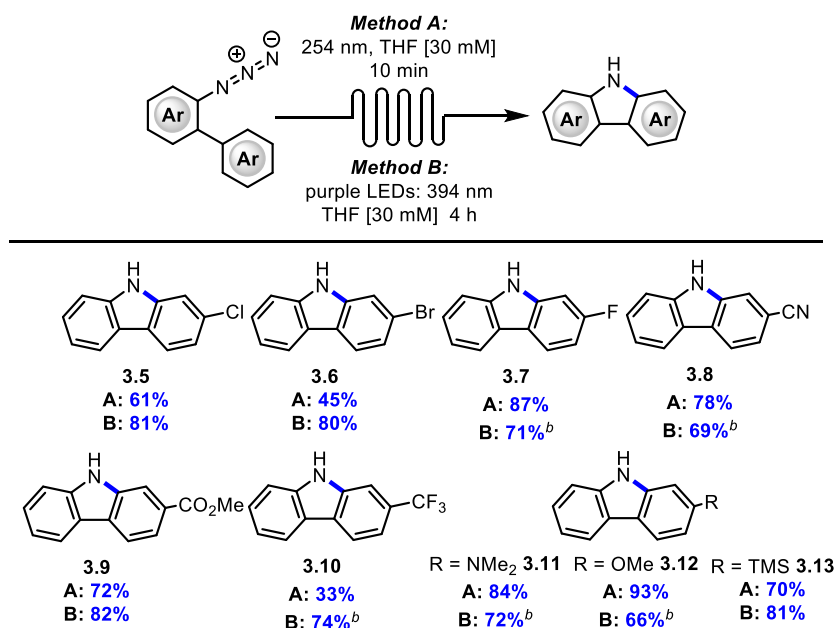
Furthermore, irradiation from the purple LEDs in either EtOAc or THF as solvent was an efficient photochemical procedure for the decomposition of azides (Table 3.1).<sup>16</sup> The chlorinated carbazole **3.5** was isolated in 81% (THF, 4 h) while irradiation of the bromo azide **3.3** in EtOAc

afforded an increased yield of the desired carbazoles (69% compared to 45% at 254 nm) and the yield could be further increased when using THF (80%). In many instances, under the 394 nm irradiation, the remainder of the mass balance was unreacted azide precursor.

Further attempts to optimize the yield of carbazoles were not fruitful: either increasing or decreasing the concentration of the reaction mixture gave lower yields, alternative solvents produced lower yields and increasing the flow rate gave lower yields, albeit again the mass balance was recovered azide starting material. Furthermore, no azo side-products were observed during any of the irradiations. It should be noted that a recent report aiming to evaluate that “greenness” of various solvents classified THF as “problematic” and EtOAc as “recommended”.<sup>17</sup> While in many cases the yields are superior in THF, the difference in yield when using EtOAc is generally within 10%, and in some cases demonstrated below, the yields can be better with EtOAc. Some differences in yield may be due to the difference in UV cutoff values for the two solvents (EtOAc 256 nm, THF 212 nm). Having optimized the conditions for the intramolecular photochemical amination at two different wavelengths in continuous flow, the scope of the transformation was explored with regards to both electron-withdrawing and electron-donating substituents (Table 3.2). Each of the cyclizations was performed at both 254 and 394 nm irradiation and in general, conversion to the desired product afforded higher yields when the latter protocol was used. In some instances, EtOAc afforded higher yields than THF as solvent for irradiation of the azidobiphenyls at 394 nm. Carbazoles bearing electron-withdrawing groups such as F (**3.7**), cyano (**3.8**), CO<sub>2</sub>Me (**3.9**) and CF<sub>3</sub> (**3.10**) all underwent cyclization (69 to 82 % yield) under 394 nm irradiation. Electron-donating substituents such as NMe<sub>2</sub> and OMe afforded carbazoles **3.11** and **3.12** products in higher yields when irradiated at 254 nm (84 to 93 % yield), while a TMS afforded the corresponding carbazoles **3.13** in higher yield at 394 nm irradiation (81%).



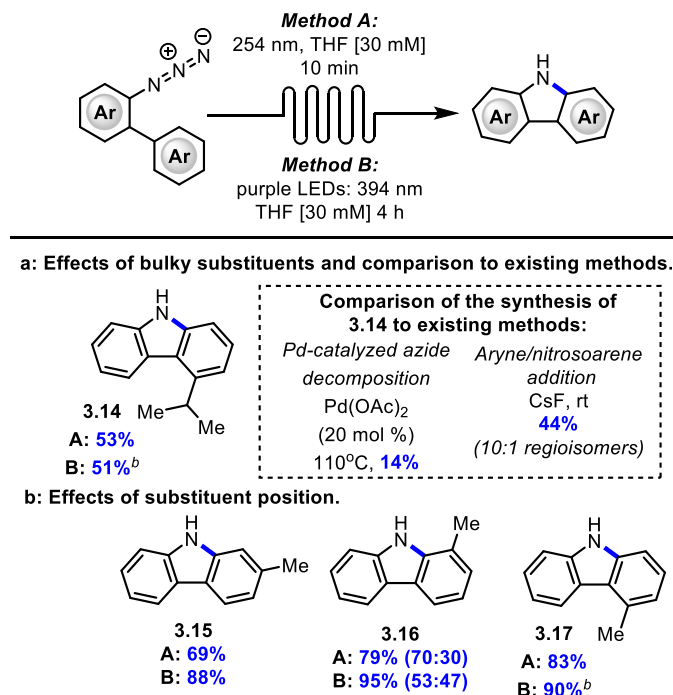
**Table 3.2** Scope of the photochemical amination: electronic effects.<sup>a</sup>



<sup>a</sup>Yields following flash chromatography. <sup>b</sup> In EtOAc

Next, the influence of alkyl group substitution was explored (Table 3.3). A sterically encumbered alkyl group, *i*-Pr, was investigated and afforded the corresponding carbazole in moderate yields (53 and 51 % at 254 and 394 nm irradiation respectively). Interestingly, carbazole **3.14** was formed as the sole product and no product resulting from C-H insertion were observed. Also noteworthy, the photochemical amination provided higher yields than existing methods involving palladium-catalyzed azide decomposition<sup>18</sup> and a bimolecular aryne/nitrosoarene addition,<sup>19</sup> in which the latter also afforded a mixture of regioisomers. In exploring the influence of alkyl substituents, a methyl group could be appended to the azidobiphenyl precursor in either the *para*-, *meta*- or *ortho*-positions and typically afforded the products in good yields.

**Table 3.3** Scope of the photochemical amination: steric effects.<sup>a</sup>



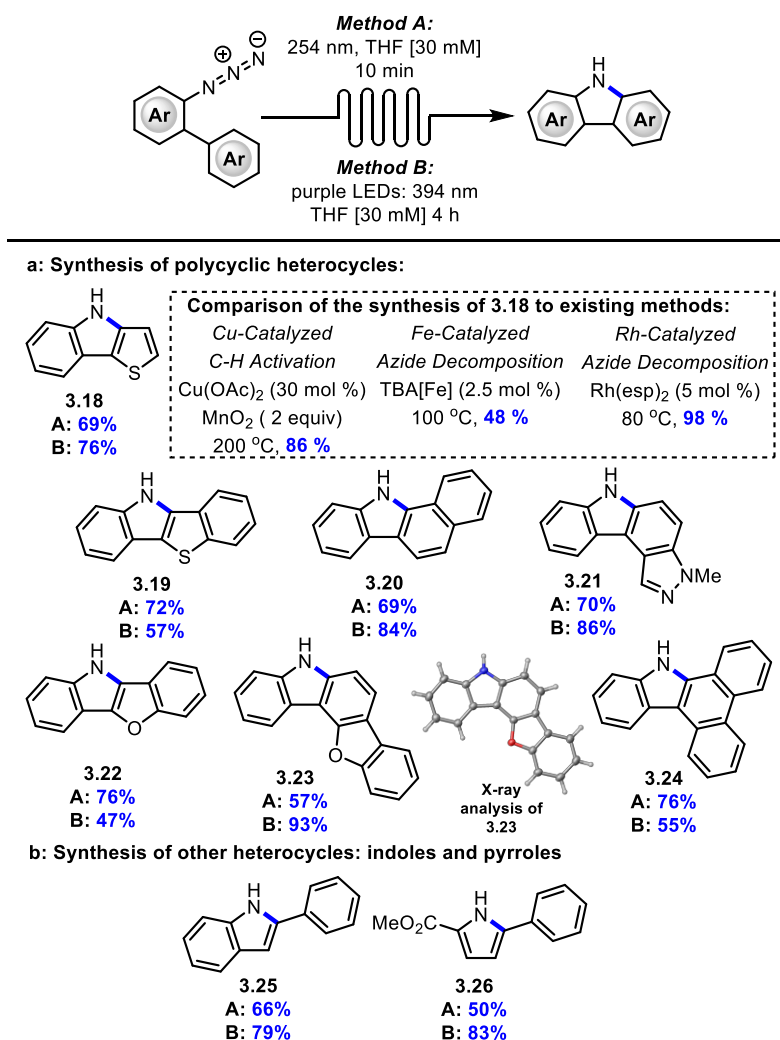
<sup>a</sup>Yields following flash chromatography. <sup>b</sup> In EtOAc

Interestingly, the photochemical decomposition of azidobiphenyls provides facile access to polycyclic heteroaromatic skeletons (Table 3.4). For example, 4*H*-thieno[3,2-*b*]indole **3.18**, previously investigated as a more electron-rich analogue of carbazole for dye-sensitized solar cells, could be formed via the photochemical amination in up to 76 % yield (394 nm irradiation). The yield fits within a range of yields found in the literature for the preparation of **3.18** via other methods,<sup>9a,20,21</sup> but has the distinction of not requiring transition metal catalysis. In addition to benzothiophene, naphthalene, indazole and benzofuran were easily annulated to form the corresponding tetracyclic heterocycles **3.19**, **3.20**, **3.21** and **3.22** as single regioisomers (76 to 86% yields, 394 nm irradiation). A dibenzofuran<sup>22</sup> and a phenanthrene could be annulated via the decomposition of the corresponding azides to form pentacyclic heterocycles (**3.23** and **3.24**; 55 to 93% yield).

Lastly, the method could also be extended to the synthesis of other aza-heterocycles. The synthesis of indole **3.25** and pyrrole **3.26** each occurred in good yields (79 and 83% yield respectively) via reaction of the corresponding azide. Again, the yields of the heterocycle products

were higher when decomposition of the azide starting materials occurred under irradiation at 394 nm (79 and 83%), rather than 254 nm (66 and 50%).

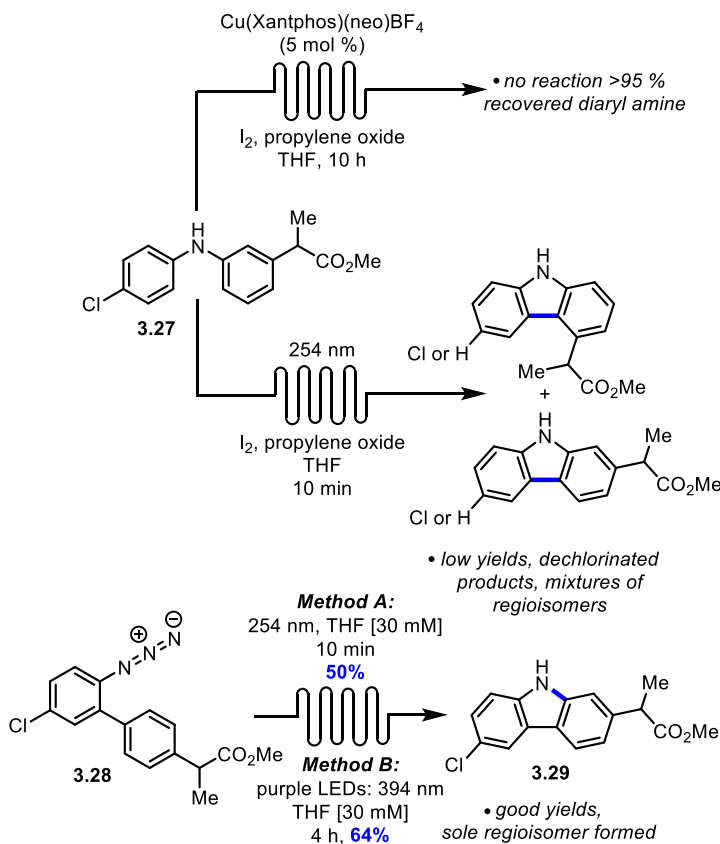
**Table 3.4** Scope of the photochemical amination: polycyclic heterocycles.<sup>a</sup>



<sup>a</sup>Yields following flash chromatography. <sup>b</sup> In EtOAc

The intramolecular photochemical amination displays useful functional group tolerance and complementarity when compared to existing photochemical methods for the synthesis of biologically active heterocycles. To illustrate the utility of the photochemical amination, different photochemical routes to the carbazole-based drug carprofen were examined (Scheme 3.1). First, synthetic routes that proceed via C-C bond formation were explored and the diaryl amine **3.27** was treated with a copper-based sensitizer under continuous flow conditions and irradiated under visible

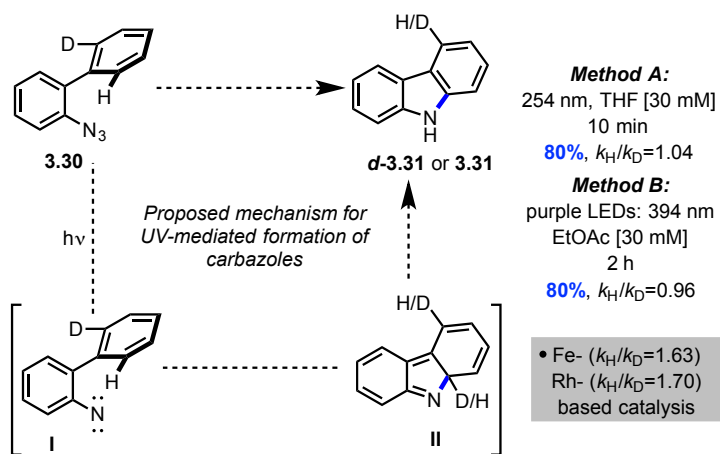
light.<sup>13a</sup> Following elution from the flow reactor, the diaryl amine was recovered almost quantitatively. Alternatively, when the same diaryl amine was excited under UV irradiation (continuous flow, 254 nm),<sup>13b,15</sup> a complex mixture forms in which carbazole products are only formed as minor products and have mostly undergone dechlorination. Importantly, the carbazoles observed are mixtures of regioisomers. When the photochemical amination was explored using the azido biphenyl **3.28**, the desired carbazole **3.29** was isolated as the major product in 50 % yield (254 nm) and 64 % (394 nm), as a sole regioisomer and without any dechlorination observed.



**Scheme 3.1** A comparison of photochemical routes to carprofen.

The mechanism of the conversion of the biphenyl azides to the corresponding carbazoles under UV-irradiation has been proposed to proceed via formation of a singlet biphenyl nitrene (**I**) which undergoes addition to an adjacent aromatic ring (Scheme 3.2).<sup>23</sup> The formed isocarbazole intermediate (**II**),<sup>24</sup> is proposed to rearrange to afford the corresponding carbazoles. In our studies, no observation of any C-H insertion products into an adjacent alkyl group such as Me (see

carbazole **3.17**, Table 3) or a *i*-Pr group (see carbazole **3.14**, Table 3) was observed, as is proposed to occur with triplet nitrene species.<sup>25</sup> It should be noted that the overlap between emission of the purple LED (394 nm) and the absorption of the biphenyl azides occurs only in the tail end of spectrum. As such, the formation of carbazoles at 394 nm could proceed via an alternative mechanism. A deuterium labelling study was performed and revealed a kinetic isotope effect of 1.04 and 0.96 (for irradiations at 254 and 394 nm respectively). While the values are considerably different from those obtained for Fe-catalyzed<sup>9a</sup> and Rh-catalyzed<sup>26</sup> aminations, alternative mechanisms may still be plausible for the process when irradiating at 394 nm. Indeed, other mechanisms involving electrocyclization and electrophilic aromatic substitution processes still remain plausible.<sup>26a</sup>



**Scheme 3.2** Proposed mechanism for the photochemical formation of carbazoles and deuterium labelling studies.

## 3.4 Conclusions

In summary, the photochemical conversion of substituted aryl or vinyl azides under a low-energy source of irradiation (394 nm) in a continuous flow reactor represents an increasingly sustainable route to heterocycles in good to excellent yields. Specifically, the strategy provided access to a range of carbazoles, including the incorporation of other heterocycles and/or polycyclic aromatics, as well as demonstrating utility towards the synthesis of an indole and pyrrole skeleton. Increased yields and improved functional group tolerance is observed when irradiation occurs with less energetic 394 nm light. The utility of the protocol was demonstrated via the photochemical synthesis of substituted carbazoles and complex tetra- and pentaheterocycles. The method was also applied to the synthesis of a known pharmaceutical agent, carprofen, and applied to the formation of indoles and pyrroles. The photochemical route is proposed to progress through a mechanism differing from the other methods of azide activation involving transition metal catalysis. The methods described herein demonstrate that underexplored photochemical methods can provide efficient, controlled and scalable routes, without the need for transition metals, to important heterocyclic frameworks.

### Supporting Information

Experimental procedures and characterization data for all new compounds. The Supporting Information is available free of charge on the RCS Publications website.

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## **4. Exploiting Photochemical Processes in Multi-Step Continuous Flow: Derivatization of the Natural Product Clausine C**

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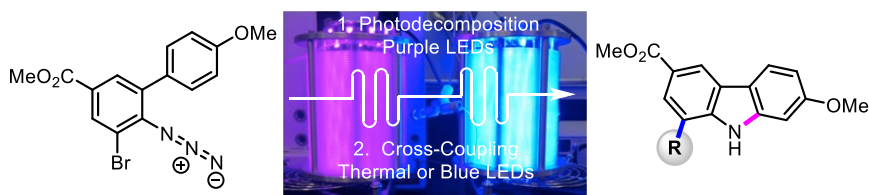
### Contributions:

-Shawn Parisien-Collette participated in the design of the experiments, did all the experimental work in the optimization, the substrate scope and contributed to the writing of the manuscript.

-Shawn K. Collins participated in the design of the experiments and writing of the manuscript.

## 4.1 Abstract

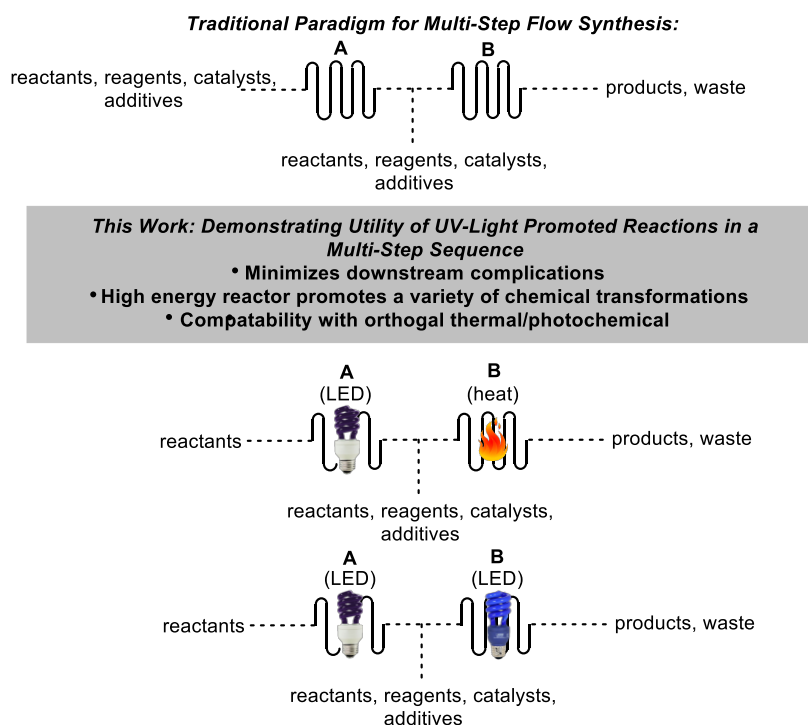
The synthesis and derivatization of carbazoles based upon the natural product clausine C has been accomplished using two different two-step continuous processes. The resulting carbazoles (9 examples, 33-74 % yield) were prepared via a continuous flow set-up integrating a UV-mediated transformation employing a purple LED reactor (394 nm) as the first step in the multi-step sequence. The second derivatization step involved cross-coupling through Pd-catalyzed Suzuki cross-coupling or Ni-catalyzed metallophotoredox cross-coupling with potassium trifluoroborate salts. The latter represents the first example of using sequential photochemical reactors, at different wavelengths, in a continuous flow process.



## 4.2 Introduction

Continuous flow methods have considerable potential to augment multi-step synthesis.<sup>1</sup> The linking of different reactions processes in sequence can improve safety, decrease reaction times and reduce waste by eliminating intermediate purification steps. However, one of the challenges of planning a continuous multi-step process is to design a sequence that minimizes downstream complications. For example, in a two-step process, a reaction mixture containing stoichiometric reagents or additives can be injected in a reactor A, however upon elution, a new host of reagents or reactants may need to be added before proceeding to reactor B (Figure 4.1). As such, care must be taken to insure that no waste or excess reagent from the first chemical reaction interferes with the subsequent chemical reaction in reactor B. There are several strategies that can reduce the chances for downstream complications arising from excess reagents, such as employing catalysis or exploiting bond-forming transformations that may require only thermal activation. Another option is to exploit packed-bed/heterogeneous catalysis systems. An elegant example was reported by Kobayashi and co-workers, who prepared the anti-inflammatory agents (*R*)- and (*S*)-rolipram employing only supported heterogeneous reagents and catalysts which included a challenging

asymmetric transformation in a four-step sequence.<sup>2</sup> Given the potential of continuous multi-step sequences in the preparation of pharmaceuticals and compounds of interest in material science,<sup>3</sup> it is surprising that photochemical processes have seen limited use. Jamison and co-workers reported the photochemical activation of a Ru-based catalyst that could be subsequently used for an ene-yne coupling.<sup>4</sup> The same group also reported a continuous three-step synthesis of deoxynucleosides in which the second step involved a photochemical deoxygenation.<sup>5</sup> Oelgemöller and co-workers reported a two-step photodecarboxylation in a meso-scale flow that concluded with a thermal dehydration/deprotection process.<sup>6</sup> Seeberger and co-workers have utilized photochemical processes in the production of artemisinin APIs.<sup>7</sup> Consequently, it was decided to further explore integrating UV-mediated processes in multi-step sequences. Herein, a two-step synthesis comprising UV-mediated decomposition of azides and subsequent cross coupling strategies to prepare and derivatize biological active alkaloids is described.

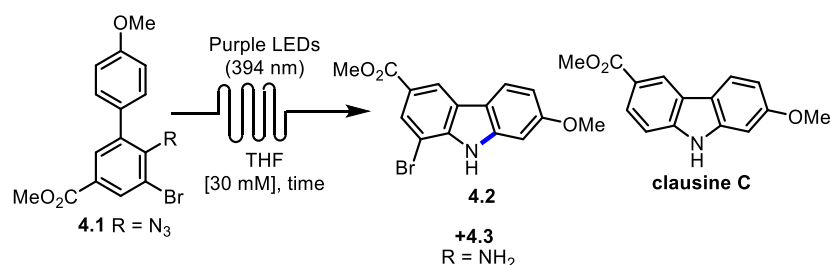


**Figure 4.1** Incorporating photochemical reactors in continuous multi-step sequences.

### 4.3 Results and Discussion

Our group has previously reported the synthesis of complex polycyclic carbazoles via photochemical decomposition of azides.<sup>8</sup> Given the importance of carbazoles as a heterocyclic framework in medicinal chemistry, we recognized that the UV-mediated process, which does not require any additional catalysts, reagents or additives, would be ideally suited in a multi-step synthetic sequence. In addition, the photochemical process involved irradiation at 394 nm which was tolerant of halogen substitution that could be exploited downstream to derivatize natural product scaffolds. To demonstrate the potential of such a synthetic strategy, the alkaloid clausine C (Table 1)<sup>9,10</sup> was targeted as it is a member of a family of carbazoles displaying a variety of biological activities including kinesin spindle protein (KSP) inhibition,<sup>11</sup> and as agonists of the cannabinoid receptor 2 (CB2).<sup>12</sup>

**Table 4.1** Optimization of the first step in continuous flow: photochemical decomposition of the azide.



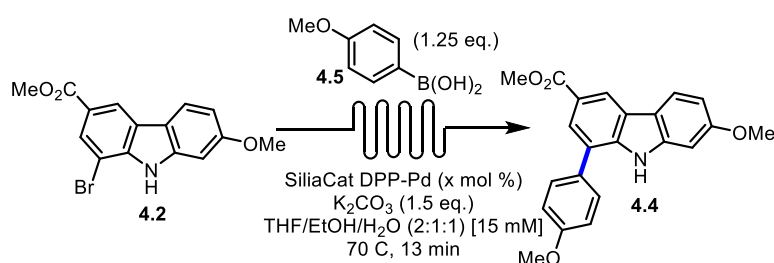
Entry	Time (h)	Yield 2 (%) <sup>a</sup>	Yield 1 (%)	Yield 3 (%)
1	2	79	11	9
2	2.5	81	8	10
3	3	82	7	10

<sup>a</sup> Yields following flash chromatography.

Preliminary investigation of a two-step process involved optimization of each individual reaction (Tables 4.1 and 4.2). First, the bromide-substituted azide **4.1** was decomposed with a continuous flow reactor employing purple LEDs with various residence times to maximize conversion (Table 4.1). When **4.1** was irradiated for 2, 2.5 and 3 h, similar isolated yields were observed (79-82 % of carbazole **4.2**). For the second derivatization process, a Suzuki cross-coupling employing the heterogeneous palladium-based SiliaCat<sup>®</sup> catalyst was selected (Figure

2).<sup>13</sup> However, the reaction conditions chosen were influenced by the solvent and concentration from the preceding photochemical process (Table 4.2). For example, the UV-mediated process employed THF as solvent, so the biphasic solvent mixture for the Suzuki cross-coupling included THF (THF/EtOH/H<sub>2</sub>O). In addition, preliminary testing was performed at 15 mM, which estimated the dilution which would occur upon injection of reagents for the Suzuki cross-coupling into the stream from the photochemical process.

**Table 4.2** Optimization of the second step in continuous flow: Suzuki cross-coupling.

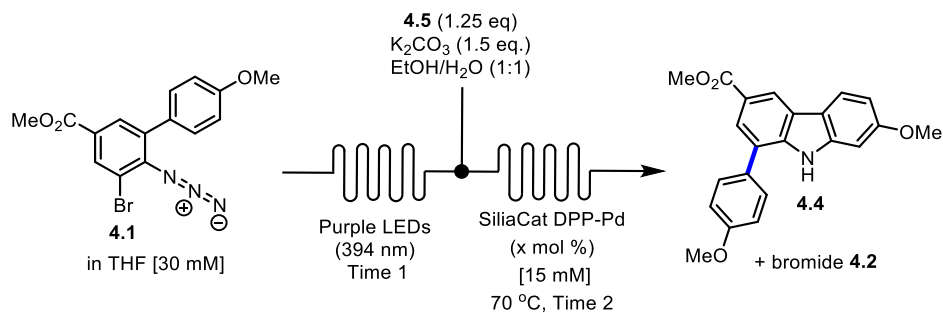


Entry	Catalyst loading (mol %)	Yield 4 (%) <sup>a</sup>
1	5	74
2	10	76 <sup>b</sup>
3	20	78

<sup>a</sup>Yields following flash chromatography. <sup>b</sup>When reaction was doped with 20% of **4.1**, the yield of coupling product **4.4** decreased to 63 %.<sup>14</sup>

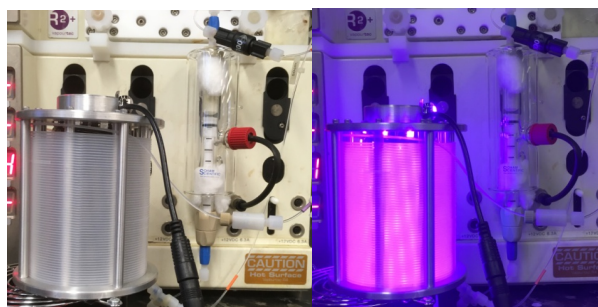
Following preliminary testing of the conversion of bromide **2** to aryl-substituted **4.**, it was found that catalyst loadings of either 5, 10 or 20 mol % all afforded good yields (74-78 %). Again, the Suzuki cross-coupling (**4.2**→**4.4**) could be done in batch with a similar yield (73 %), but required 14 h. When the two-step process starting from azide **4.1** to the derivatized clausine C **4.4** was investigated (Table 4.3), good yield of the desired product (60 %) could be obtained when the residence time in the Suzuki cross-coupling step was extended (13→21 min). It should be noted that the two-step flow process represents a significant improvement over the batch processes affording a similar overall yield while reducing reaction time (17 h vs. ~3.3 h residence time) and eliminating a purification step.

**Table 4.3** Optimization of the two-step continuous process in continuous flow.



Entry	Time 1 (h)	Time 2 (min)	Catalyst loading (mol %)	yield 4.1 (%) <sup>a</sup>	Yield 4.2 (%) <sup>a</sup>	yield 4.4 (%) <sup>a</sup>
1	2	13	10	10	41	35
2	2.5	17	20	-	-	52
3	3	21	20	-	-	60

<sup>a</sup>Yields following flash chromatography.

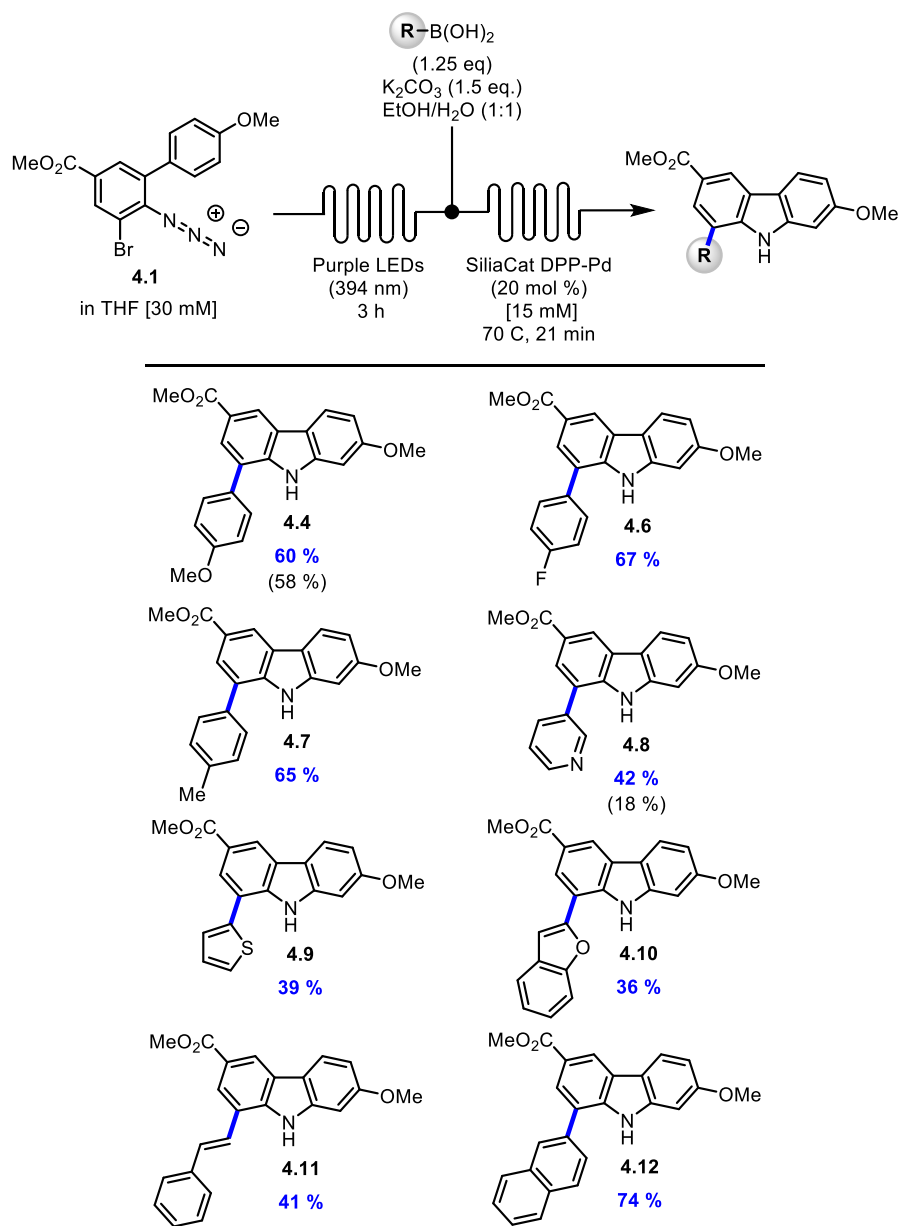


**Figure 4.2** Experimental set-up for continuous two-step synthesis employing a photochemical reactor for irradiation at 394 nm (purple LEDs), followed by Suzuki-coupling using a supported Pd-based catalyst, SiliaCat.

With optimized conditions in hand, it was decided to demonstrate the applicability of the two-step flow process method with the cross-coupling of other boronic acids (Table 4.4). As mentioned previously, the anisyl-substituted carbazole **4.4** was obtained in 60 % isolated yield. Carbazoles having a *p*-F aryl or *p*-Me aryl motif also underwent coupling productively (**4.6**, 67 % or **7**, 65 %). Heteroaromatic boronic acids were also viable coupling partners in the two-step process, and carbazoles adorned with pyridyl (**4.8**, 42 %), thiophene (**4.9**, 39 %) and benzofuran (**4.10**, 36 %) motifs were isolatable. Other boronic acids based upon styrenyl- and naphthyl-motifs also underwent coupling in good yields (41 % and 74 % for **4.11** and **4.12** respectively). Furthermore, the two-step flow process allowed for better yields than what would have been obtained through two sequential reactions involving a cross-coupling in batch. For example, the

cross-coupling of carbazole bromide **4.2** in batch with 3-pyridyl boronic acid afforded the pyridine-carbazole derivative in only 23 %, which amounts to an 18 % cumulative yield over two steps (see yield in parentheses in Table 4.4). In contrast the two-step flow process afforded **4.8** in 42 % (greater than two-fold increase in yield).

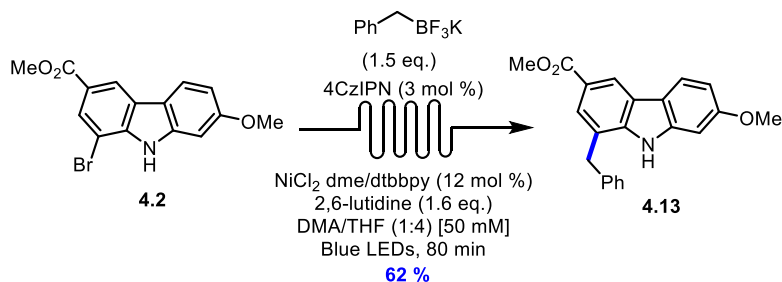
**Table 4.4** Scope of a two-step process in continuous flow.<sup>a</sup>



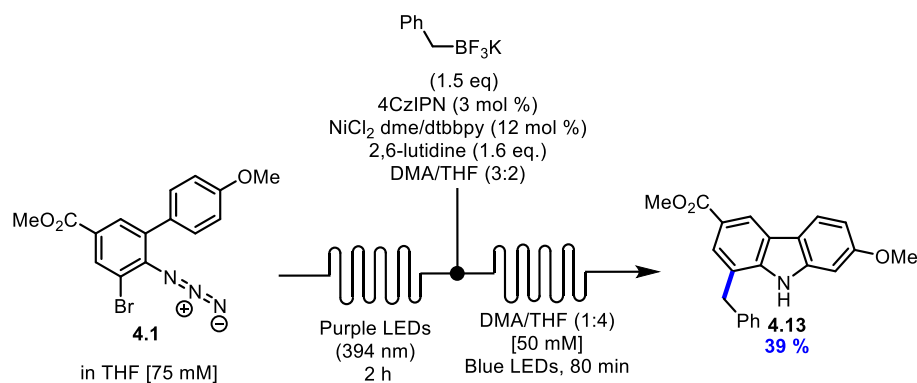
<sup>a</sup>Yields following flash chromatography. Yield in parentheses represent yields for the two-step process when the Suzuki cross-coupling step is performed in batch



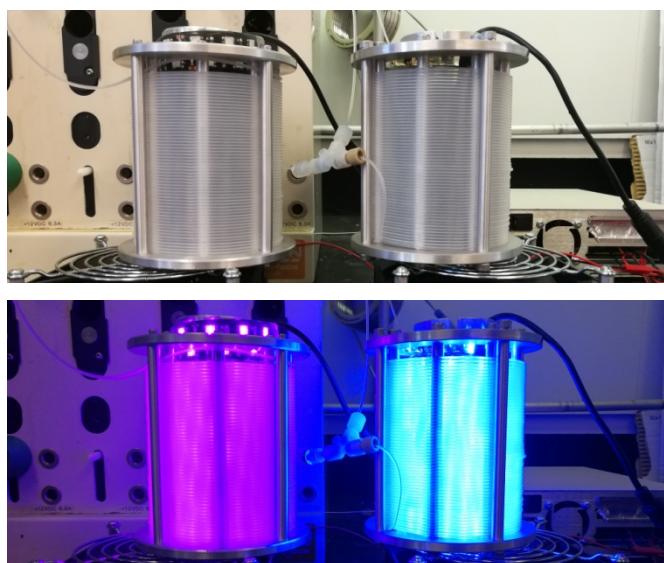
Lastly, it was envisioned that other cross-coupling processes could be incorporated with the two-step process that function via other modes of activation. One such process would involve metallophotoredox chemistry<sup>15</sup> once again exploiting the halogen functionality of clausine derivative **2**. Boyd and co-workers<sup>16</sup> had already demonstrated the feasibility of cross-coupling aryl bromides with potassium alkyl trifluoroborates using a Ni-based catalyst system ( $\text{NiCl}_2 \cdot \text{dme}/\text{dtbbpy}$ , 2,6-lutidine) and an Ir-based photocatalyst, in an operationally simplified flow process. As such, the coupling of the bromide **4.2** and benzyl trifluoroborate was performed under analogous reaction conditions, with the exception of replacing the Ir-based catalyst with the organic dye 4CzIPN (1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; Scheme 4.1).<sup>17</sup> When the metallophotoredox coupling was performed in flow, the desired coupling product **4.13** was obtained in 62 % yield. Due to the importance of the concentration for the nickel/photoredox dual catalysis protocol, some modifications were necessary before incorporation in the two-step flow process. To achieve optimal concentration required for the second step, the concentration of the initial photochemical decomposition of azides had to be doubled. Although the increase of concentration produced a slight drop in yield (**4.1**→**4.2**, 70 %, 2 h), when combined with the nickel/photoredox coupling, the desired product could still be obtained in synthetically useful yields (**4.13**, 39 %, 43 % theoretical yield for two steps). Interestingly, to the best of our knowledge, the two-step protocol represents the first multi-step flow sequence employing different wavelengths for each process (Scheme 4.2, Figure 4.3).



**Scheme 4.1** Nickel/photoredox cross-coupling with bromo-carbazole **2**.



**Scheme 4.2** Nickel/photoredox cross-coupling in continuous flow utilizing two different photochemical reactors.



**Figure 4.3** Experimental set-up for continuous two-step synthesis employing two photochemical reactors: 394 nm (purple LEDs) and 450 nm (blue LEDs).

During the flow procedure, deposits of a white precipitate could be observed in the tubing. Isolation revealed the solid to be the benzyl BF<sub>3</sub>K salt. To improve solubility, the THF in the two step process could be exchanged for dioxane, with minimal changes in the first photochemical decomposition of the azide **4.1**. Although the reaction mixture remained homogeneous throughout the flow process, no change in the global yield was observed. In addition, other iridium-based catalysts could be used as photocatalyst, but also did not improve the yield of **4.13**.<sup>18</sup>

## 4.4 Conclusions

In summary, the preparation and derivatization of biologically active carbazoles clausine C has been accomplished using two different two-step continuous processes. The resulting carbazoles (9 examples, 33-74 % yield) were isolated in yields that were typically equal or greater than what would have been obtained in two separate batch reactions requiring an intermediate purification by chromatography. Importantly, the flow set-up integrates a UV-mediated transformation, a decomposition of an aryl azide, as the first step in the multi-step sequence. Of note is that the first photochemical transformation requires no additional reagents, catalysts or additives, which highlights how UV-processes can be ideal for minimizing downstream complications in the following steps. The use of a purple LED reactor (394 nm) was selected as it was found to be tolerant of functionality (halides) needed for subsequent derivatization. Two cross-coupling processes were then integrated: a Pd-catalyzed Suzuki cross coupling employing a silica-supported catalyst and a Ni-catalyzed metallophotoredox cross coupling with potassium trifluoroborate salts. The latter is noteworthy, as it represents to the best of our knowledge, the first example of using sequential photochemical reactors, at different wavelengths, in a continuous flow process. Given their tunability, chemoselectivity and functional group tolerance, as well as their enhanced rates and yields in flow, it is likely that there will be increase in the use of photochemical processes in multi-step continuous processes.

### Supporting Information

Experimental procedures and characterization data for all new compounds. The Supporting Information is available free of charge on the RCS Publications website.

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18. See the Supporting Information.

## 5. Conclusions et perspectives

### 5.1 Conclusions

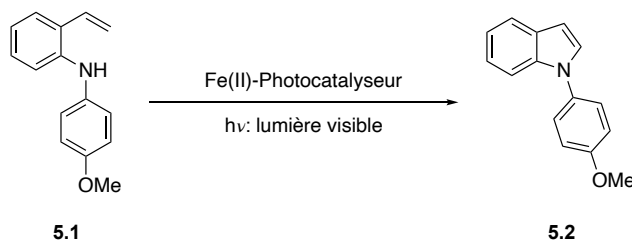
Pour le premier projet de cette thèse (chapitre 2), les objectifs établis précédemment ont été atteints. Une série de cinq photocatalyseurs à base de fer(II) a été développée suivant les travaux antérieurs du professeur McCusker.<sup>1</sup> Ces complexes utilisent comme ligands des dérivés de pyridyle (bpy, dmbpy, dtbbpy, terpy et phen). Le  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2$  a été identifié comme le plus efficace pour la photocyclisation de diaryles et triarylamines. Treize exemples ont été cyclisés avec des rendements entre 63 et 91 %. L'iode a été remplacé avec succès par de l'oxygène moléculaire pour servir d'oxydant. Pour utiliser de façon efficace l'oxygène gazeux en flux continu, un réacteur de type « tube-in-tube » a été utilisé. Celui-ci permet d'introduire le gaz de façon homogène dans le mélange réactionnel et d'assurer la reproductibilité du processus. Puis, la stratégie de « numbering-up » a été employée pour effectuer l'agrandissement d'échelle du processus en flux continu. Celle-ci a permis d'effectuer la synthèse du 9-phénylcarbazole (**2.2**) avec un rendement de 90 % sur une échelle de 1 g (4,11 mmol) en diminuant de 50 % le temps du procédé de la transformation.

Le deuxième projet de cette thèse (chapitres 3 et 4) a été étudié en atteignant les objectifs précédemment mentionnés. Le développement d'une décomposition photochimique d'azotures a été effectué en utilisant la lumière ultraviolette comme source d'énergie. Le photoréacteur UV précédemment développé<sup>2</sup> a été utilisé en comparaison avec un nouveau photoréacteur formé de DELs mauves (394 nm). Ce processus permet d'effectuer la synthèse de carbazoles (21 exemples) avec des rendements entre 33 à 95 %. De plus, d'autres hétérocycles tels que des indoles et des pyrroles peuvent être synthétisés avec cette méthodologie. L'étendue de cette transformation a été évaluée avec les deux photoréacteurs pour obtenir une compréhension de la réactivité des composés comportant un lien carbone-halogène. L'utilisation du photoréacteur de DELs mauves permet d'obtenir 80 % de rendement du 2-bromocabazole **3.6** sans bris du lien C-Br. Ceci permet l'utilisation potentielle de ce lien dans une seconde transformation (post-fonctionnalisation). L'utilisation du processus de photodécomposition d'azotures a été démontrée dans une séquence multi-étapes (chapitre 4). La synthèse comportant deux étapes permet dans un premier temps de

former l'hétérocycle carbazole comportant un lien C-Br. Ce lien est par la suite modifié par un couplage croisé de type Suzuki catalysé par un complexe de palladium supporté sur silice (SiliaCat DPP-Pd) pour fournir des dérivés du produit naturel Clausine C. Huit exemples ont été synthétisés au total, avec des rendements variants entre 36 et 74 %. Le développement d'une synthèse multi-étapes utilisant deux processus photochimiques séquentiels a été effectué. La première étape est la photodécomposition d'azoture fournissant le carbazole **4.2**. Subséquemment, ce carbazole est transformé en dérivé benzylique de la Clausine C avec un rendement total de 39 % sur deux étapes. Ce processus multi-étapes est l'un des premiers utilisant deux réactions photochimiques.

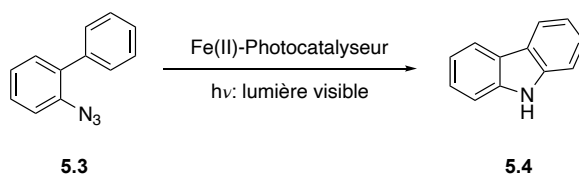
## 5.2 Perspectives et travaux futurs

Pour étudier davantage la réactivité des photocatalyseurs à base de fer(II), d'autres réactions ont été investiguées. Dans un premier temps, la synthèse d'indole par la formation d'un lien C-N a été imaginée (Schéma 5.1). Après avoir essayé des conditions réactionnelles variées (photocatalyseur et oxydant), il s'est avéré que le photocatalyseur de fer(II) ne catalysait pas la réaction, mais plutôt que seul l'iode moléculaire était nécessaire pour effectuer cette transformation.



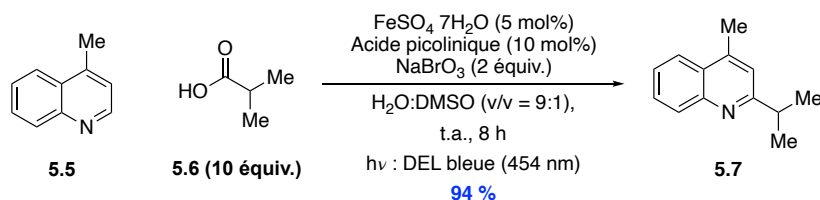
**Schéma 5.1** Synthèse de l'indole **5.2** par la formation du lien C-N.

Dans un deuxième temps, la synthèse de carbazoles par la décomposition d'azoture pour la formation du lien C-N a été étudiée (Schéma 5.2). Ce type de transformation pourrait permettre l'obtention de carbazoles avec une amine libre (N-H). Cette étude nous a fourni de bons résultats, cependant, en effectuant les contrôles réactionnels, il s'est avéré que seul la source d'énergie lumineuse est nécessaire pour effectuer la transformation. C'est dans cette optique que ce projet a été approfondi dans le chapitre **3** de cette thèse.



**Schéma 5.2** Synthèse du carbazole **5.4** par la formation du lien C-N.

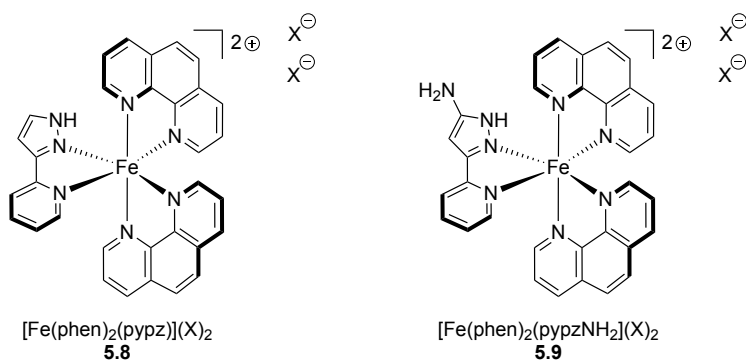
Depuis le commencement de l'investigation de la réactivité des photocatalyseurs de fer(II), d'autres groupes de recherche se sont penchés sur le sujet. En 2019, le groupe du professeur Jin a utilisé un photocatalyseur de fer(II) formé *in situ* en mélangeant du sulfate de fer(II) et de l'acide picolinique (Schéma 5.3).<sup>3</sup> Les chercheurs ont démontré le potentiel décarboxylateur de ce complexe pour effectuer l'alkylation d'hétérocycles.



**Schéma 5.3** Réaction d'alkylation d'hétérocycles photocatalytique développée par Jin.

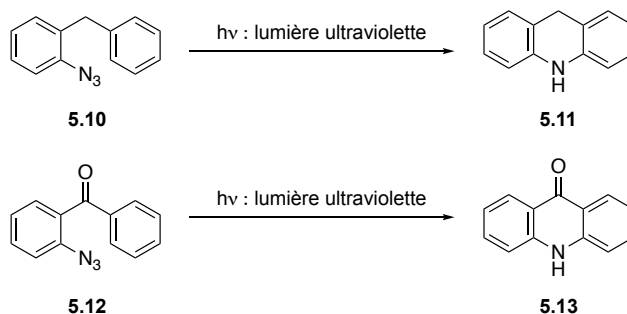
Chacun des projets abordés dans la thèse représente de nouvelles directions pour la synthèse photochimique, que ce soit en utilisant des complexes à base de métaux pour la photocatalyse ou en exploitant la chimie en flux continu pour rendre les processus photochimiques plus efficaces. Par conséquent, il existe plusieurs directions pour le futur de chaque projet. Dans le cas des photocatalyseurs à base de fer, l'activité pourrait être augmentée en améliorant la capacité de transfert de charge d'un catalyseur par l'assistance d'un pont hydrogène.<sup>4</sup> On peut envisager une pré-organisation d'une molécule de réactif et d'un catalyseur par le biais d'un pont hydrogène, ce qui vient contrebalancer les facteurs de temps de demi-vie et de diffusion. Ceci peut se faire en synthétisant une nouvelle série de catalyseurs hétéroleptiques (Figure 5.1) utilisant des ligands de type 2-pyridylpyrazole (pypz) ou 5-amino-2-pyridylpyrazole (pypzNH<sub>2</sub>).





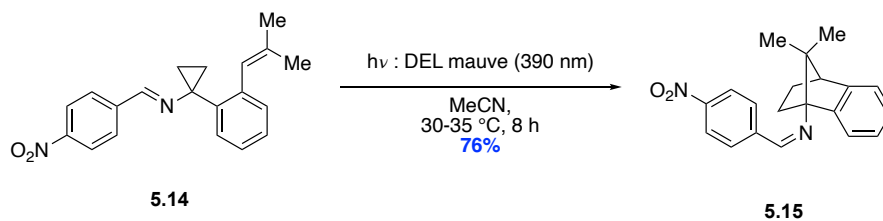
**Figure 5.1** Photocatalyseurs hétéroleptiques de fer(II) incorporant des ligand formant des ponts hydrogène.

Pour approfondir la réactivité des azotures aromatiques en condition photochimique (DELS mauve), l'étude de formation d'hétérocycles azotés à six chaînons a été effectuée (Schéma 5.4). L'azoture **5.10** a été utilisé pour la photodécomposition, mais aucune réactivité n'a été observée. Ceci pourrait être due au manque de conjugaison du système  $\pi$ , ce qui diminue la longueur d'onde pouvant être absorbée. Pour augmenter la conjugaison du système  $\pi$ , un motif cétone a été ajouté entre les deux cycles aromatiques (azoture **5.12**) dans l'espoir de former le composé **5.13**, sans succès.



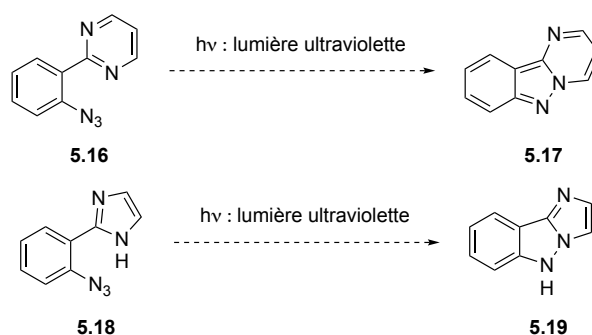
**Schéma 5.4** Formation de cycles à six chaînons par photodécomposition d'azoture.

Cette source d'énergie lumineuse (DEL mauve) en équilibre entre la lumière ultraviolette et la lumière visible a connu un intérêt accru depuis le début de cette étude. Tout récemment, le professeur Stephenson a étudié la réactivité des imines face à la photochimie utilisant des DELs mauves.<sup>5</sup> Ce type de transformations permet une cyclisation intramoléculaire formant un bicycle via la réactivité radicalaire de l'imine.



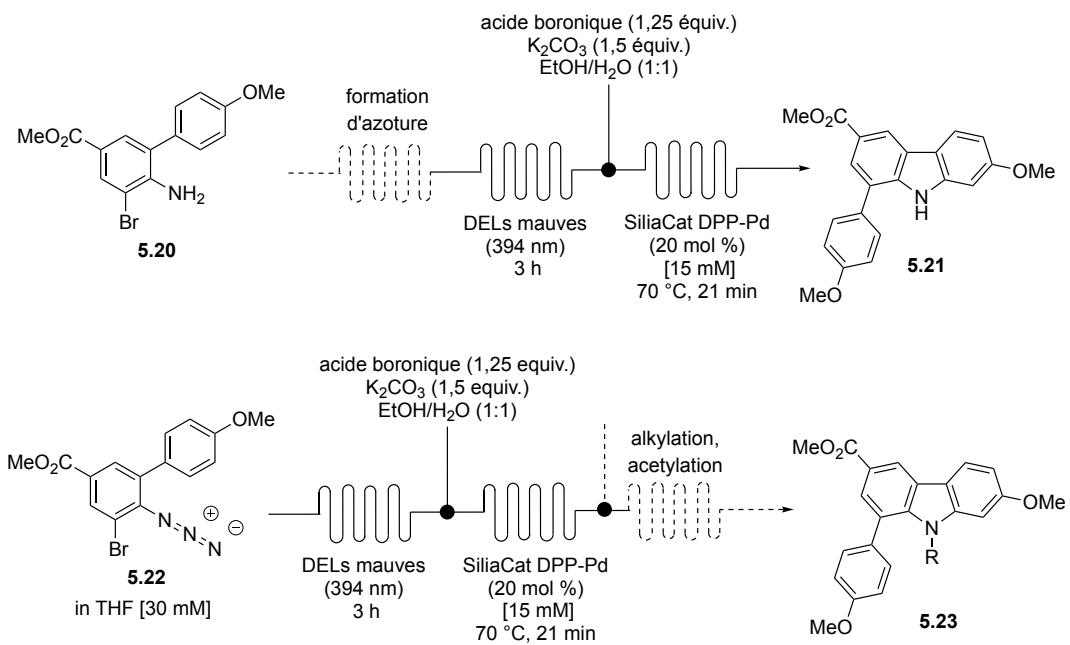
**Schéma 5.5** Réaction de cyclisation intramoléculaire photochimique développée par Stephenson.

La photodécomposition UV des azotures pourrait trouver une nouvelle application dans la synthèse d'hétérocycles possédant une liaison N-N. Ce type de lien a été récemment étudié pour la formation du pyrimido[1,2-*b*]indazole **5.17**.<sup>6</sup> Pour effectuer la synthèse de ce produit, une décomposition photochimique de l'azoture peut être envisagée. De plus, l'utilisation de l'azoture **5.18** permettrait la formation de l'imidazo[1,2-*b*]indazole **5.19** peu synthétisé auparavant (Schéma 5.6).



**Schéma 5.6** Formation de liens N-N par photodécomposition d'azotures.

Étant donné que le développement de séquences multi-étapes incorporant des processus photochimiques en est encore à ses balbutiements, il existe plusieurs façons d'ajouter des étapes à une séquence multi-étapes. Compte tenu de l'importance de la création de bibliothèques de molécules pour leur évaluation biologique, une famille de dérivés de carbazoles pourrait être préparée en impliquant d'autres événements de formation de liaison. Il serait possible d'ajouter une réaction de formation d'un azoture<sup>7</sup> au début du processus, permettant de débiter la synthèse avec l'amine **5.20** correspondante. Il serait aussi envisageable d'effectuer cette troisième réaction à la suite d'un couplage croisé de type Suzuki catalysé par un complexe de palladium. Une alkylation ou une acétylation de l'amine pourrait être effectuée pour augmenter le niveau de complexité du produit final (Schéma 5.7).



**Schéma 5.7** Extension de la séquence multi-étapes en flux continu.

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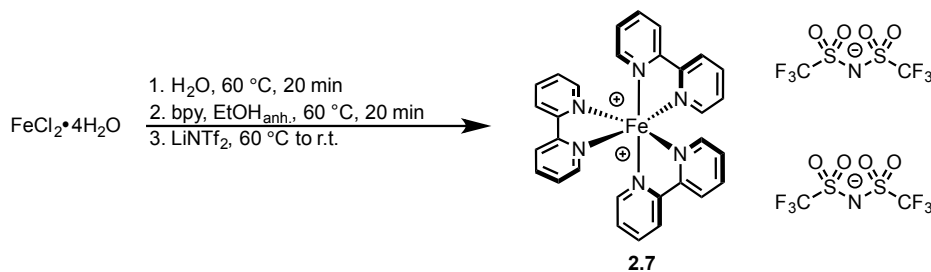
## 6. Supporting Information of Chapter 2

### 6.1 General

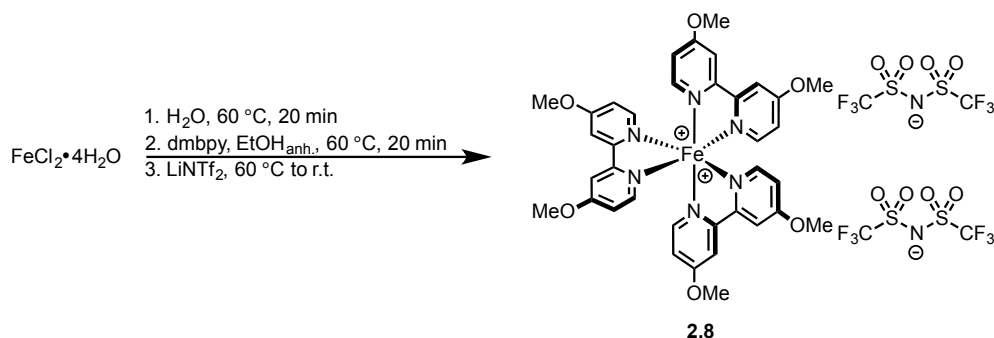
All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.<sup>1</sup> All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. The following products were prepared according to their respective literature procedures: 4-methoxy-*N,N*-diphenylaniline,<sup>2</sup> 4-methyl-*N,N*-diphenylaniline,<sup>2</sup> 4-methoxy-*N*-(4-methoxyphenyl)-*N*-phenylaniline,<sup>3</sup> 3,5-dimethoxy-*N,N*-diphenylaniline,<sup>3</sup> Tris-(4-methoxyphenyl)amine,<sup>2</sup> *N,N*-diphenylpyrimidin-5-amine,<sup>2</sup> 4-fluoro-*N,N*-diphenylaniline,<sup>3</sup> 4-chloro-*N,N*-diphenylaniline,<sup>3</sup> 2,4,6-Trimethyl-*N,N*-diphenylaniline,<sup>2</sup> *N*-(4-methylphenyl)-*N*-methylaniline,<sup>2</sup> *N*-ethyl-*N*-phenylaniline,<sup>2</sup> 1-phenyl-1,2,3,4-tetrahydroquinoline,<sup>2</sup> *N*-(2,5-Xylyl)-*p*-anisidine.<sup>4</sup> Technical solvents were obtained from VWR International Co. Anhydrous solvents (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, THF, DMF, Toluene, and n-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still<sup>5</sup> and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F<sub>254</sub>). Visualization of TLC plate was performed by UV (254 nm), KMnO<sub>4</sub> or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by <sup>1</sup>H NMR. NMR spectra were taken in deuterated CDCl<sub>3</sub> using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard (CHCl<sub>3</sub>: δ 7.27 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. The <sup>1</sup>H NMR assignments were made based on chemical shift and multiplicity. The <sup>13</sup>C NMR assignments were

made on the basis of chemical shift and multiplicity. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted. All photochemical experiments using visible light were carried out using common household energy saving lightbulbs. Typically, the experiments conducted utilized "Blue Planet Energy Saving Lightbulbs" (23W, Model number: 052-5510-2, Bulb type: Bare Spiral, Base Type: E26/24 (Medium), Technology: CFL, Light Output: 1600 Lumens).

## 6.2 Synthesis of Photosensitizers

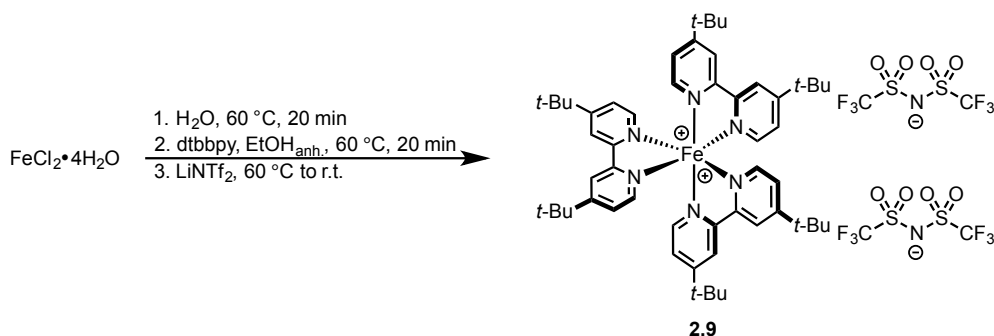


**Tris(2,2'-bipyridyl)iron(II)bis(bis(trifluoromethane)sulfonimide) (2.7):** In a round bottom flask equipped with a stir bar was charged with iron(II) chloride tetrahydrate (298 mg, 1.50 mmol, 1.0 equiv.) and distilled water (30.0 mL, 0.05 M). The reaction mixture was placed in a pre-heated oil bath at 60°C during 20 minutes. Then, to the reaction mixture was added a solution of 2,2'-bipyridyl (714 mg, 4.57 mmol, 3.05 equiv) in anhydrous EtOH (45.7 mL, 0.10 M). The reaction mixture temperature was maintained at 60°C during another 20 minutes. LiNTf<sub>2</sub> (1289 mg, 4.49 mmol, 3.0 equiv) was added in one portion and the heating was stopped. The reaction mixture was left to cool at room temperature (without removing the oil bath). The reaction mixture was filtered with a Buchner funnel with a fritted disk and the precipitate was washed with Et<sub>2</sub>O. The red precipitate was dried under vacuum overnight to afford the desired product as a red powder (1.14 g, 70 %). <sup>1</sup>H NMR (300 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ ppm 8.85 (d, *J* = 7.7 Hz, 6H), 8.28 (t, *J* = 7.2 Hz, 6H), 7.74 (d, *J* = 4.6 Hz, 6H), 7.59 (d, *J* = 5.9 Hz, 6H); <sup>13</sup>C NMR (75 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ ppm 161.30, 156.18, 140.79, 129.58, 125.98; <sup>19</sup>F NMR (282 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ ppm -81.27 (s, 3F); HRMS (ESI) *m/z* calculated for C<sub>30</sub>H<sub>24</sub>[<sup>56</sup>Fe]N<sub>6</sub> [M]<sup>2+</sup>, 262.0700; found: 262.0697. ; HRMS (ESI) *m/z* calculated for C<sub>2</sub>F<sub>6</sub>N<sub>1</sub>O<sub>4</sub>S<sub>2</sub> [M]<sup>-</sup>, 279.9178; found: 279.9177.

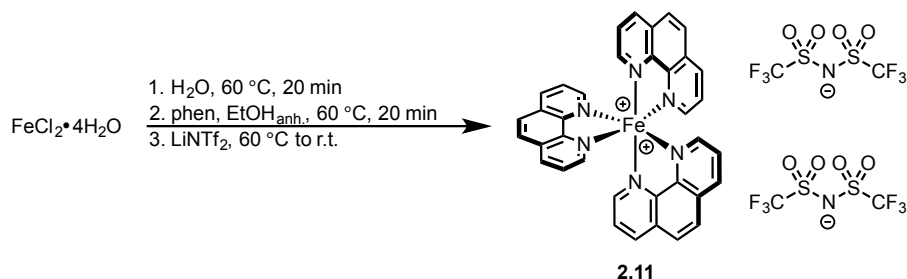


**Tris(4,4'-dimethoxy-2,2'-bipyridyl)iron(II)bis(bis(trifluoromethane)sulfonimide) (2.8):** In a round bottom flask equipped with a stir bar was charged with iron(II) chloride tetrahydrate (302 mg, 1.52 mmol, 1.0 equiv.) and distilled water (30.4 mL, 0.05 M). The reaction mixture was placed in a pre-heated oil bath at 60°C during 20 minutes. Then, to the reaction mixture was added a solution of 4,4'-dimethoxy-2,2'-bipyridyl (1002 mg, 4.64 mmol, 3.05 equiv) in anhydrous EtOH (46.4 mL, 0.10 M). The reaction mixture temperature was maintained at 60°C during another 20 minutes.  $\text{LiNTf}_2$  (1309 mg, 4.56 mmol, 3.0 equiv) was added in one portion and the heating was stopped. The reaction mixture was left to cool at room temperature (without removing the oil bath). The reaction mixture was filtered with a Buchner funnel with a fritted disk and the precipitate was washed with  $\text{Et}_2\text{O}$ . The red precipitate was dried under vacuum overnight to afford the desired product as a dark purple powder (1.55 g, 81 %).  $^1\text{H}$  NMR (300 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm 8.42 (s, 6H), 7.50 (d,  $J = 6.0$  Hz, 6H), 7.16 (d,  $J = 6.0$  Hz, 6H), 4.06 (s, 18H);  $^{13}\text{C}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm 169.98, 162.40, 156.59, 116.05, 112.88, 58.19;  $^{19}\text{F}$  NMR (282 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm -81.31 (s, 3F); HRMS (ESI)  $m/z$  calculated for  $\text{C}_{36}\text{H}_{36}[^{56}\text{Fe}]\text{N}_6\text{O}_6$   $[\text{M}]^{+2}$ , 352.1017; found: 352.1022. ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_2\text{F}_6\text{N}_1\text{O}_4\text{S}_2$   $[\text{M}]^-$ , 279.9178; found: 279.9184.

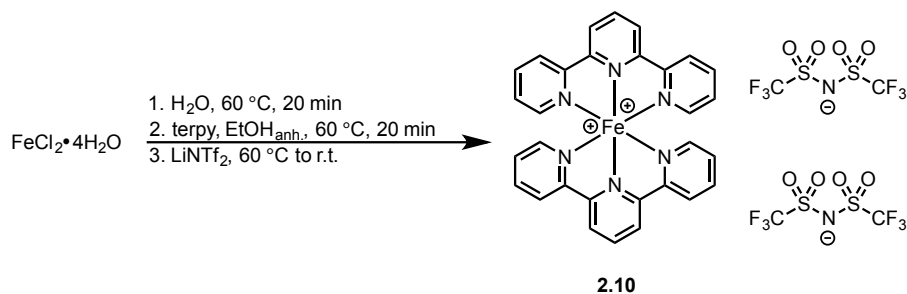




**Tris(4,4'-di-*tert*-butyl-2,2'-bipyridyl)iron(II)bis(bis(trifluoromethane)sulfonimide) (2.9):** In a round bottom flask equipped with a stir bar was charged with iron(II) chloride tetrahydrate (252 mg, 1.27 mmol, 1.0 equiv.) and distilled water (25.4 mL, 0.05 M). The reaction mixture was placed in a pre-heated oil bath at 60°C during 20 minutes. Then, to the reaction mixture was added a solution of 4,4'-di-*tert*-butyl-2,2'-bipyridyl (1038 mg, 3.87 mmol, 3.05 equiv) in anhydrous EtOH (38.7 mL, 0.10 M). The reaction mixture temperature was maintained at 60°C during another 20 minutes. LiNTf<sub>2</sub> (1094 mg, 3.81 mmol, 3.0 equiv) was added in one portion and the heating was stopped. The reaction mixture was left to cool at room temperature (without removing the oil bath). The reaction mixture was filtered with a Buchner funnel with a fritted disk and the precipitate was washed with Et<sub>2</sub>O. The red precipitate was dried under vacuum overnight to afford the desired product as a red powder (1.34 g, 74 %). <sup>1</sup>H NMR (300 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ ppm 8.91 (s, 6H), 7.53 (d, *J* = 15.0 Hz, 12H), 1.41 (s, 54H); <sup>13</sup>C NMR (75 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ ppm 156.27, 161.21, 155.69, 126.83, 123.37, 37.14, 31.57; <sup>19</sup>F NMR (282 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ ppm -81.21 (s, 3F); HRMS (ESI) *m/z* calculated for C<sub>54</sub>H<sub>72</sub>[<sup>56</sup>Fe]N<sub>6</sub> [M]<sup>+2</sup>, 430.2578; found: 430.2596. ; HRMS (ESI) *m/z* calculated for C<sub>2</sub>F<sub>6</sub>N<sub>1</sub>O<sub>4</sub>S<sub>2</sub> [M]<sup>-</sup>, 279.9178; found: 279.9170.

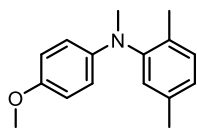


**Tris(1,10-phenanthroline)iron(II) bis(bis(trifluoromethane)sulfonimide) (2.11):** In a round bottom flask equipped with a stir bar was charged iron(II) chloride tetrahydrate (334 mg, 1.68 mmol, 1.0 equiv.) and distilled water (33.6 mL, 0.05 M). The reaction mixture was placed in a pre-heated oil bath at 60°C for 20 minutes. Then, to the reaction mixture was added a solution of 1,10-phenanthroline (924 mg, 5.13 mmol, 3.05 equiv) in anhydrous EtOH (51.3 mL, 0.10 M). The reaction mixture temperature was maintained at 60°C for another 20 minutes.  $\text{LiNTf}_2$  (1447 mg, 5.04 mmol, 3.0 equiv) was added in one portion and the heating was stopped. The reaction mixture was left to cool at room temperature (without removing the oil bath). The reaction mixture was filtered on a Buchner funnel with a fritted disk and the precipitate was washed with  $\text{Et}_2\text{O}$ . The red precipitate was dried under vacuum overnight to afford the desired product **3** as a red powder (1.34 g, 69%).  $^1\text{H}$  NMR (300 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm 8.84-8.82 (d,  $J = 7.8$  Hz, 6H), 8.43 (s, 6H), 8.05 (d,  $J = 4.2$  Hz, 6H), 7.80 (t,  $J = 5.4$  Hz, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm 158.18, 151.78, 139.41, 132.48, 130.09, 128.07;  $^{19}\text{F}$  NMR (282 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm -81.03 (s, 3F); HRMS (ESI)  $m/z$  calculated for  $\text{C}_{36}\text{H}_{24}\text{FeN}_6$   $[\text{M}]^{+2}$ , 298.0700; found: 298.0697. HRMS (ESI)  $m/z$  calculated for  $\text{C}_2\text{F}_6\text{N}_1\text{O}_4\text{S}_2$   $[\text{M}]^-$ , 279.9178; found: 279.9189.



**Bis(2,2':6',2''-terpyridyl)iron(II)bis(bis(trifluoromethane)sulfonimide) (2.10):** In a round bottom flask equipped with a stir bar was charged with iron(II) chloride tetrahydrate (199 mg, 1.00 mmol, 1.0 equiv.) and distilled water (20.0 mL, 0.05 M). The reaction mixture was placed in a pre-heated oil bath at 60°C during 20 minutes. Then, to the reaction mixture was added a solution of 2,2':6',2''-terpyridyl (707 mg, 3.03 mmol, 3.03 equiv) in anhydrous EtOH (30.3 mL, 0.10 M). The reaction mixture temperature was maintained at 60°C during another 20 minutes.  $\text{LiNTf}_2$  (862 mg, 3.00 mmol, 3.0 equiv) was added in one portion and the heating was stopped. The reaction mixture was left to cool at room temperature (without removing the oil bath). The reaction mixture was filtered with a Buchner funnel with a fritted disk and the precipitate was washed with  $\text{Et}_2\text{O}$ . The purple precipitate was dried under vacuum overnight to afford the desired product as a purple powder (1.14 g, 70 %).  $^1\text{H}$  NMR (300 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm 9.25 (d,  $J = 8.1$  Hz, 4H), 8.87 (t,  $J = 8.1$  Hz, 2H), 8.79 (d,  $J = 7.8$  Hz, 4H), 8.03 (td,  $J = 7.8, 1.2$  Hz, 4H), 7.43 (d,  $J = 5.6$  Hz, 4H), 7.24 (td,  $J = 6.6, 1.2$  Hz, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm 161.47, 159.08, 154.17, 139.93, 139.33, 128.60, 124.88, 124.86;  $^{19}\text{F}$  NMR (282 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  ppm -81.30 (s, 3F); HRMS (ESI)  $m/z$  calculated for  $\text{C}_{30}\text{H}_{22}[\text{Fe}]_6 [\text{M}]^{2+}$ , 261.0631; found: 261.0622. ; HRMS (ESI)  $m/z$  calculated for  $\text{C}_2\text{F}_6\text{N}_1\text{O}_4\text{S}_2 [\text{M}]^-$ , 279.9187; found: 279.9178.

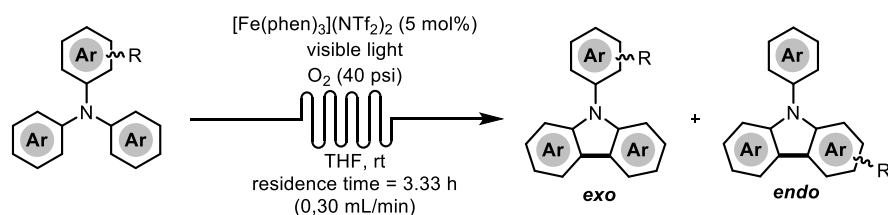
### 6.3 Synthesis of Precursors



2.24

**N-(4-methoxyphenyl)-N,2,5-trimethylaniline (2.24):** A solution of *N*-(2,5-xylyl)-*p*-anisidine (1.00 g, 4.4 mmol, 1 eq.) and NaH (352 mg, 2 eq.) in anhydrous DMF (1 M) was stirred at room temperature for 1 hour. Iodomethane (0.41 mL, 1.5 eq.) was then added to the solution and the mixture was heated at 70 °C of 16 hours. The solution was cooled down to room temperature and was diluted with EtOAc/H<sub>2</sub>O. The organic phase was washed with water (3x). The combined organic phases were washed with brine (1x) and dried with anhydrous sodium sulfate. The resulting suspension was filtered. The filtrate was concentrated under vacuum to provide a crude reaction mixture, which was purified by column chromatography on silica-gel (100 % hexanes to 5 % diethyl ether in hexanes) to afford the desired product as a colorless oil (273 mg, 26 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.14 (d, *J* = 7.6 Hz, 1H), 6.96 (m, 2H), 6.78 (d, *J* = 9.3 Hz, 2H), 6.53 (d, *J* = 9.1 Hz, 2H), 3.76 (s, 3H), 3.18 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm 151.74, 147.54, 144.08, 136.98, 132.99, 131.04, 127.87, 126.46, 114.81 (2C), 114.53 (2C), 55.76, 39.74, 20.88, 17.53; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>19</sub>NO [M+H]<sup>+</sup>, 242.1547; found: 242.1539.

## 6.4 Synthesis of Carbazoles



**General Procedure for Visible Light Mediated Synthesis of carbazole under continuous-flow using  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2$  catalyst procedure (A):** A solution of  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2$  **2.11** (9.3 mg, 0.01 mmol, 5 mol %), triarylamine (0.16 mmol, 1 equiv.) and tetrahydrofuran (32 mL, 5 mM) was prepared and injected via a VapourTec R2+ pumping module. The solution was first pumped through a 15 mL gas-liquid reactor connected to an oxygen supply (40 psi), and then through five PFA coiled reactors (13 mL volume), each having a compact fluorescent lamp (energy saving lightbulb, 23W) located in its center. A 8 bar back pressure regulator was connected at the end of the line. The reaction mixture was pumped at a flow rate of 0.325 mL/min for an “oxygenation” time of 0.77 h and an “irradiation” time of 3.33 h. Following elution through the flow reactor, the crude reaction mixture was quenched by the addition of silica gel. The resulting slurry was concentrated under reduced pressure and purified by column chromatography to afford the desired product.



**Figure 6.1** Continuous-flow reactor set-up used for the visible light mediated synthesis of carbazoles. (left: VapourTec module connected to five PFA coils; right: disposition of CFL inside PFA coils)

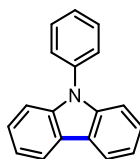


**Figure 6.2** Continuous-flow reactor. (left: Vapourtec PFA coil (10 mL, 1 mm I.D.) ; right: homemade PFA coil (12 mL, 1 mm I.D.)

**General Procedure for Large-Scale Visible Light Mediated Synthesis of carbazole under continuous-flow using  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2$  catalyst procedure (B):** A solution of  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2$  **2.11** (243 mg, 0.21 mmol, 5 mol %), triarylamine (4.1 mmol, 1 equiv.) and tetrahydrofuran (820 mL, 5 mM) was prepared and injected via a VapourTec R2+ pumping module. The solution was first pumped through a 15 mL gas-liquid reactor connected to an oxygen supply (100 psi), then through a T-shaped split in which each reaction mixture stream was pumped through four PFA coiled reactors (13 mL volume), each having a compact fluorescent lamp (energy saving lightbulb, 23W) located in its center. Following elution from the coiled reactors, the streams were recombined via a T-shaped junction equipped with two 8 bar back pressures regulators in series. The reaction mixture was pumped at a flow rate of 0.65 mL/min for an “oxygenation” time of 0.38 h and an “irradiation” time of 2.67 h. Following elution through the flow reactor, the crude reaction mixture was quenched by the addition of silica gel. The resulting slurry was concentrated under reduced pressure and purified by column chromatography to afford the desired product.

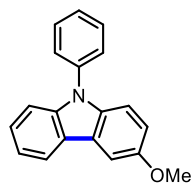


**Figure 6.3** Continuous-flow reactor numbering-up set-up used for the visible light mediated synthesis of carbazoles.



**2.2**

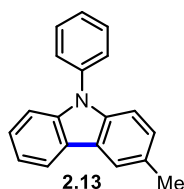
**9-Phenylcarbazole (2.2):** Following the general procedure **A** using continuous-flow with amine **2.1** (39 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes) to afford the desired product **2.2** as a white solid (35.4 mg, 91 %). Following the general procedure **B** using continuous-flow with amine **2.1** (1.006 g, 4.1 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes) to afford the desired product **2.2** as a white solid (897.9 mg, 90 %). The NMR data obtained for carbazole **2.2** were in agreement with that found in the literature.<sup>6</sup>



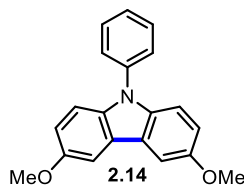
**2.12**

**3-Methoxy-9-phenylcarbazole (2.12):** Following the general procedure **A** using continuous-flow with 4-methoxy-*N,N*-diphenylaniline (51 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes to 5 % diethyl ether/hexanes) to afford the desired carbazole **2.12** as colorless oil (37.2 mg, 85 %) in a 11:89 ratio for the "endo"

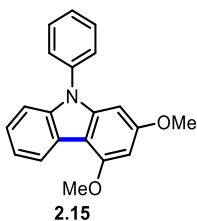
product 3-methoxy-9-phenylcarbazole. The NMR data obtained for carbazole **2.12** were in agreement with that found in the literature.<sup>7</sup>



**3-Methyl-9-phenylcarbazole (2.13):** Following the general procedure **A** using continuous-flow with 4-methyl-*N,N*-diphenylaniline (41.5 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes to 5 % diethyl ether/hexanes) to afford the desired carbazole **2.13** as a colorless oil (33.4 mg, 81 %) in a 33:67 ratio for the "endo" product 3-methyl-9-phenylcarbazole. The NMR data obtained for carbazole **2.13** were in agreement with that found in the literature.<sup>8</sup>



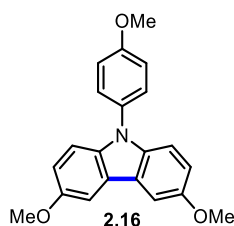
**3,6-Dimethoxy-9-phenylcarbazole (2.14):** Following the general procedure **A** using continuous-flow with 4-methoxy-*N*-(4-methoxyphenyl)-*N*-phenylaniline (48.9 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (5 % ethyl acetate/hexanes) to afford the desired carbazole **2.14** as a yellow oil (24.3 mg, 50 %) in a 50:50 ratio. The NMR data obtained for carbazole **2.14** were in agreement with that found in the literature.<sup>9</sup>



**2,4-Dimethoxy-9-phenylcarbazole (2.15):** Following the general procedure **A** using continuous-flow with 3,5-dimethoxy-*N,N*-diphenylaniline (48.9 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (5 % to 15 % diethyl ether/hexanes) to afford the desired carbazole **2.15** as a colorless oil (26.7 mg, 55 %) in a 33:67 ratio for the "endo"



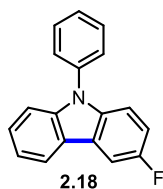
product 2,4-dimethoxy-9-phenylcarbazole. The NMR data obtained for carbazole **2.15** were in agreement with that found in the literature.<sup>6</sup>



**3,6-Dimethoxy-9-(4-methoxyphenyl)carbazole (2.16):** Following the general procedure **A** using continuous-flow with tris-(4-methoxyphenyl)amine (53.7 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (5 % to 20 % diethyl ether/hexanes) to afford the desired carbazole **2.16** as pale yellow oil (33.6 mg, 63 %). The NMR data obtained for carbazole **2.16** were in agreement with that found in the literature.<sup>10</sup>

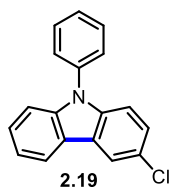


**5-Phenylpyrimido[5,4-b]indole (2.17):** Following the representative procedure **A** using continuous-flow with *N,N*-diphenylpyrimidin-5-amine (40 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (30 % ethyl acetate/hexanes to 100 % ethyl acetate) to afford the desired carbazole **2.17** as an off-white solid (36.0 mg, 91 %). The NMR data obtained for carbazole **2.17** were in agreement with that found in the literature.<sup>2</sup>

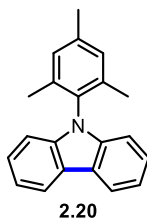


**3-fluoro-9-phenylcarbazole (2.18):** Following the general procedure **A** using continuous-flow with 4-fluoro-*N,N*-diphenylaniline (42.1 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes) to afford the desired carbazole **2.18** as a colorless oil (31.8 mg, 76 %) in a 7:93 ratio for the "endo" product 3-fluoro-9-

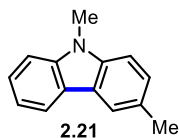
phenylcarbazole. The NMR data obtained for carbazole **2.18** were in agreement with that found in the literature.<sup>3</sup>



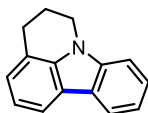
**3-chloro-9-phenylcarbazole (2.19):** Following the representative procedure **A** using continuous-flow with 4-chloro-*N,N*-diphenylaniline (44.8 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes) to afford the desired carbazole **2.19** as a colorless oil (38.7 mg, 87 %) in a 5:95 ratio for the "endo" product 3-chloro-9-phenylcarbazole. The NMR data obtained for carbazole **2.19** were in agreement with that found in the literature.<sup>3</sup>



**9-Mesitylcarbazole (2.20):** Following the representative procedure **A** using continuous-flow with 2,4,6-Trimethyl-*N,N*-diphenylaniline (46.0 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes to 5 % diethyl ether/hexanes) to afford the desired carbazole **2.20** as an off-white solid (35.2 mg, 77 %). The NMR data obtained for carbazole **2.20** were in agreement with that found in the literature.<sup>2</sup>

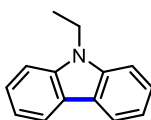


**3,9-Dimethylcarbazole (2.21):** Following the general procedure **A** using continuous-flow with *N*-(4-methylphenyl)-*N*-methylaniline (31.6 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes to 5 % diethyl ether/hexanes) to afford the desired alkyl carbazole **2.21** as a white solid (25.0 mg, 80 %). The NMR data obtained for carbazole **2.21** were in agreement with that found in the literature.<sup>11</sup>



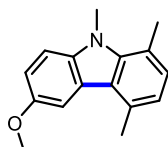
2.22

**5,6-Dihydro-4H-pyrido[3,2,1-jk]carbazole (2.22):** Following the general procedure **A** using continuous-flow with 1-phenyl-1,2,3,4-tetrahydroquinoline (33.6 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes to 5 % diethyl ether/hexanes) to afford the desired carbazole **2.22** as an off-white solid (22.2 mg, 67%). The NMR data obtained for carbazole **2.22** were in agreement with that found in the literature.<sup>12</sup>



2.23

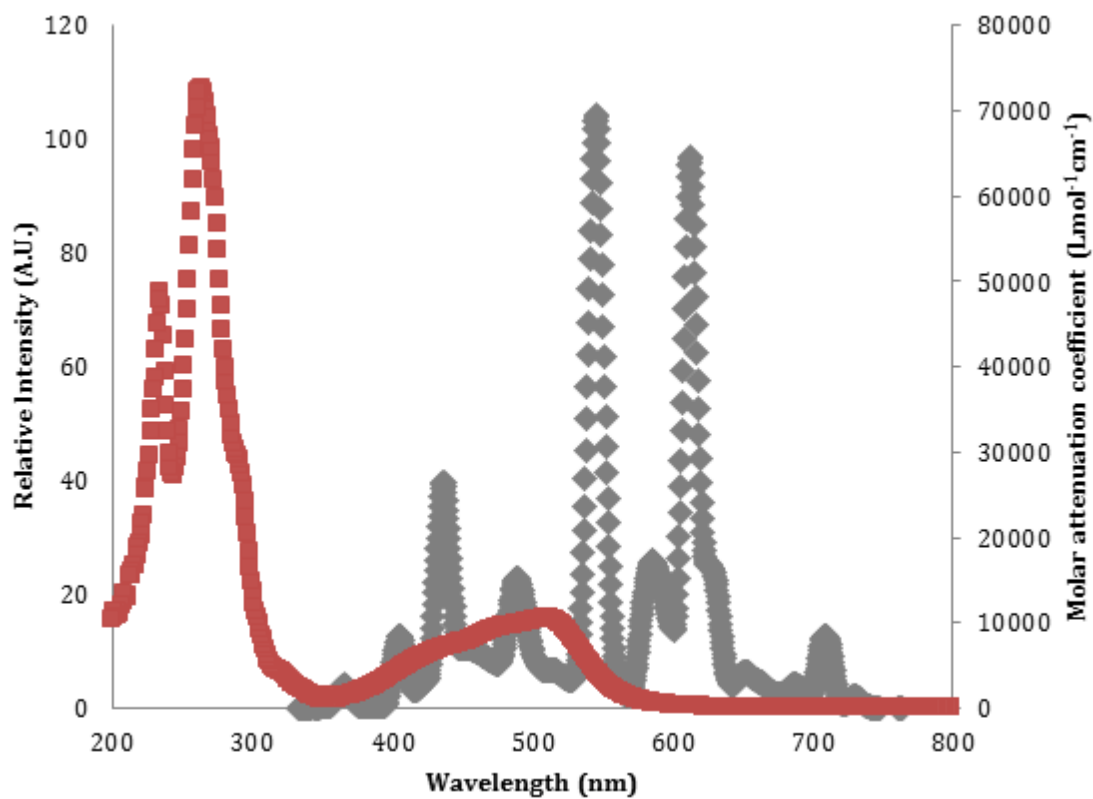
**9-Ethylcarbazole (2.23):** Following the general procedure **A** using continuous-flow with *N*-ethyl-*N*-phenylaniline (31.6 mg, 0.16 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (100 % hexanes to 5 % diethyl ether/hexanes) to afford the desired carbazole **2.23** as a white solid (25.0 mg, 80 %). The NMR data obtained for carbazole **2.23** were in agreement with that found in the literature.<sup>13</sup>



2.25

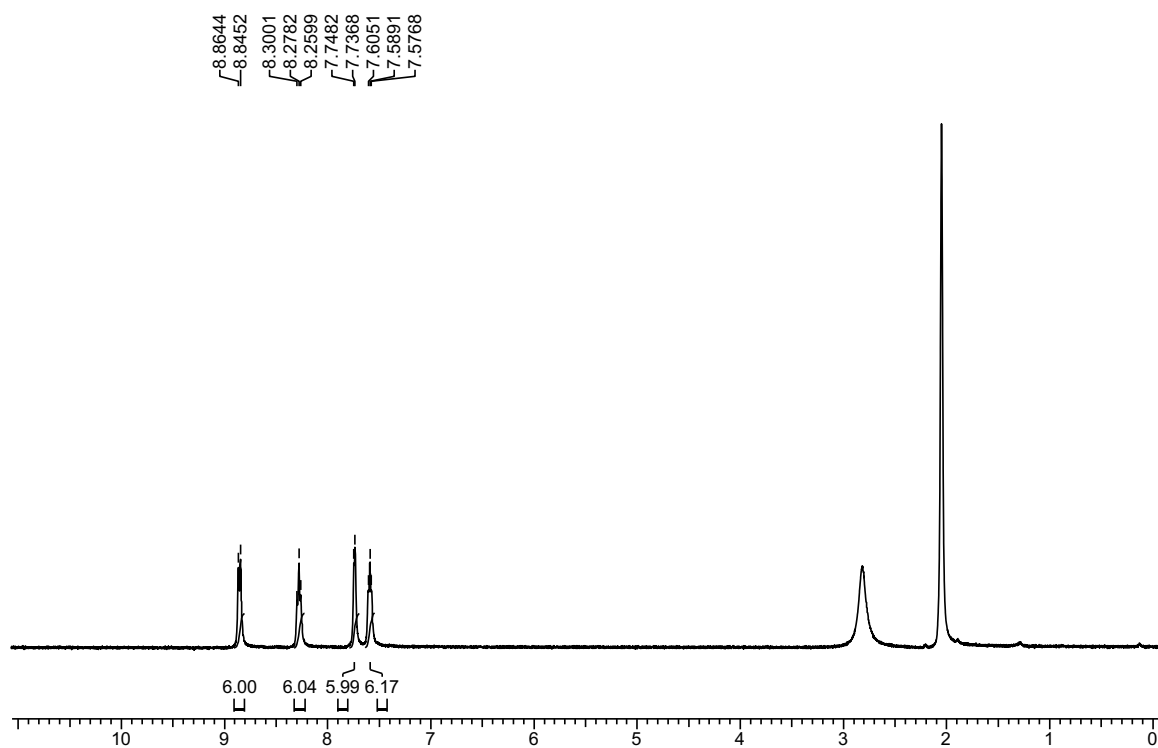
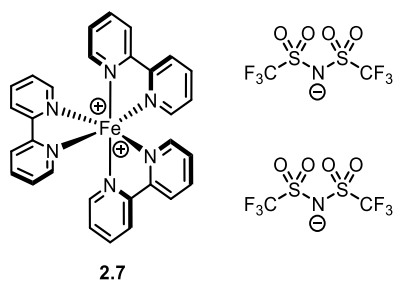
**6-Methoxy-1,4,9-trimethylcarbazole (2.25):** Following the general procedure **B** using continuous-flow with amine **2.24** (268 mg, 1.0 mmol, 1.0 equiv.), the crude reaction mixture was purified by silica gel column chromatography (5% diethyl ether/hexanes) to afford the desired product **2.25** as a white solid (129 mg, 54 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.73 (d, *J* = 2.5 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 7.3 Hz, 1H), 4.09 (s, 3H), 3.96 (s, 3H), 2.86 (s, 3H), 2.84 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm 153.30, 140.32, 136.92, 131.15, 128.53, 123.88, 121.72, 120.19, 117.75, 113.17, 108.71, 106.48, 56.23, 32.40, 20.78, 20.32; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>17</sub>NO [M+H]<sup>+</sup>, 240.1372; found: 240.1383.

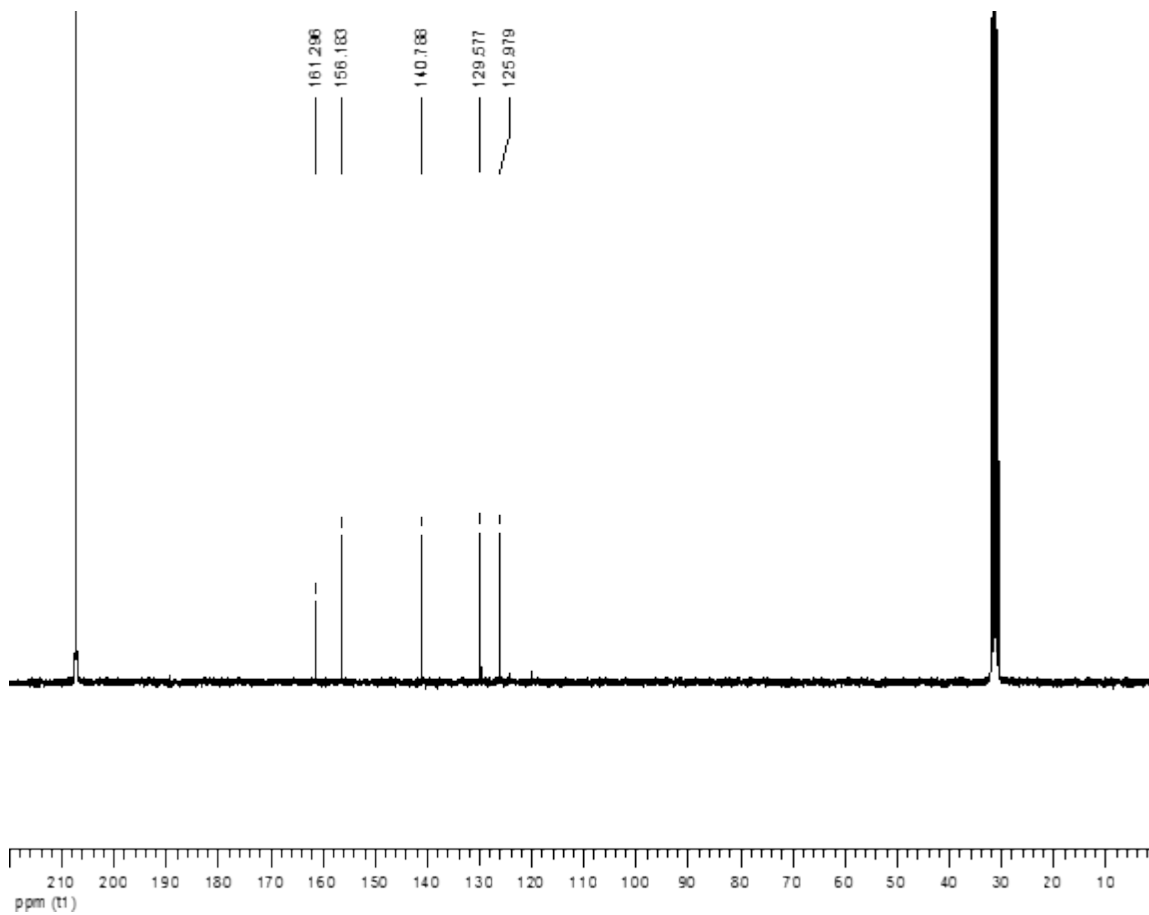
## 6.5 Uv-Vis Spectra

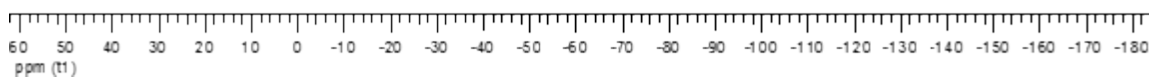
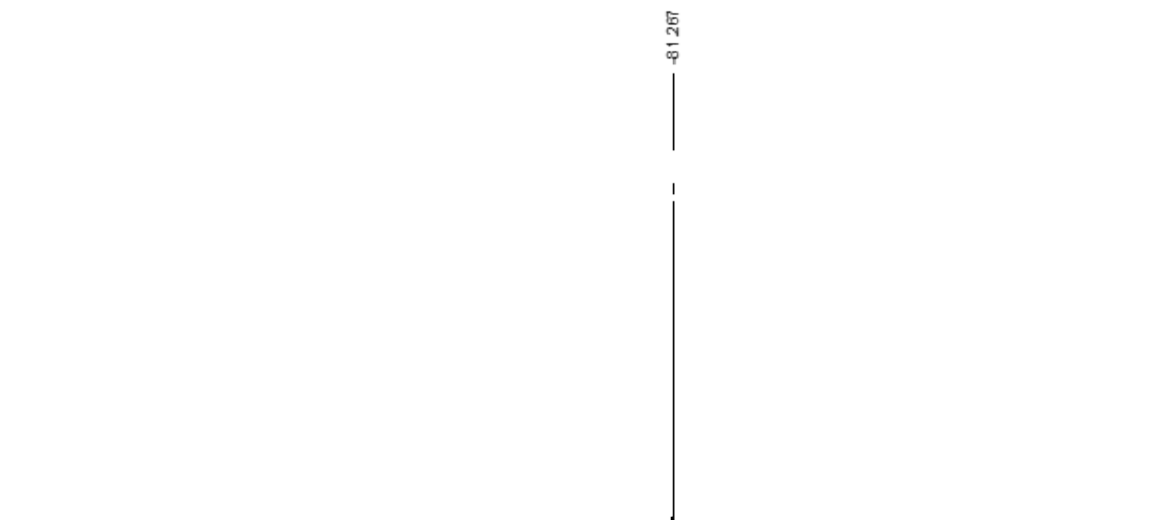


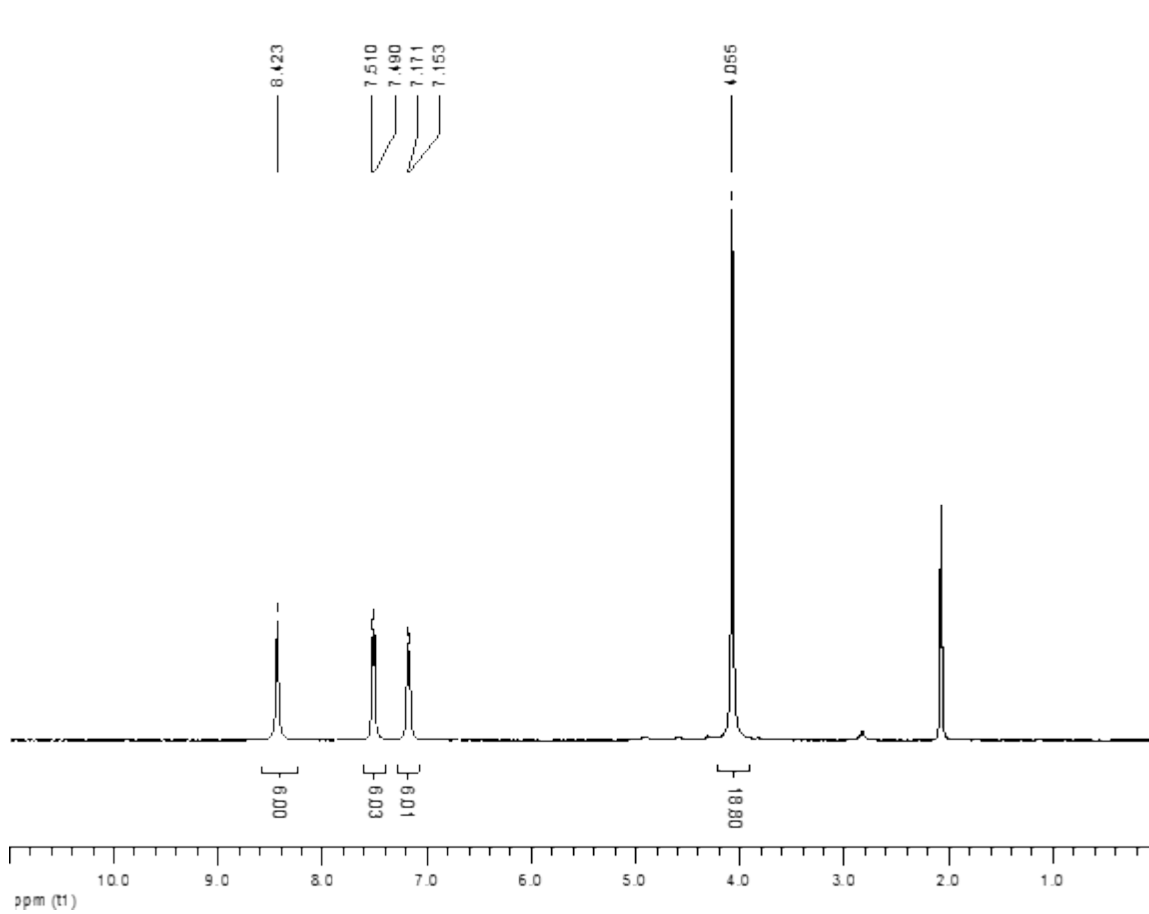
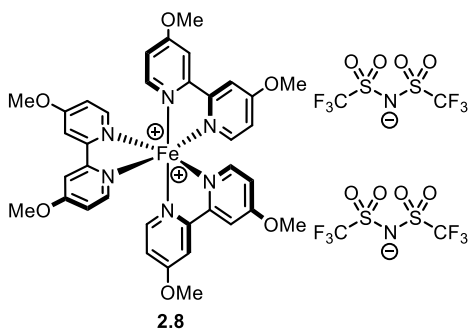
**Figure 6.4** Absorption spectra of **2.11**  $[\text{Fe}(\text{phen})_3](\text{NTf}_2)_2$   $5 \times 10^{-5} \text{ M}$  (red) and emission spectra for CFL blub light (grey).

## 6.6 NMR Data for all New Compounds

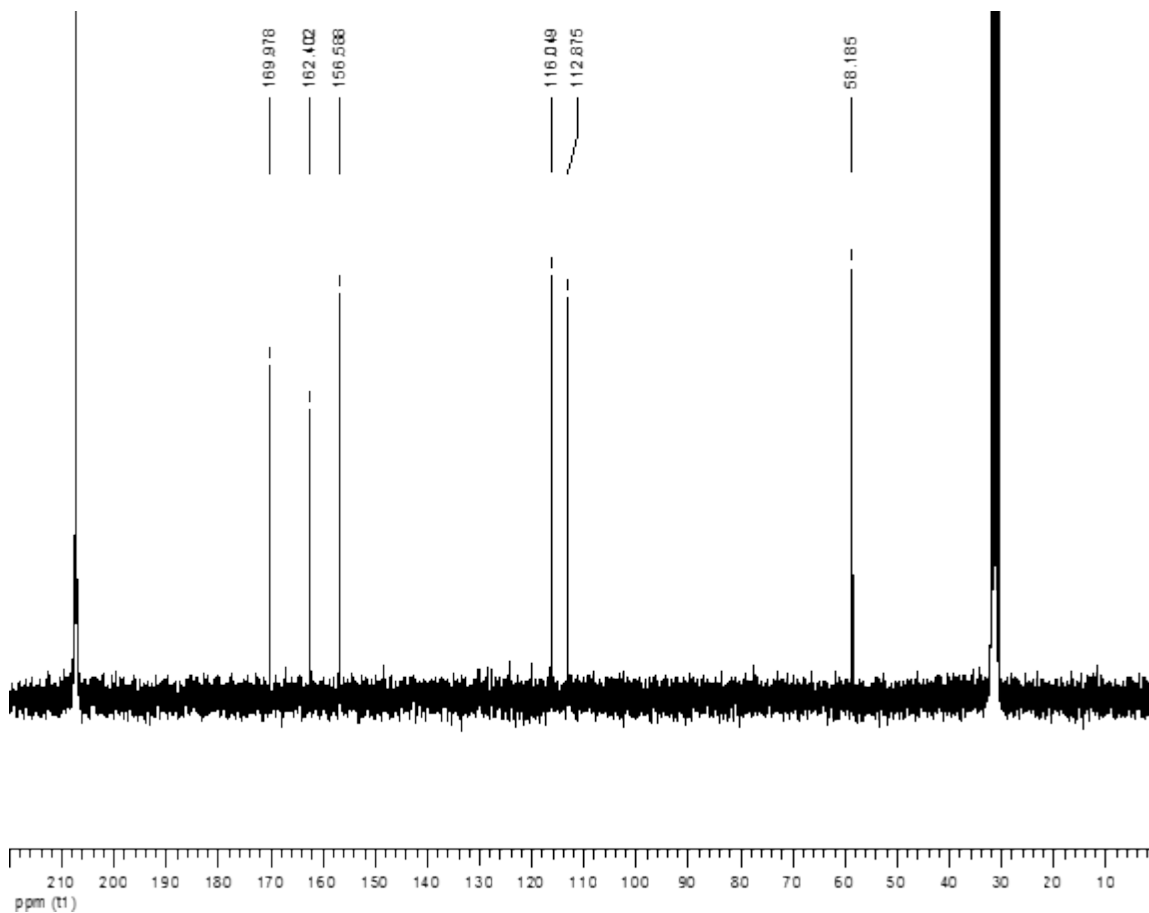


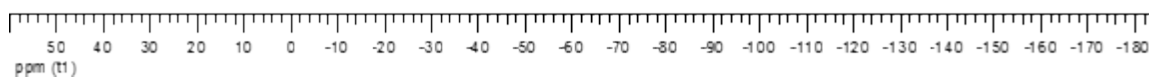
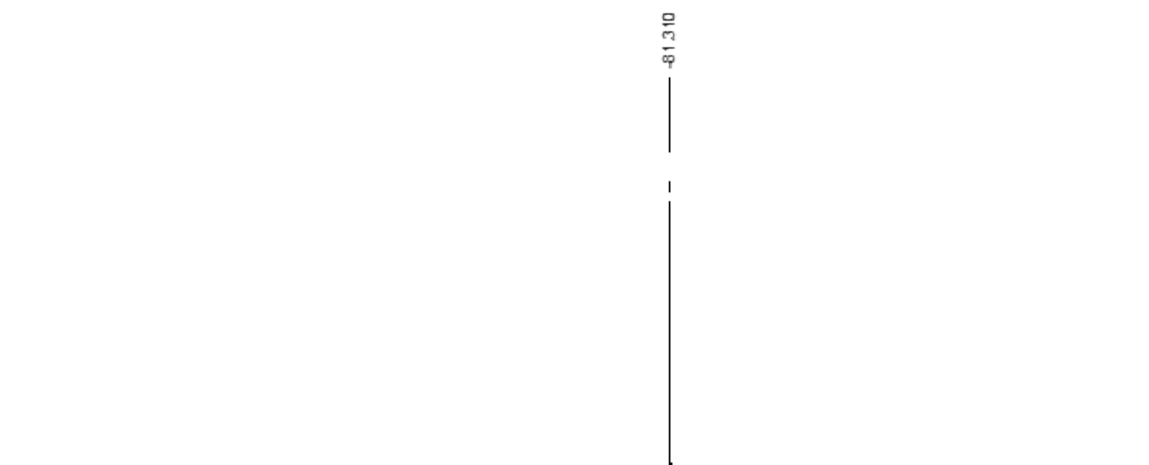


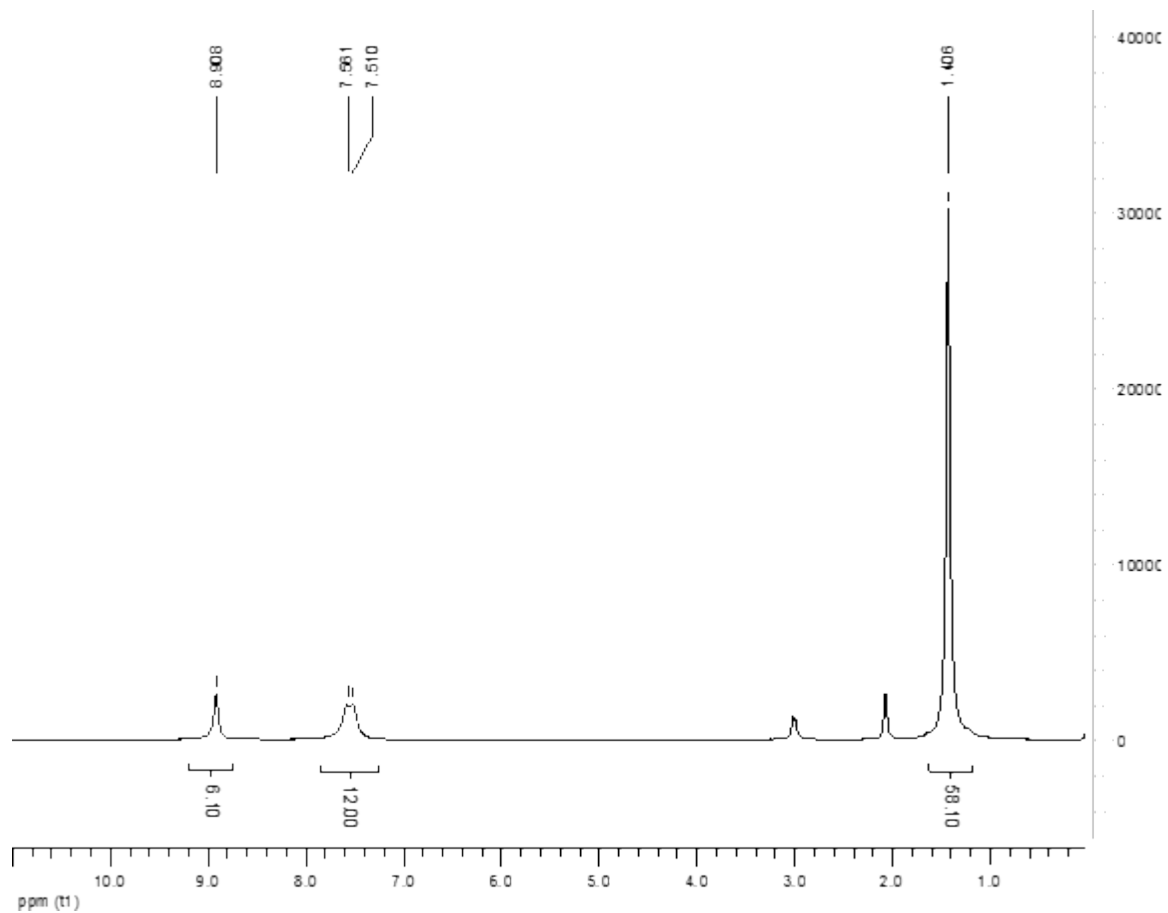
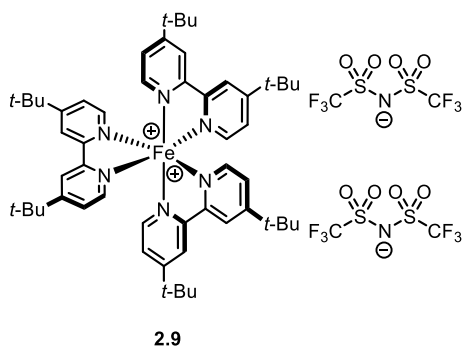


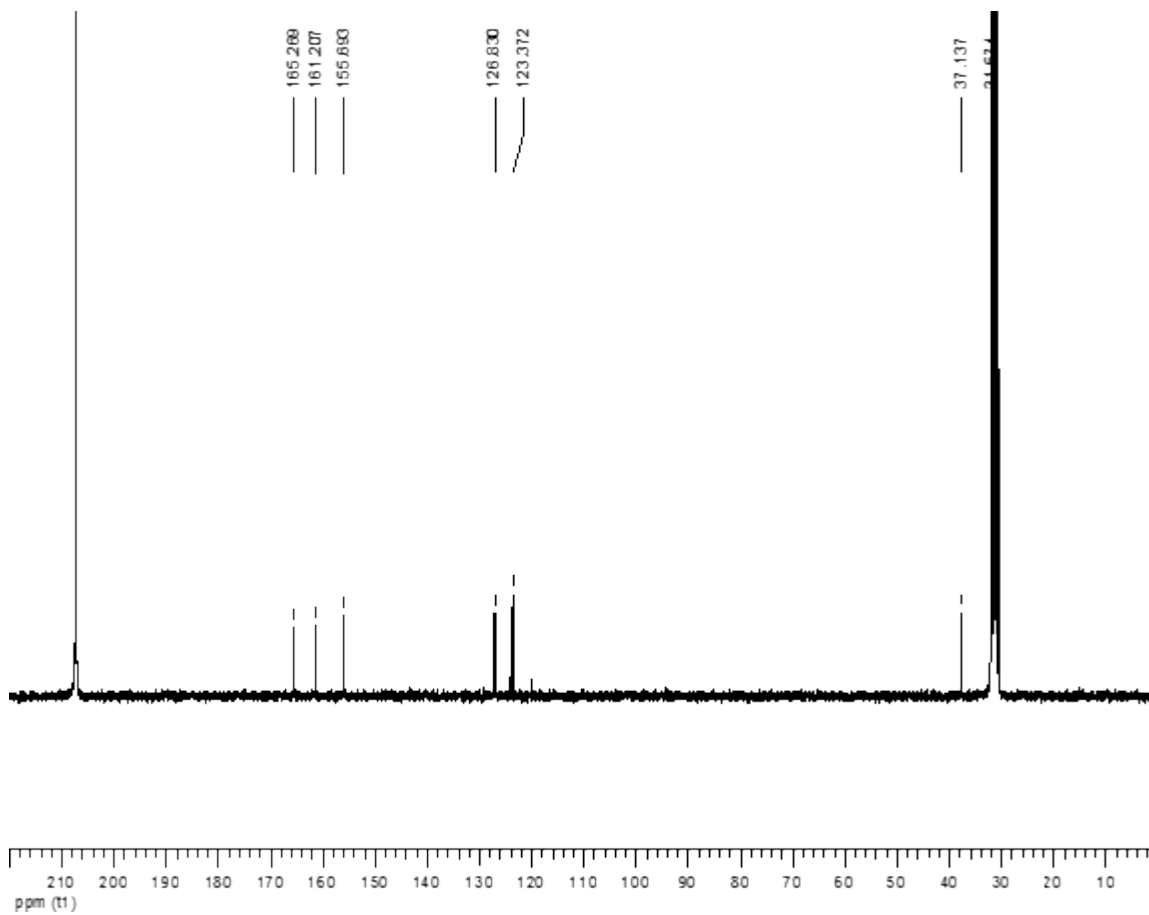


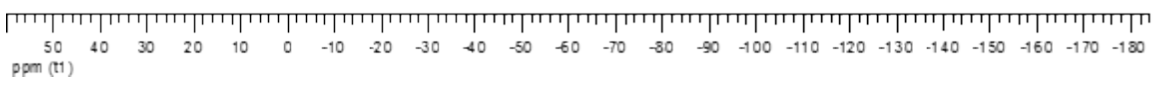
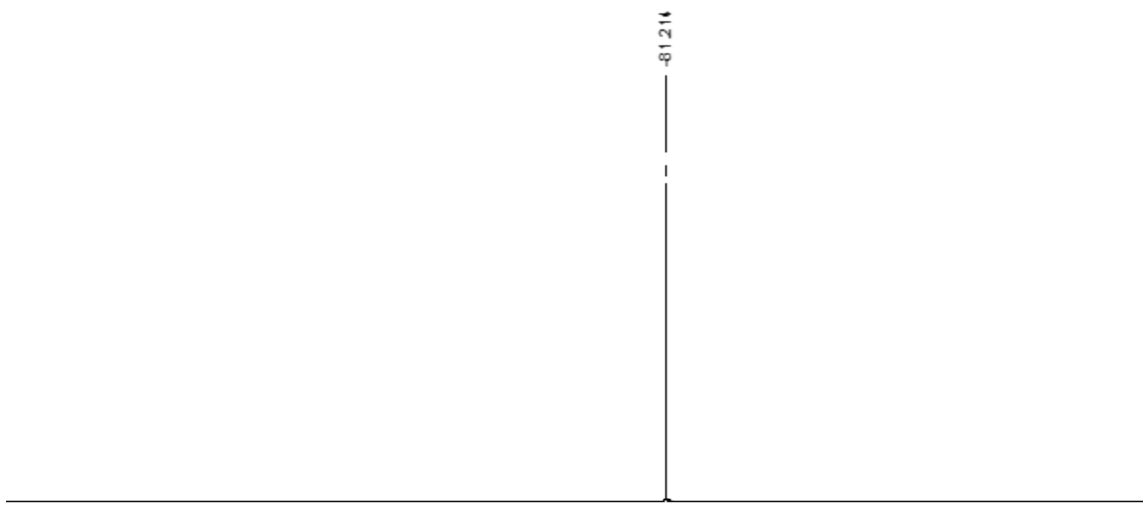


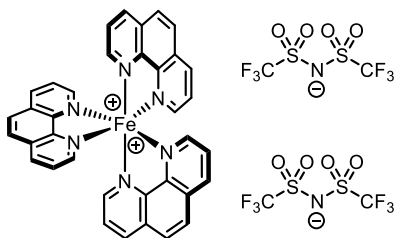




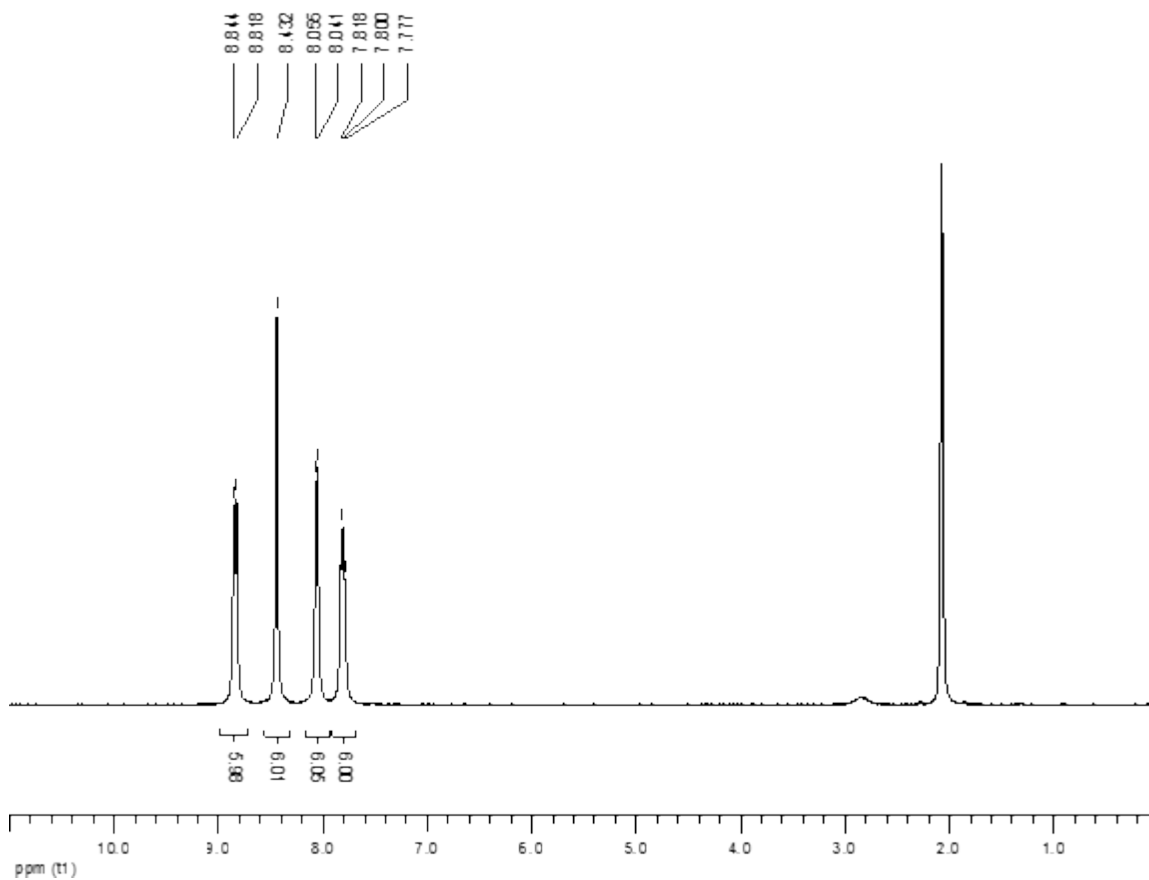


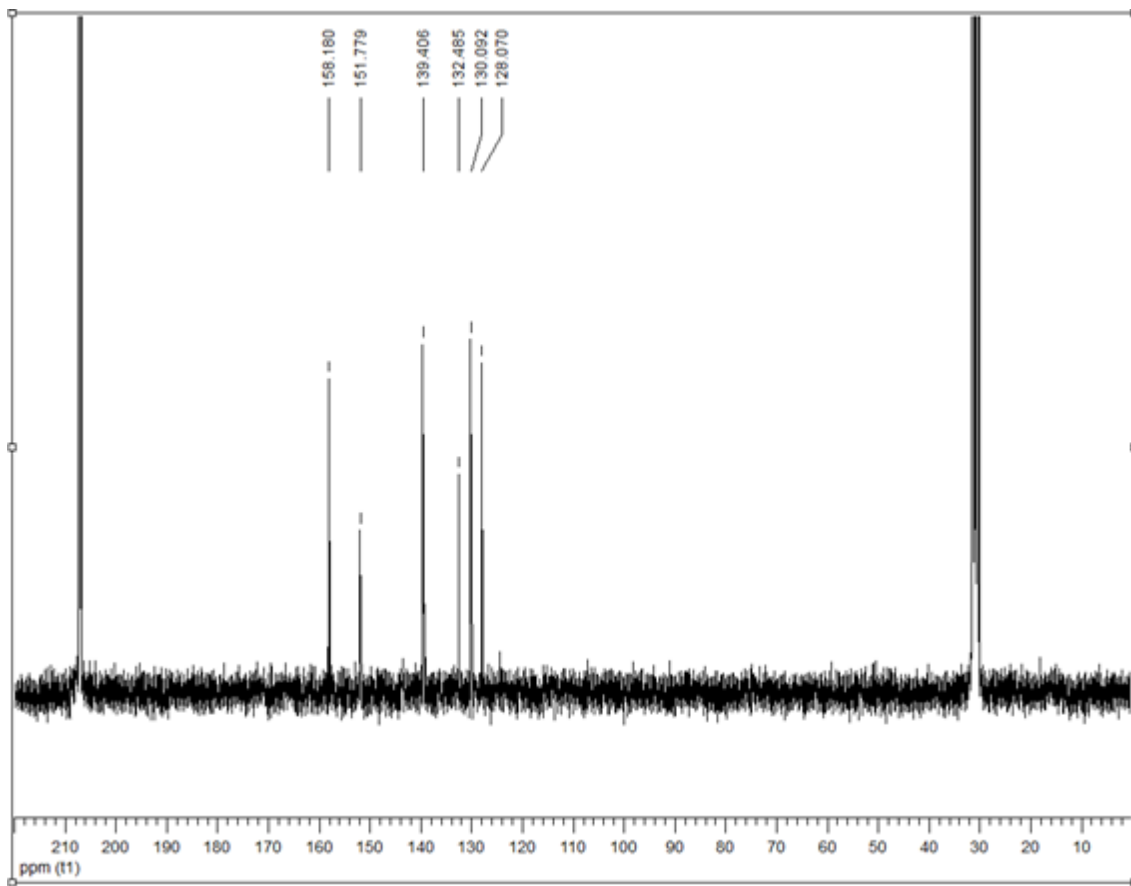


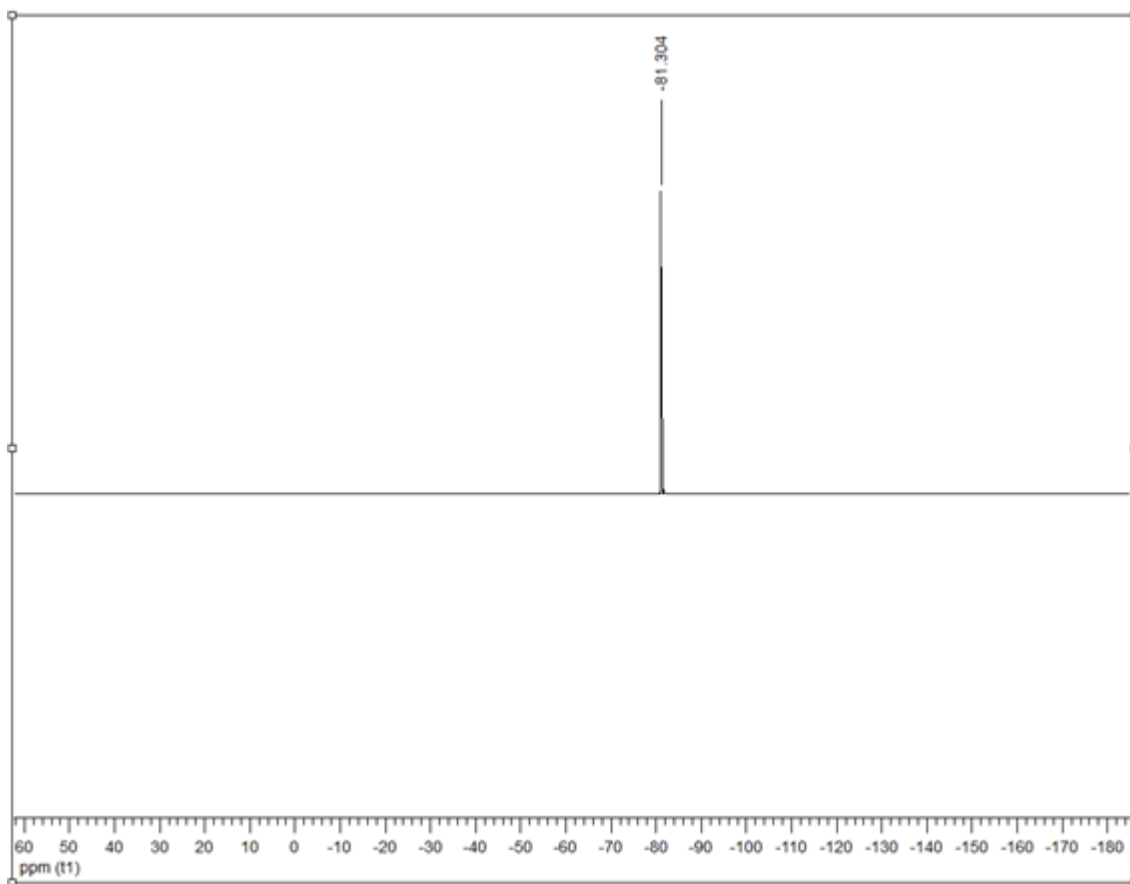




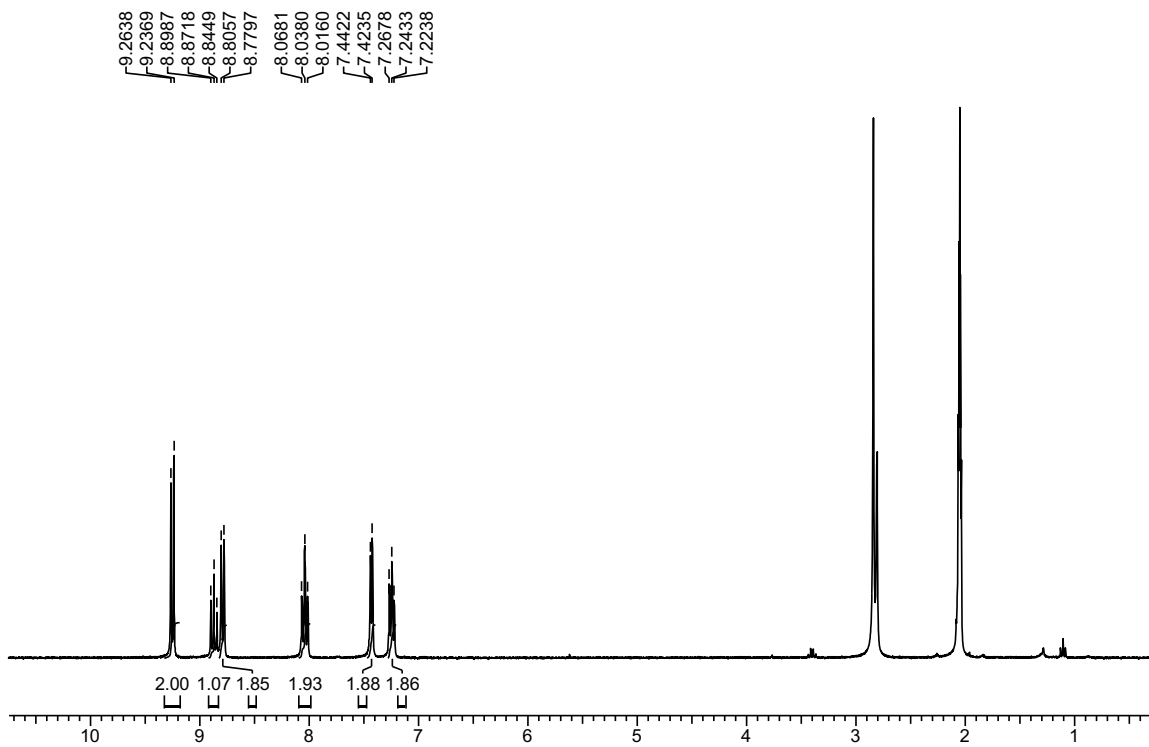
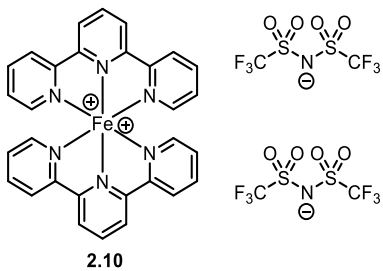
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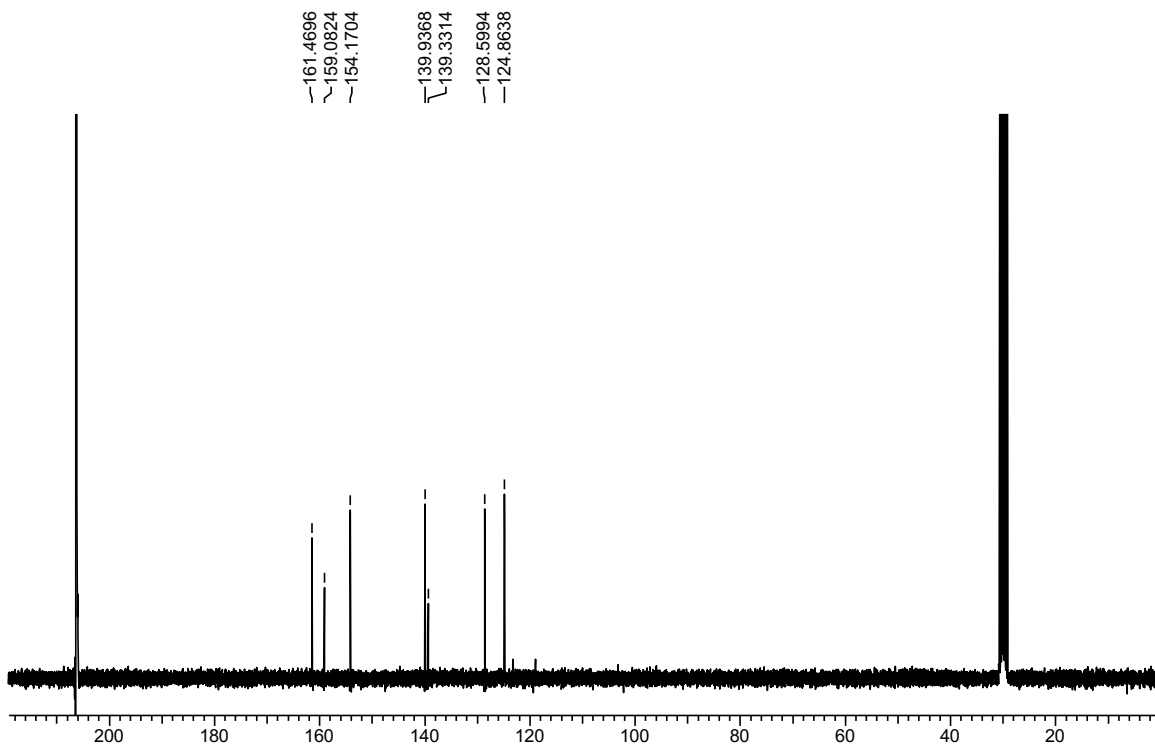


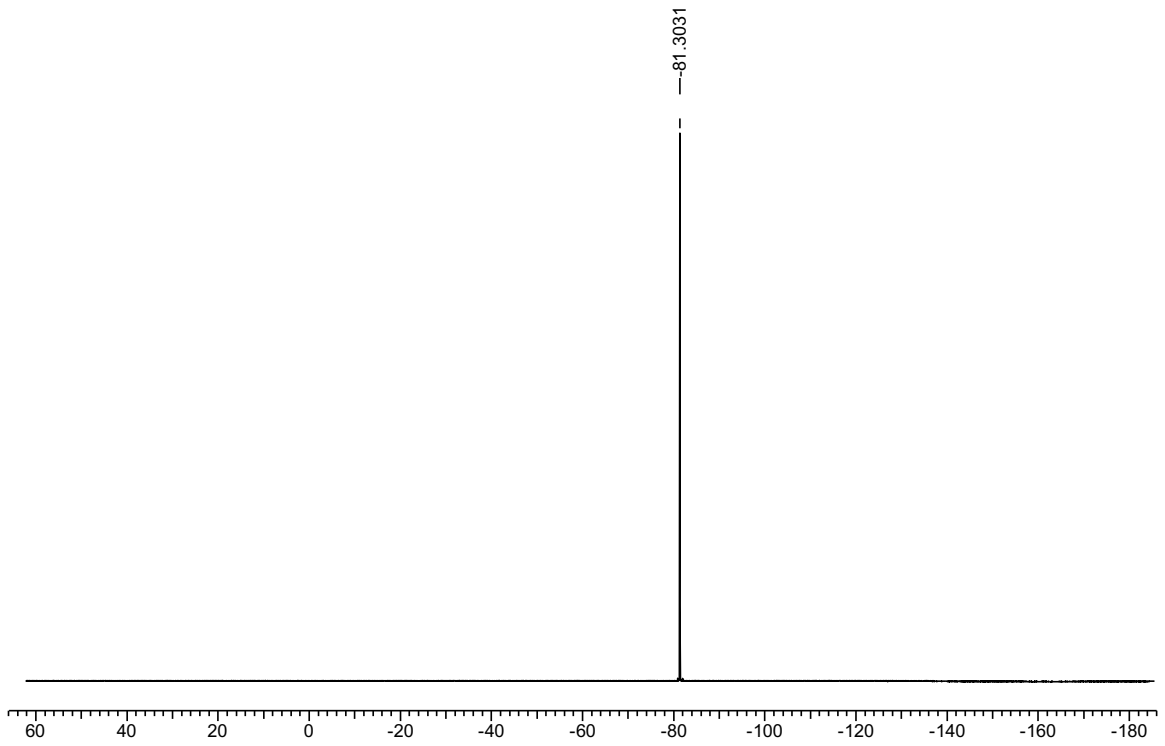


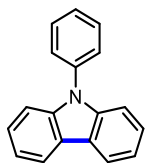




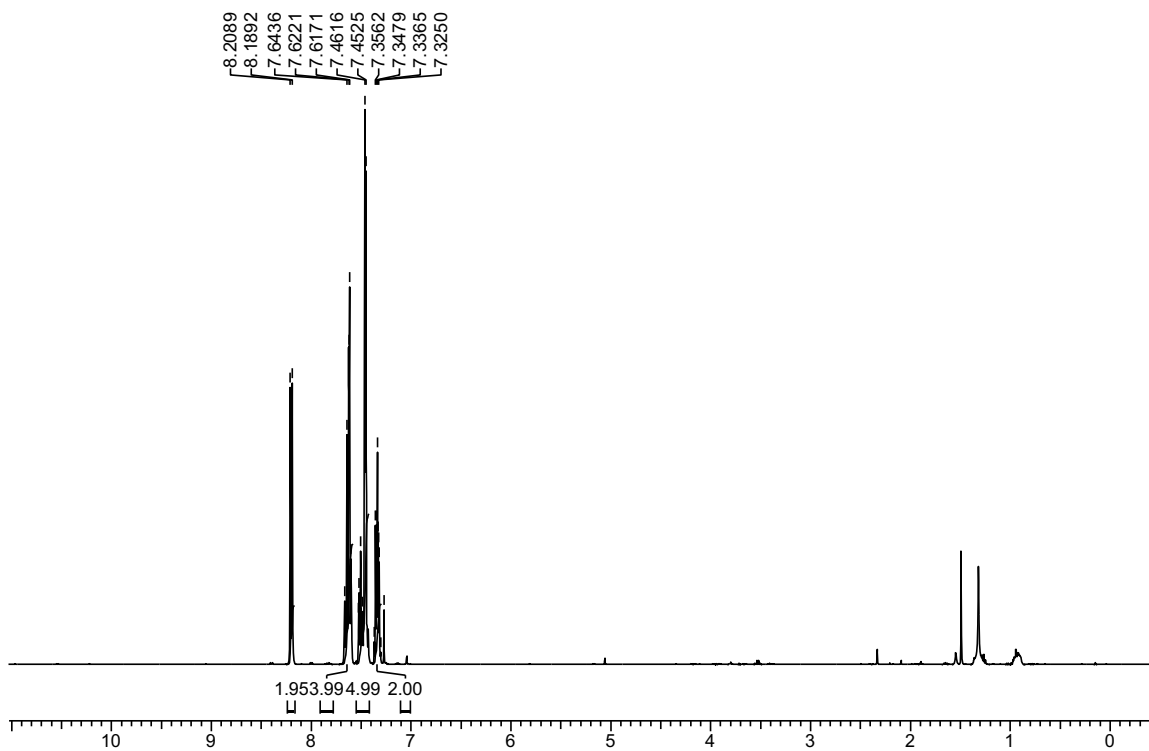


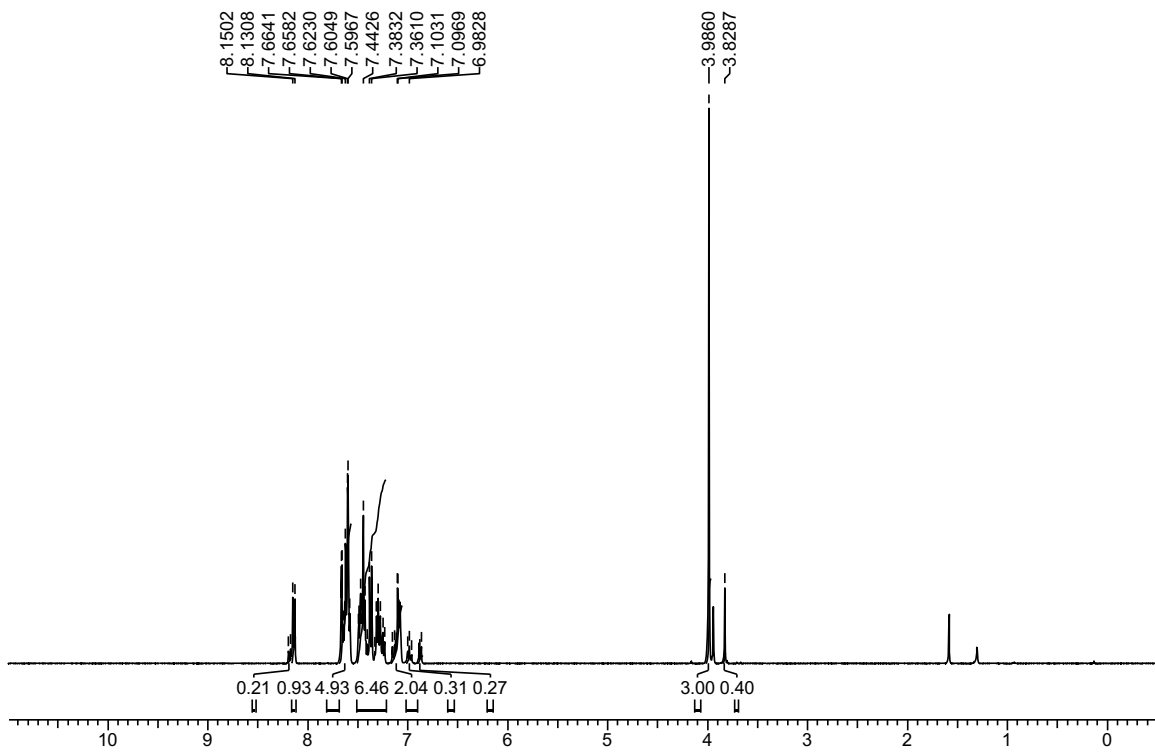
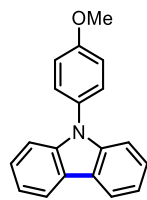
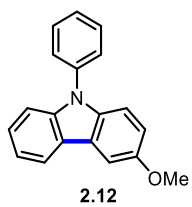


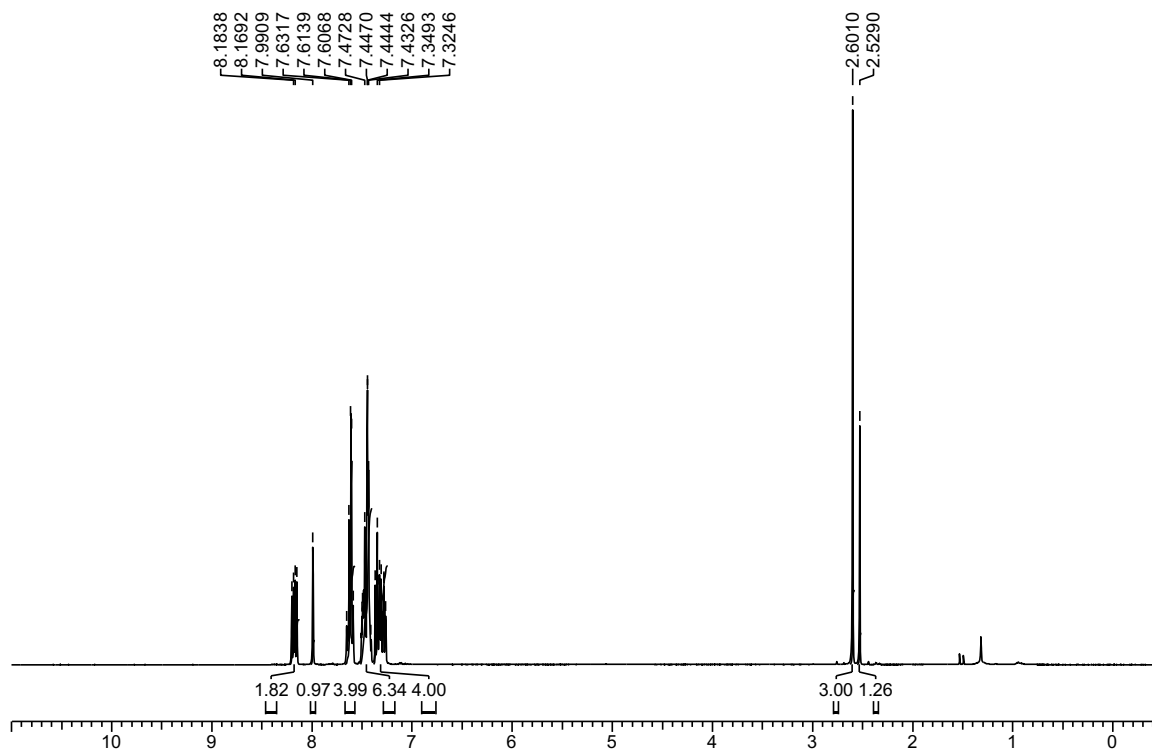
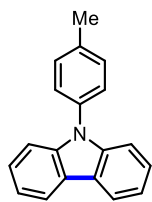
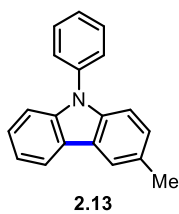


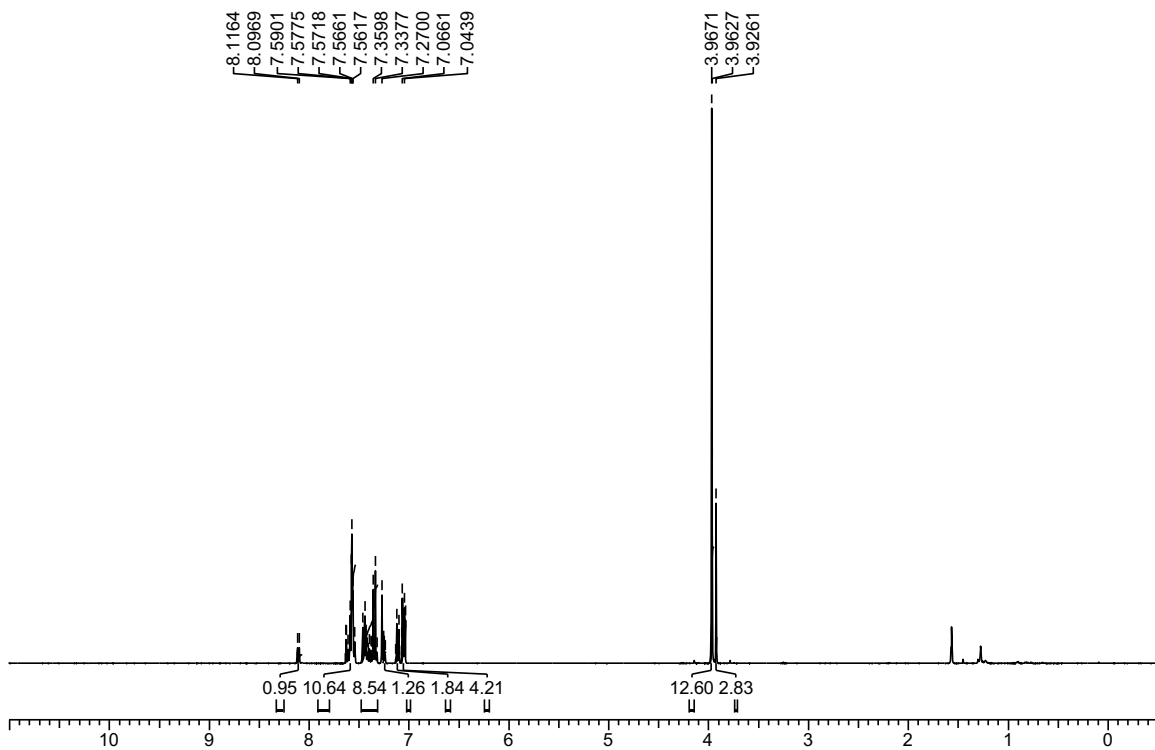
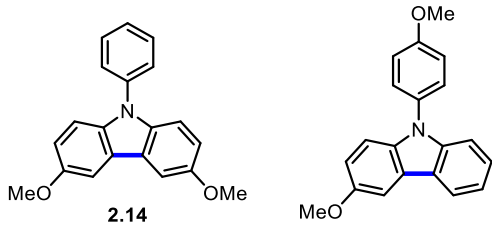


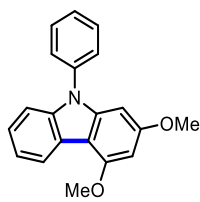
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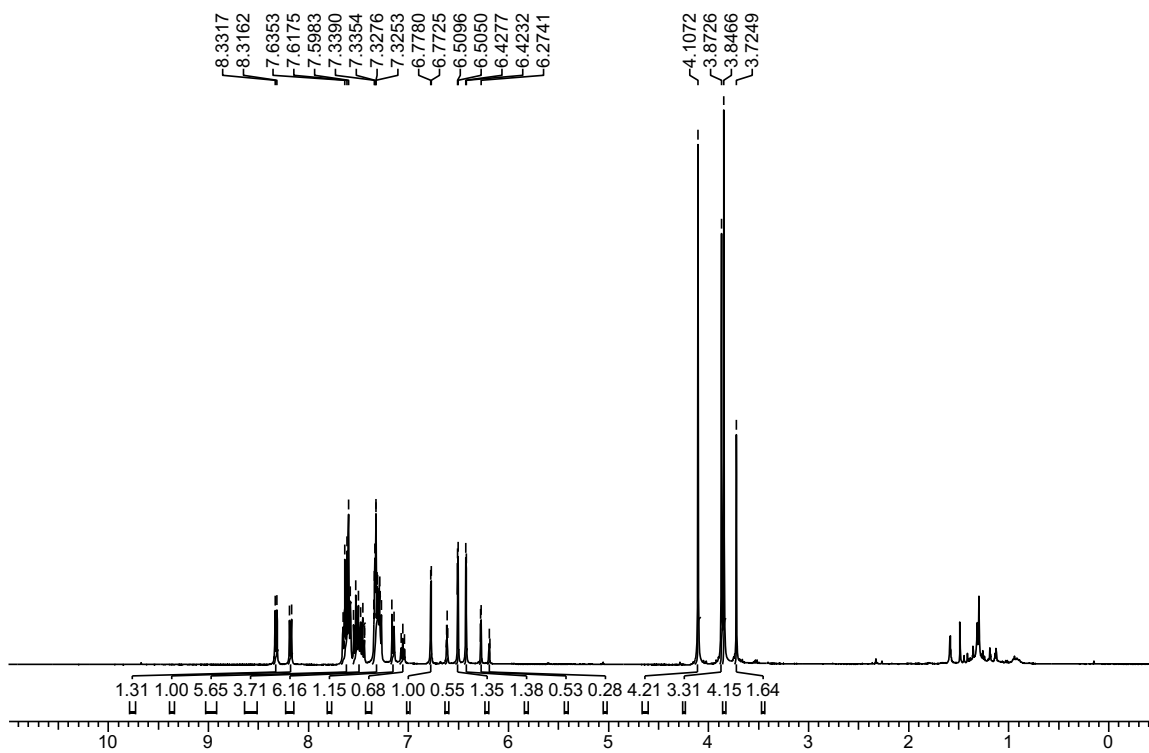
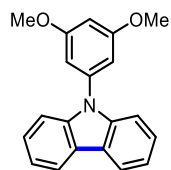




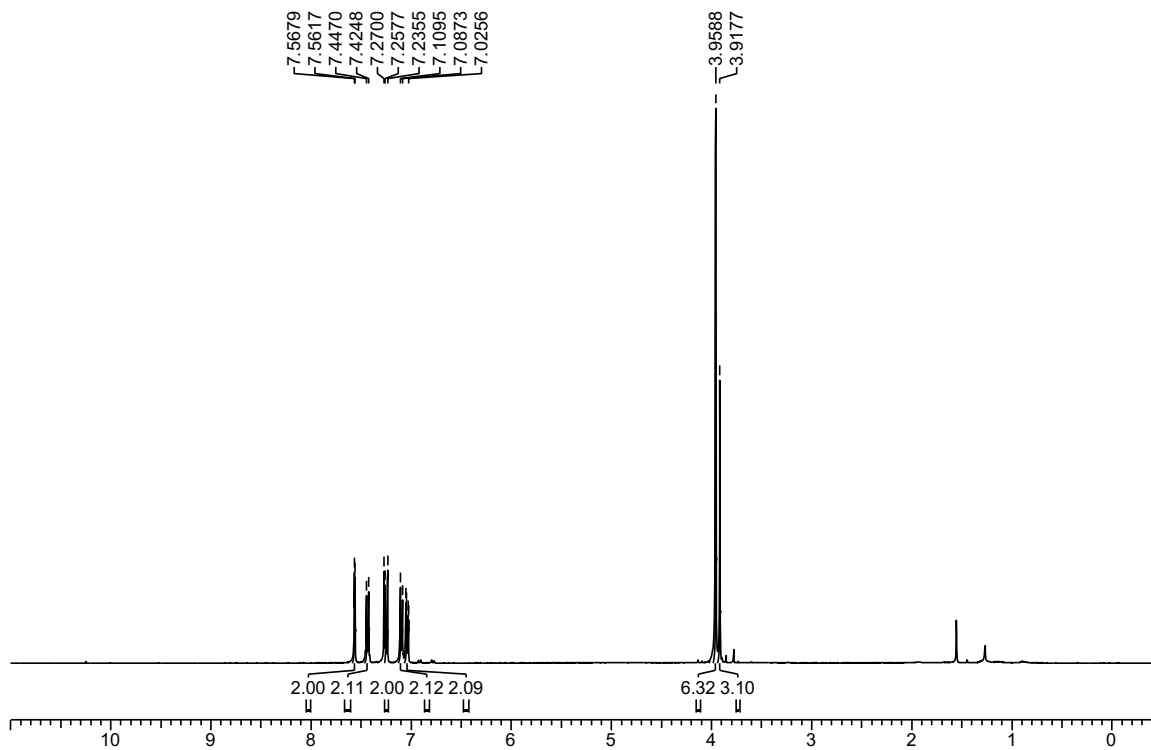
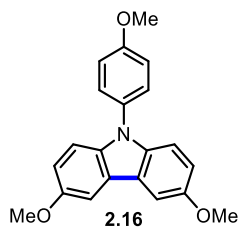


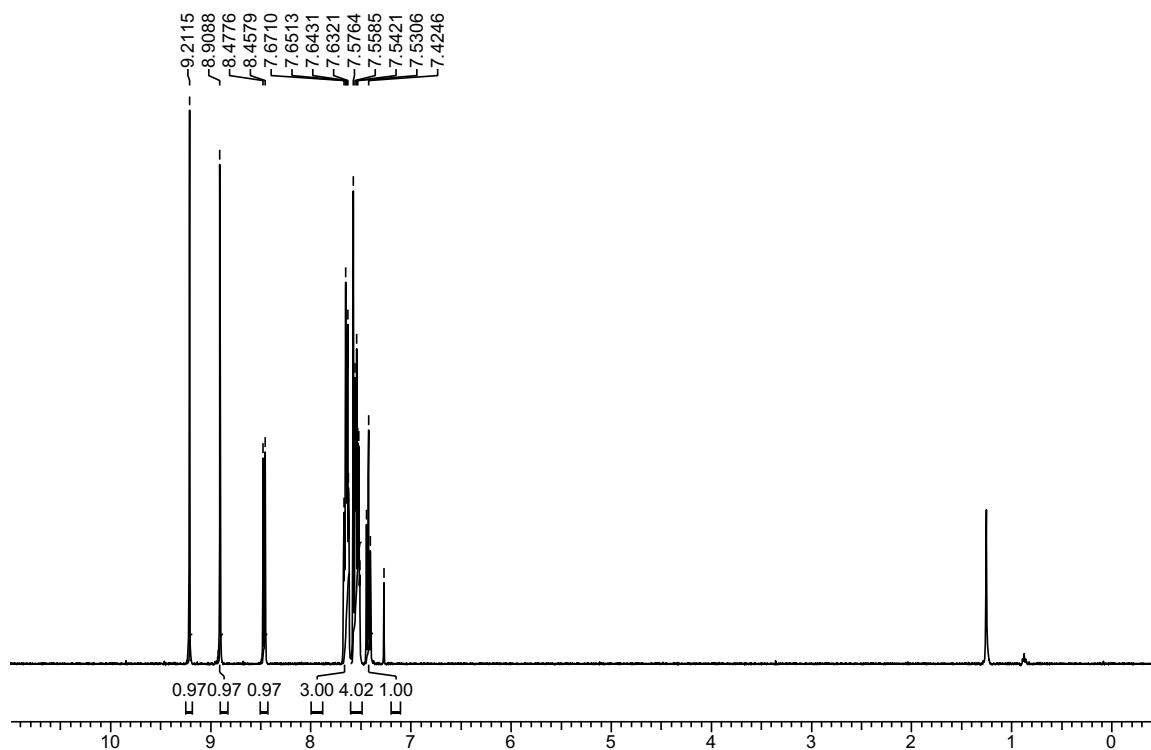
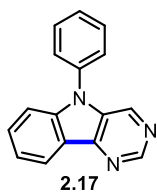


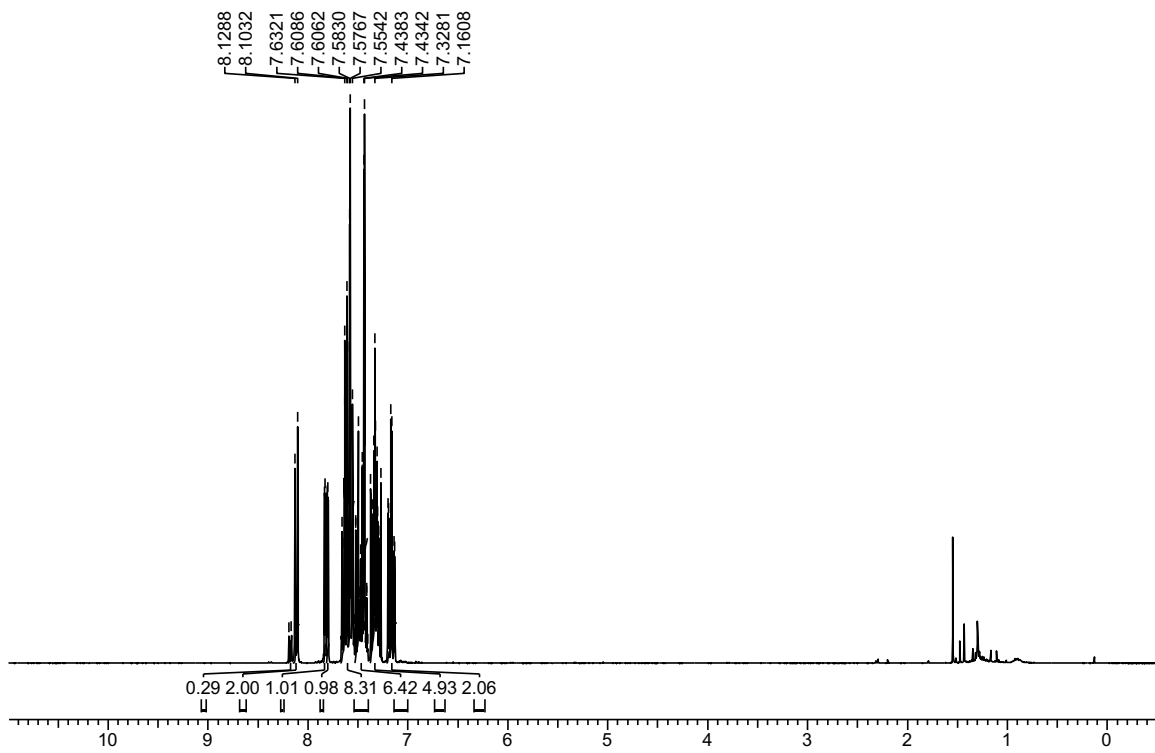
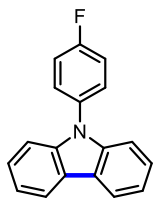
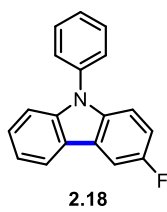
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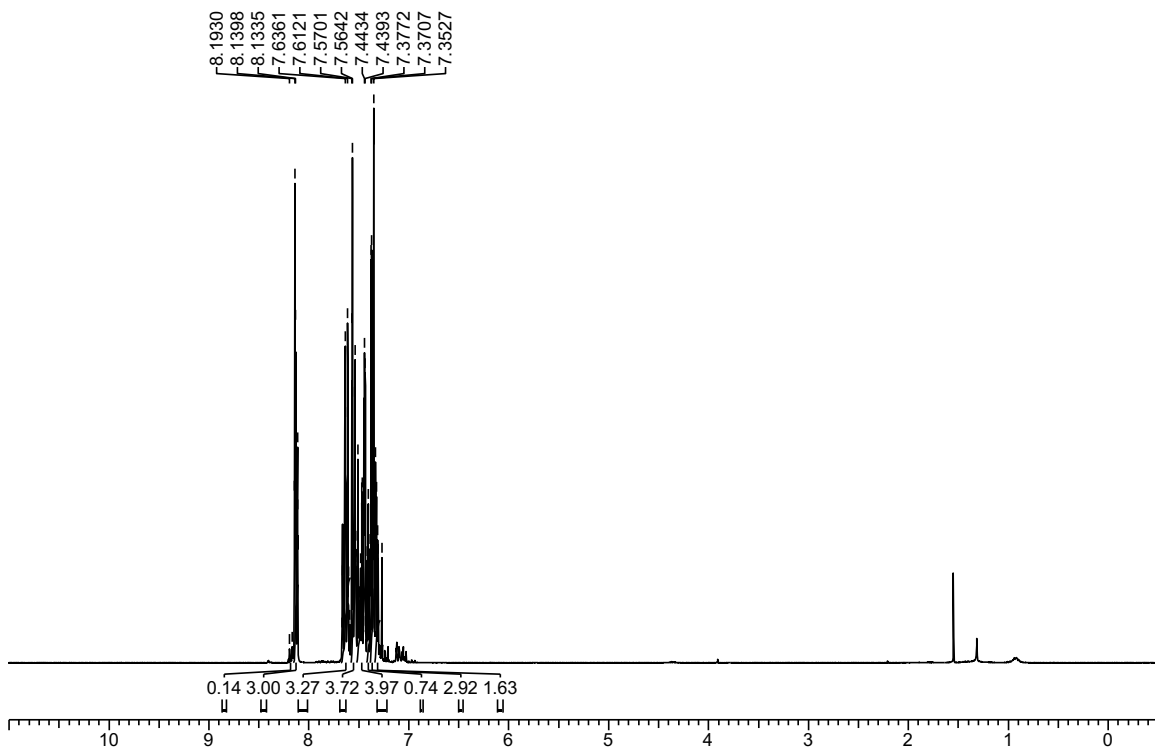
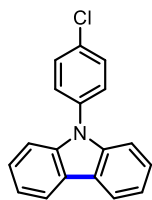
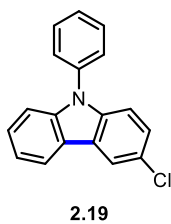


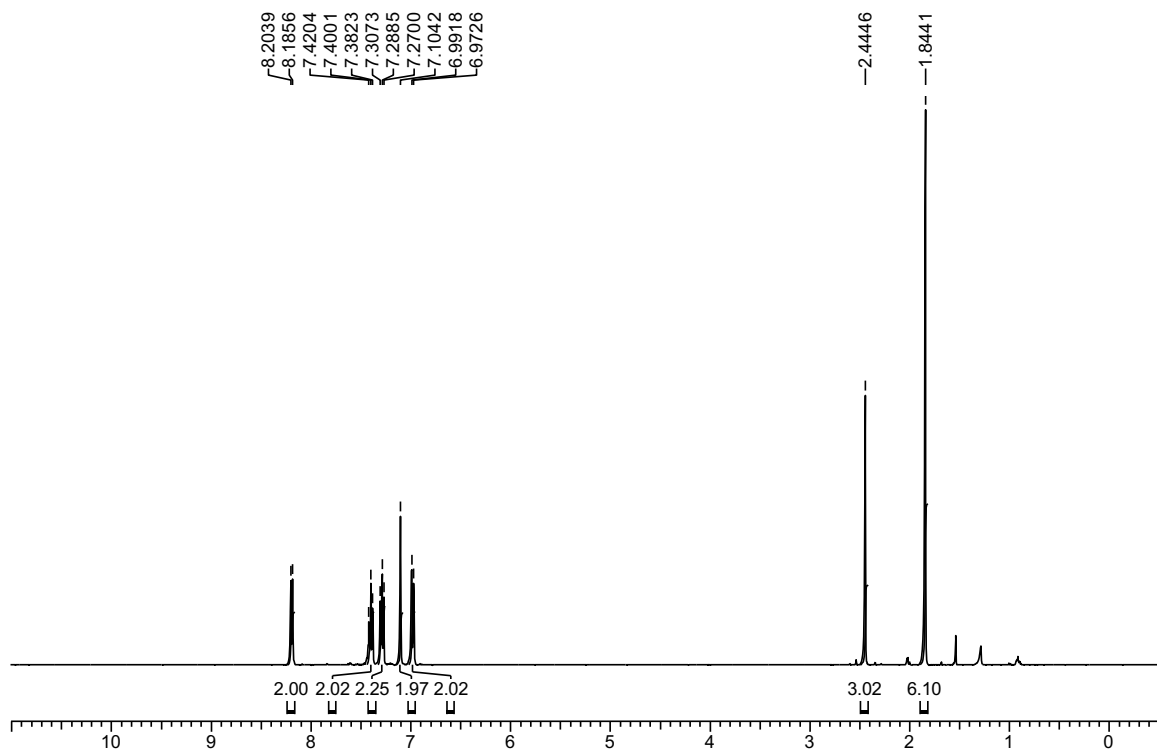
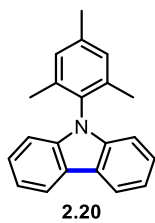


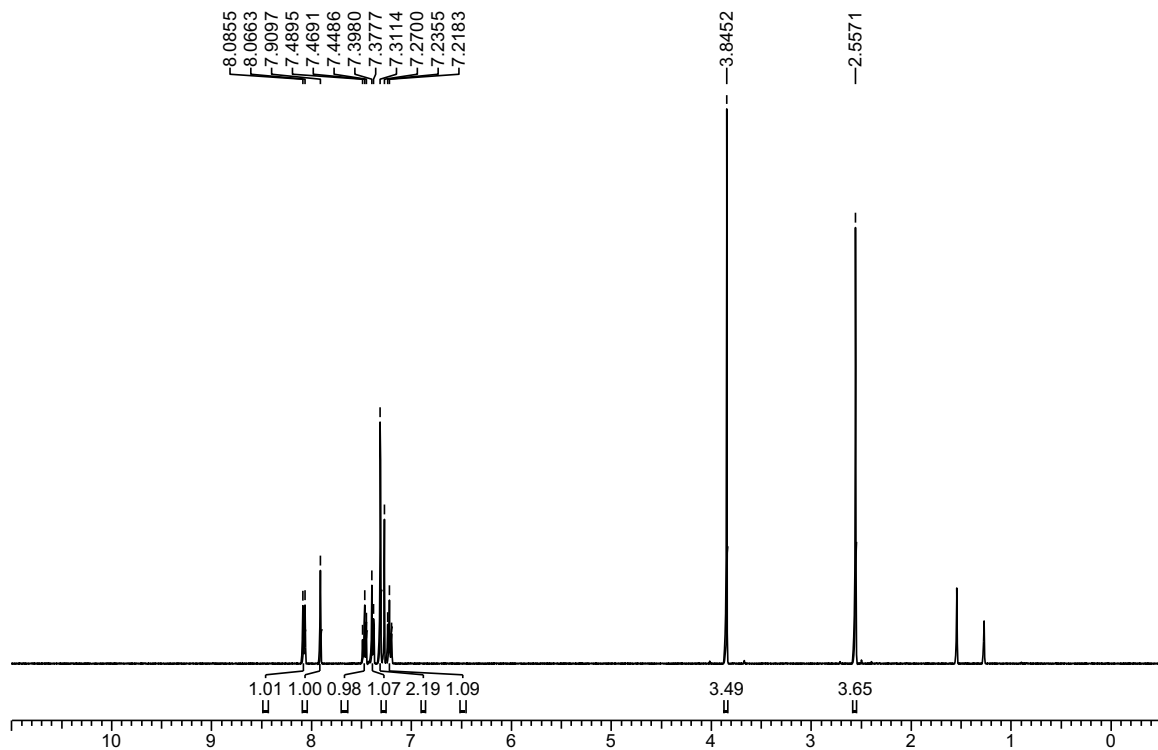
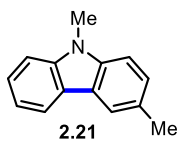


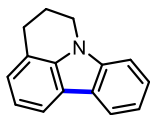




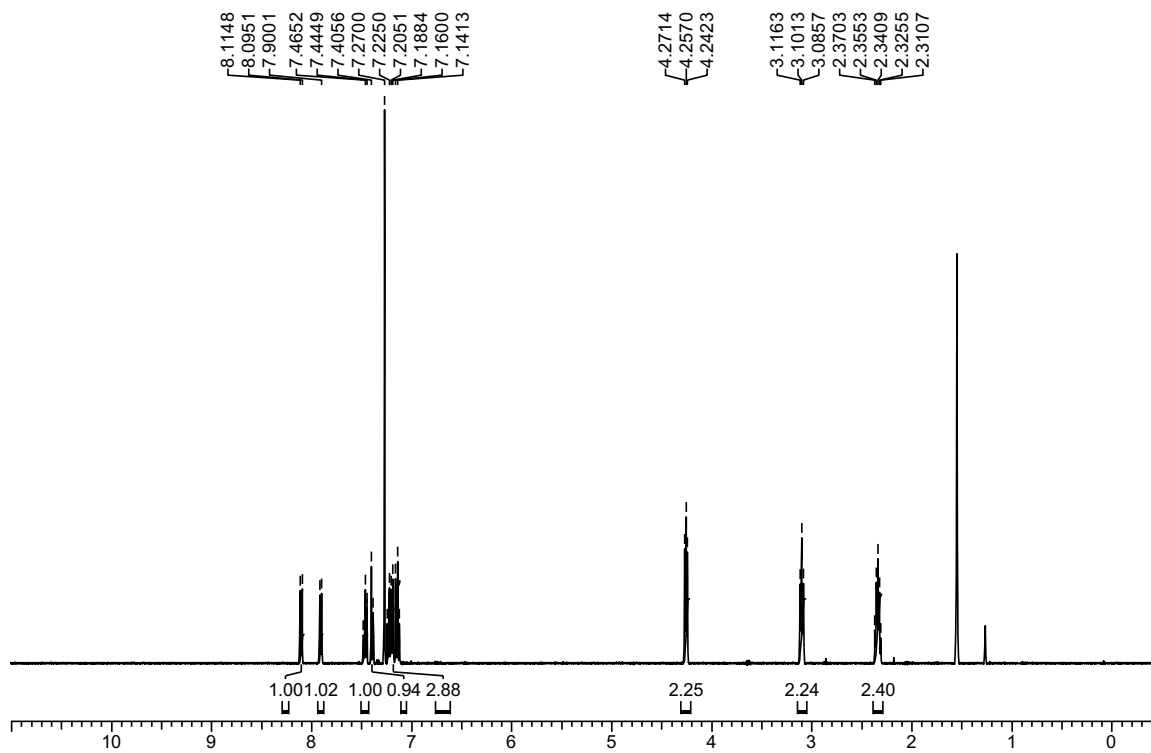


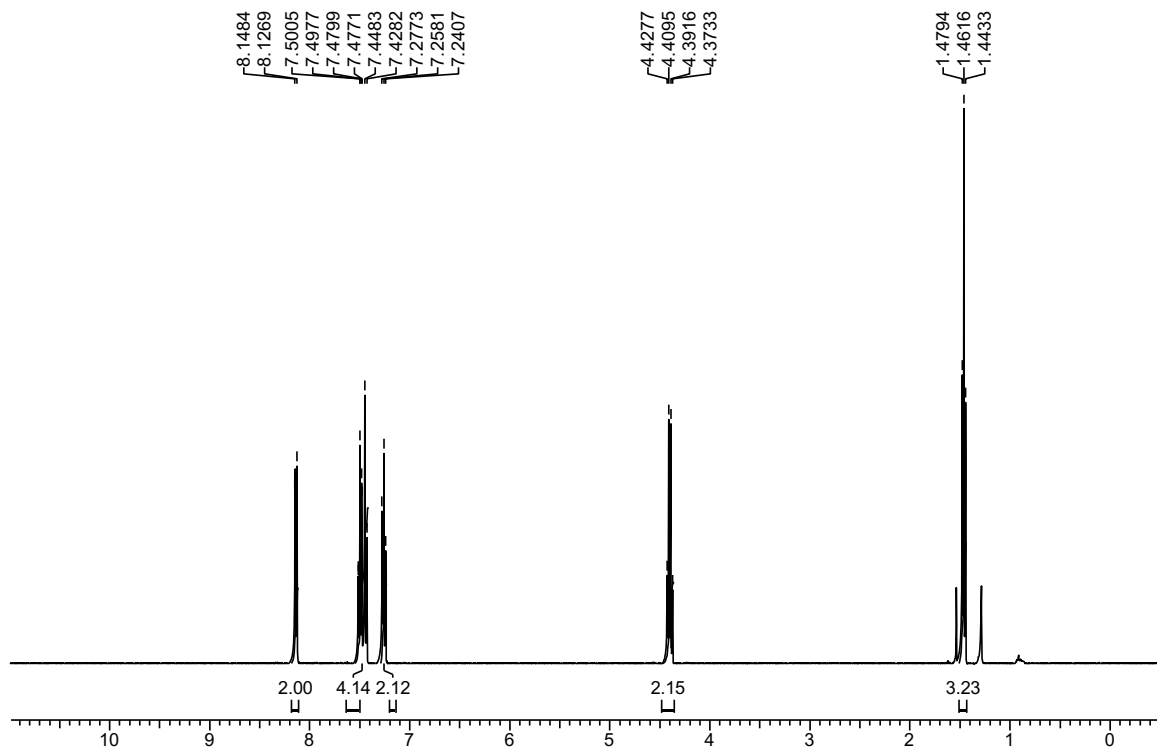
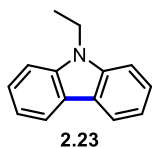




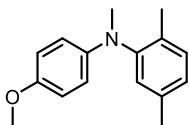


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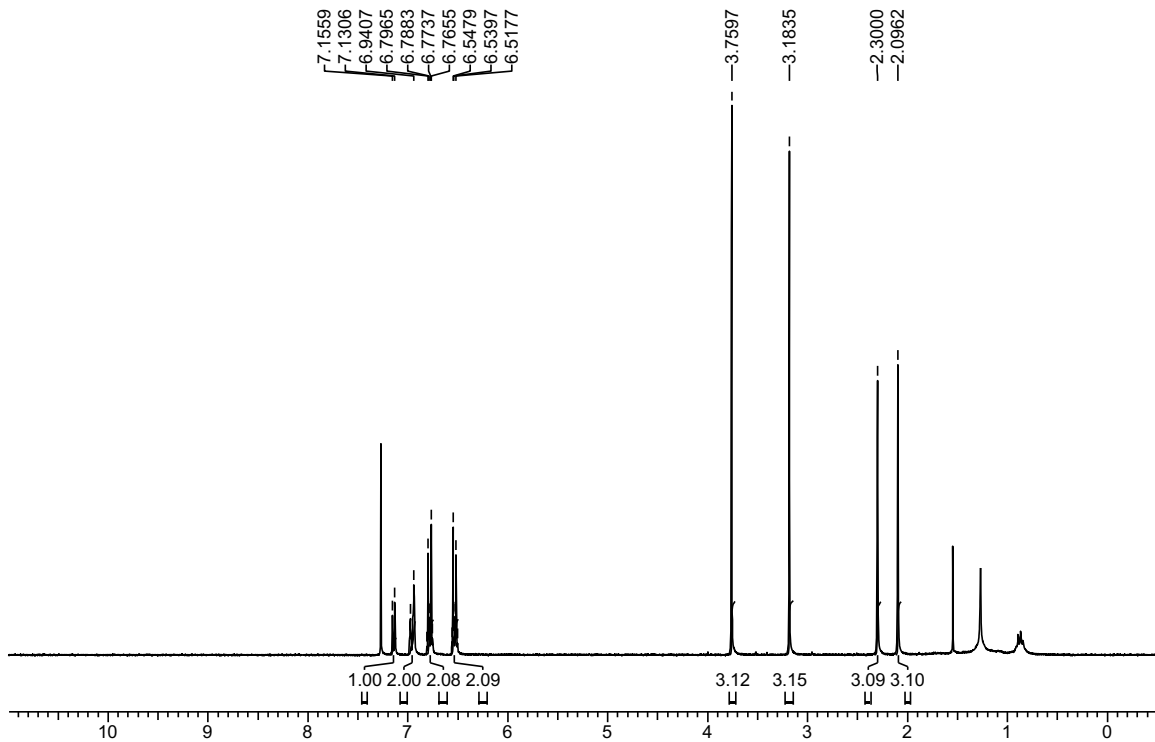


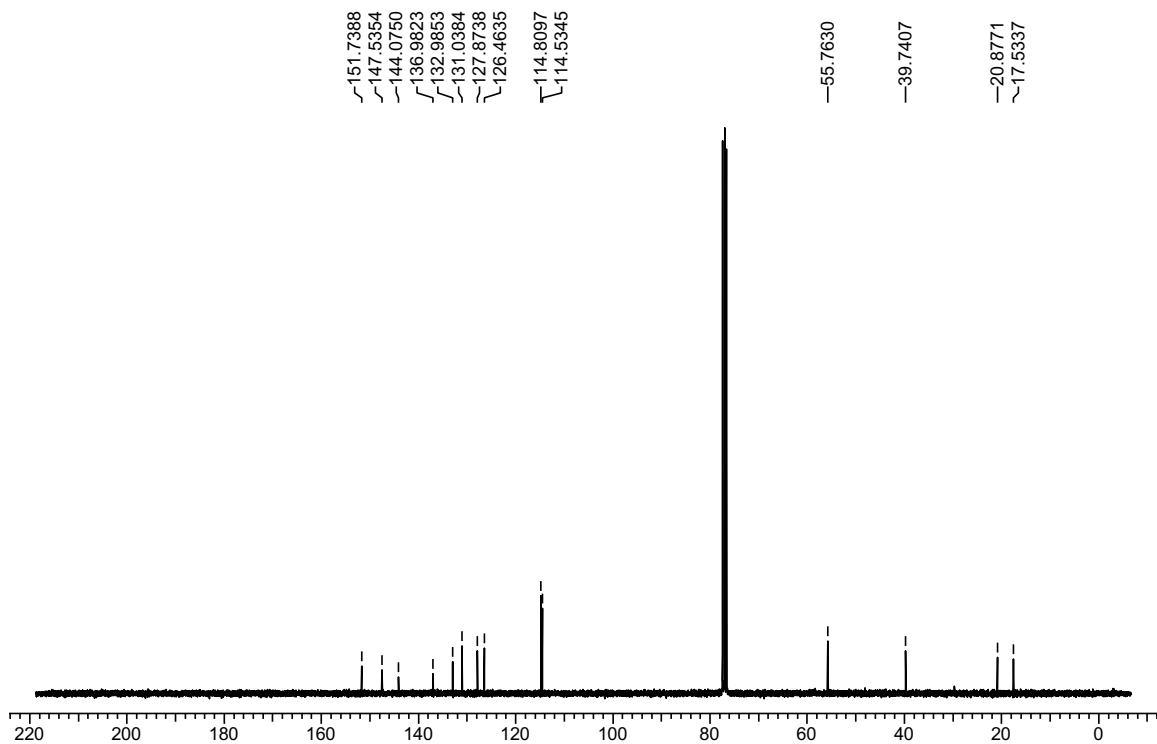


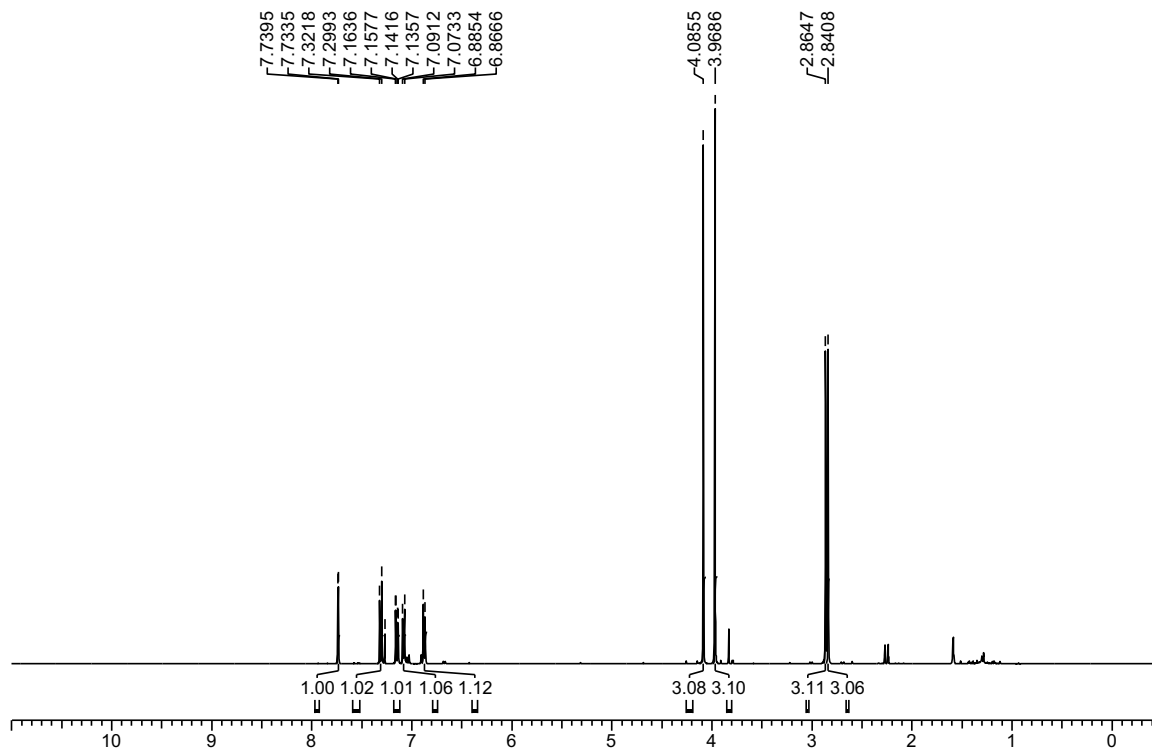
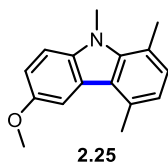


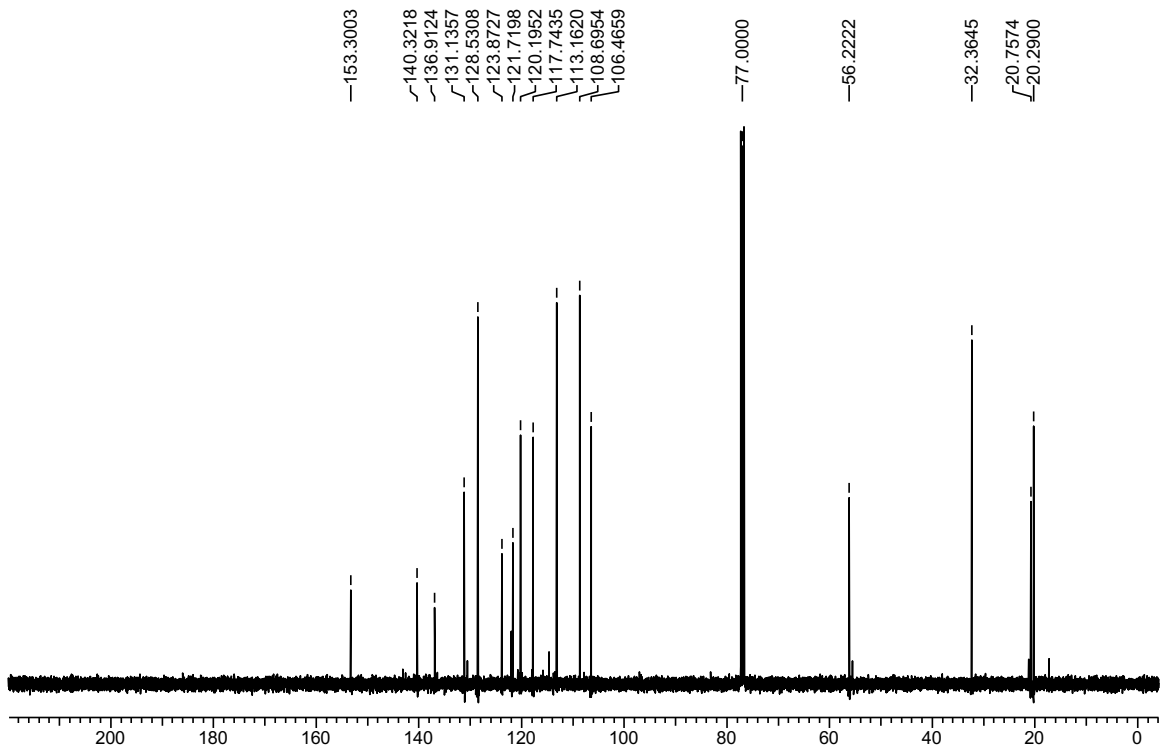


2.24









## 6.7 Bibliography

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## 7. Supporting Information of Chapter 3

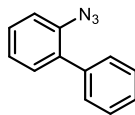
### 7.1 General

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.<sup>1</sup> All chemical products were obtained from Sigma-Aldrich Chemical Company or Alfa Aesar and were reagent quality. The following products were prepared according to their respective literature procedures: Methyl (2*Z*,4*E*)-2-azido-5-phenylpenta-2,4-dienoate. Technical solvents were obtained from VWR International Co. Anhydrous solvents (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still<sup>2</sup> and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F<sub>254</sub>). Visualization of TLC plate was performed by UV (254 nm), KMnO<sub>4</sub> or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by <sup>1</sup>H NMR. NMR spectra were taken in deuterated CDCl<sub>3</sub> using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard (CHCl<sub>3</sub>: δ 7.27 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). The acquisition parameters are shown on all spectra. The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.

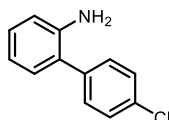
## 7.2 Synthesis of Precursors

**General Procedure for Suzuki Cross-Coupling (C):** An oven-dried sealed tube was charged with 2-iodoaniline (1 equiv.), arylboronic acid (1.2 equiv.),  $K_2CO_3$  (4 equiv.),  $Pd(PPh_3)_2Cl_2$  (2 mol %) and a mixture of dimethoxyethane/water (1:1 [0.25 M]) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 18 h under nitrogen. Upon cooling, the biphasic solution was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted twice with EtOAc (20 mL) and the combined organic phases were washed with brine (50 mL). The organic phases were dried over  $Na_2SO_4$ , filtered and concentrated. The crude mixture was purified by silica gel column chromatography (hexanes/ethyl acetate) to afford corresponding product.

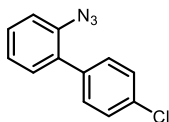
**General Procedure for Sandmeyer reaction (D):** The corresponding 2-aminobiaryl (1.0 equiv.) was dissolved in a mixture of acetic acid / water (2:1, 0.1 M) and cooled to 0 °C.  $NaNO_2$  (1.4 equiv.) was added and the resulting was stirred at 0 °C for one hour.  $NaN_3$  (1.5 equiv.) was then added slowly, the resulting mixture was warmed to room temperature and stirred for an additional hour. The solution was diluted with  $CH_2Cl_2$  (20 mL) and made basic by the slow addition of saturated aqueous  $K_2CO_3$  until bubbling ceased. The phases were separated and the aqueous phase was extracted twice with  $CH_2Cl_2$  (20 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL). The organic phases were dried over  $Na_2SO_4$ , filtered and concentrated. The crude mixture was purified by silica gel column chromatography (hexanes/ethyl acetate) to afford corresponding product.



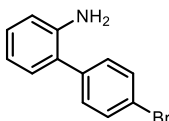
**2-Azido-1,1'-biphenyl (3.1):** Following the General Procedure D, starting from [1,1'-biphenyl]-2-amine (1.0 g, 5.9 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (1.08 g, 94 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



**4'-Chloro-[1,1'-biphenyl]-2-amine (7.1):** Following the General Procedure C, starting from 4-chlorophenylboronic acid (0.28 g, 1.8 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a brown oil (0.25 g, 81 % yield). NMR data was in accordance with what was previously reported.<sup>4</sup>

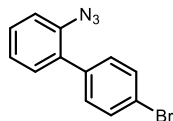


**2-Azido-4'-chloro-1,1'-biphenyl (3.2):** Following the General Procedure D, starting from 4'-chloro-[1,1'-biphenyl]-2-amine 7.1 (0.25 g, 1.2 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.20 g, 74 % yield). NMR data was in accordance with what was previously reported.<sup>5</sup>

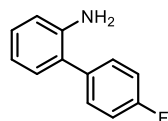


**4'-Bromo-[1,1'-biphenyl]-2-amine (7.2):** Following the General Procedure C, starting from 4-bromophenylboronic acid (0.36 g, 1.8 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.25 g, 68 % yield). NMR data was in accordance with what was previously reported.<sup>6</sup>

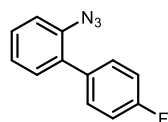




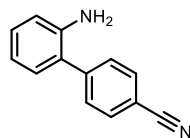
**2-Azido-4'-bromo-1,1'-biphenyl (3.3):** Following the General Procedure D, starting from 4'-bromo-[1,1'-biphenyl]-2-amine **7.2** (0.25 g, 1.0 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.23 g, 84 % yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.55 (d, *J* = 8.5 Hz, 2H), 7.44-7.38 (m, 1H), 7.34-7.29 (m, 3H), 7.26-7.18 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 137.1, 137.0, 132.4, 131.3, 131.0, 129.1, 125.0, 121.8, 118.8; HRMS (ESI) *m/z* calculated for C<sub>12</sub>H<sub>7</sub>BrN [M-N<sub>2</sub>-H]<sup>+</sup> 243.9751; found 243.9762.



**4'-Fluoro-[1,1'-biphenyl]-2-amine (7.3):** Following the General Procedure C, starting from 4-fluorophenylboronic acid (0.17 g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a brown solid (0.15 g, 83 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

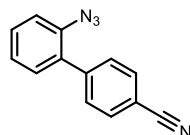


**2-Azido-4'-fluoro-1,1'-biphenyl (7.4):** Following the General Procedure D, starting from 4'-fluoro-[1,1'-biphenyl]-2-amine **7.3** (0.15 g, 0.8 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (0.15 g, 87 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

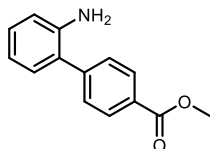


**2'-Amino-[1,1'-biphenyl]-4-carbonitrile (7.5):** Following the General Procedure C, starting from 4-cyanophenylboronic acid (0.18 g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica

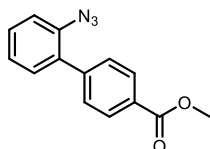
gel column chromatography (100 % hexanes → 30 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.18 g, 92 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



**2'-Azido-[1,1'-biphenyl]-4-carbonitrile (7.6):** Following the General Procedure D, starting from 2'-amino-[1,1'-biphenyl]-4-carbonitrile **7.5** (0.18 g, 0.9 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.08 g, 41 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

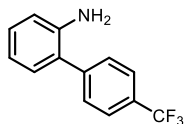


**Methyl 2'-amino-[1,1'-biphenyl]-4-carboxylate (7.7):** Following the General Procedure C, starting from 4-methoxycarbonylphenylboronic acid (0.43 g, 2.4 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 15 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (0.29 g, 65 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.12 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H) 7.20 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.85 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.79 (dd, *J* = 7.9, 0.9 Hz, 1H), 3.96 (s, 3H), 3.76 (brs, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 166.7, 144.3, 143.3, 130.2, 129.9, 129.0, 128.9, 128.7, 126.1, 118.6, 115.7, 51.9; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub>H [M+H]<sup>+</sup> 228.1015; found 228.1019.

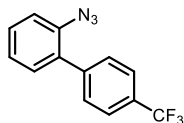


**Methyl 2'-azido-[1,1'-biphenyl]-4-carboxylate (7.8):** Following the General Procedure D, starting from methyl 2'-amino-[1,1'-biphenyl]-4-carboxylate **7.7** (0.29 g, 1.3 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate

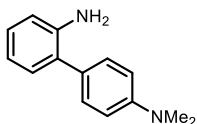
in hexanes), to afford the desired product as a yellow solid (0.29 g, 88 % yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.11 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.47-7.41 (m, 1H), 7.36 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.30-7.21 (m, 2H), 3.95 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 166.9, 142.8, 137.2, 132.6, 131.1, 129.5, 129.4, 129.3, 129.1; 125.0, 118.8, 52.1; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>H [M+H]<sup>+</sup> 254.0921; found 254.0924.



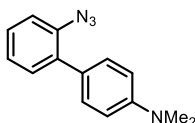
**4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-amine (7.9):** Following the General Procedure C, starting from 4-(trifluoromethyl)phenylboronic acid (0.23 g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.20 g, 83 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



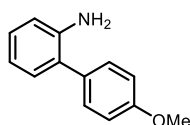
**2-Azido-4'-trifluoromethyl-1,1'-biphenyl (7.10):** Following the General Procedure D, starting from 4'-(trifluoromethyl)-[1,1'-biphenyl]-2-amine **7.9** (0.20 g, 0.8 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a clear oil (0.16 g, 78 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



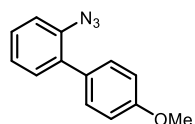
**N',N'-Dimethyl-[1,1'-biphenyl]-2,4'-diamine (7.11):** Following the General Procedure C, starting from 4-(dimethylamino)phenylboronic acid (0.20 g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a red oil (0.19 g, 88 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.36 (d, *J* = 8.6 Hz, 1H), 7.15-7.10 (m, 2H), 6.84-6.76 (m, 4H), 3.79 (brs, 2H), 3.01 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 149.5, 143.7, 130.3, 129.6, 127.7, 127.6, 127.2, 118.4, 115.3, 112.6, 40.4; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>H [M+H]<sup>+</sup> 213.1377; found 213.1386.



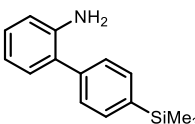
**2'-Azido-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine (7.12):** Following the General Procedure D, starting from *N,N'*-dimethyl-[1,1'-biphenyl]-2,4'-diamine **7.11** (0.19 g, 0.9 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.19 g, 90 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.38-7.32 (m, 4H), 7.25-7.17 (m, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.01 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 149.8, 136.8, 133.9, 190.9, 130.1, 127.6, 125.8, 124.8, 118.6, 111.9, 40.4; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>H [M+H]<sup>+</sup> 239.1296; found 239.1291.



**4'-Methoxy-[1,1'-biphenyl]-2-amine (7.13):** Following the General Procedure C, starting from 4-methoxyphenylboronic acid (0.18g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a pale yellow oil (0.19 g, 97 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

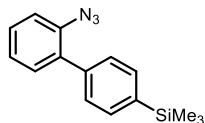


**2-Azido-4'-methoxy-1,1'-biphenyl (7.14):** Following the General Procedure D, starting from 4'-methoxy-[1,1'-biphenyl]-2-amine **7.13** (0.19 g, 0.97 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.19 g, 89 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

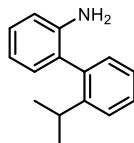


**4'-(Trimethylsilyl)-[1,1'-biphenyl]-2-amine (7.15):** Following the General Procedure C, starting from (4-(trimethylsilyl)phenyl)boronic acid (0.35 g, 1.8 mmol, 1.2 equiv.), the crude mixture was

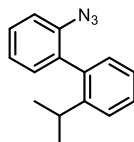
purified by silica gel column chromatography (100 % hexanes → 5 % ethyl acetate in hexanes), to afford the desired product as a yellow oil (0.31 g, 86 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.61 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.19-7.14 (m, 2 H), 6.83 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 6.78 (dd, *J* = 8.0, 0.8 Hz, 1 H), 3.78 (brs, 2H), 0.32 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 143.5, 139.9, 139.2, 133.8, 130.4, 128.5, 128.3, 127.6, 118.6, 115.6, -1.1; HRMS (ESI) *m/z* calculated for C<sub>15</sub>H<sub>19</sub>NSiH [M+H]<sup>+</sup> 242.1356; found 242.1359.



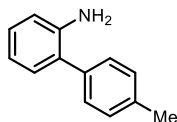
**(2'-Azido-[1,1'-biphenyl]-4-yl)trimethylsilane (7.16):** Following the General Procedure D, starting from 4'-(trimethylsilyl)-[1,1'-biphenyl]-2-amine **7.15** (0.31 g, 1.3 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 5 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (0.26 g, 74 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.61 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.43-7.39 (m, 1H), 7.36 (dd, *J*<sub>1</sub> = 7.6 Hz, *J*<sub>2</sub> = 1.5 Hz, 1H), 7.29-7.27 (m, 1H), 7.25-7.21 (m, 1H), 0.32 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 139.5, 138.5, 137.1, 133.6, 133.1, 131.2, 128.7, 128.6, 124.9, 118.6, -1.1; HRMS (ESI) *m/z* calculated for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>SiNH<sub>4</sub> [M+NH<sub>4</sub>]<sup>+</sup> 285.1522; found 285.1530.



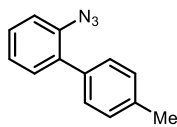
**2'-Isopropyl-[1,1'-biphenyl]-2-amine (7.17):** Following the General Procedure C, starting from 1-bromo-2-isopropylbenzene (0.17 mL, 1.1 mmol, 1.1 equiv.) and 2-aminophenylboronic acid hydrochloride (0.17 g, 1.0 mmol, 1.0 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.22 g, 99 % yield). NMR data was in accordance with what was previously reported.<sup>7</sup>



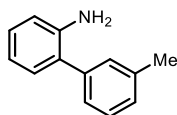
**2-Azido-2'-isopropyl-1,1'-biphenyl (7.18):** Following the General Procedure D, starting from 2'-isopropyl-[1,1'-biphenyl]-2-amine **7.17** (0.22 g, 1.0 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a pale brown solid (0.15 g, 68 % yield). NMR data was in accordance with what was previously reported.<sup>7</sup>



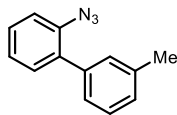
**4'-Methyl-[1,1'-biphenyl]-2-amine (7.19):** Following the General Procedure C, starting from 4-methylphenylboronic acid (0.16 g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a clear oil (0.15 g, 83 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



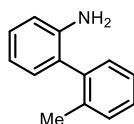
**2-Azido-4'-methyl-1,1'-biphenyl (7.20):** Following the General Procedure D, starting from 4'-methyl-[1,1'-biphenyl]-2-amine **7.19** (0.15 g, 0.8 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a clear oil (0.13 g, 79 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



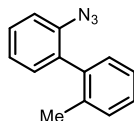
**3'-Methyl-[1,1'-biphenyl]-2-amine (7.21):** Following the General Procedure C, starting from 3-methylphenylboronic acid (0.16 g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.14 g, 76 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



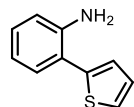
**2-Azido-3'-methyl-1,1'-biphenyl (7.22):** Following the General Procedure D, starting from 3'-methyl-[1,1'-biphenyl]-2-amine **7.21** (0.14 g, 0.8 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.12 g, 77 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



**2'-Methyl-[1,1'-biphenyl]-2-amine (7.23):** Following the General Procedure C, starting from 2-methylphenylboronic acid (0.16 g, 1.2 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.15 g, 84 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

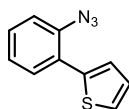


**2-Azido-2'-methyl-1,1'-biphenyl (7.24):** Following the General Procedure D, starting from 2'-methyl-[1,1'-biphenyl]-2-amine **7.23** (0.15 g, 0.8 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.15 g, 84 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

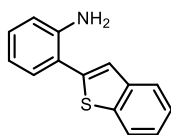


**2-(Thiophen-2-yl)aniline (7.25):** Following the General Procedure C, starting from 2-thienylboronic acid (0.31 g, 2.4 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired

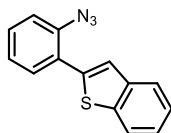
product as a tan oil (0.30 g, 84 % yield). NMR data was in accordance with what was previously reported.<sup>8</sup>



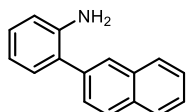
**2-(2-Azidophenyl)thiophene (7.26):** Following the General Procedure D, starting from 2-(thiophen-2-yl)aniline **7.25** (0.30 g, 1.7 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.30 g, 89 % yield). NMR data was in accordance with what was previously reported.<sup>9</sup>



**2-(Benzo[b]thiophen-2-yl)aniline (7.27):** Following the General Procedure C, starting from benzo[b]thiophen-2-ylboronic acid (0.43 g, 2.4 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (0.36 g, 79 % yield). NMR data was in accordance with what was previously reported.<sup>10</sup>

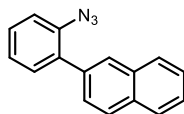


**2-(2-Azidophenyl)benzo[b]thiophene (7.28):** Following the General Procedure D, starting from 2-(benzo[b]thiophen-2-yl)aniline **7.27** (0.36 g, 1.6 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (0.14 g, 35 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.88-7.82 (m, 2H), 7.72 (s, 1H), 7.68 (dd, *J*<sub>1</sub> = 7.7, 1.5 Hz, 1H) 7.43-7.33 (m, 3H), 7.30 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.24-7.20 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 140.0, 139.9, 139.2, 136.9, 130.7, 129.2, 125.9, 125.0, 124.5, 124.4, 123.8, 123.7, 121.9, 119.1; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>8</sub>NS [M-N<sub>2</sub>-H]<sup>+</sup> 222.0376; found 222.0378.

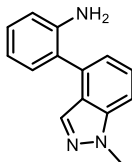




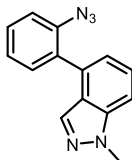
**2-(Naphthalen-2-yl)aniline (7.29):** Following the General Procedure C, starting from 2-naphthylboronic acid (0.41 g, 2.4 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow oil (0.36 g, 82 % yield). NMR data was in accordance with what was previously reported.<sup>9</sup>



**2-(2-Azidophenyl)naphthalene (7.30):** Following the General Procedure D, starting from 2-(naphthalen-2-yl)aniline **7.29** (0.36 g, 1.6 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow oil (0.34 g, 93 % yield). NMR data was in accordance with what was previously reported.<sup>9</sup>

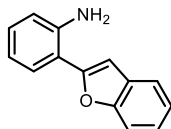


**2-(1-Methyl-1*H*-indazol-4-yl)aniline (7.31):** Following the General Procedure C, starting from 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-indazole (0.57 g, 2.2 mmol, 1.1 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 20 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.39 g, 87 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.90 (d, *J* = 0.7 Hz, 1H), 7.48 (dd, *J* = 8.4, 7.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1 H), 7.27-7.19 (m, 3H), 6.90-6.83 (m, 2H), 4.13 (s, 3H), 3.76 (brs, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 143.8, 140.2, 132.9, 132.8, 130.7, 128.9, 126.6, 124.8, 123.2, 121.1, 118.4, 115.7, 107.9, 35.7; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>H [M+H]<sup>+</sup> 224.1186; found 224.1182.

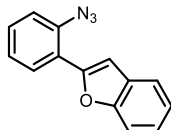


**4-(2-Azidophenyl)-1-methyl-1*H*-indazole (7.32):** Following the General Procedure D, starting from 2-(1-methyl-1*H*-indazol-4-yl)aniline **7.31** (0.39 g, 1.7 mmol), the crude mixture was purified

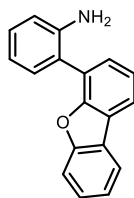
by silica gel column chromatography (100 % hexanes → 15 % ethyl acetate in hexanes), to afford the desired product as a tan solid (0.29 g, 71 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.84 (d, *J* = 0.7 Hz, 1H), 7.51-7.42 (m, 4H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.30-7.26 (m, 1H), 7.16 (dd, *J* = 6.8, 0.9 Hz, 1H), 4.13 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 139.9, 137.7, 132.6, 131.6, 131.5, 131.4, 129.2, 126.0, 124.9, 123.4, 121.6, 118.9, 108.4, 35.6; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>H [M+H]<sup>+</sup> 250.1092; found 250.1087.



**2-(Benzofuran-2-yl)aniline (7.33):** Following the General Procedure C, starting from 2-benzofuranylboronic acid (0.39 g, 2.4 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a brown solid (0.41 g, 99 % yield). NMR data was in accordance with what was previously reported.<sup>11</sup>

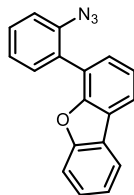


**2-(2-Azidophenyl)benzofuran (7.34):** Following the General Procedure D, starting from 2-(benzofuran-2-yl)aniline **7.33** (0.41 g, 1.99 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.34 g, 72 % yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.63 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.54-7.51 (m, 2H), 7.43-7.22 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 154.0, 151.3, 136.3, 129.3, 129.1, 127.8, 124.9, 124.6, 122.9, 121.9, 121.3, 118.9, 110.9, 106.9; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>9</sub>N<sub>3</sub>OH [M+H]<sup>+</sup> 236.0818; found 236.0822.

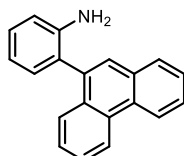


**2-(Dibenzo[*b,d*]furan-4-yl)aniline (7.35):** Following the General Procedure C, starting from 4-(dibenzofuranyl)boronic acid (0.35 g, 1.7 mmol, 1.2 equiv.), the crude mixture was purified by

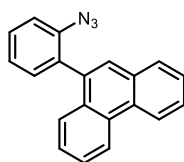
silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (0.26 g, 73 % yield). NMR data was in accordance with what was previously reported.<sup>12</sup>



**4-(2-Azidophenyl)dibenzo[*b,d*]furan (7.36):** Following the General Procedure D, starting from 2-(dibenzo[*b,d*]furan-4-yl)aniline **7.35** (0.26 g, 1.0 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (0.25 g, 89 % yield). NMR data was in accordance with what was previously reported.<sup>13</sup>

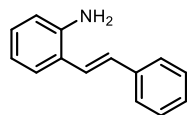


**2-(Phenanthren-9-yl)aniline (7.37):** Following the General Procedure C, starting from 9-phenanthracenylboronic acid (0.53 g, 2.4 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (0.45 g, 84 % yield). NMR data was in accordance with what was previously reported.<sup>14</sup>

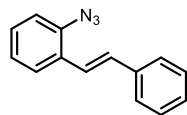


**9-(2-Azidophenyl)phenanthrene (7.38):** Following the General Procedure D, starting from 2-(phenanthren-9-yl)aniline **7.37** (0.45 g, 1.7 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (0.40 g, 81 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.79 (d, *J* = 8.2 Hz, 1H), 8.75 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.72-7.61 (m, 4H), 7.56-7.52 (m, 3H), 7.41

(dd,  $J = 7.5, 1.5$  Hz, 1H), 7.35 (d,  $J = 7.9$  Hz, 1 H), 7.33-7.29 (m, 1H); (100 MHz,  $\text{CDCl}_3$ )  $\delta = 138.9, 134.9, 132.4, 132.2, 131.3, 131.1, 130.3$  (2C), 129.2, 128.8, 128.1, 126.8 (2C), 126.7, 126.6, 126.5, 124.8, 122.9, 122.6, 118.4; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{20}\text{H}_{13}\text{N}_3\text{NH}_4$   $[\text{M}+\text{NH}_4]^+$  313.1438; found 313.1448.

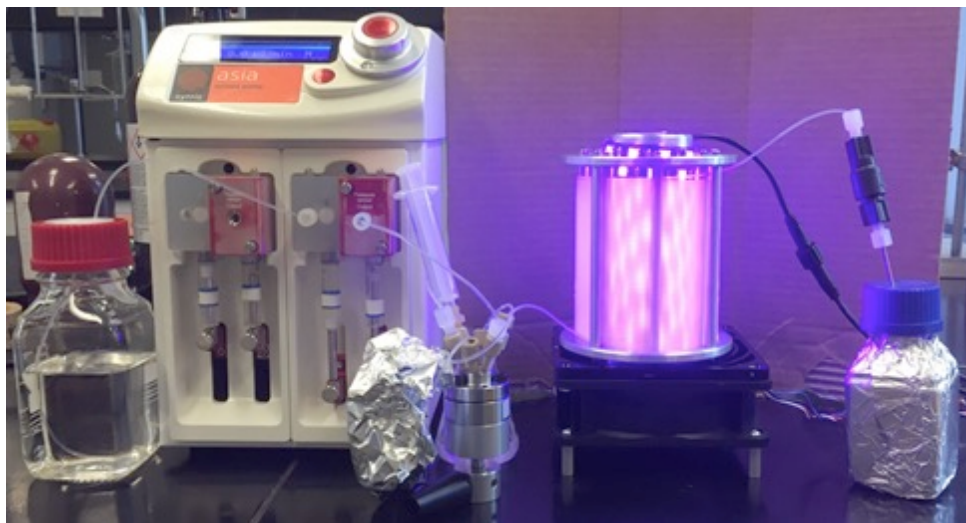


**(E)-2-Styrylaniline (7.39):** Following the General Procedure C, starting from trans-2-phenylvinylboronic acid (0.53 g, 3.6 mmol, 1.2 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (0.49 g, 83 % yield). NMR data was in accordance with what was previously reported.<sup>9</sup>



**(E)-1-Azido-2-styrylbenzene (7.40):** Following the General Procedure D, starting from (E)-2-styrylaniline **7.39** (0.20 g, 1.0 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.2 g, 88 % yield). NMR data was in accordance with what was previously reported.<sup>9</sup>

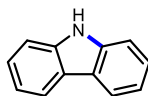
### 7.3 Synthesis of Carbazoles



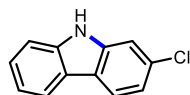
**Figure 7.1** Continuous-flow reactor set-up used for the UV-light-mediated synthesis of heterocycles.

**Photodecomposition Procedure at 254 nm under Continuous-Flow (A):** A solution of biarylazide (0.15 mmol, 1.0 equiv.) and THF (5 mL, 30 mM) was injected via a syringe into an aluminium foil-covered 5 mL injection loop (6-way valve). The carrier solvent was pumped by a Syrris Asia pumping module. The pump was turned on at a flow rate of 1.6 mL/min. The reaction mixture was pumped through a 16 mL FEP-coiled reactor irradiated with 254 nm light source for a 10 minutes residence time. The collected solution was concentrated under vacuum to provide a crude reaction mixture which was purified by column chromatography on silica-gel (hexanes/ethyl acetate) to afford corresponding product.

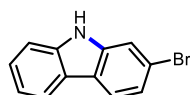
**Photodecomposition Procedure at 394 nm under Continuous-Flow (B):** A solution of biarylazide (0.15 mmol, 1.0 equiv.) and THF (5 mL, 30 mM) was injected via a syringe into an aluminium foil-covered 5 mL injection loop (6-way valve). The carrier solvent was pumped by a Syrris Asia pumping module. The pump was turned on at a flow rate of 0.0542 mL/min. The reaction mixture was pumped through a 13 mL PFA-coiled reactor irradiated with 394 nm (purple LED light source) for a 4 hours residence time. The collected solution was concentrated under vacuum to provide a crude reaction mixture which was purified by column chromatography on silica-gel (hexanes/ethyl acetate) to afford corresponding product.



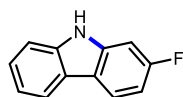
**9H-Carbazole (3.4):** Following the Photodecomposition Procedure A, starting from 2-azido-1,1'-biphenyl **3.1**, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (20.0 mg, 80 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-1,1'-biphenyl **3.1**, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (20.0 mg, 80 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



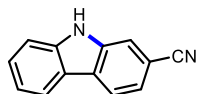
**2-Chloro-9H-carbazole (3.5):** Following the Photodecomposition Procedure A, starting from 2-azido-4'-chloro-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (18.5 mg, 61 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-4'-chloro-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (22.8 mg, 81 % yield). NMR data was in accordance with what was previously reported.<sup>15</sup>



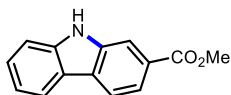
**2-Bromo-9H-carbazole (3.6):** Following the Photodecomposition Procedure A, starting from 2-azido-4'-bromo-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (16.6 mg, 45 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-4'-bromo-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (29.6 mg, 80 % yield). NMR data was in accordance with what was previously reported.<sup>15</sup>



**2-Fluoro-9H-carbazole (3.7):** Following the Photodecomposition Procedure A, starting from 2-azido-4'-fluoro-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (24.2 mg, 87 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-4'-fluoro-1,1'-biphenyl and using ethyl acetate as the solvent, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (19.7 mg, 71 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

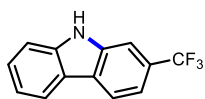


**2-Cyano-9H-carbazole (3.8):** Following the Photodecomposition Procedure A, starting from 2'-azido-[1,1'-biphenyl]-4-carbonitrile, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (22.5 mg, 78 % yield). Following the Photodecomposition Procedure B, starting from 2'-azido-[1,1'-biphenyl]-4-carbonitrile and using ethyl acetate as the solvent, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (19.9 mg, 69 % yield). NMR data was in accordance with what was previously reported.<sup>16</sup>

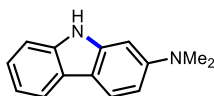


**Methyl 9H-carbazole-2-carboxylate (3.9):** Following the Photodecomposition Procedure A, starting from Methyl 2'-azido-[1,1'-biphenyl]-4-carboxylate, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (24.3 mg, 72 % yield). Following the Photodecomposition Procedure B, starting from Methyl 2'-azido-[1,1'-biphenyl]-4-carboxylate, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes),

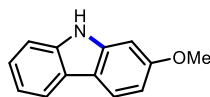
to afford the desired product as a white solid (27.7 mg, 82 % yield). NMR data was in accordance with what was previously reported.<sup>16</sup>



**2-(Trifluoromethyl)-9H-carbazole (3.10):** Following the Photodecomposition Procedure A, starting from 2-azido-4'-trifluoromethyl-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (11.5 mg, 33 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-4'-trifluoromethyl-1,1'-biphenyl and using ethyl acetate as the solvent, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (26.2 g, 74 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



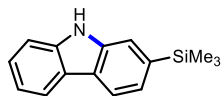
**2-(Dimethylamino)-9H-carbazole (3.11):** Following the Photodecomposition Procedure A, starting from 2'-azido-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (26.5 mg, 84 % yield). Following the Photodecomposition Procedure B, starting from 2'-azido-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine and using ethyl acetate as the solvent, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (22.7 mg, 72 % yield). NMR data was in accordance with what was previously reported.<sup>16</sup>



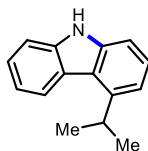
**2-Methoxy-9H-carbazole (3.12):** Following the Photodecomposition Procedure A, starting from 2-azido-4'-methoxy-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (27.5 mg, 93 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-4'-methoxy-1,1'-biphenyl and using ethyl acetate as the solvent, the crude mixture



was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (19.5 mg, 66 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

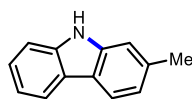


**2-Methoxy-9H-carbazole (3.13):** Following the Photodecomposition Procedure A, starting from 2-azido-4'-methoxy-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (25.1 mg, 70 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-4'-methoxy-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a pale yellow solid (29.1 mg, 81 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ = 11.17 (s, 1H), 8.09 (m, 2H), 7.62 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.40-7.37 (m, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.16-7.13 (m, 1H), 0.32 (s, 9H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ = 139.8, 139.5, 136.4, 125.7, 122.9 (2C), 122.2, 120.2, 119.6, 118.4, 115.6, 110.9, -0.8; HRMS (ESI) *m/z* calculated for C<sub>15</sub>H<sub>17</sub>NSi [M-H]<sup>-</sup> 238.1052; found 238.1052.

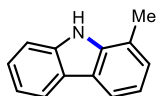


**4-Isopropyl-9H-carbazole (3.14):** Following the Photodecomposition Procedure A, starting from 2-azido-2'-isopropyl-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (16.6 mg, 53 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-2'-isopropyl-1,1'-biphenyl and using ethyl acetate as the solvent, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (16.0 mg, 51 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ = 11.29 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.39-7.31 (m, 3H), 7.19-7.15 (m, 1H), 7.08-7.03 (m, 1H), 3.92-3.82 (m, 1H), 1.41 (d, *J* = 6.8 Hz, 6H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ = 143.9, 140.3, 140.1, 126.0, 125.2, 122.8, 122.2, 119.9, 119.1,

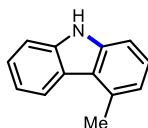
114.9, 111.2, 108.9, 30.2, 22.8 (2C); HRMS (ESI)  $m/z$  calculated for  $C_{15}H_{15}N$   $[M-H]^-$  208.1130; found 208.1126.



**2-Methyl-9H-carbazole (3.15):** Following the Photodecomposition Procedure A, starting from 2-azido-4'-methyl-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford the desired product as a white solid (18.8 mg, 69 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-4'-methyl-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford the desired product as a white solid (23.9 mg, 88 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>

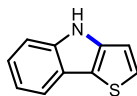


**1-Methyl-9H-carbazole (3.16):** Following the Photodecomposition Procedure A, starting from 2-azido-3'-methyl-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford an inseparable mixture of regioisomers as a pale yellow solid (21.5 mg, 79 % yield, 70:30). Following the Photodecomposition Procedure B, starting from 2-azido-3'-methyl-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford an inseparable mixture of regioisomers as a pale yellow solid (25.8 mg, 95 % yield, 53:47). NMR data was in accordance with what was previously reported.<sup>3</sup>

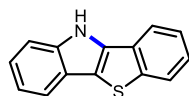


**4-Methyl-9H-carbazole (3.17):** Following the Photodecomposition Procedure A, starting from 2-azido-2'-methyl-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford the desired product as a white solid (22.6 mg, 83 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-2'-methyl-1,1'-biphenyl and using ethyl acetate as the solvent, the crude mixture was

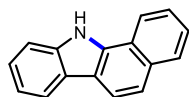
purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (24.5 mg, 90 % yield). NMR data was in accordance with what was previously reported.<sup>3</sup>



**4H-Thieno[3,2-b]indole (3.18):** Following the Photodecomposition Procedure A, starting from 2-(2-azidophenyl)thiophene, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (17.9 mg, 69 % yield). Following the Photodecomposition Procedure B, starting from 2-(2-azidophenyl)thiophene, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (19.7 mg, 76 % yield). NMR data was in accordance with what was previously reported.<sup>16</sup>

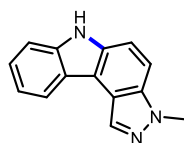


**10H-Benzo[4,5]thieno[3,2-b]indole (3.19):** Following the Photodecomposition Procedure A, starting from 2-(2-azidophenyl)benzo[*b*]thiophene, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (24.1 mg, 72 % yield). Following the Photodecomposition Procedure B, starting from 2-(2-azidophenyl)benzo[*b*]thiophene, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (19.1 mg, 57 % yield). NMR data was in accordance with what was previously reported.<sup>16</sup>

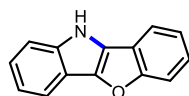


**11H-Benzo[*a*]carbazole (3.20):** Following the Photodecomposition Procedure A, starting from 2-(2-azidophenyl)naphthalene, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (22.5 mg, 69 % yield). Following the Photodecomposition Procedure B, starting from 2-(2-azidophenyl)naphthalene, the crude mixture was purified by silica gel column chromatography

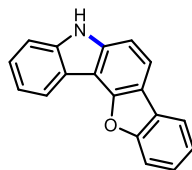
(100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (27.4 mg, 84 % yield). NMR data was in accordance with what was previously reported.<sup>17</sup>



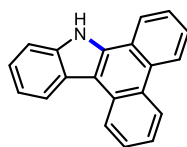
**3-Methyl-3,6-dihydropyrazolo[3,4-*c*]carbazole (3.21):** Following the Photodecomposition Procedure A, starting from 4-(2-azidophenyl)-1-methyl-1*H*-indazole, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 25 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (23.2 mg, 70 % yield). Following the Photodecomposition Procedure B, starting from 4-(2-azidophenyl)-1-methyl-1*H*-indazole, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 25 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (28.5 mg, 86 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.49 (s, 1H) 8.57 (d, *J* = 0.9 Hz, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 7.67 (dd, *J* = 9.0, 0.7 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H) 7.57 (d, *J* = 8.1 Hz, 1H) 7.40-7.37 (m, 1H), 7.24-7.20 (m, 1H), 4.15 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 138.8, 135.7, 134.2, 129.7, 124.4, 121.8, 121.1, 118.6, 116.8, 112.2, 111.5, 111.3, 108.1, 35.8; HRMS (ESI) *m/z* calculated for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>H [M+H]<sup>+</sup> 222.1036; found 222.1026.



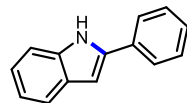
**10*H*-Benzofuro[3,2-*b*]indole (3.22):** Following the Photodecomposition Procedure A, starting from 2-(2-azidophenyl)benzofuran, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (23.6 g, 76 % yield). Following the Photodecomposition Procedure B, starting from 2-(2-azidophenyl)benzofuran, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (14.6 mg, 47 % yield). NMR data was in accordance with what was previously reported.<sup>16</sup>



**5H-Benzofuro[3,2-*c*]carbazole (3.23):** Following the Photodecomposition Procedure A, starting from 4-(2-azidophenyl)dibenzo[*b,d*]furan, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow crystalline solid (22.0 mg, 57 % yield). Following the Photodecomposition Procedure B, starting from 4-(2-azidophenyl)dibenzo[*b,d*]furan, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow crystalline solid (35.9 mg, 93 % yield). NMR data was in accordance with what was previously reported.<sup>13</sup>

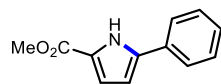


**9H-Dibenzo[*a,c*]carbazole (3.24):** Following the Photodecomposition Procedure A, starting from 9-(2-Azidophenyl)phenanthrene, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (30.5 mg, 76 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (22.1 mg, 55 % yield). NMR data was in accordance with what was previously reported.<sup>17</sup>



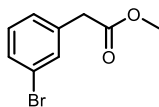
**2-Phenyl-1H-indole (3.25):** Following the Photodecomposition Procedure A, starting from (*E*)-1-Azido-2-styrylbenzene, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (19.6 mg, 66 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes →

10 % ethyl acetate in hexanes), to afford the desired product as a white solid (22.9 mg, 79 % yield). NMR data was in accordance with what was previously reported.<sup>18</sup>

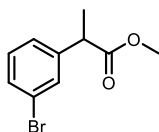


**Methyl 5-phenyl-1H-pyrrole-2-carboxylate (3.26):** Following the Photodecomposition Procedure A, starting from 2-azido-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (15.1 mg, 50 % yield). Following the Photodecomposition Procedure B, starting from 2-azido-1,1'-biphenyl, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (25.1 mg, 83 % yield). NMR data was in accordance with what was previously reported.<sup>19</sup>

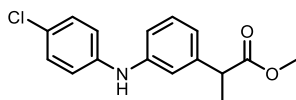
## 7.4 Synthesis of Carprofen Methyl Ester



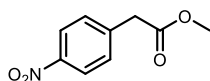
**Methyl 2-(3-bromophenyl)acetate (7.41):** An oven-dried sealed tube was charge with 3-bromophenyl acetic acid (2.15 g, 10 mmol, 1 equiv.), sulfuric acid (catalytic amount) and methanol (20 mL, 0.5 M). The mixture was stirred at 65 °C for 16 h. Upon cooling, the reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL), the phases were separated. The aqueous phase was extracted twice with EtOAc (20 mL) and the combined organic phases were washed with brine (50 mL). The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a clear oil (2.07 g, 90 % yield). NMR data was in accordance with what was previously reported.<sup>20</sup>



**Methyl 2-(3-bromophenyl)propanoate (7.42):** Methyl 2-(3-bromophenyl)acetate **7.41** (1.77 g, 7.7 mmol) in dry THF (15 mL) was added dropwise to a stirred solution of lithium diisopropylamide (LDA) (8.9 mmol, 1.15 equiv.) in THF (20 mL) at -78 °C under nitrogen (N<sub>2</sub>), and after 30 min, iodomethane (0.5 mL, 8.1 mmol) was added slowly. The resulting solution was stirred for 2 h with the temperature changed from -78 to 0 °C, then evaporated to dryness, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a clear oil (1.28 g, 68 % yield). NMR data was in accordance with what was previously reported.<sup>21</sup>

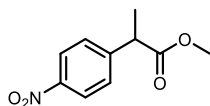


**Methyl 2-(3-((4-chlorophenyl)amino)phenyl)propanoate (3.27):** An oven-dried sealed tube was charged with 4-chloroaniline (0.42 g, 3.3 mmol, 1.1 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (1.47 g, 4.5 mmol, 1.5 equiv.), xPhos (0.11 mg, 0.24 mmol, 8 mol %), Pd<sub>2</sub>(dba)<sub>3</sub> (27.0 mg, 0.12 mmol, 4 mol %), anhydrous toluene (15 mL, 0.20 M) and methyl 2-(3-bromophenyl)propanoate **7.42** (0.73 g, 3.0 mmol, 1.0 equiv.) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 24 h under nitrogen. Upon cooling, the reaction mixture was diluted with dichloromethane (30 mL), filtered on Celite® and then dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure afforded the crude product that was purified by silica gel column chromatography (5% ethyl acetate in hexanes) to afford the desired product as yellow oil (0.67 g, 77 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.25-7.21 (m, 3H), 7.01-6.95 (m, 4H), 6.89-6.87 (m, 1H), 5.61 (brs, 1H), 3.71-3.66 (m, 4H), 1.49 (d, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 174.9, 142.9, 141.7, 141.5, 129.5, 129.1, 125.3, 120.2, 118.7, 116.8, 116.2, 51.9, 45.2, 18.3; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>16</sub>ClNO<sub>2</sub>H [M+H]<sup>+</sup> 290.0929; found 290.0942.

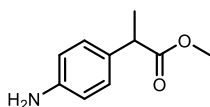


**Methyl 2-(4-nitrophenyl)acetate (7.43):** An oven-dried sealed tube was charged with 4-nitrophenyl acetic acid (5.44 g, 30 mmol, 1 equiv.), sulfuric acid (catalytic amount) and methanol (30 mL, 1 M). The mixture was stirred at 65 °C for 16 h. Upon cooling, the reaction mixture was diluted with ethyl acetate (60 mL) and water (60 mL), the phases were separated. The aqueous phase was extracted twice with EtOAc (30 mL) and the combined organic phases were washed with brine (60 mL). The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (5.6 g, 96 % yield). NMR data was in accordance with what was previously reported NMR data was in accordance with what was previously reported.<sup>20</sup>

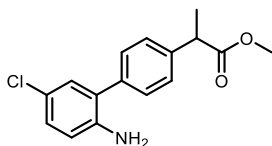




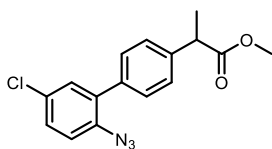
**Methyl 2-(4-nitrophenyl)propanoate (7.44):** An oven-dried round-bottom flask, was charged with methyl 2-(4-nitrophenyl)acetate **7.43** (1.01 g, 5.17 mmol, 1.0 equiv.), sodium hydride (0.20 g, 4.92 mmol, 0.95 equiv.) and anhydrous THF (10 mL, 0.52 M). The mixture was stirred at 0 °C and iodomethane (0.48 mL, 7.76 mmol, 1.5 equiv.) was added dropwise. The mixture was warmed to room temperature and the reaction was followed by TLC until completion. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL), the phases were separated. The aqueous phase was extracted twice with EtOAc (20 mL) and the combined organic phases were washed with brine (50 mL). The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude mixture was purified by silica gel column chromatography (100 % hexanes → 20 % ethyl acetate in hexanes), to afford the desired product as a yellow oil (1.08 g, 94 % yield). NMR data was in accordance with what was previously reported.<sup>22</sup>



**Methyl 2-(4-aminophenyl)propanoate (7.45):** An oven-dried round-bottom flask, was charged with methyl 2-(4-nitrophenyl)propanoate **7.44** (0.30 g, 1.4 mmol, 1.0 equiv.), palladium on charcoal (10% Pd, 0.15 g) and methanol (14 mL, 0.125 M). The mixture was hydrogenated (1 atm of H<sub>2</sub>) until complete disappearance (4-5h) of the starting material (TLC). After filtration on a pad of Celite, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 20 % ethyl acetate in hexanes), to afford the desired product as a yellow solid (0.22 g, 89 % yield). NMR data was in accordance with what was previously reported.<sup>23</sup>

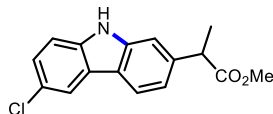


**Methyl 2-(2'-amino-5'-chloro-[1,1'-biphenyl]-4-yl)propanoate (7.46):** A round-bottom flask was charged with methyl 2-(4-aminophenyl)propanoate **7.45** (0.11 g, 0.6 mmol, 1.0 equiv.), sodium nitrite (46 mg, 0.66 mmol, 1.1 equiv.) and a mixture of methanol/HCl [6M] (0.33 M, 2:1). The mixture was cooled to 0 °C and stirred for 1 hour. Bis(pinacolato)diboron (0.17 g, 0.66 mmol, 1.1 equiv.) was added to the mixture and stirred for an additional 2 hours at room temperature. The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and basified by the slow addition of saturated aqueous K<sub>2</sub>CO<sub>3</sub> until bubbling ceased. The phases were separated and the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL). The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude mixture was submitted to General Procedure C, starting from methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (0.25 g, 1.1 mmol, 1.1 equiv.), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 20 % ethyl acetate in hexanes), to afford the desired product as a pale yellow oil (0.14 g, 62 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.39 (s, 4H), 7.11-7.09 (m, 2H), 6.69-6.67 (m, 1H), 3.81-3.76 (m, 3H), 3.71 (s, 3H), 1.55 (d, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 174.8, 142.2, 139.9, 137.1, 129.9, 129.1, 128.4, 128.1, 128.0, 123.1, 116.6, 52.1, 45.1, 18.5; HRMS (ESI) *m/z* calculated for C<sub>16</sub>H<sub>16</sub>ClNO<sub>2</sub>H [M+H]<sup>+</sup> 290.0930; found 290.0942.



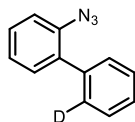
**Methyl 2-(2'-azido-5'-chloro-[1,1'-biphenyl]-4-yl)propanoate (3.28):** Following the General Procedure D, starting from methyl 2-(2'-amino-5'-chloro-[1,1'-biphenyl]-4-yl)propanoate **7.46** (0.25 g, 0.87 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % diethyl ether in hexanes), to afford the desired product as a clear oil (0.22 g, 79 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.42-7.32 (m, 6H), 7.18 (d, *J* = 8.4 Hz, 1H), 3.79 (q, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 1.55 (d, *J* = 7.2 Hz, 3H); (100 MHz, CDCl<sub>3</sub>) δ = 174.8, 140.3, 135.7,

135.6, 134.7, 131.0, 130.2, 129.5, 128.5, 127.4, 120.0, 52.1, 45.1, 18.5; HRMS (ESI)  $m/z$  calculated for  $C_{16}H_{14}ClN_3O_2NH_4 [M+NH_4]^+$  333.1123; found 333.1113.

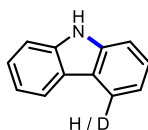


**Methyl 2-(6-chloro-9H-carbazol-2-yl)propanoate (3.29):** Following the Photodecomposition Procedure A, starting from methyl 2-(2'-azido-5'-chloro-[1,1'-biphenyl]-4-yl)propanoate **3.28**, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  15 % ethyl acetate in hexanes), to afford the desired product as a white solid (21.6 mg, 50 % yield). Following the Photodecomposition Procedure B, starting from methyl 2-(2'-azido-5'-chloro-[1,1'-biphenyl]-4-yl)propanoate **3.28**, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  15 % ethyl acetate in hexanes), to afford the desired product as a white solid (27.6 mg, 64 % yield). NMR data was in accordance with what was previously reported.<sup>24</sup>

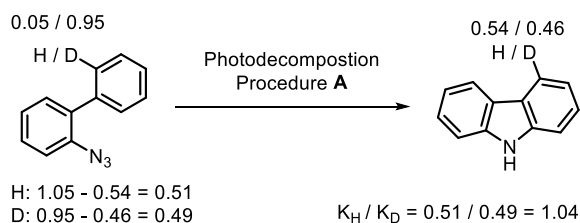
## 7.5 Kinetic Isotope Effects

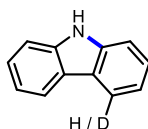
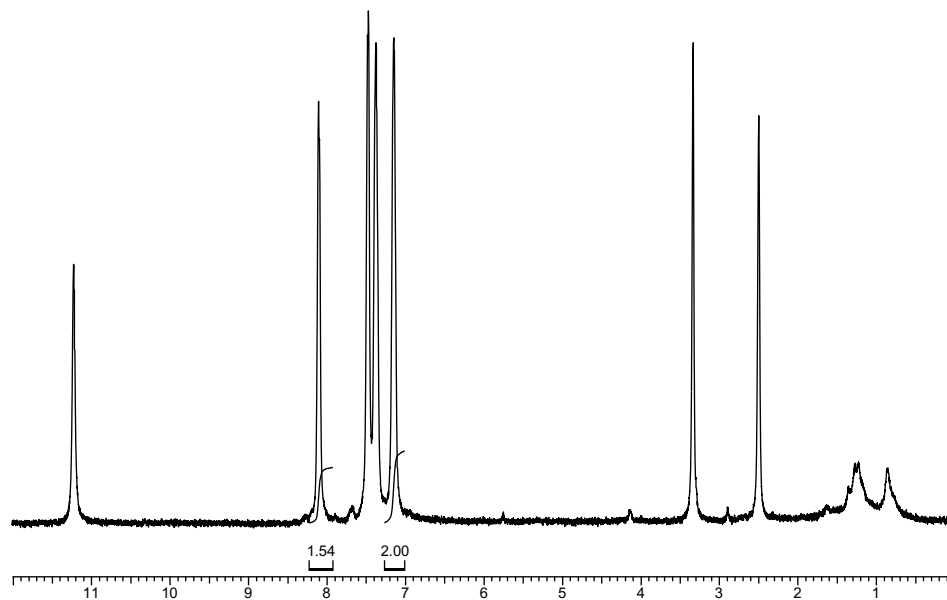


**2-Azido-1,1'-biphenyl-2'-d (3.30):** Following the General Procedure D, starting from [1,1'-biphenyl]-2'-d-2-amine (0.27 g, 1.6 mmol), the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford the desired product as a tan oil (0.23 g, 74 % yield),  $^1\text{H}$  NMR showed 95 % deuterium incorporation. NMR data was in accordance with what was previously reported.<sup>9</sup>

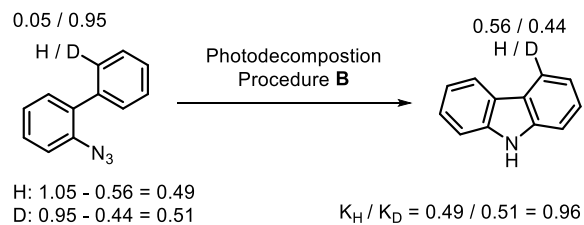


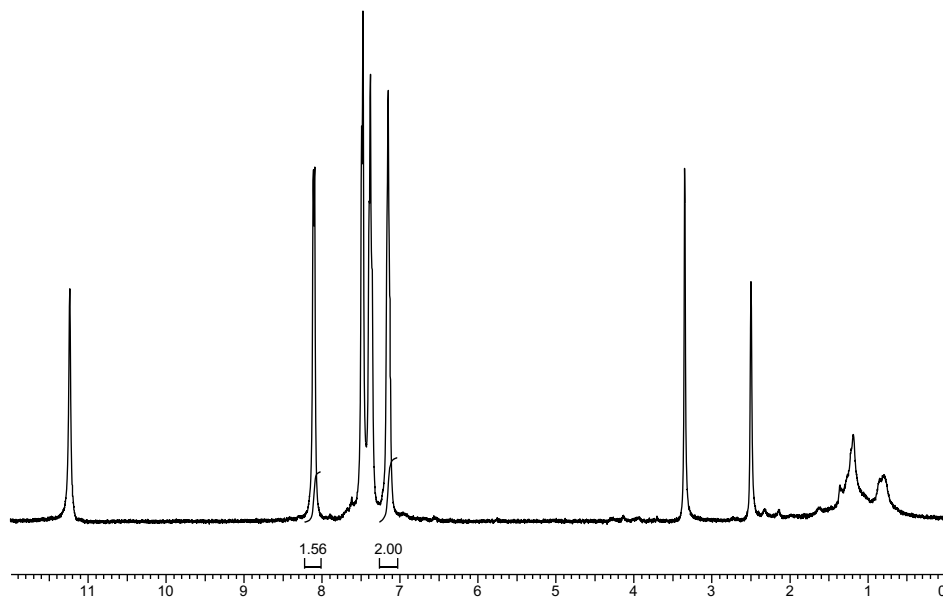
**9H-Carbazole-4-d (d-3.31 or 3.31):** Following the Photodecomposition Procedure A, starting from 2-azido-1,1'-biphenyl-2'-d **3.30**, the crude mixture was purified by silica gel column chromatography (100 % hexanes  $\rightarrow$  10 % ethyl acetate in hexanes), to afford the desired product as a white solid (20.1 mg, 80 % yield,  $K_{\text{H}} / K_{\text{D}} = 1.04$ ). NMR data was in accordance with what was previously reported.<sup>3</sup>





**9H-Carbazole-4-d (*d*-3.31 or 3.31):** Following the Photodecomposition Procedure B for 2 hours (0.108 mL/min), starting from 2-azido-1,1'-biphenyl-2'-d **3.30** and using ethyl acetate as the solvent, the crude mixture was purified by silica gel column chromatography (100 % hexanes → 10 % ethyl acetate in hexanes), to afford the desired product as a white solid (20.1 mg, 80 % yield,  $K_H / K_D = 0.96$ ). NMR data was in accordance with what was previously reported.<sup>3</sup>





## 7.6 Background on Light Source

For reactions using irradiation at 254 nm, a previously published experimental set up was used: [A. Caron, A. C. Hernandez-Perez and S. K. Collins](#) *Org. Process Res. Dev.* 2014, **18**, 1571. The UV light sources was purchased from Luzchem (<http://www.luzchem.com/>). The following data is available online for the UVC lamp used:

Chamber Temp. 25 °C

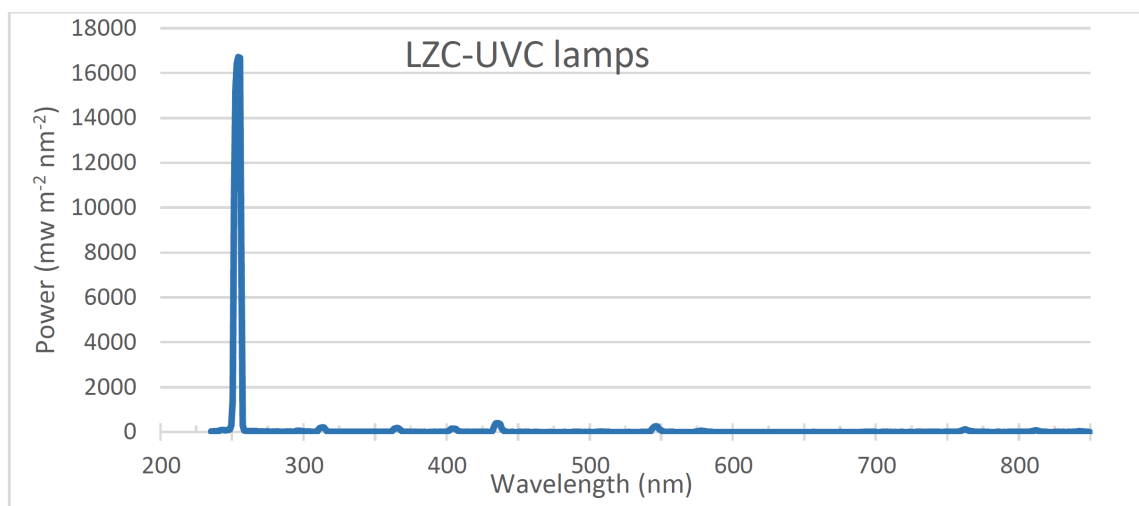
Photoreactor model LZC-ICH2

Monitored range 235 to 850 nm

Resolved peaks: 254, 313, 365, 405, 435, 546, 762 nm

The following data was reproduced from the Luzchem website :

(<http://www.luzchem.com/ExposureStandards.php> )



Region	Range, nm	Dose mw*m <sup>-2</sup>	% energy
UVA	315-400	1,300	1%
UVB	280-315	1,430	2%
UVC	235-280	88,340	90%
Visible	400-700	5,070	5%
NIR	700-850	1,680	2%

For reactions using irradiation at 394 nm, the light sources was purchased from Creative Lightings (<https://www.creativelightings.com/>). The LED strips used were: <http://www.creativelightings.com/Purple-UV-LED-Flex-Strips-12vdc-WP-300-Meter-p/cl-frs5050wpdd-5m-12v-uv.htm>. The following data was reproduced from the Creative Lightings website :

Purple/UV Water Resistant LED Flexible Ribbon Spool - 5050 Series - 300 Purple/UV LEDs 400-410nm

Standard length: 5 meters (16.4ft)/reel

Strip width: single color 10mm,(3/8in)

Color of PCB: Black, Silicone PVC encapsulated, super flexible

Color: Purple **Ultra Violet / Purple** (1/2 the normal brightness - MORE UV REACTIVE) 400-410nm

Working voltage: 12 Volt DC (24v Optional)

LED quantity of entire strip: single color **300pcs**, RGB 150pcs or 300pcs

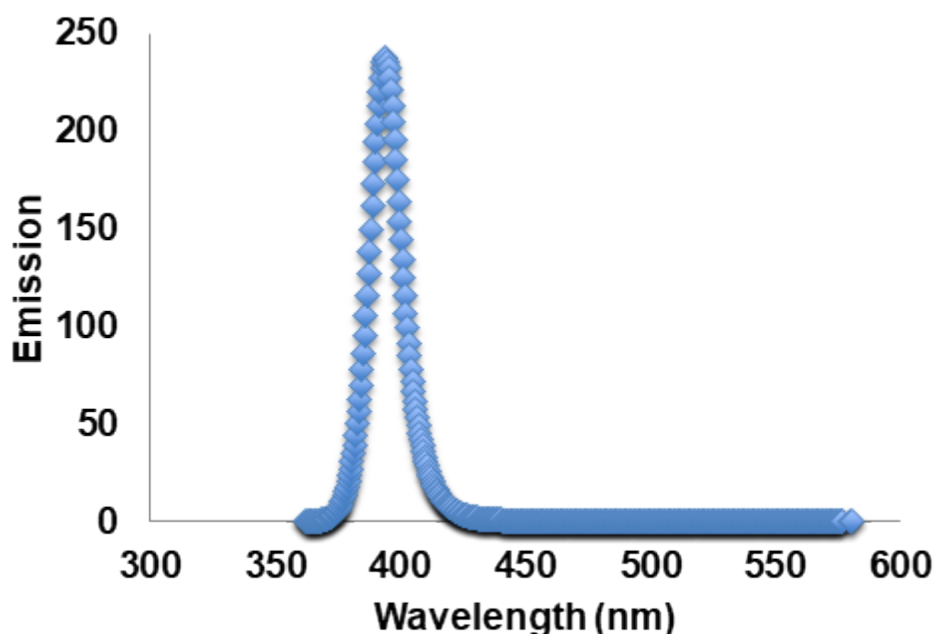
LED Density: Double Density = .75"

LED spacing - Provides high output and more even light output

Lifespan (approx. 100,000 hours)

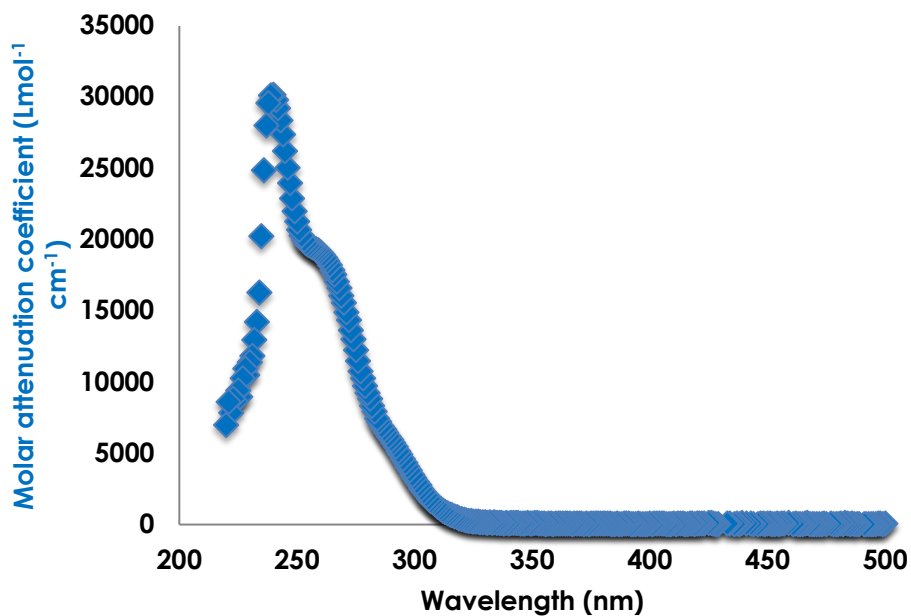
Wattage: 72 Watts per 5 Meter Spool

Water resistant/Rustproof IP-66 rated

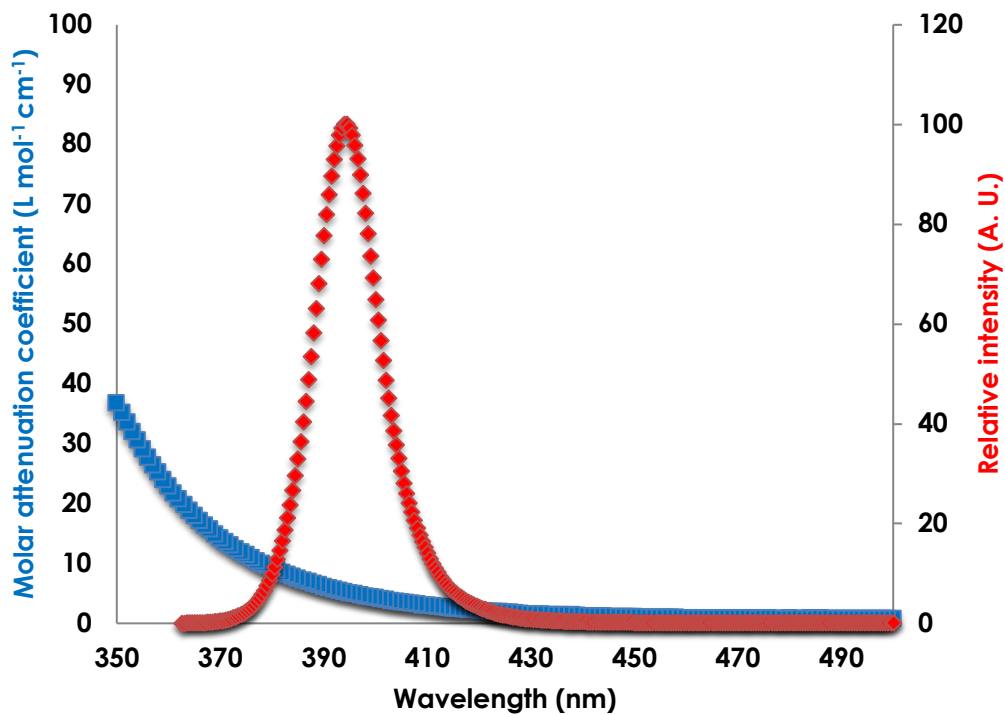




## 7.7 Absorption/Emission Spectra

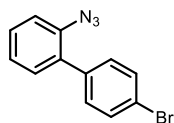


**Figure 7.2** Absorption spectrum for 2-azido-1,1'-biphenyl (**1**) (25  $\mu\text{M}$  in THF)

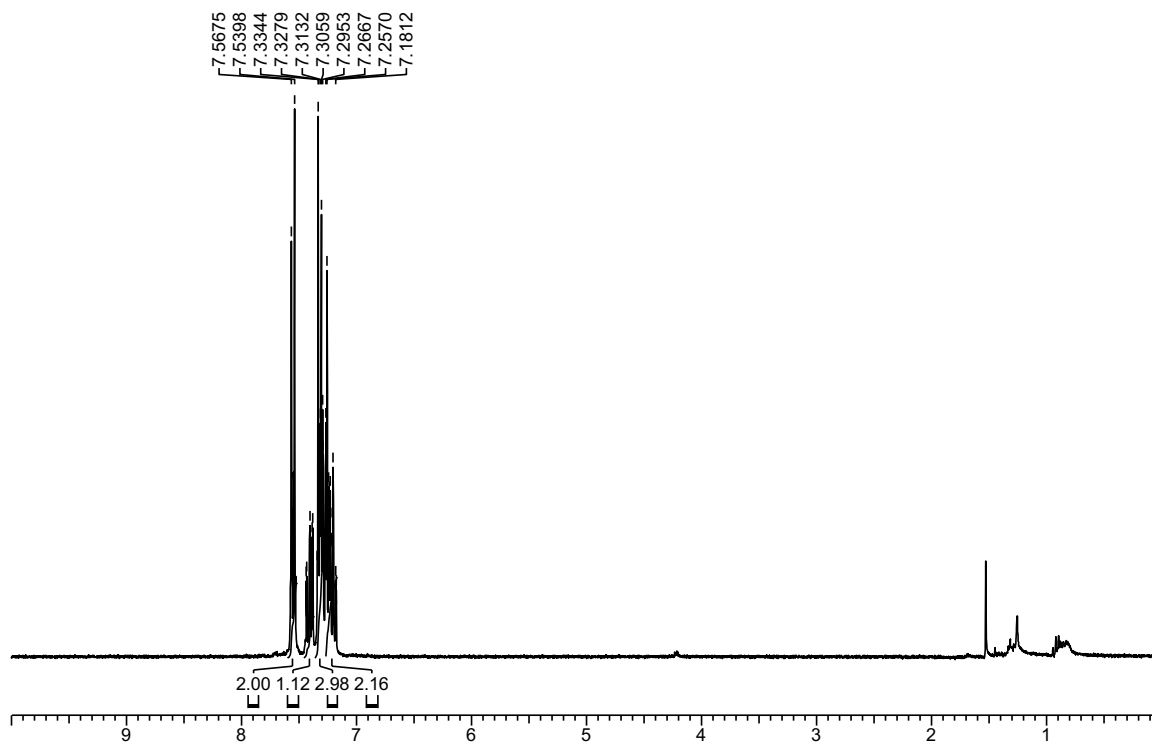


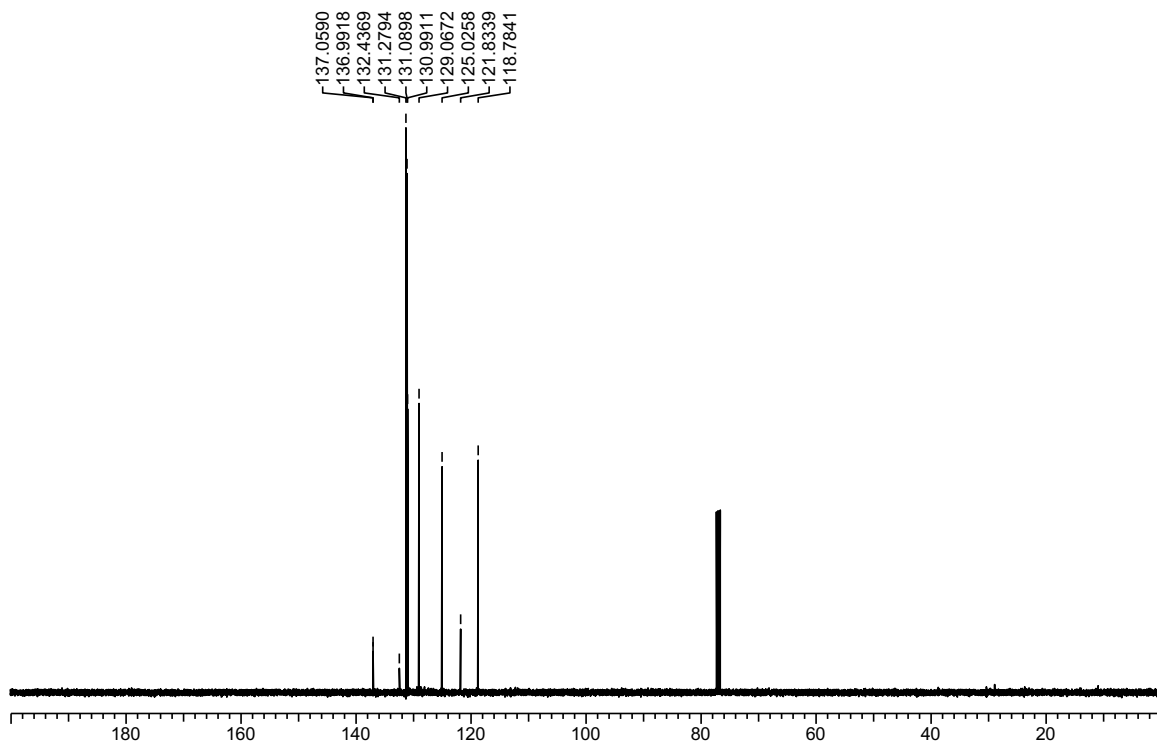
**Figure 7.3** Overlapping the absorption spectrum for 2-azido-1,1'-biphenyl (**1**) with the emission spectrum of the purple LED at the concentration used for the photochemical decomposition of the azide (30 mM in THF)

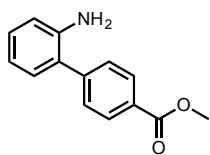
## 7.8 NMR Data for all New Compounds



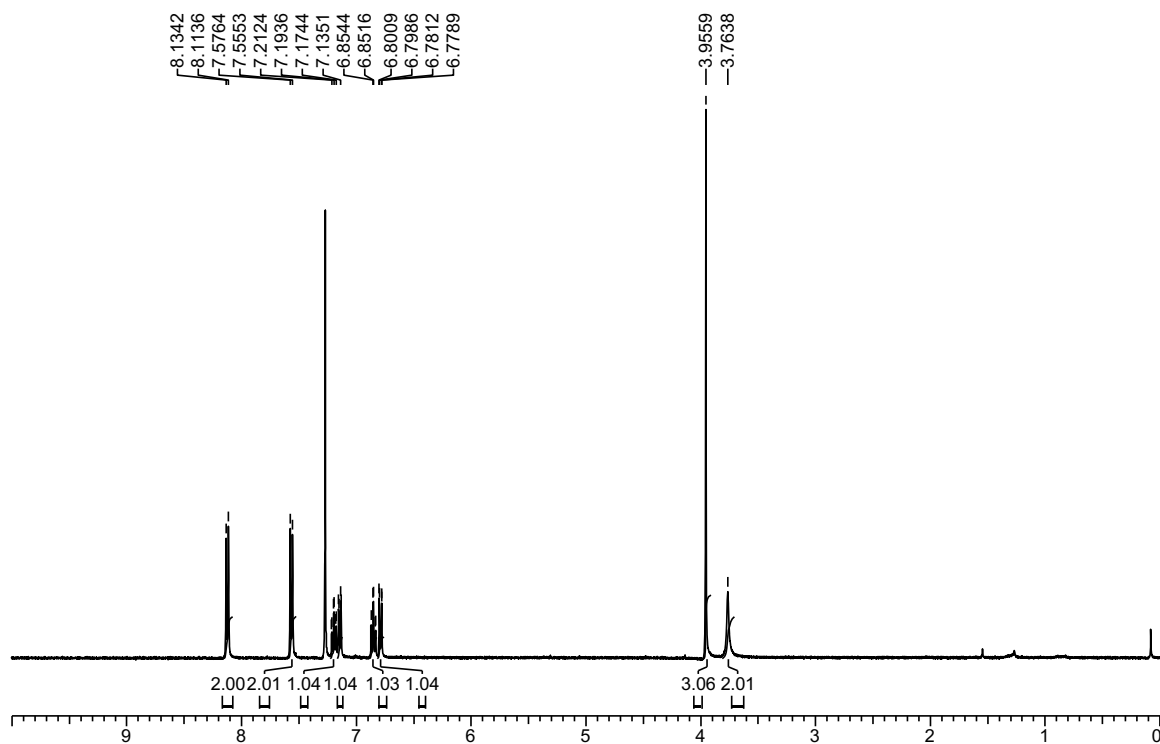
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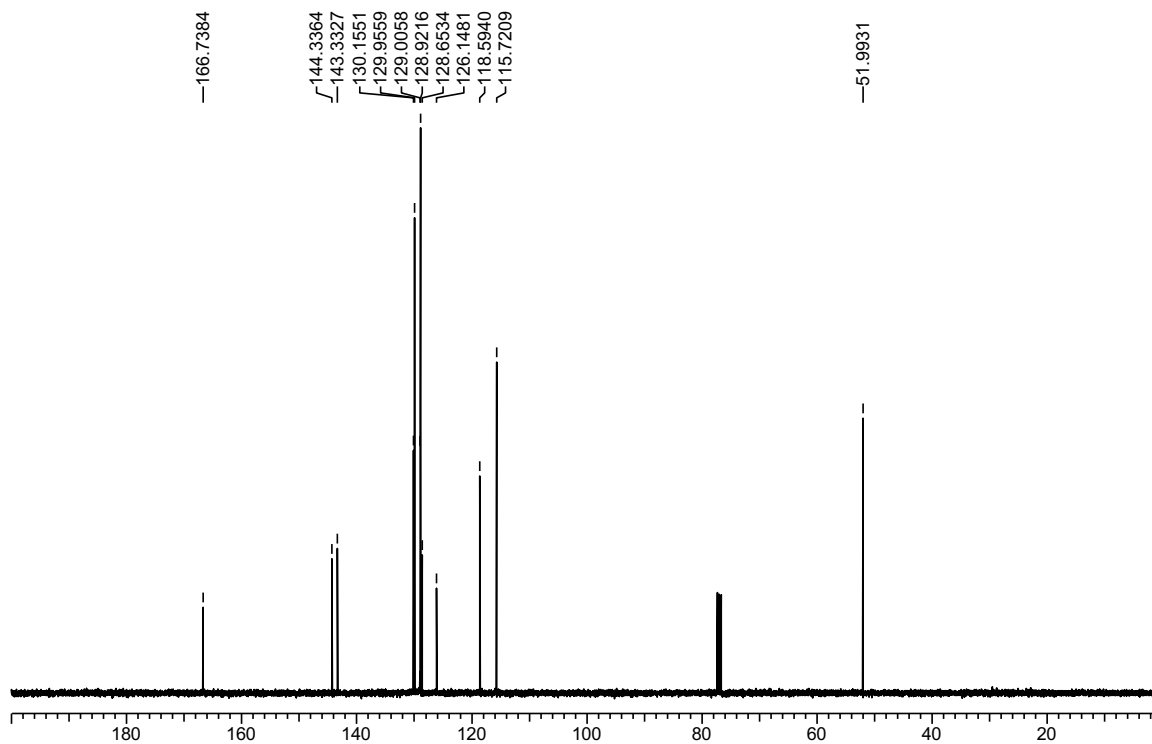


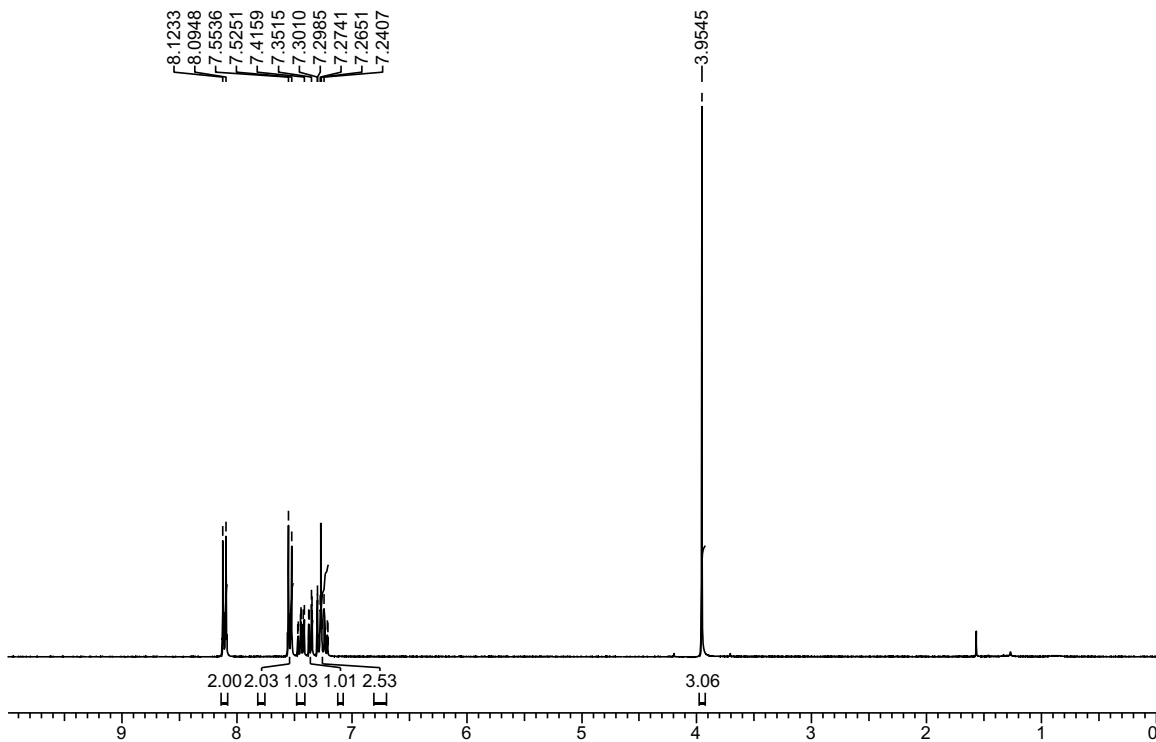
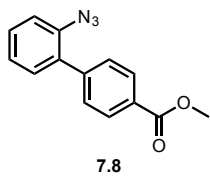


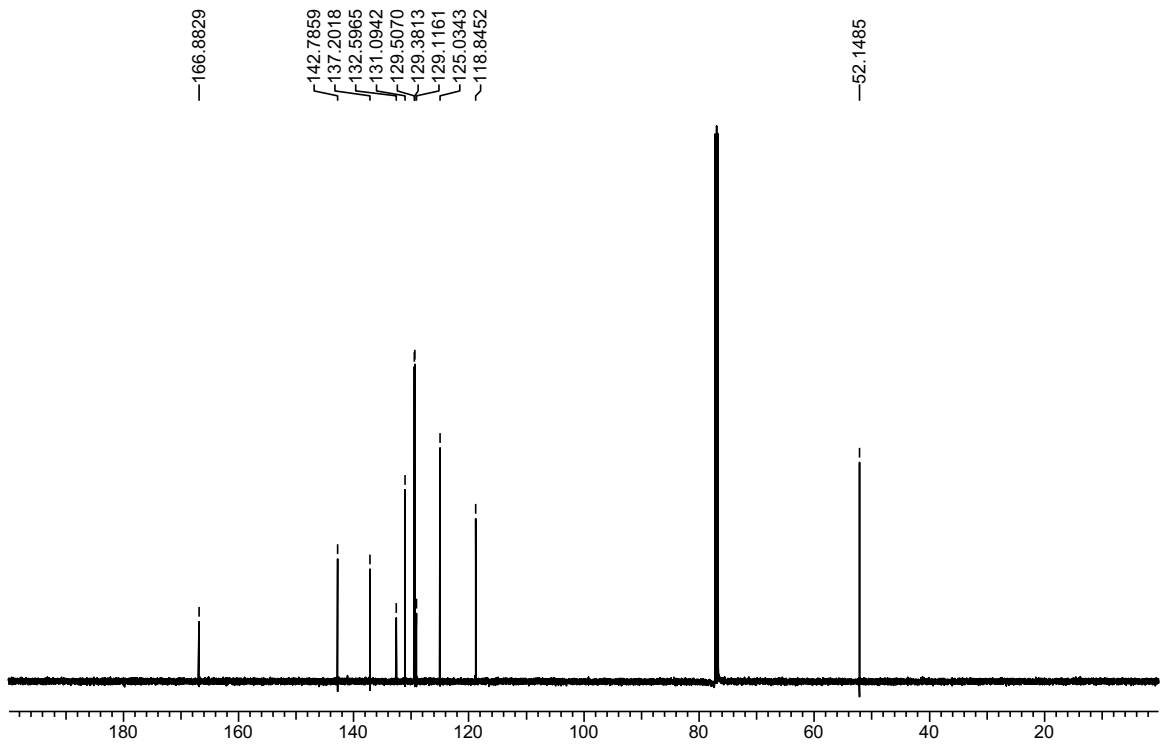


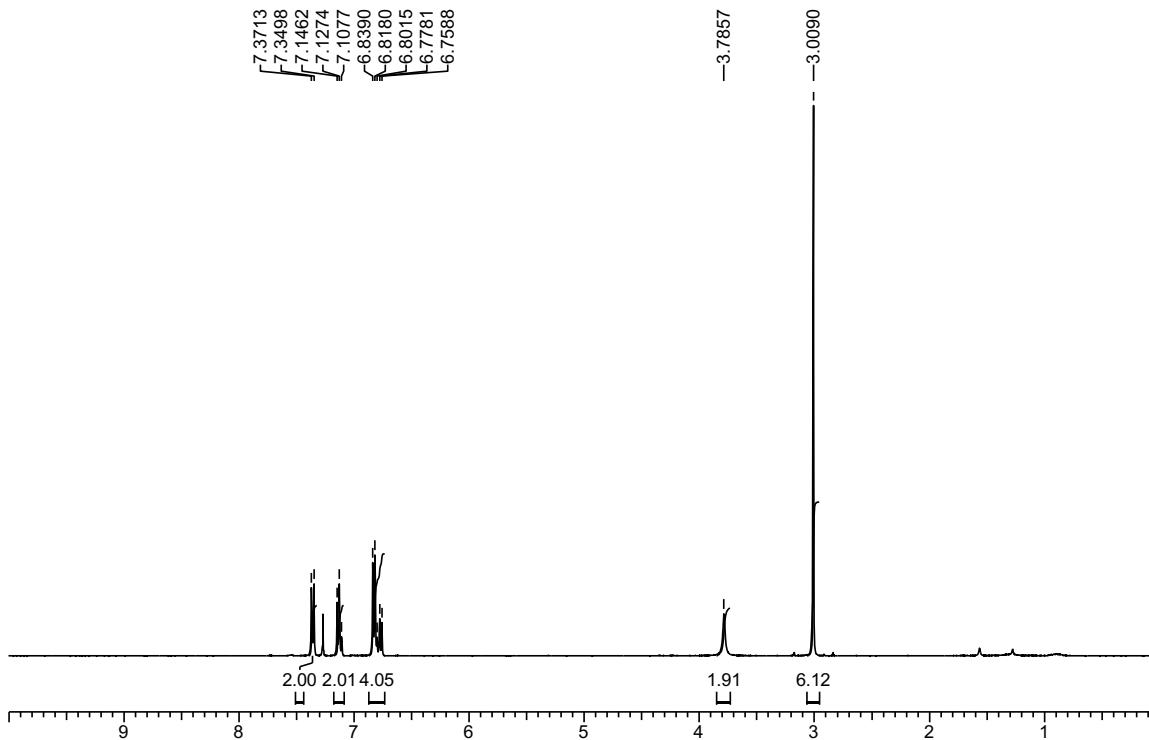
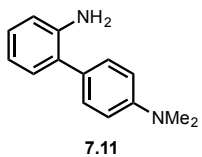
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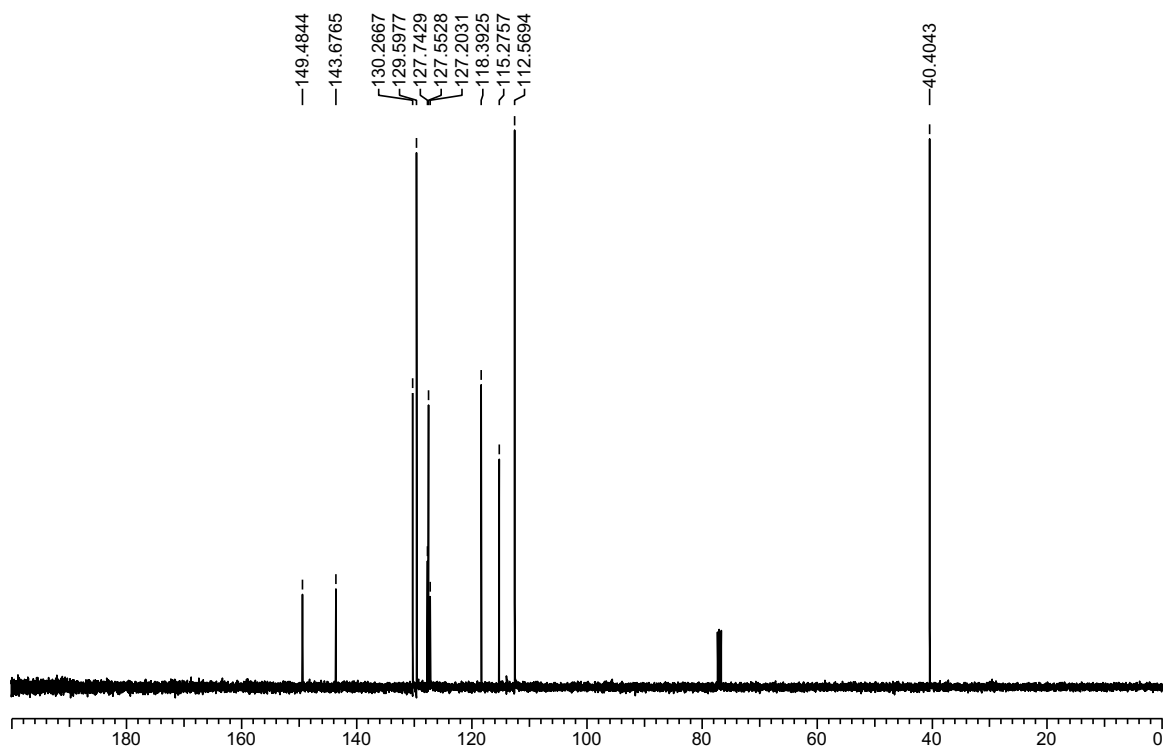


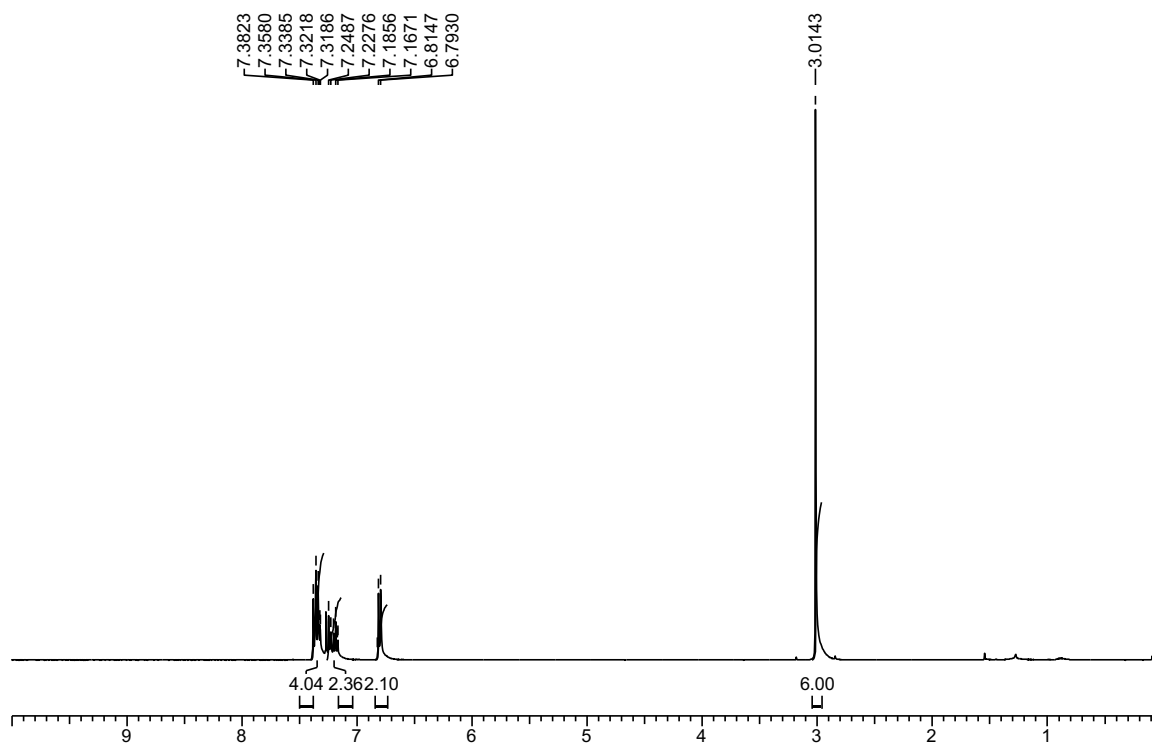
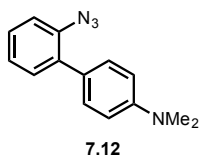


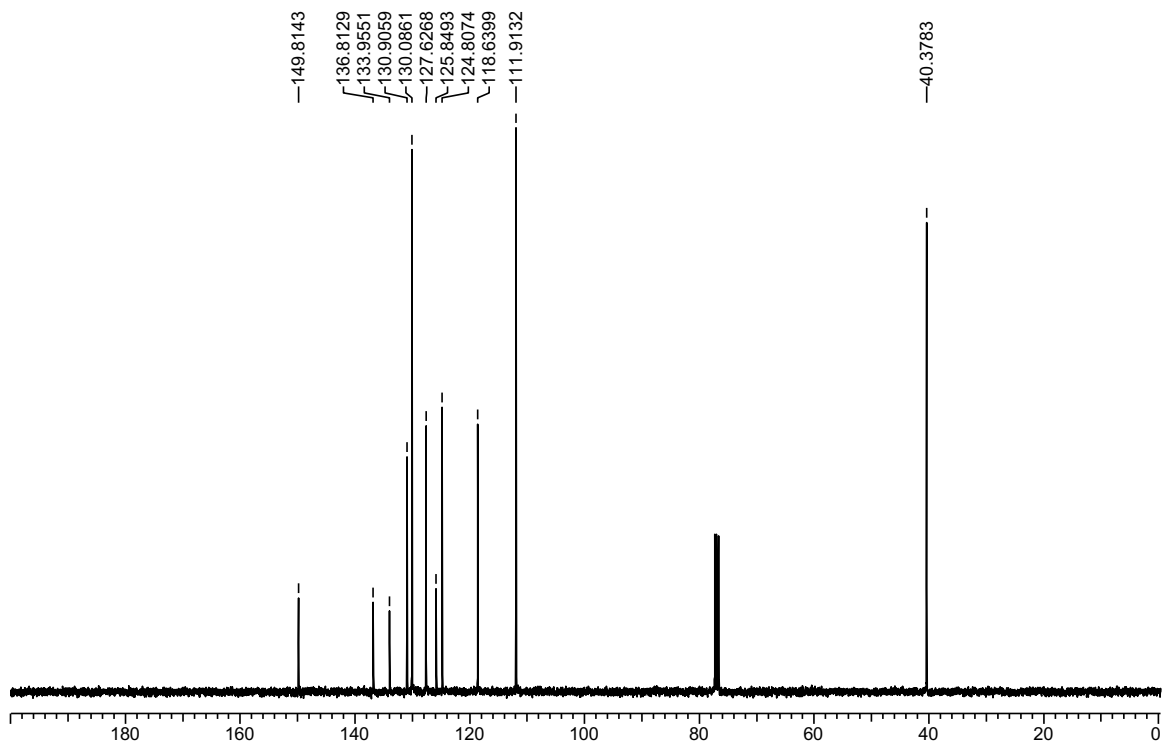


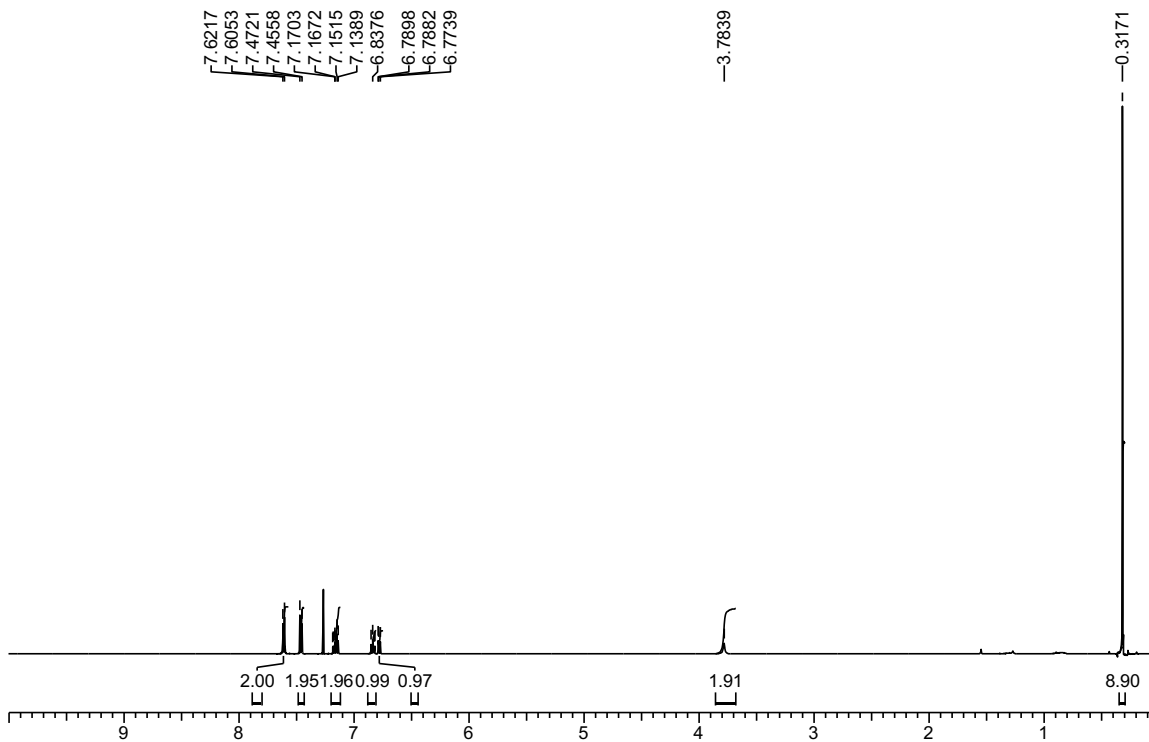
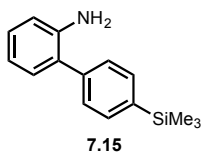


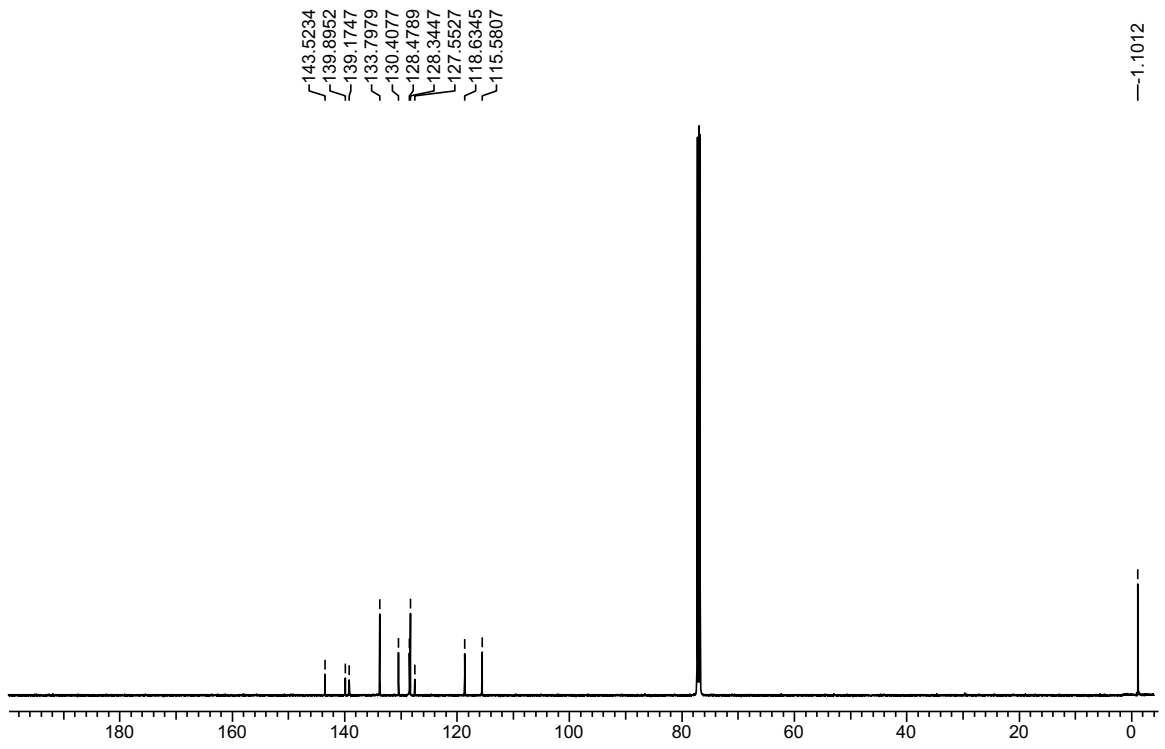


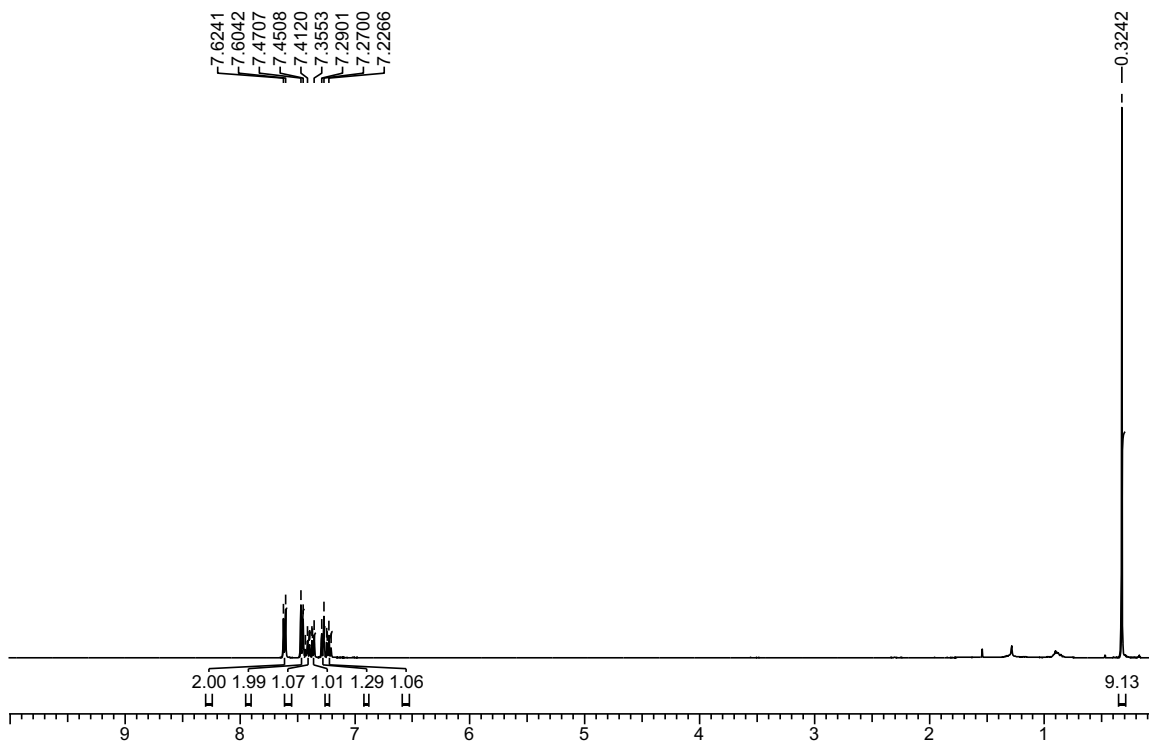
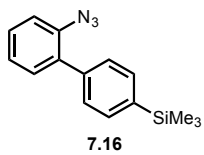


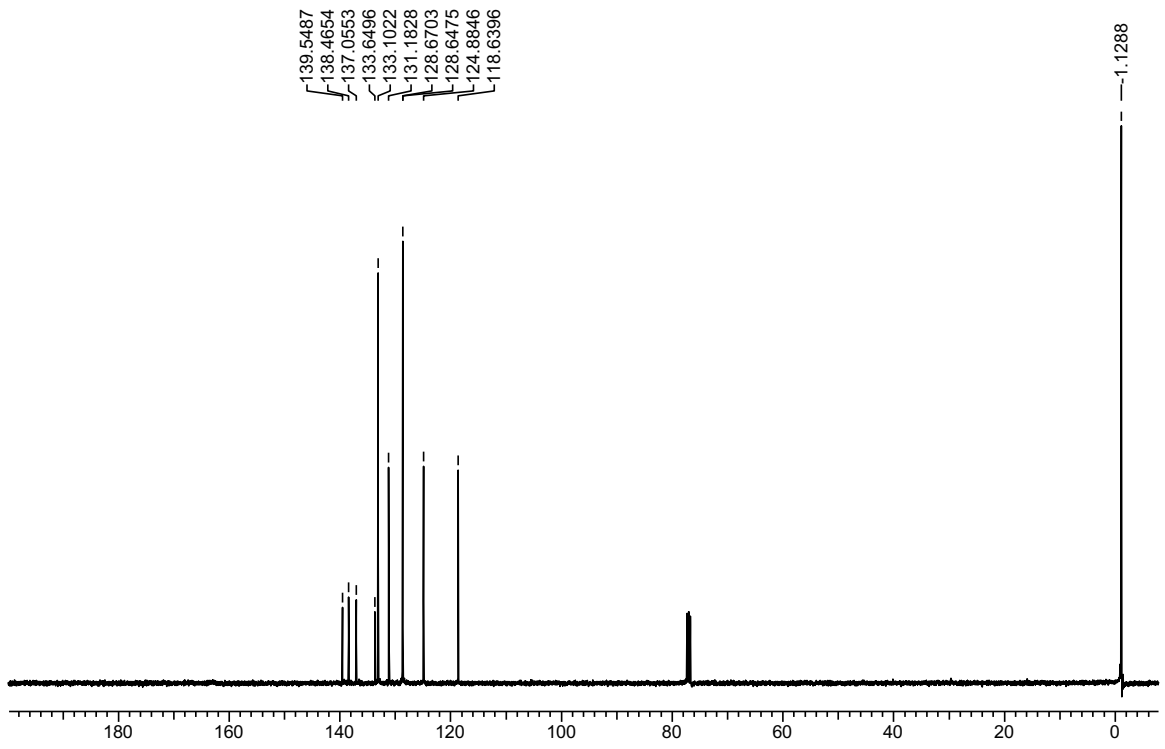


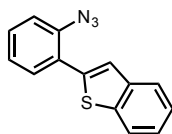




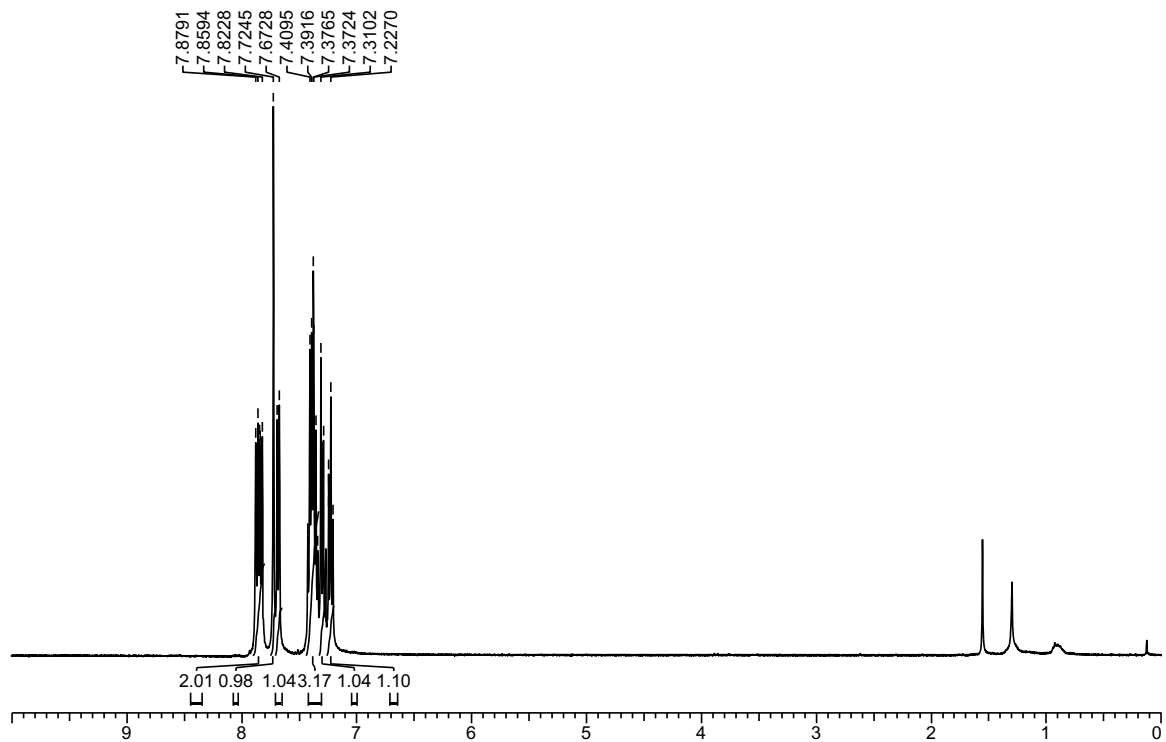




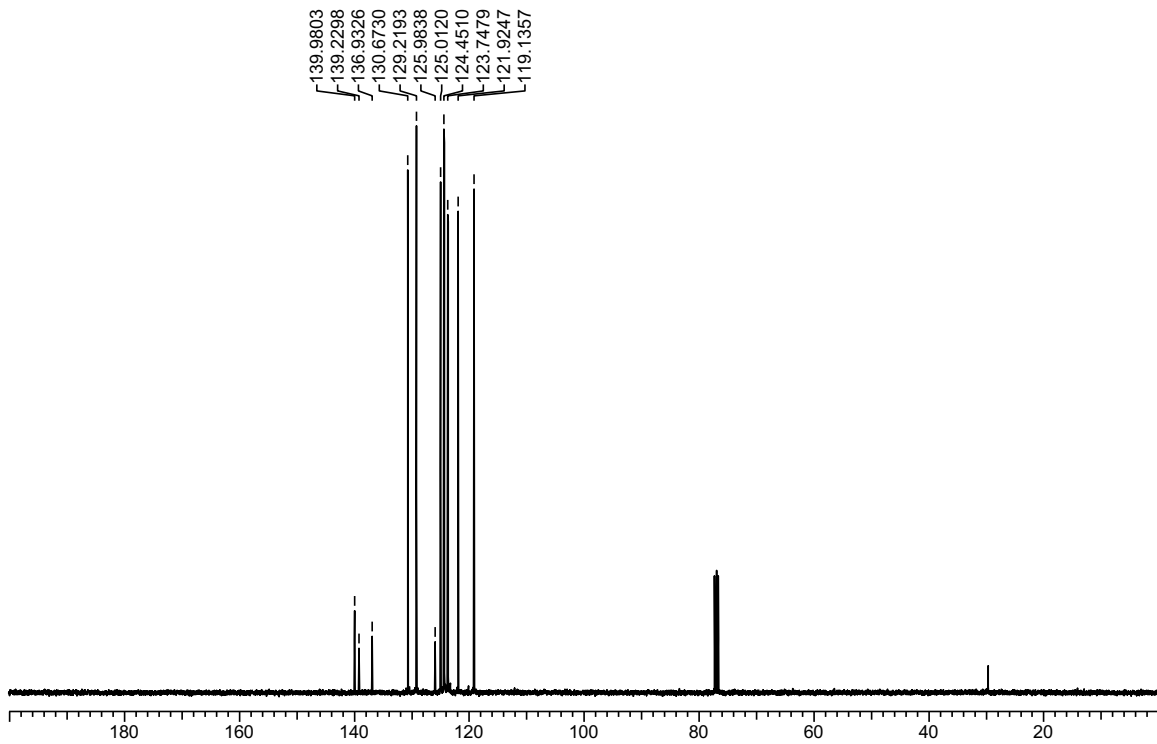


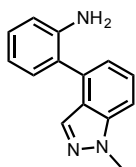


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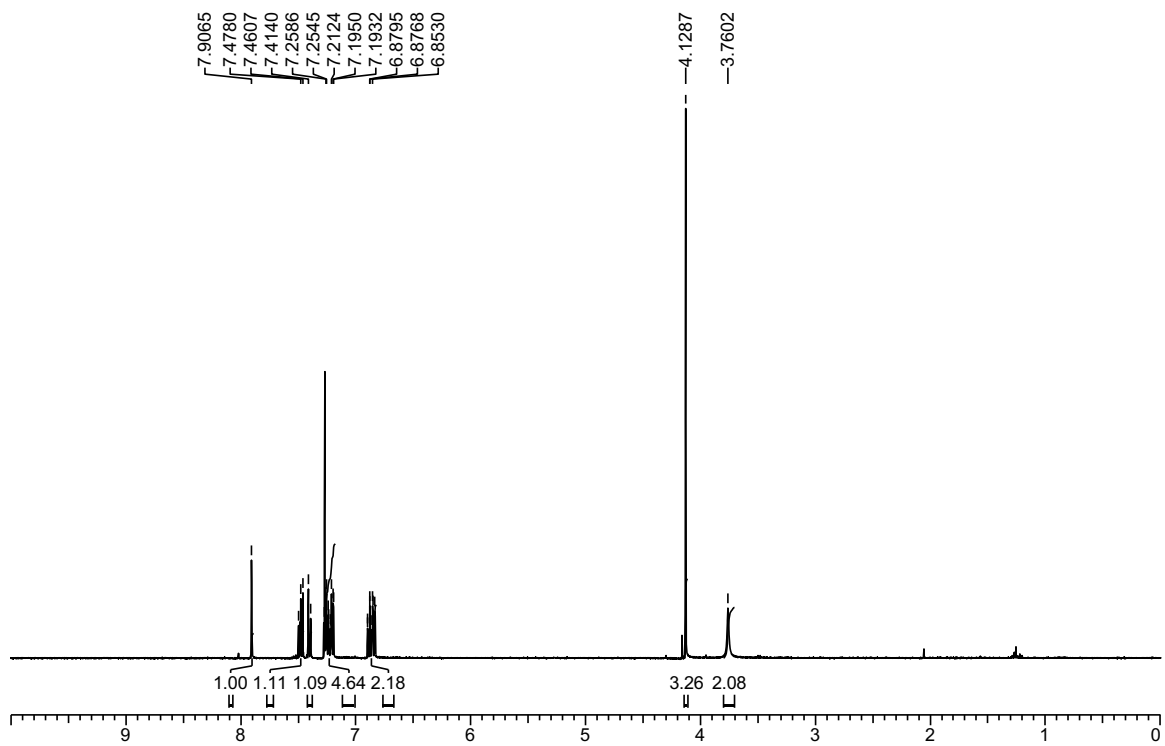


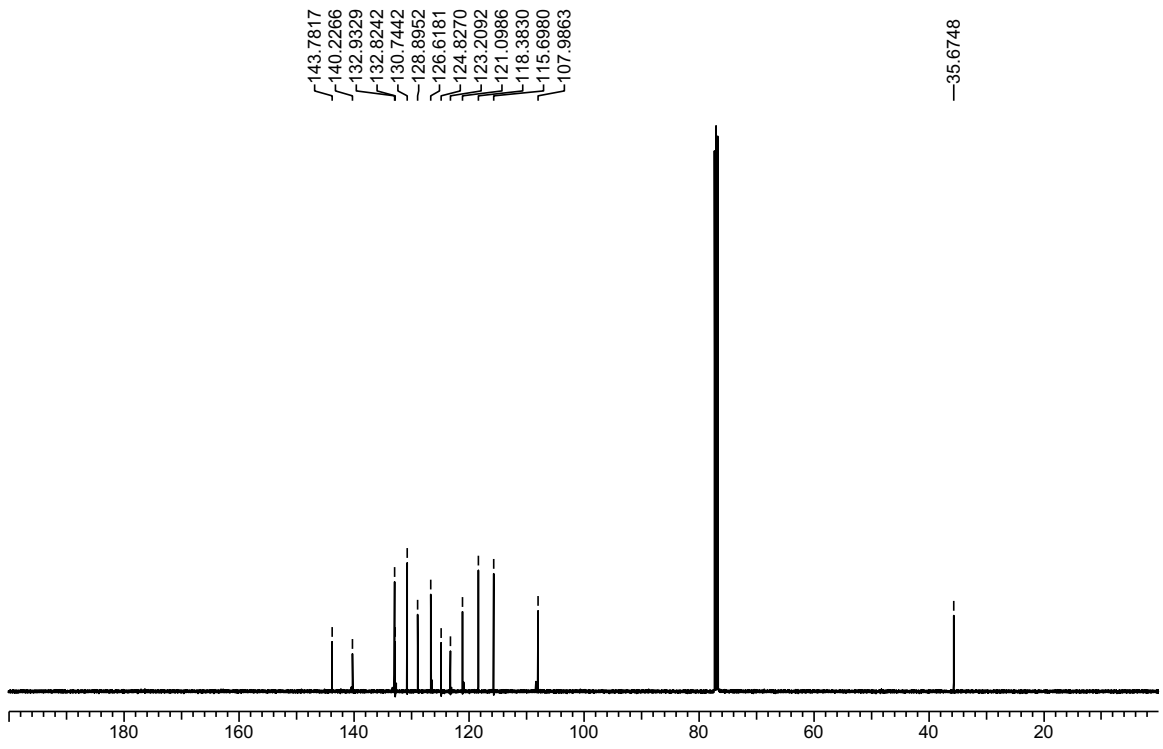


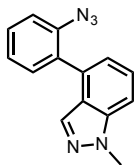




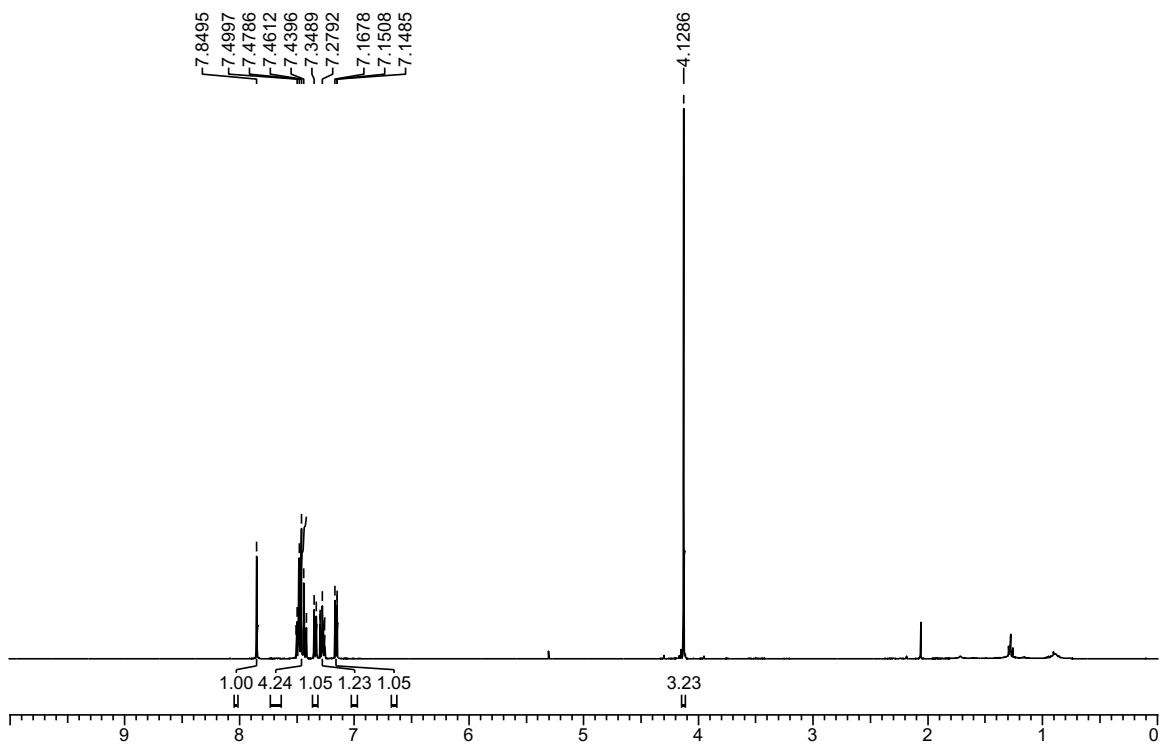
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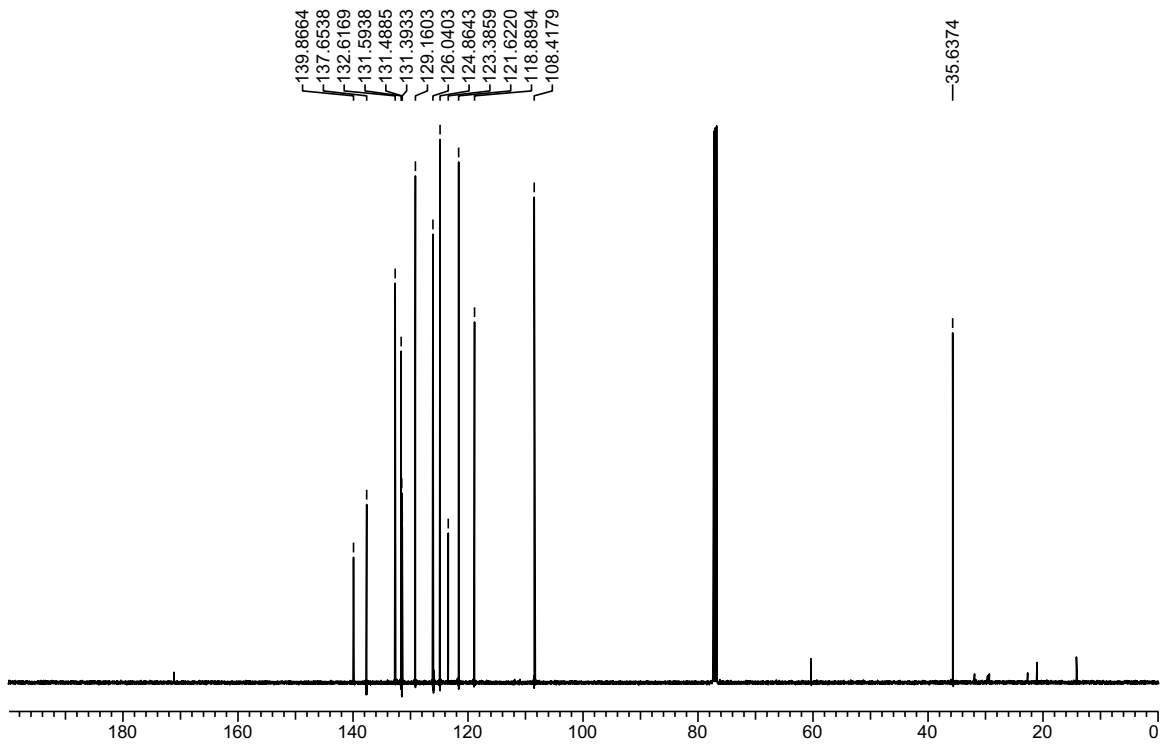


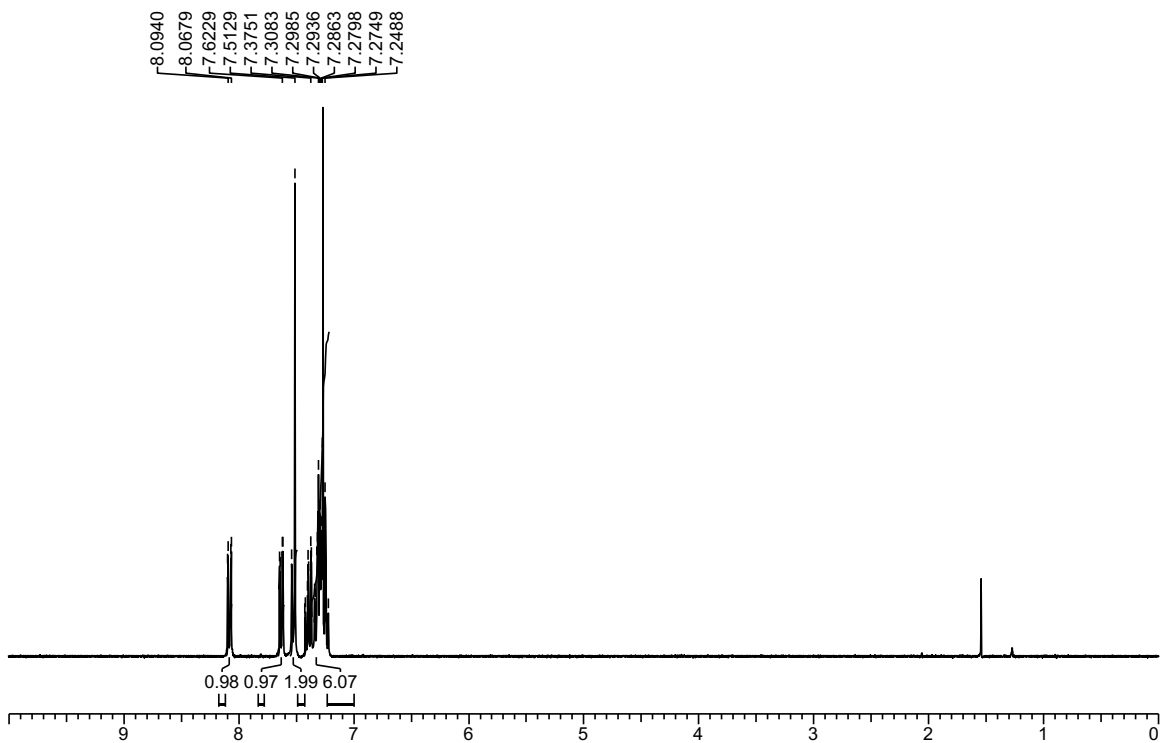
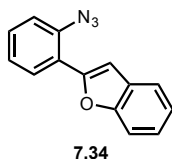


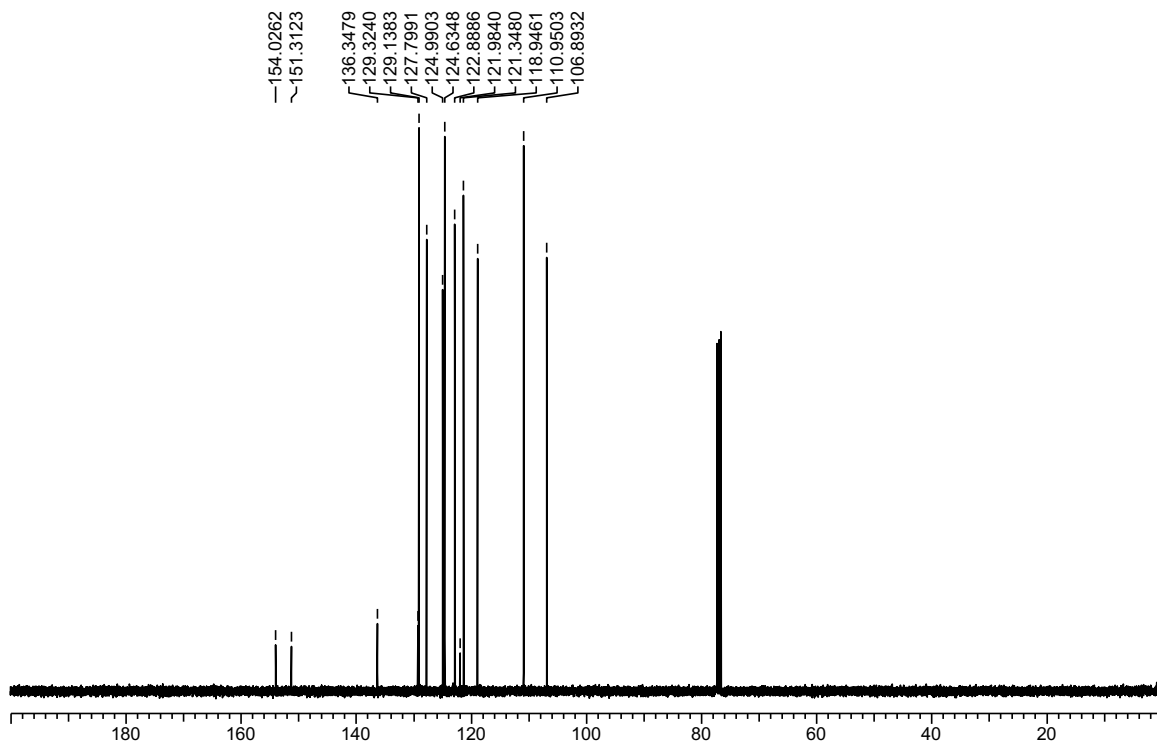


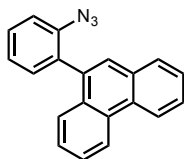
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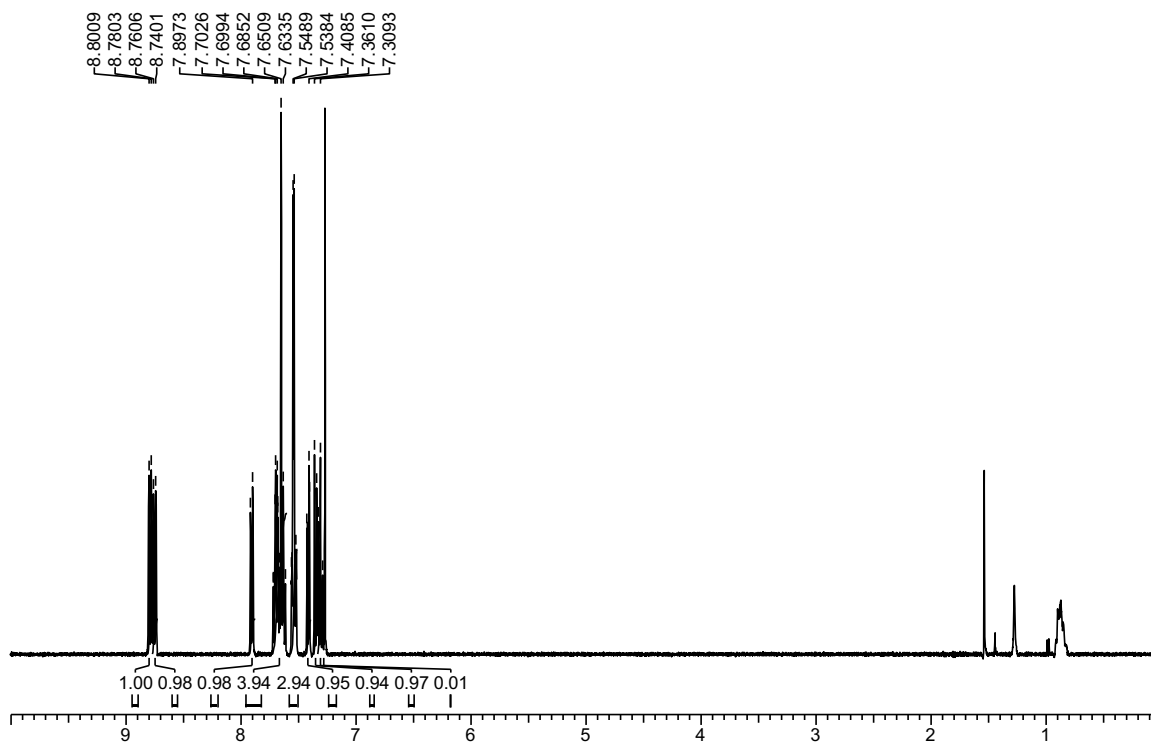




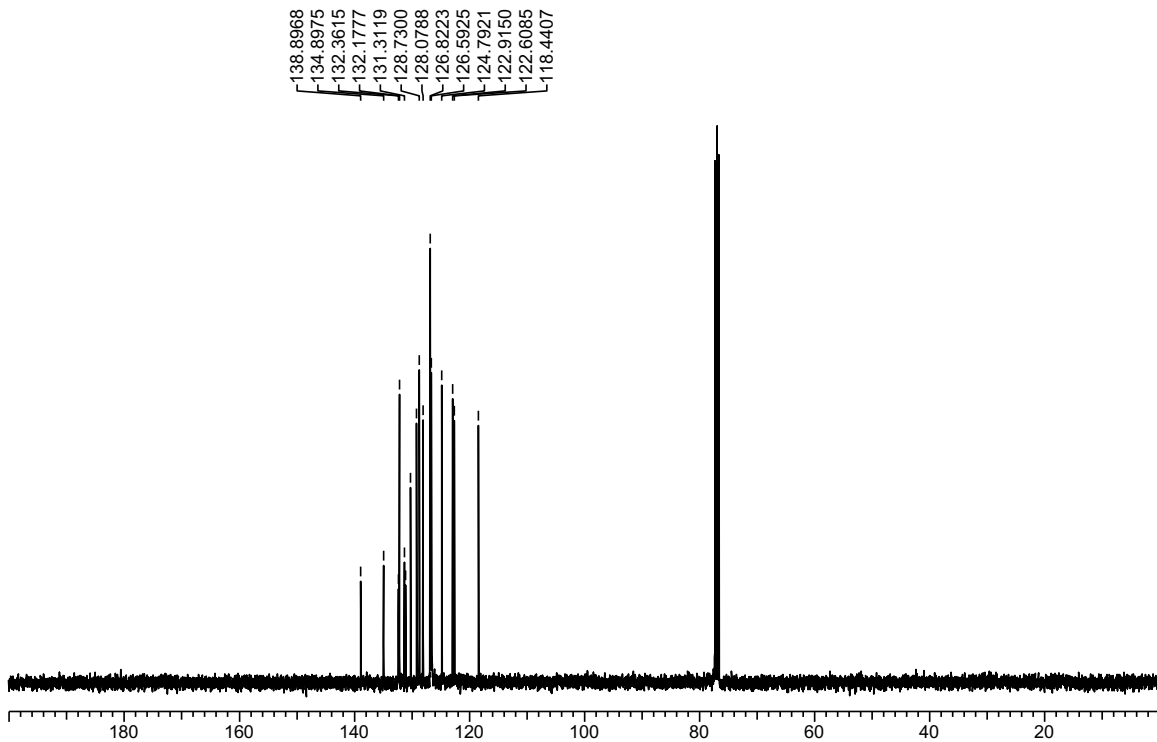


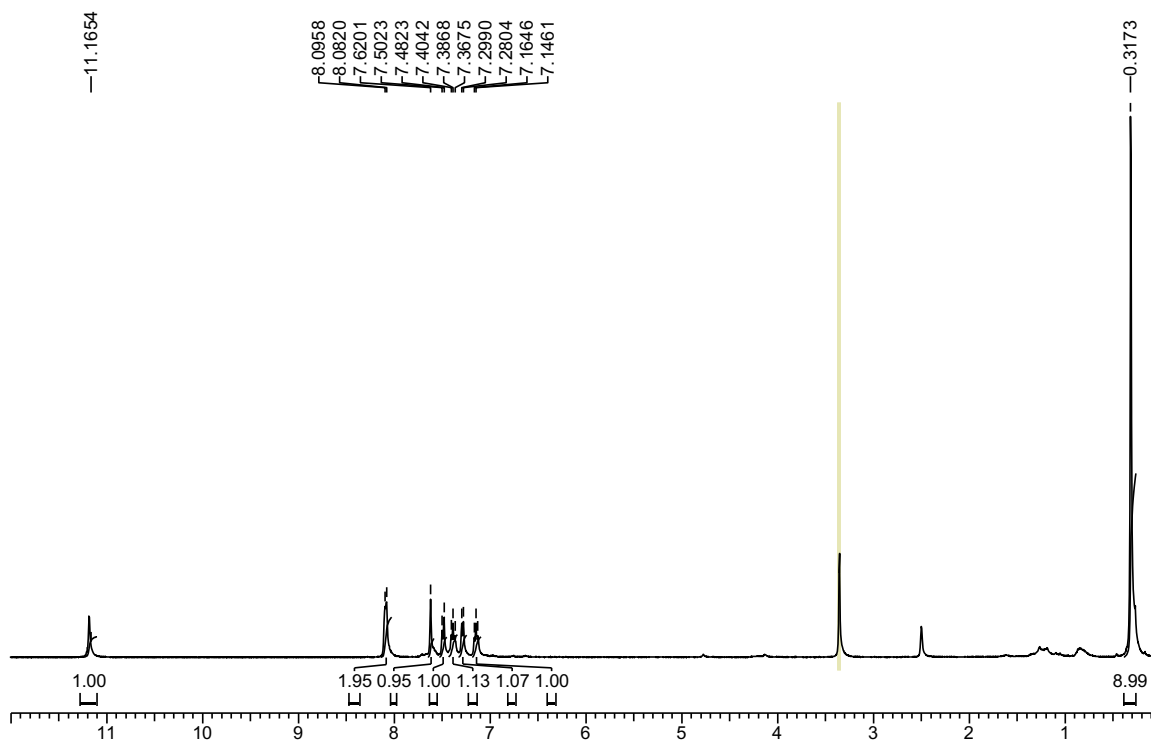
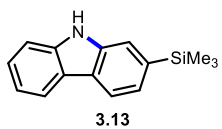


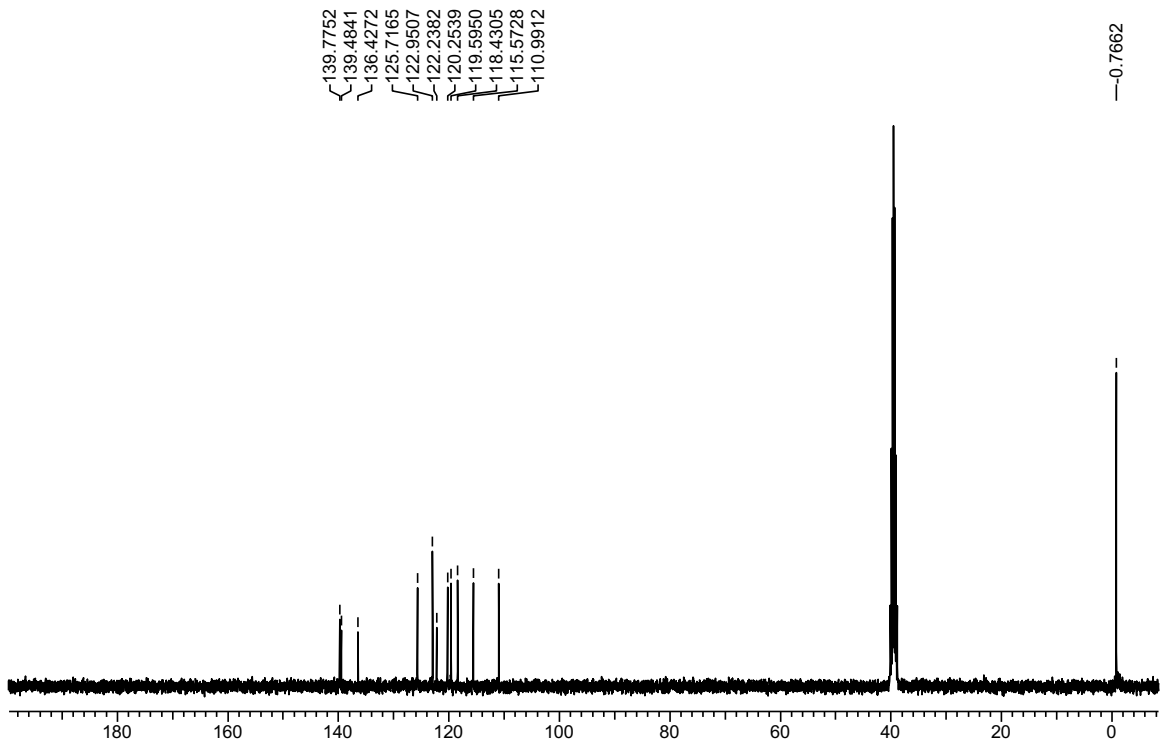
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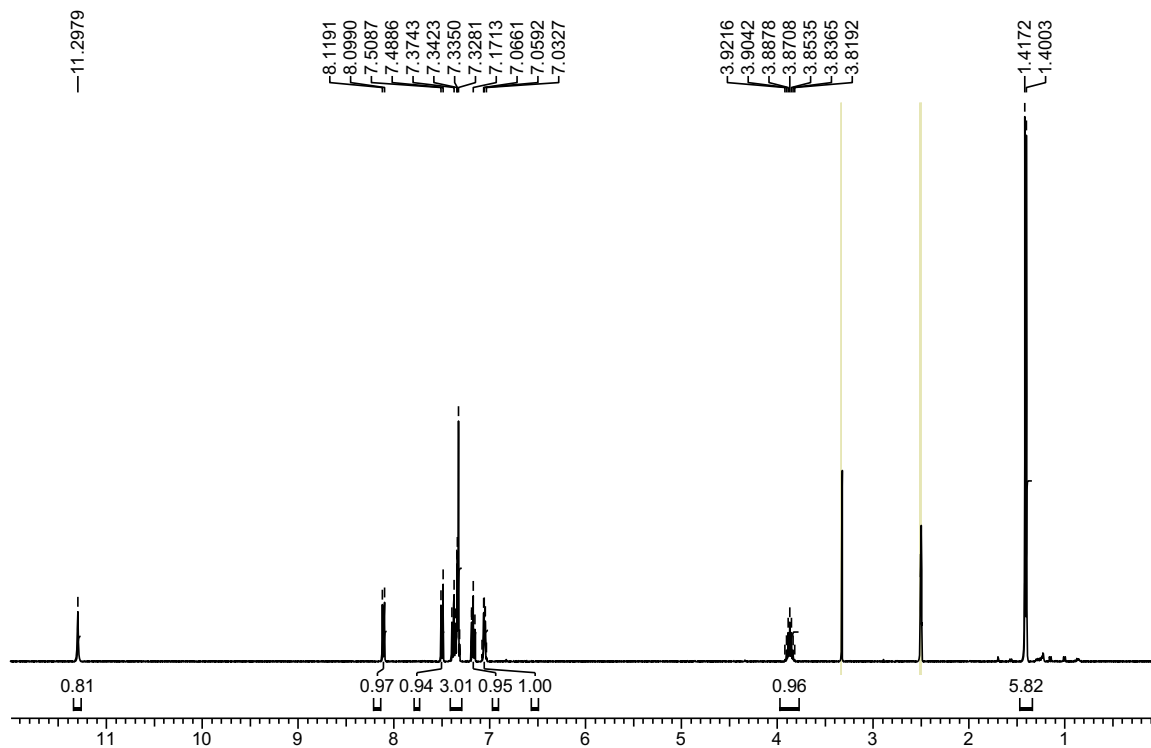
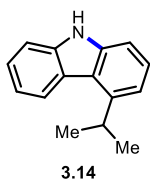


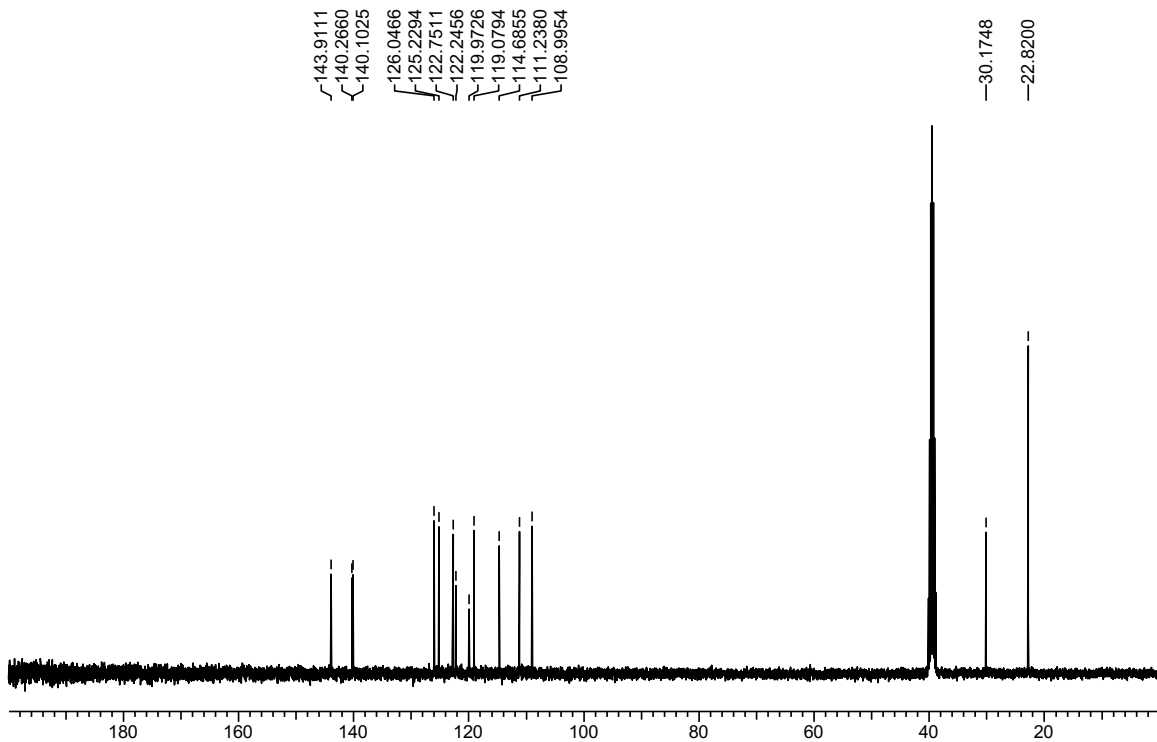


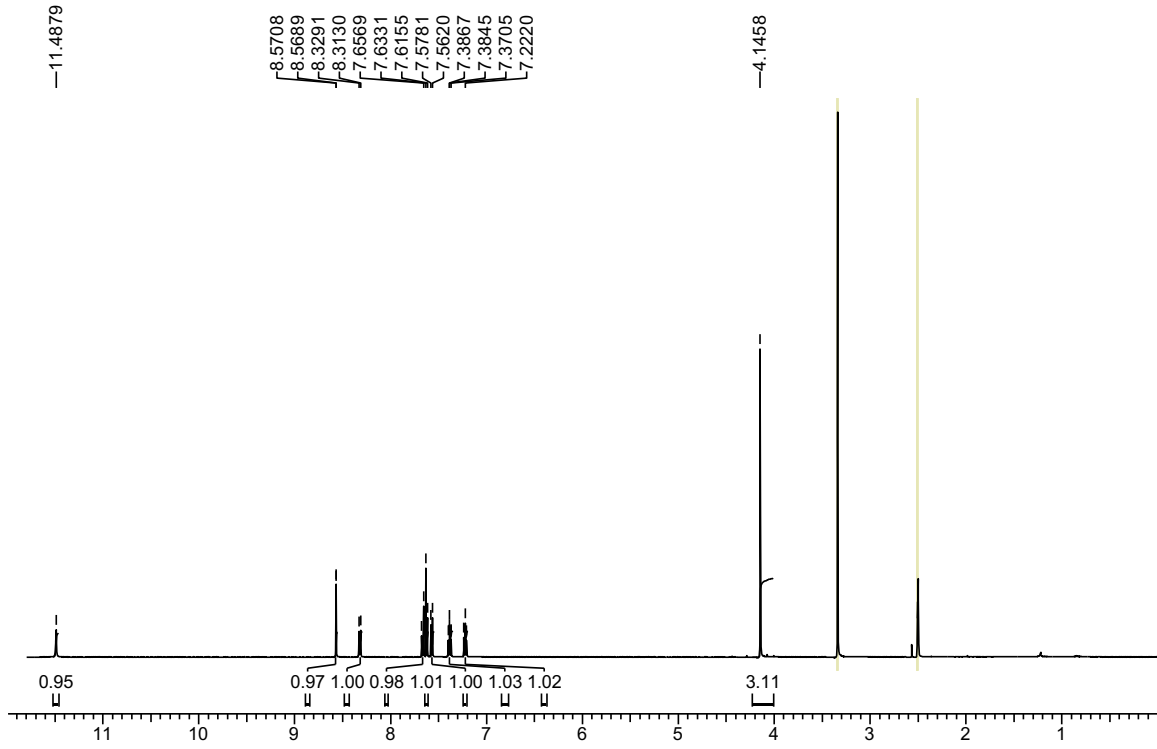
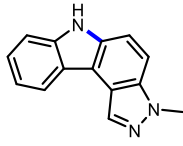


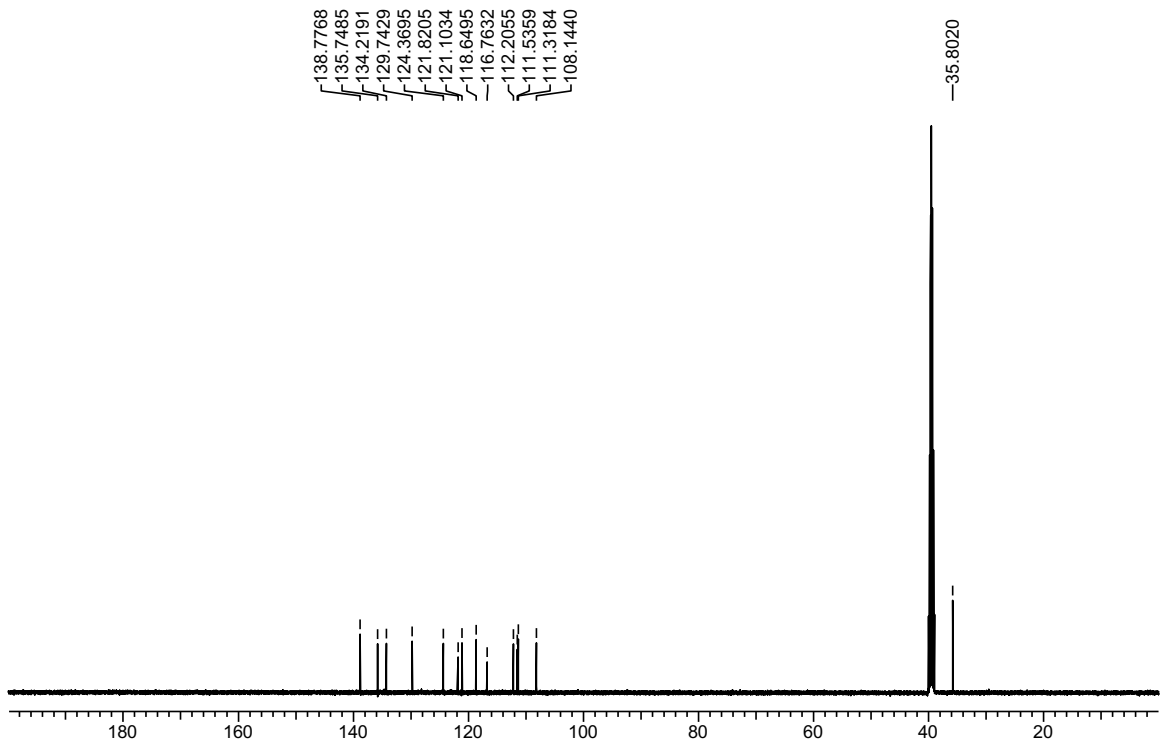


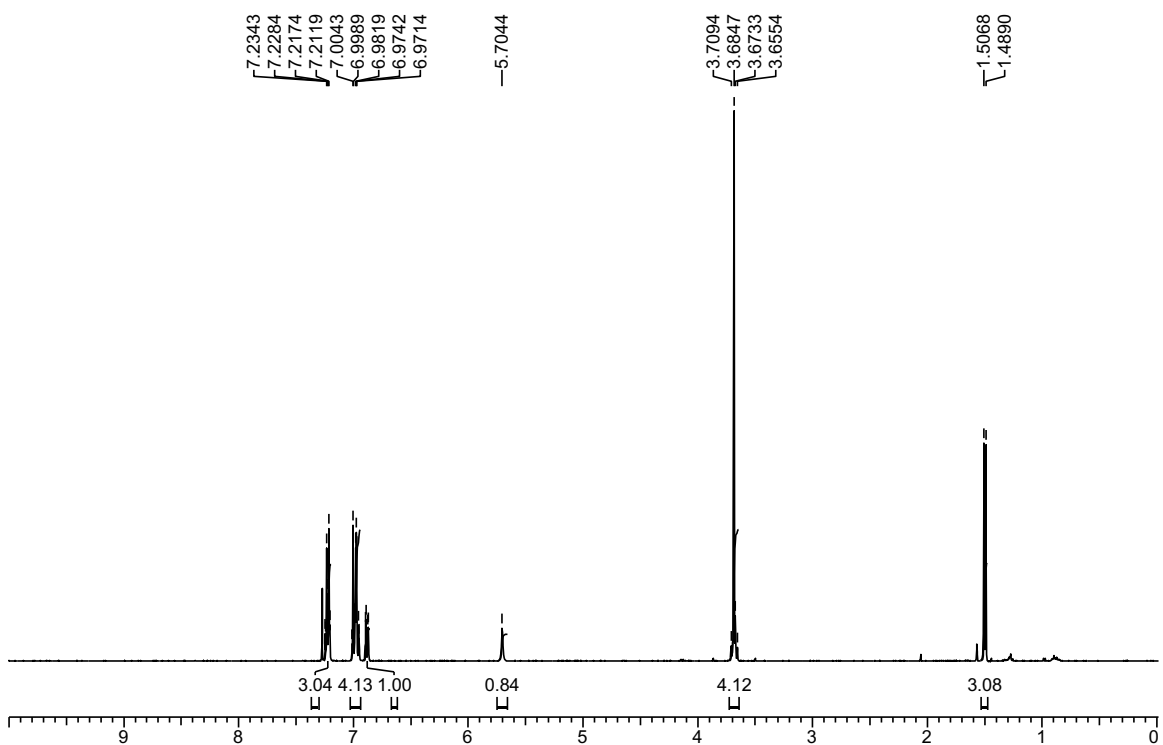
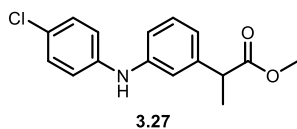




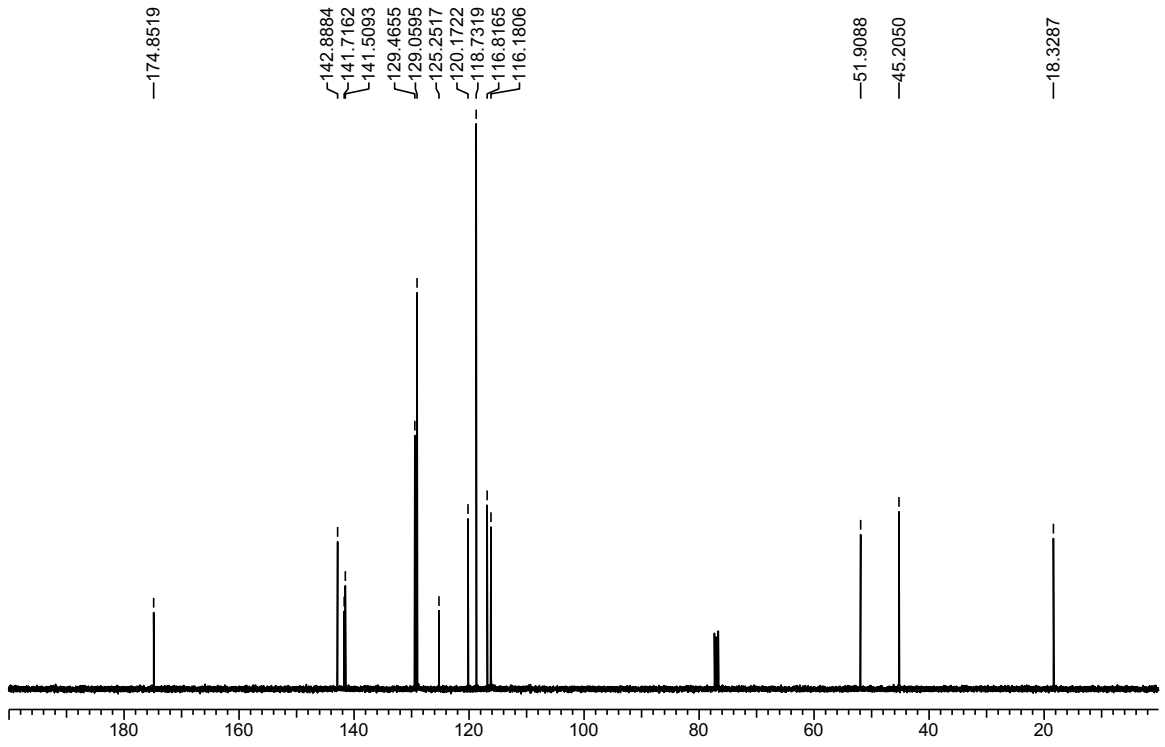


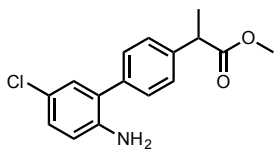




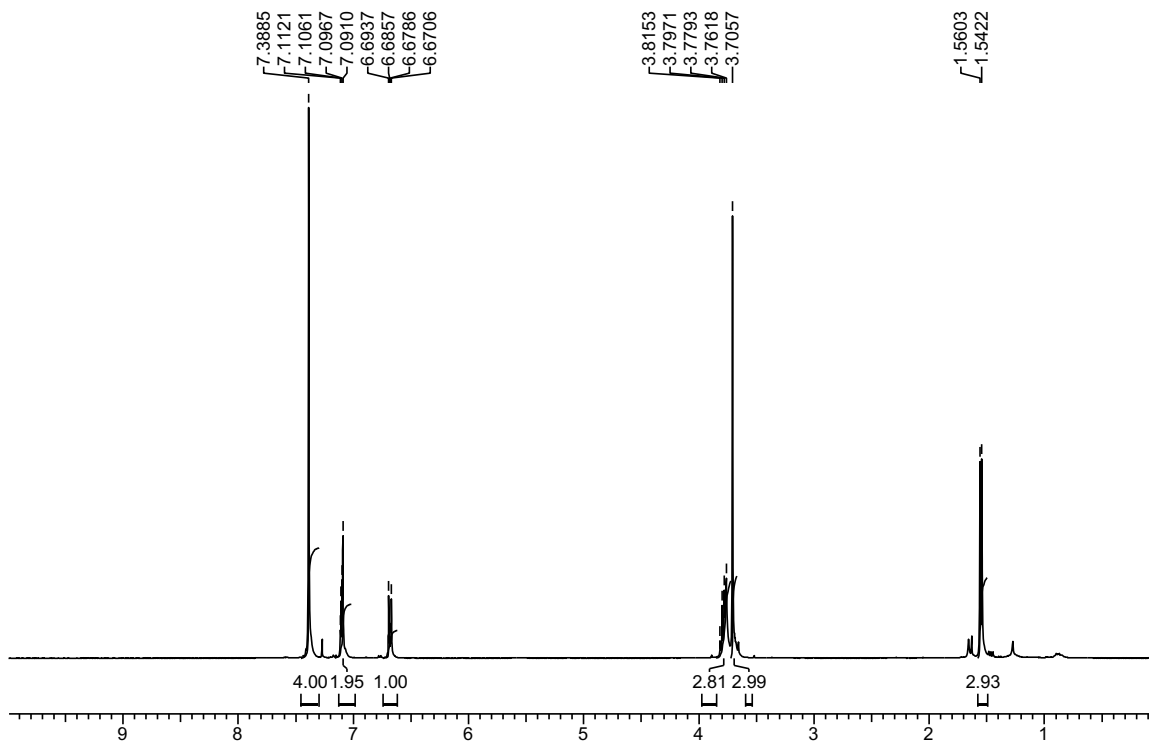


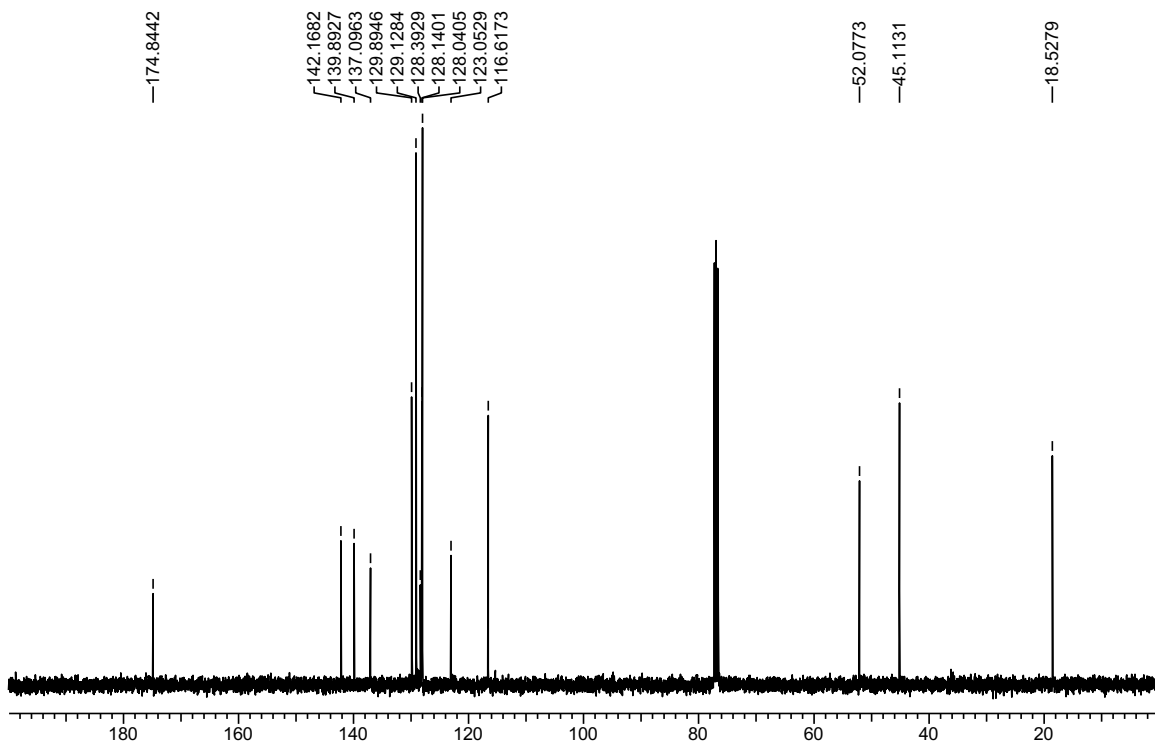


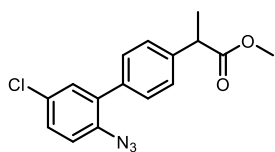




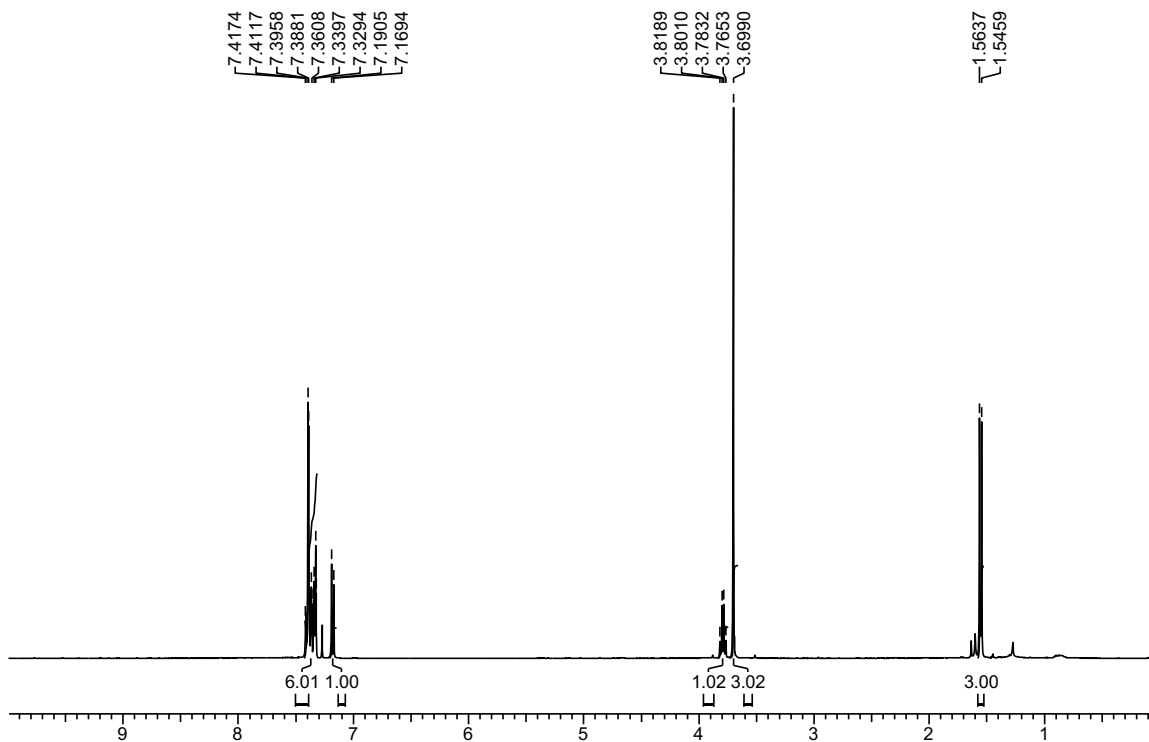
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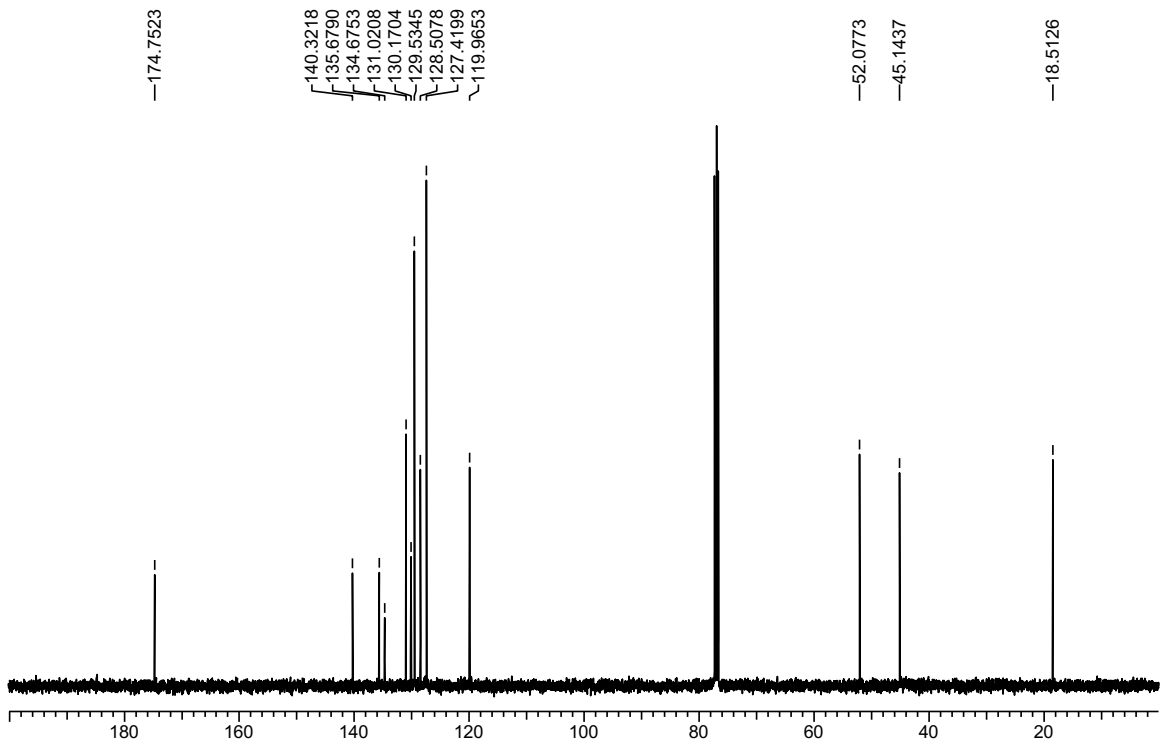






3.28





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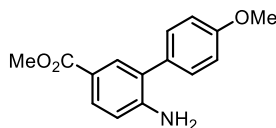
## 8. Supporting Information of Chapter 4

### 8.1 General

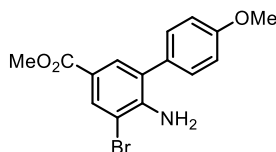
All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.<sup>1</sup> All chemical products were obtained from Sigma-Aldrich Chemical Company, Alfa Aesar or Oakwood Chemical and were reagent quality. Technical solvents were obtained from VWR International Co. Anhydrous solvents (CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>2</sub>O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still<sup>2</sup> and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F<sub>254</sub>). Visualization of TLC plate was performed by UV (254 nm), KMnO<sub>4</sub>, *p*-anisaldehyde or ninhydrin stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by <sup>1</sup>H NMR. NMR spectra were taken in deuterated CDCl<sub>3</sub> using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard (CHCl<sub>3</sub>: δ 7.27 for <sup>1</sup>H, δ 77.0 for <sup>13</sup>C). The acquisition parameters are shown on all spectra. The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.



## 8.2 Synthesis of Precursors

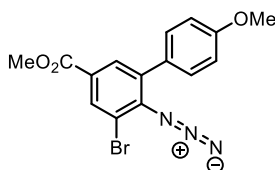


**Methyl 6-amino-4'-methoxy-[1,1'-biphenyl]-3-carboxylate (8.1):** An oven-dried open sealed tube was charged with methyl 4-amino-3-bromobenzoate (3.45 g, 15 mmol, 1 equiv.), 4-methoxyphenylboronic acid (2.51 g, 16.5 mmol, 1.1 equiv.),  $\text{K}_2\text{CO}_3$  (8.3 g, 60 mmol, 4 equiv.),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (0.105 g, 0.15 mmol, 1 mol %) and a mixture of dimethoxyethane/water (1:1 [0.5 M]) under a nitrogen atmosphere. The tube was sealed and the mixture was stirred at 80 °C for 18 h under nitrogen. Upon cooling, the biphasic mixture was diluted with ethyl acetate (50 mL) and the phases were separated. The aqueous phase was extracted twice with EtOAc (50 mL) and the combined organic phases were washed with brine (150 mL). The organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude mixture was purified by silica gel column chromatography (7.5 → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (1.72 g, 45 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.85-7.82 (m, 2H), 7.37 (d,  $J$  = 8.8 Hz, 2H) 7.00 (d,  $J$  = 8.8 Hz, 2H), 6.73 (d,  $J$  = 8.1 Hz, 1H), 4.16 (brs, 2H), 3.86 (s, 3H), 3.86 (s, 3H) ;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 167.2, 159.1, 148.2, 132.4, 130.6, 130.2, 130.1, 126.3, 119.8, 114.4, 114.3, 55.3, 51.6; HRMS (ESI)  $m/z$  calculated for  $\text{C}_{15}\text{H}_{15}\text{NO}_3$   $[\text{M}+\text{H}]^+$  258.1125; found 258.1131.



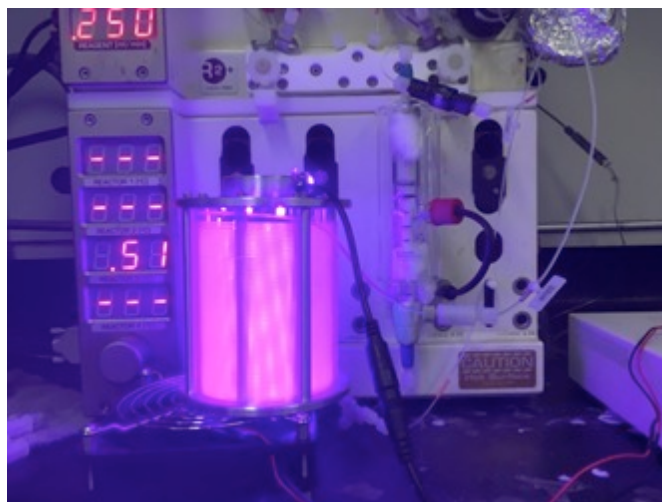
**Methyl 6-amino-5-bromo-4'-methoxy-[1,1'-biphenyl]-3-carboxylate (4.3):** A round bottom flask was charged with methyl 6-amino-4'-methoxy-[1,1'-biphenyl]-3-carboxylate (1.00 g, 3.9 mmol, 1 equiv.), *N*-bromosuccinimide (0.69 g, 3.9 mmol, 1.0 equiv.) and 10 mL dichloromethane [0.5 M]. The mixture was stirred at room temperature for 4 h. The solution was then diluted with dichloromethane (25 mL) and wash with water (25 mL). The organic phase was dried over  $\text{Na}_2\text{SO}_4$ ,

filtered and concentrated. The crude mixture was purified by silica gel column chromatography (7.5 → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (1.21 g, 93 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.11 (d, *J* = 1.9 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H) 7.33 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.63 (brs, 2H), 3.87 (s, 3H), 3.87 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 166.2, 159.4, 145.8, 133.3, 131.1, 130.2, 130.1, 127.1, 120.1, 114.5, 108.3, 55.3, 51.9; HRMS (ESI) *m/z* calculated for C<sub>15</sub>H<sub>14</sub>BrNO<sub>3</sub> [M+H]<sup>+</sup> 336.0230 found 336.0237.

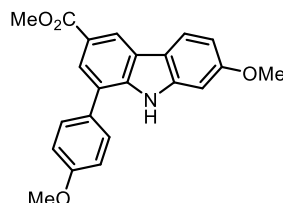


**Methyl 6-azido-5-bromo-4'-methoxy-[1,1'-biphenyl]-3-carboxylate (4.1):** A round bottom flask was charged with methyl 6-amino-5-bromo-4'-methoxy-[1,1'-biphenyl]-3-carboxylate (1.00 g, 2.97 mmol, 1 equiv.) in 10 mL acetonitrile [0.3 M] and cooled to 0 °C in an ice bath. To the stirred mixture was added *tert*-butyl nitrite (0.46 g, 531 μL, 4.46 mmol, 1.5 equiv.) followed by azidotrimethylsilane (0.68 g, 782 μL, 5.95 mmol, 2 equiv.) dropwise. The mixture was stirred at room temperature for 1 h. The solution was then concentrated under vacuum and the crude mixture was purified by silica gel column chromatography (5 → 15 % ethyl acetate in hexanes), to afford the desired product as a white solid (1.08 g, 96 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.20 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 1.9 Hz, 1H) 7.37 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 165.2, 159.9, 140.1, 137.3, 133.5, 131.7, 130.4, 128.9, 127.9, 117.0, 114.1, 55.4, 52.4; HRMS (ESI) *m/z* calculated for C<sub>15</sub>H<sub>12</sub>BrN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup> 362.0135; found 362.0133.

### 8.3 Synthesis of Clausine C Derivatives via Two-Step Photodecomposition and Pd-Catalyzed Cross Coupling

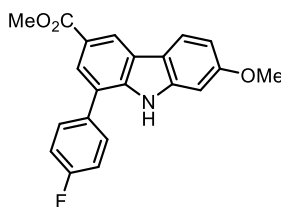


**Figure 8.1** Experimental set-up for continuous two-step synthesis employing a photochemical reactor for irradiation at 394 nm (purple LEDs), followed by Suzuki-coupling using a supported Pd-based catalyst, SiliaCat.

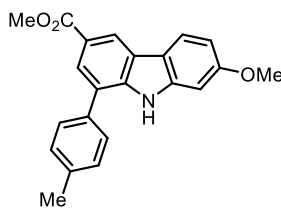


**General Procedure for the Two-Step Photodecomposition/Pd-Catalyzed Cross-Coupling in Continuous-Flow (4.4):** A solution of methyl 6-azido-5-bromo-4'-methoxy-[1,1'-biphenyl]-3-carboxylate **4.1** (54.3 mg, 0.15 mmol, 1.0 equiv.) in THF (5 mL, 30 mM) was injected via a syringe into an aluminium foil-covered 5 mL injection loop (6-way valve). The carrier solvent was pumped by a Vapourtec R2+ pumping module. The pump was turned on at a flow rate of 0.077 mL/min. The reaction mixture was pumped through a 13.8 mL PFA-coiled reactor irradiated with 394 nm light source for a 3 h residence time. A solution of 4-methoxyphenylboronic acid **4.5** (0.188 mmol, 1.25 equiv.), potassium carbonate (31.1 mg, 0.225 mmol, 1.5 equiv.) in H<sub>2</sub>O/EtOH (1:1, 5 mL, 30mM) was injected via a syringe into a second 5 mL injection loop (6-way valve). A second pump

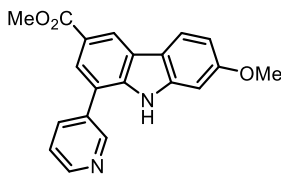
was turned on at a flow rate of 0.077 mL/min to introduce the second solution via a T-mixer to the exiting stream from the photoreactor. The solution then entered a glass column reactor (0.7854 ID x 7 cm) containing a mixture of SiliaCatDpp-Pd (120 mg, 0.03 mmol, 20 mol%) and 1.5 g of Celite. With a total flow rate of 0.154 mL/min, the reaction mixture was pumped through the 3.14 mL packed-bed reactor heated at 70 °C for a 20.4 minutes residence time. The collected solution was concentrated under vacuum to provide a crude reaction mixture which was purified by column chromatography on silica-gel (7.5 % → 30 % ethyl acetate in hexanes), to afford methyl 7-methoxy-1-(4-methoxyphenyl)-9*H*-carbazole-3-carboxylate **4.4** as a white solid (32.5 mg, 60 % yield): <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.35 (s, 1H), 8.64 (s, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 7.85 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H) 7.15 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 1.6, 1H), 6.85 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 167.0, 159.0 (2C), 142.3, 139.9, 130.0, 129.3, 124.9, 124.1, 123.4, 121.4, 120.6, 119.9, 116.3, 114.6, 108.9, 95.4, 55.3, 55.2, 51.8; HRMS (ESI) *m/z* calculated for C<sub>22</sub>H<sub>19</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 362.1387; found 362.1398.



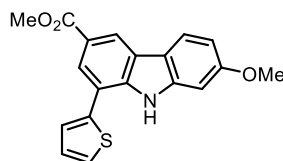
**Methyl 1-(4-fluorophenyl)-7-methoxy-9*H*-carbazole-3-carboxylate (4.6):** Following the two-step procedure, using 4-fluorophenylboronic acid (26.2 mg, 0.188 mmol, 1.25 equiv.) the crude mixture was purified by silica gel column chromatography (7.5 % → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (35.0 mg, 67 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.41 (s, 1H), 8.68 (d, *J* = 1.2 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H) 7.87 (d, *J* = 1.6 Hz, 1H), 7.77-7.73 (m, 2H), 7.42 (dd, *J* = 8.9, 8.8 Hz, 2H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.2 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 167.0, 159.1, 142.4, 139.9, 134.1, 130.6, 125.2, 123.5, 123.3, 121.5, 120.6, 120.5, 116.2, 116.1, 115.9, 109.0, 95.3, 55.3, 51.9; <sup>19</sup>F NMR (376.4 MHz, DMSO-*d*<sub>6</sub>) δ = -114.5; HRMS (ESI) *m/z* calculated for C<sub>21</sub>H<sub>16</sub>FNO<sub>3</sub> [M+H]<sup>+</sup> 350.1187; found 350.1200.



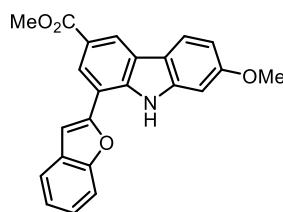
**Methyl 7-methoxy-1-(*p*-tolyl)-9*H*-carbazole-3-carboxylate (4.7):** Following the two-step procedure, using *p*-tolylboronic acid (25.5 mg, 0.188 mmol, 1.25 equiv.) the crude mixture was purified by silica gel column chromatography (7.5 % → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (33.5 mg, 65 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.35 (s, 1H), 8.65 (d, *J* = 1.1 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H) 7.87 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 2.1 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 2.43 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 167.0, 159.0, 142.3, 139.9, 137.1, 134.8, 129.7, 128.3, 125.0, 124.2, 123.4, 121.4, 120.5, 120.2, 116.2, 108.9, 95.4, 55.2, 51.8, 20.8; HRMS (ESI) *m/z* calculated for C<sub>22</sub>H<sub>19</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 346.1438; found 346.1444.



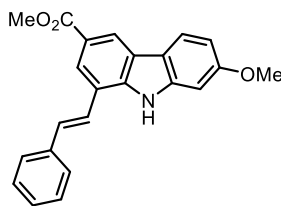
**Methyl 7-methoxy-1-(pyridin-3-yl)-9*H*-carbazole-3-carboxylate (4.8):** Following the two-step procedure, using 3-pyridinylboronic acid (25.6 mg, 0.188 mmol, 1.25 equiv.) the crude mixture was purified by silica gel column chromatography (7.5 % → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (20.8 mg, 42 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.58 (s, 1H), 8.92 (d, *J* = 1.9 Hz, 1H), 8.73 (d, *J* = 1.3 Hz, 1H) 8.70 (dd, *J* = 4.5, 1.2 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 1.3 Hz, 1H), 7.64-7.61 (m, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 8.18 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H) ; <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 166.8, 159.1, 149.0, 148.8, 142.4, 140.0, 136.2, 125.5, 124.1, 123.6, 121.6, 121.0, 120.9, 120.7, 116.1, 109.1, 95.3, 55.2, 51.9; HRMS (ESI) *m/z* calculated for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> 333.1234; found 333.1242.



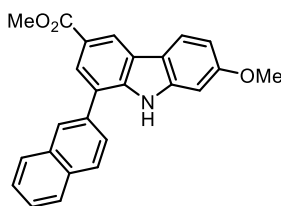
**Methyl 7-methoxy-1-(thiophen-2-yl)-9H-carbazole-3-carboxylate (4.9):** Following the two-step procedure, using 2-thienylboronic acid (25.3 mg, 0.188 mmol, 1.25 equiv.) the crude mixture was purified by silica gel column chromatography (7.5 % → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (19.6 mg, 39 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ = 11.44 (s, 1H), 8.66 (d, *J* = 1.5 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H) 8.00 (d, *J* = 1.5 Hz, 1H), 7.74 (d, *J* = 4.5 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.35-7.32 (m, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 6.88 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ = 166.7, 159.2, 142.4, 139.2, 138.9, 128.5, 126.3, 126.1, 124.5, 123.9, 121.6, 120.6, 117.2, 116.1, 109.3, 95.5, 55.2, 51.9; HRMS (ESI) *m/z* calculated for C<sub>19</sub>H<sub>15</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> 338.0845; found 338.0854.



**Methyl 1-(benzofuran-2-yl)-7-methoxy-9H-carbazole-3-carboxylate (4.10):** Following the two-step Procedure A, using 2-benzofuranylboronic acid (30.4 mg, 0.188 mmol, 1.25 equiv.) the crude mixture was purified by silica gel column chromatography (7.5 % → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (20.1 mg, 36 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ = 11.61 (s, 1H), 8.72 (s, 1H), 8.46 (s, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H) 7.76 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.41 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.34 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.1 Hz, 1H) 3.93 (s, 3H), 3.89 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ = 166.7, 159.4, 154.1, 152.8, 142.5, 137.7, 128.8, 124.9, 124.5, 123.5, 122.5, 121.7, 121.5, 121.2, 120.7, 115.9, 112.9, 111.5, 109.6, 103.7, 95.6, 55.4, 52.1; HRMS (ESI) *m/z* calculated for C<sub>23</sub>H<sub>17</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 372.1230; found 372.1247.

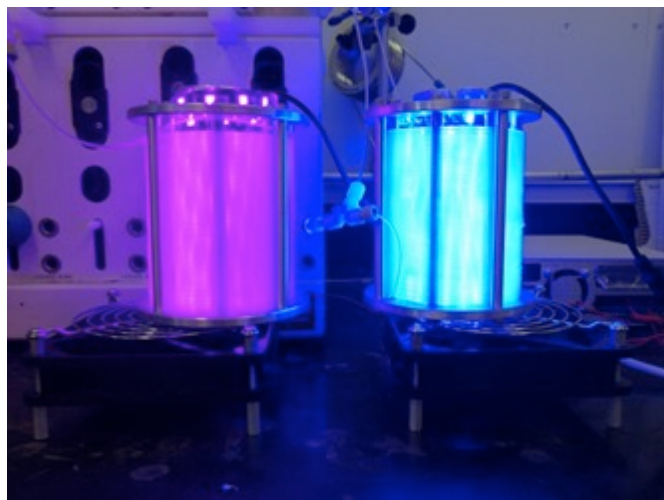


**Methyl (*E*)-7-methoxy-1-styryl-9*H*-carbazole-3-carboxylate (4.11):** Following the two-step Procedure A, using *trans*-2-phenylvinylboronic acid (27.7 mg, 0.188 mmol, 1.25 equiv.) the crude mixture was purified by silica gel column chromatography (7.5 % → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (22.2 mg, 41 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.85 (s, 1H), 8.60 (s, 1H), 8.28 (s, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 7.84-7.76 (m, 3H), 7.47-7.43 (m, 3H), 7.33 (dd, *J* = 7.3, 7.2 Hz, 1H), 7.05 (d, *J* = 1.9 Hz, 1H), 6.87 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 167.0, 159.2, 141.9, 140.6, 137.2, 129.6, 128.7, 127.8, 126.7, 123.4, 123.0, 121.6, 121.1, 120.6, 120.3, 120.0, 116.2, 108.9, 94.9, 55.3, 51.8; HRMS (ESI) *m/z* calculated for C<sub>23</sub>H<sub>19</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 358.1438; found 358.1454.

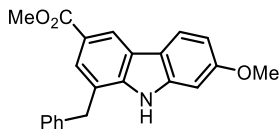


**Methyl 7-methoxy-1-(naphthalene-2-yl)-9*H*-carbazole-3-carboxylate (4.12):** Following the two-step Procedure A, using 2-naphthylboronic acid (32.2 mg, 0.188 mmol, 1.25 equiv.) the crude mixture was purified by silica gel column chromatography (7.5 % → 30 % ethyl acetate in hexanes), to afford the desired product as a white solid (42.5 mg, 74 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.52 (s, 1H), 8.72 (d, *J* = 1.5 Hz, 1H), 8.27 (d, *J* = 1.0 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.09-8.02 (m, 3H), 7.84 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62-7.59 (m, 2H), 7.06 (d, *J* = 2.2, 1H), 6.87 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 167.0, 159.1, 142.4, 140.1, 135.1, 133.2, 132.4, 128.7, 128.4, 127.6, 127.3, 126.6, 126.4, 126.4, 125.4, 124.1, 123.6, 121.5, 120.7, 120.5, 116.3, 109.0, 95.3, 55.2, 51.8; HRMS (ESI) *m/z* calculated for C<sub>25</sub>H<sub>19</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 382.1438; found 382.1446.

## 8.4 Synthesis of Clausine C Derivatives via Two-Step Photodecomposition and Ni-Catalyzed Cross Coupling



**Figure 8.2** Experimental set-up for continuous two-step synthesis employing two photochemical reactors: 394 nm (purple LEDs) and 450 nm (blue LEDs).

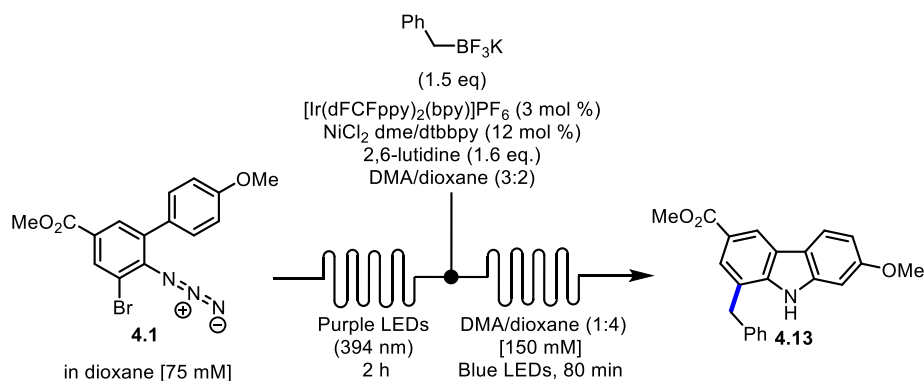


**General Procedure for the Two-Step Photodecomposition/Ni-Catalyzed Cross-Coupling in Continuous-Flow (4.13):** A solution of methyl 6-azido-5-bromo-4'-methoxy-[1,1'-biphenyl]-3-carboxylate **4.1** (54.3 mg, 0.15 mmol, 1.0 equiv.) in THF (2 mL, 75 mM) was injected via a syringe into an aluminium foil-covered 2 mL injection loop (6-way valve). The carrier solvent was pumped by a Vapourtec R2+ pumping module. The pump was turned on at a flow rate of 0.115 mL/min. The reaction mixture was pumped through a 13.9 mL PFA-coiled reactor irradiated with 394 nm light source for a 2 hours residence time. A solution of potassium benzyltrifluoroborate (0.225 mmol, 1.5 equiv.), nickel(II) chloride ethylene glycol dimethyl ether complex (4.04 mg, 0.018 mmol, 12 mol%), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (4.93 mg, 0.018 mmol, 12 mol%), 4CzIPN (3.55 mg, 0.0045 mmol, 3 mol%), 2,6-lutidine (25.7 mg, 28  $\mu$ L, 0.24 mmol, 1.6 equiv.) in DMA/THF (3:2, 1 mL, 150 mM) was injected via a syringe into an aluminium foil-covered 1 mL injection loop (6-way valve). A second pump was turned on at a flow rate of 0.0575 mL/min to introduce



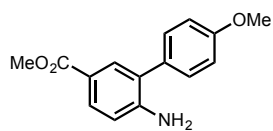
the second solution via a T-mixer to the exiting stream from the photoreactor. With a total flow rate of 0.1725 mL/min, the reaction mixture was pumped through a 13.9 mL PFA-coiled reactor irradiated with 450 nm light source for a 1.33 h residence time. The collected solution was concentrated under vacuum to provide a crude reaction mixture which was purified by silica gel column chromatography (5 % → 20 % acetone in hexanes) to afford methyl 1-benzyl-7-methoxy-9*H*-carbazole-3-carboxylate **4.13** as a white solid (20.1 mg, 39 % yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.62 (s, 1H), 8.56 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.74 (s, 1H), 7.34-7.27 (m, 4H), 7.21-7.17 (m, 1H), 7.05 (d, *J* = 2.0 Hz, 1H) 6.84 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.32 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 167.1, 159.0, 141.9, 141.5, 140.0, 128.7, 128.5, 126.2, 125.5, 123.4, 122.7, 121.5, 120.3, 119.5, 116.5, 108.9, 94.9, 55.3, 51.2, 36.1; HRMS (ESI) *m/z* calculated for C<sub>22</sub>H<sub>19</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 346.1438; found 346.1449

#### Additional attempts to improve yield:

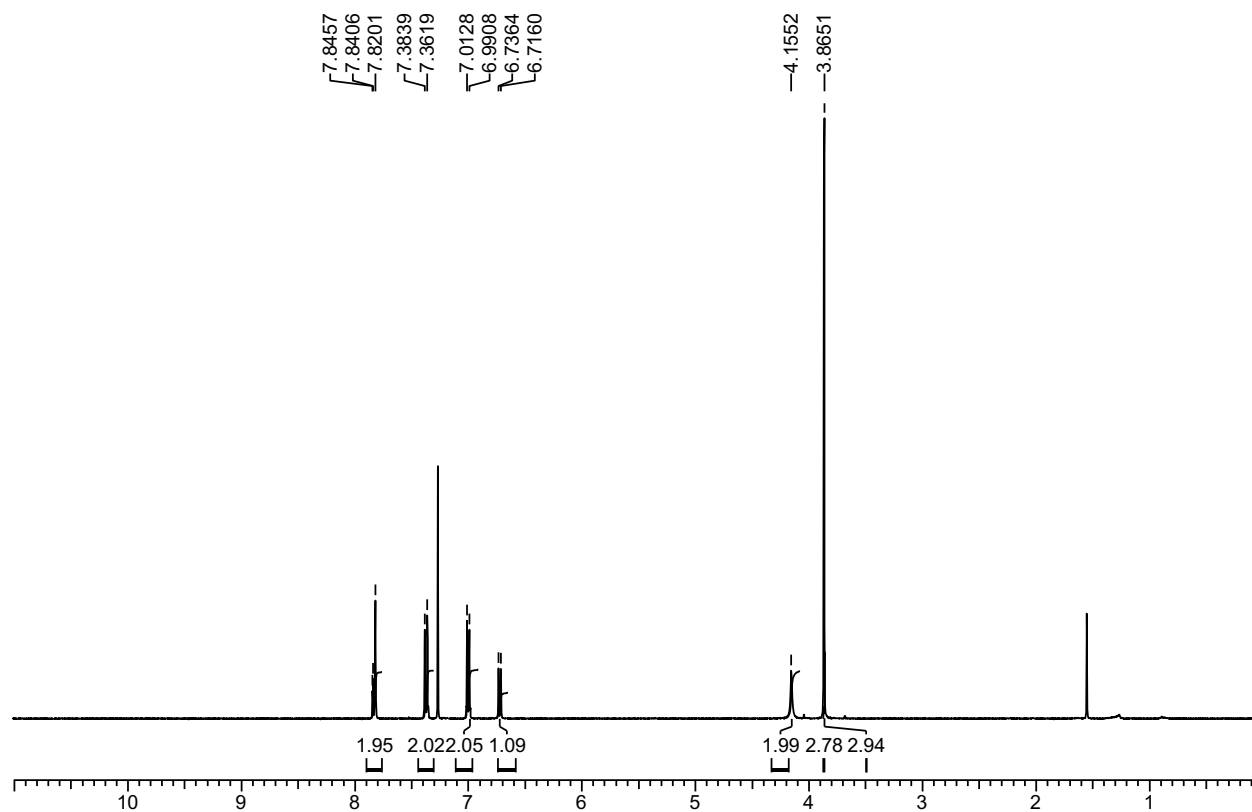


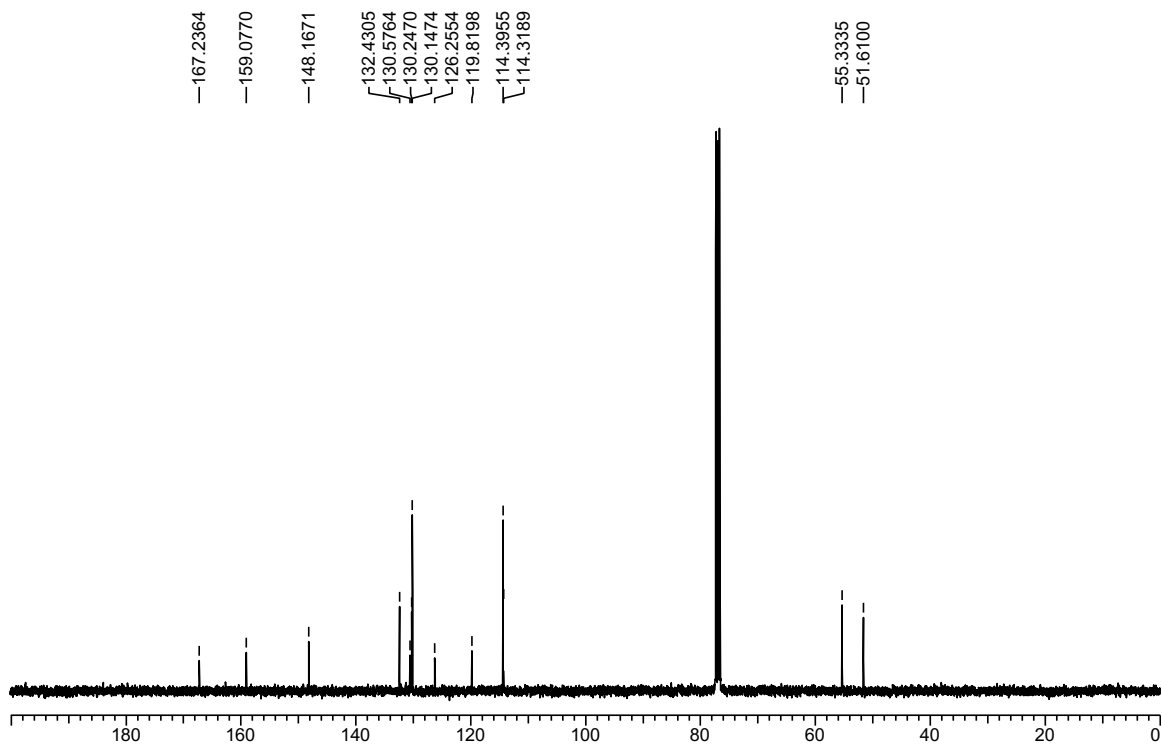
Light Source	Time for 2 <sup>nd</sup> photochemical step (min)	Yield (%)
one Blue LED column (6 W)	80	36
CFL	80	15
two Blue LED columns (6 W each)	160	37
one Blue LED column (20 W)	80	38

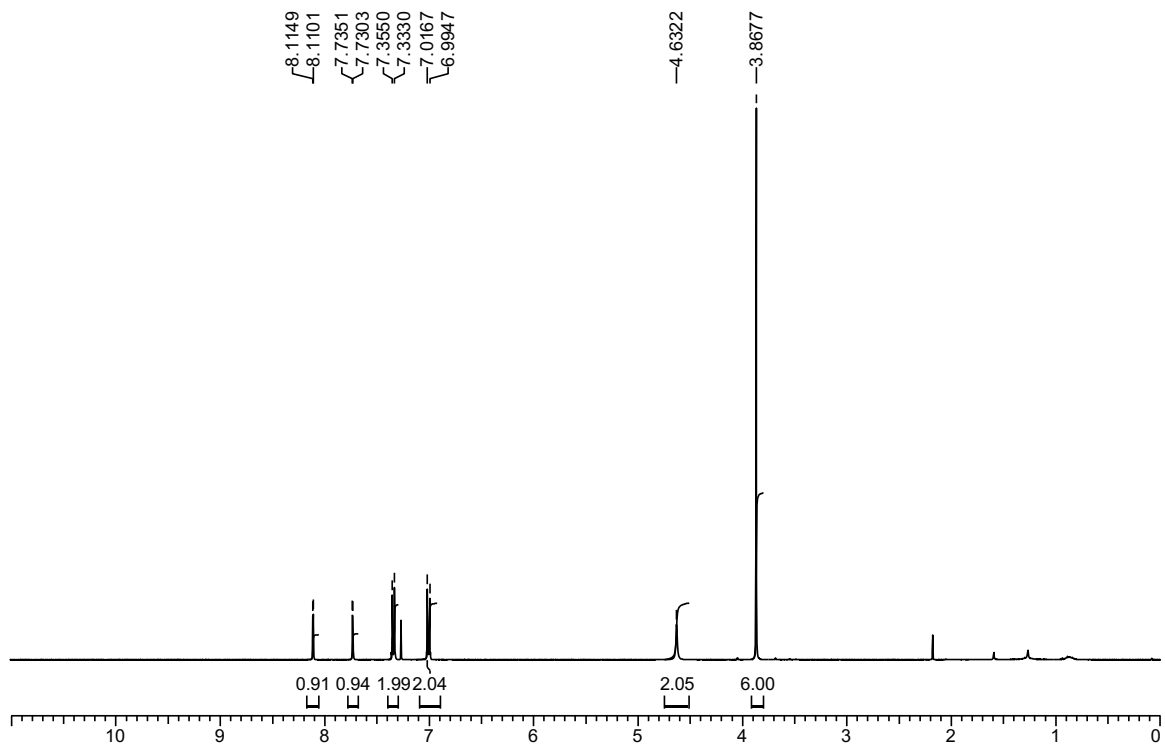
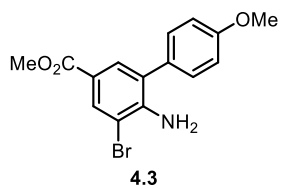
## 8.5 NMR Data for all New Compounds

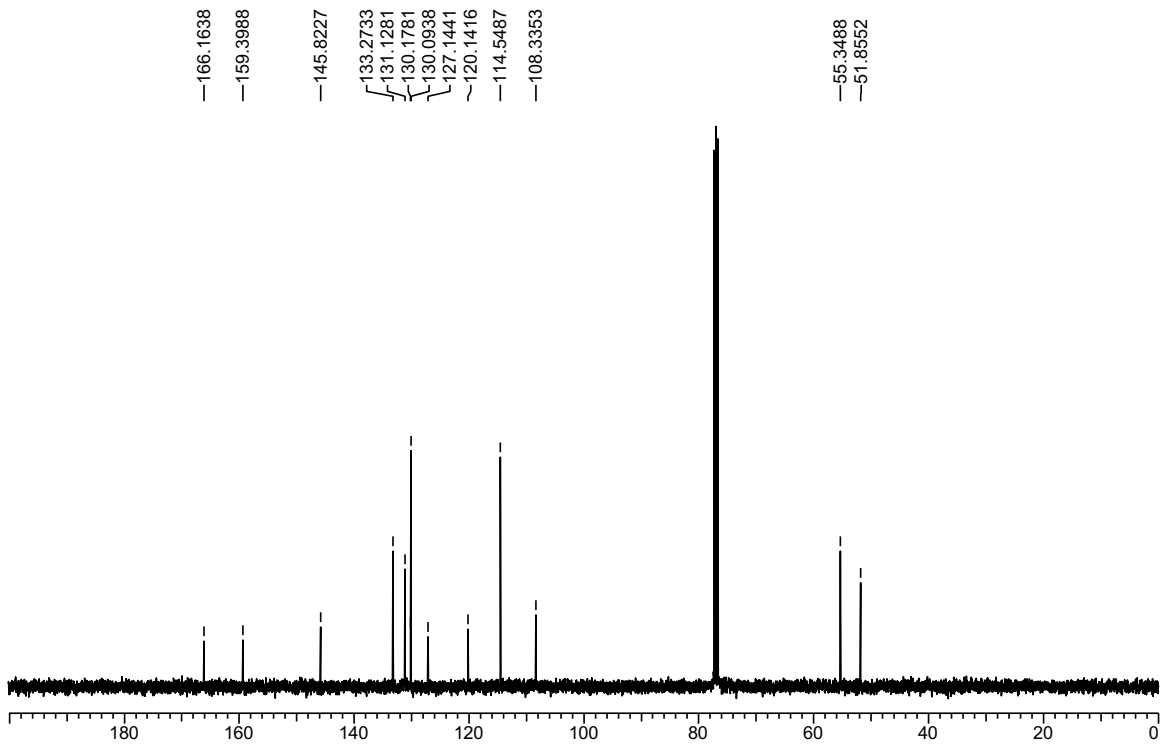


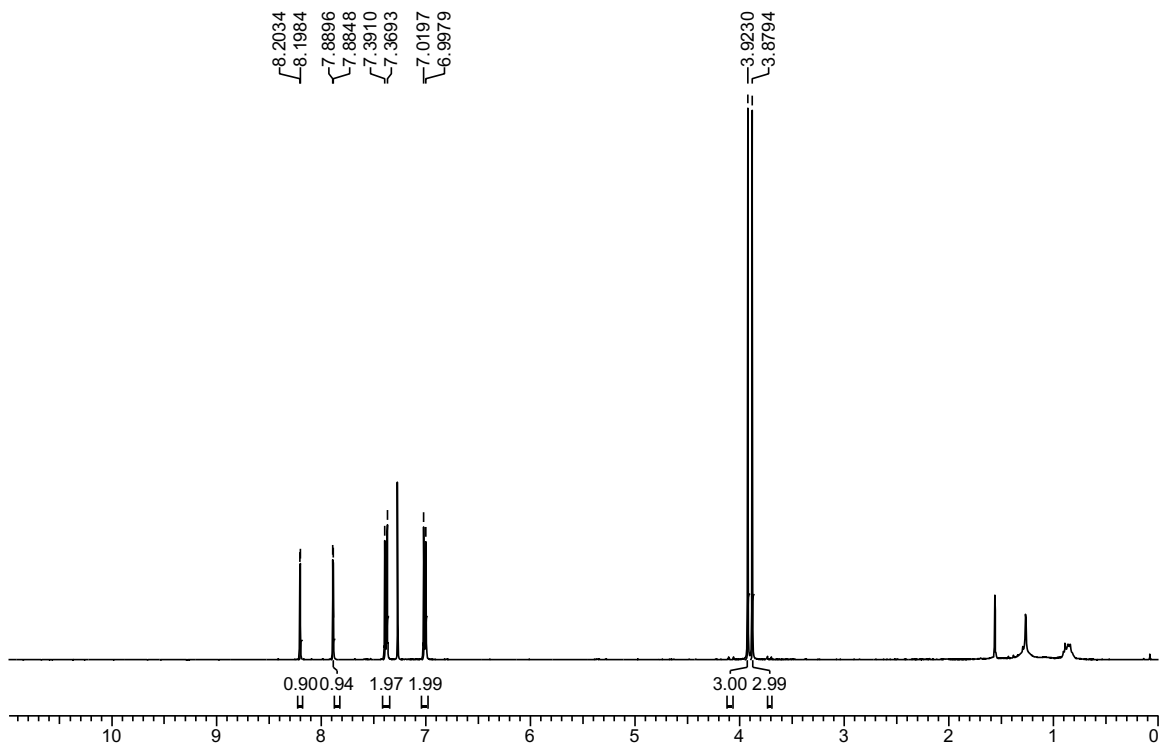
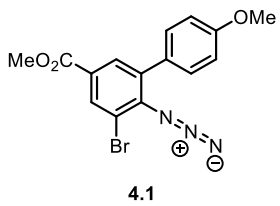
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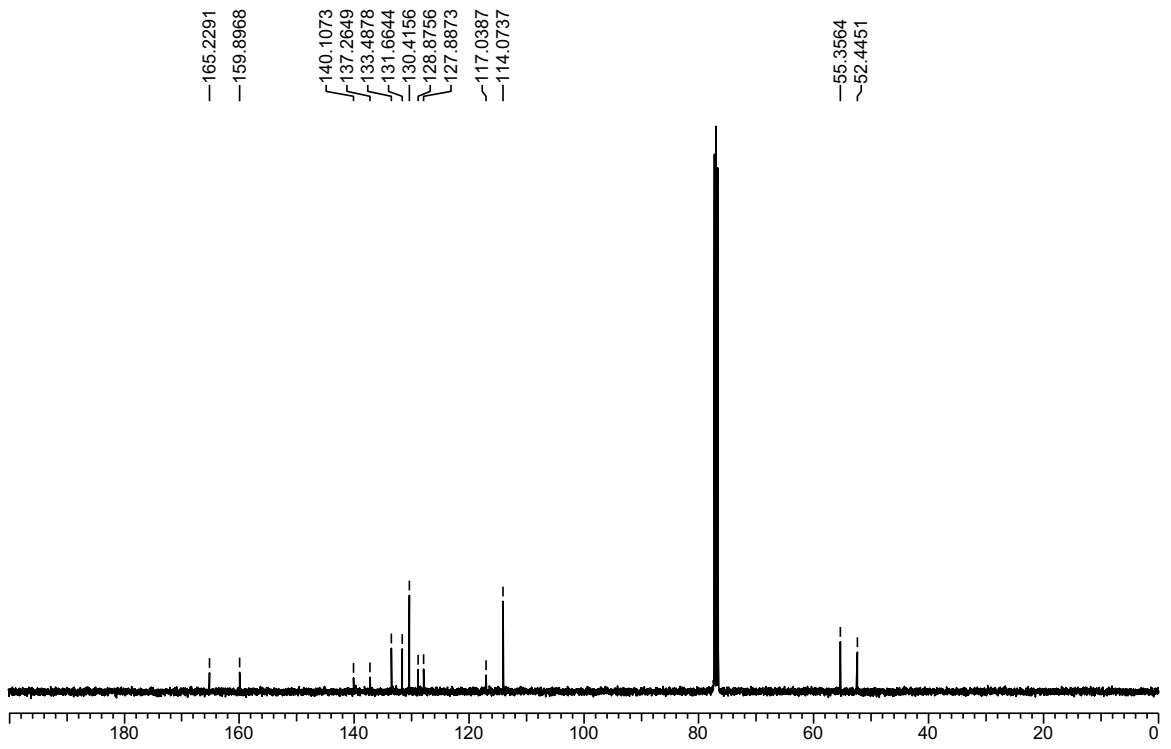


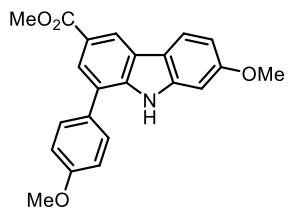




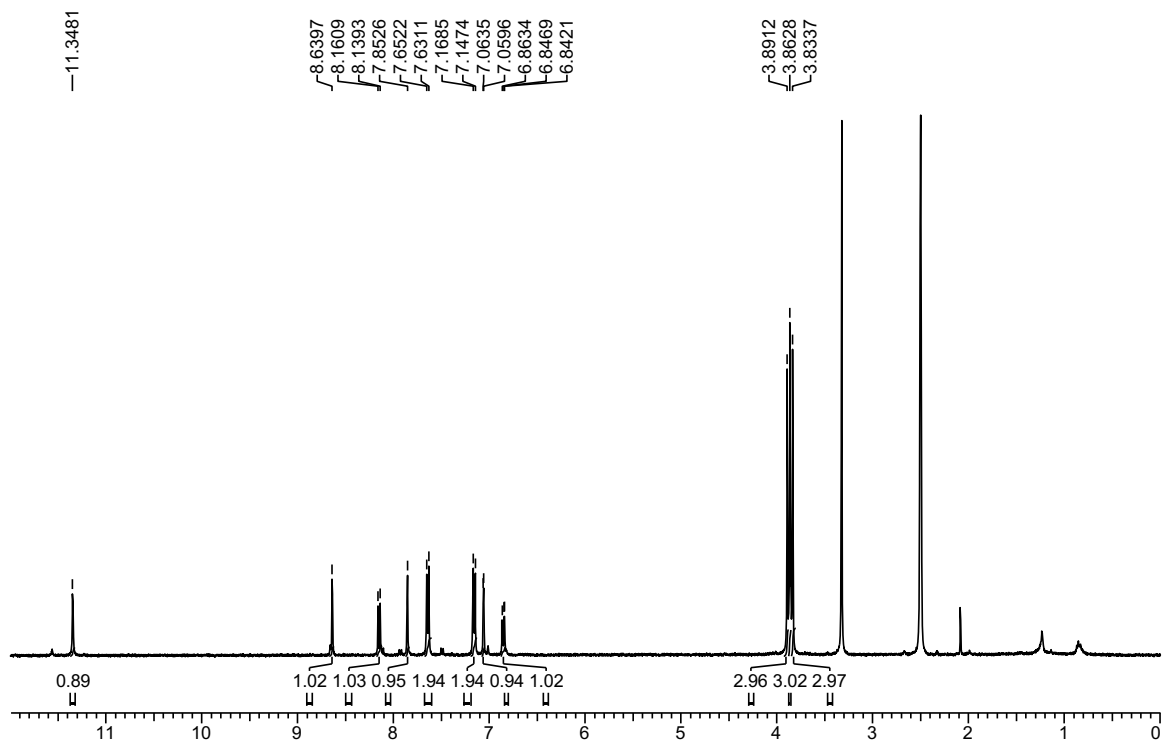




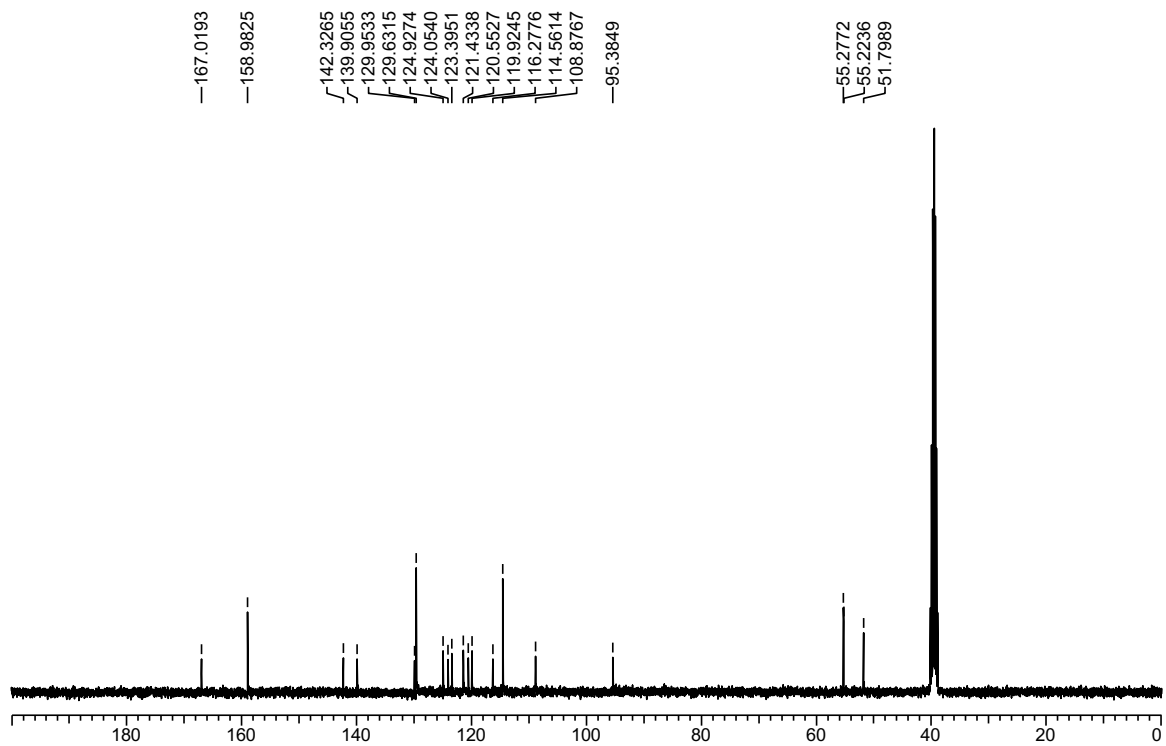


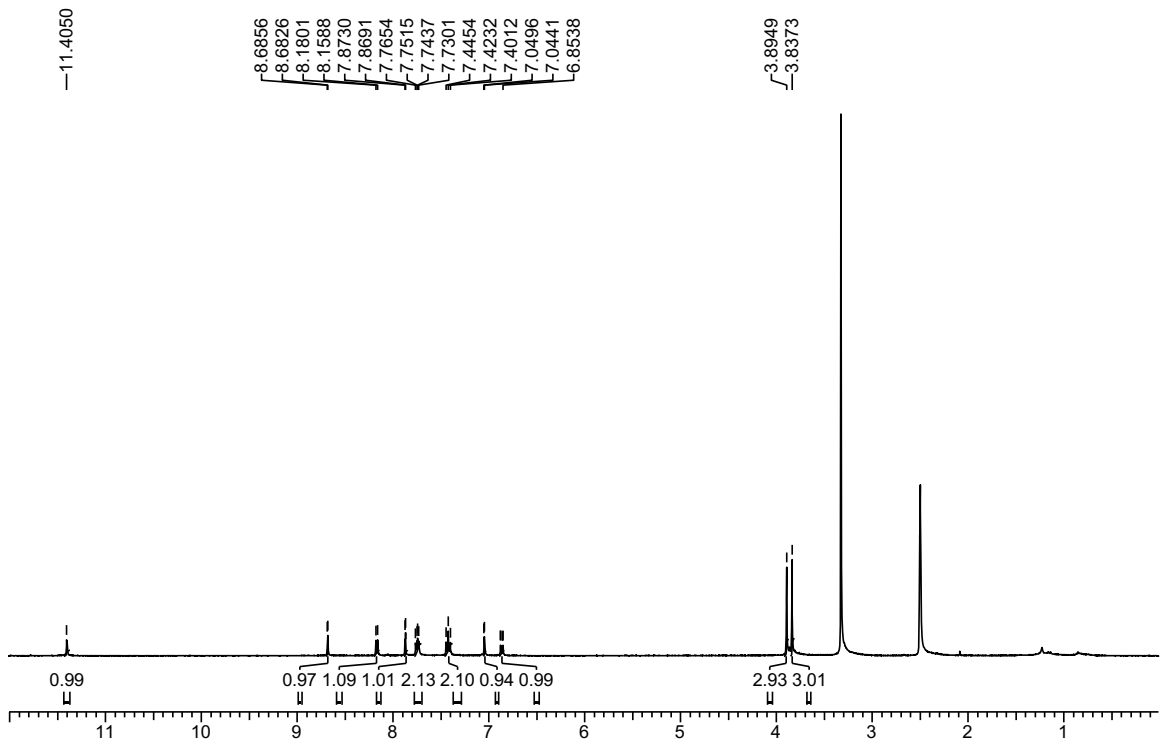
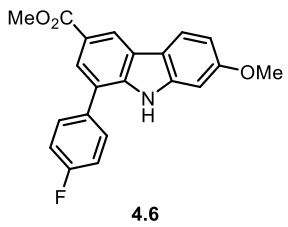


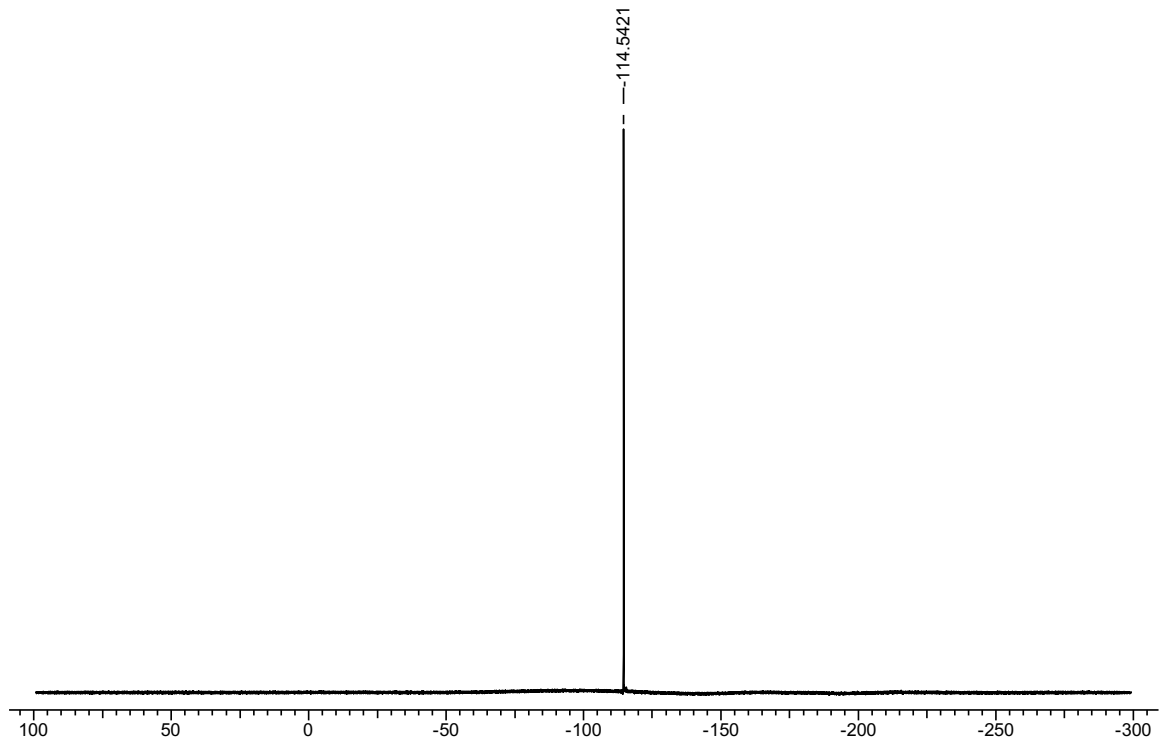
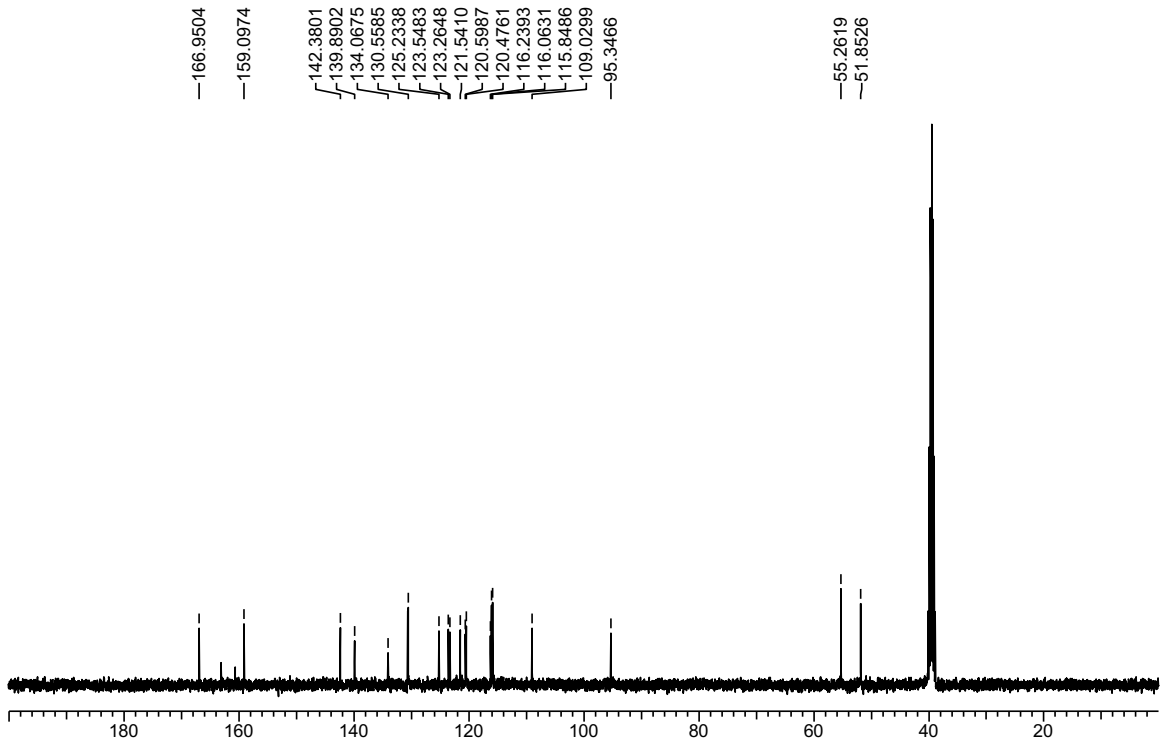
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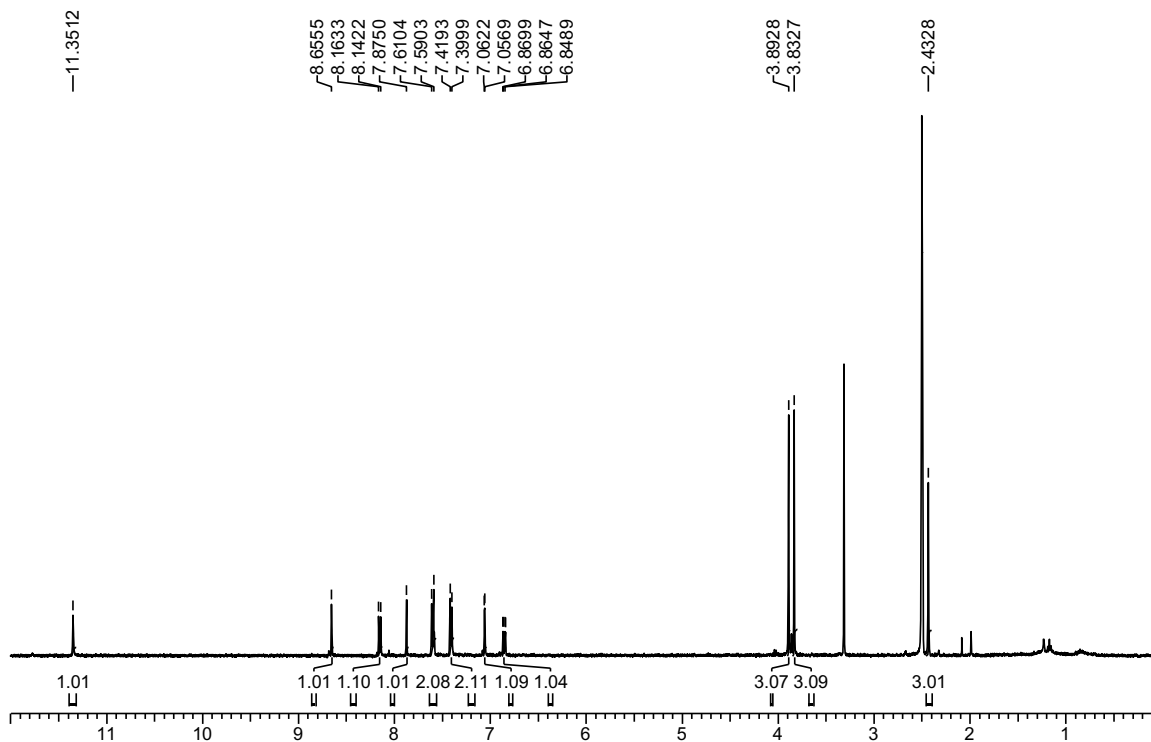
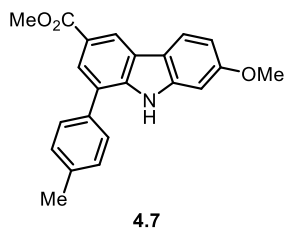


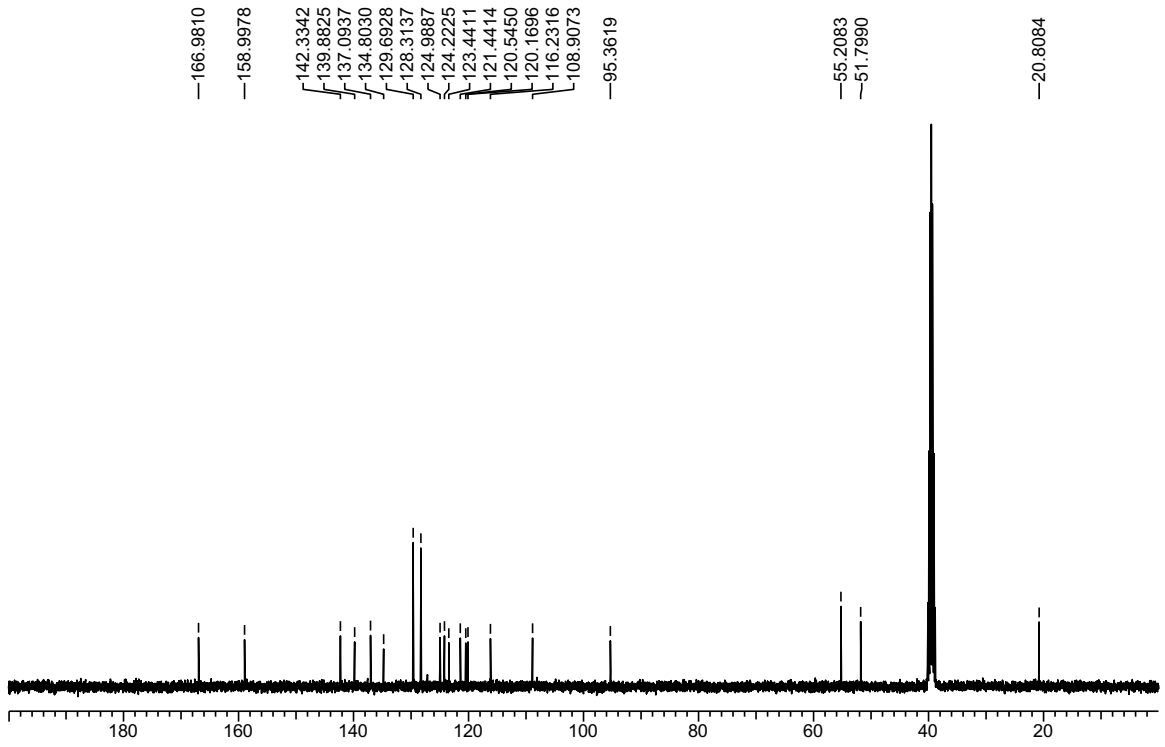


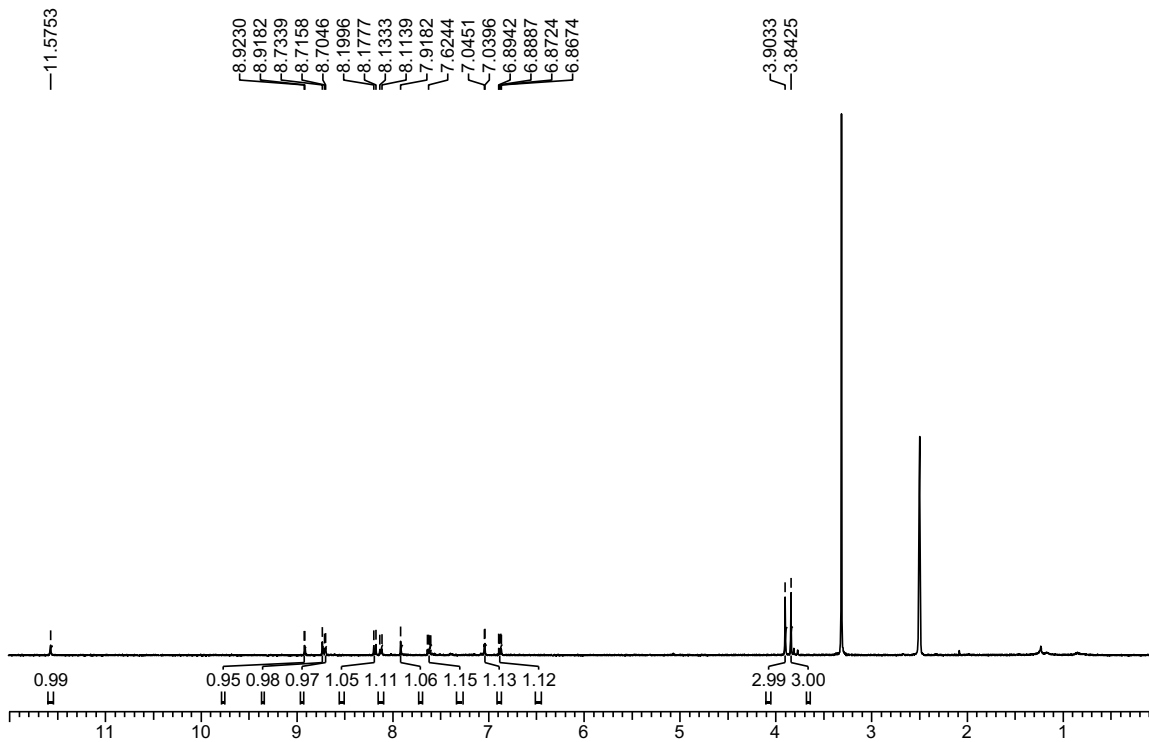
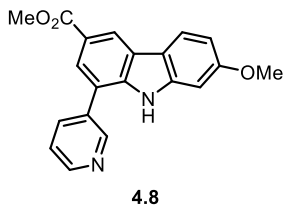


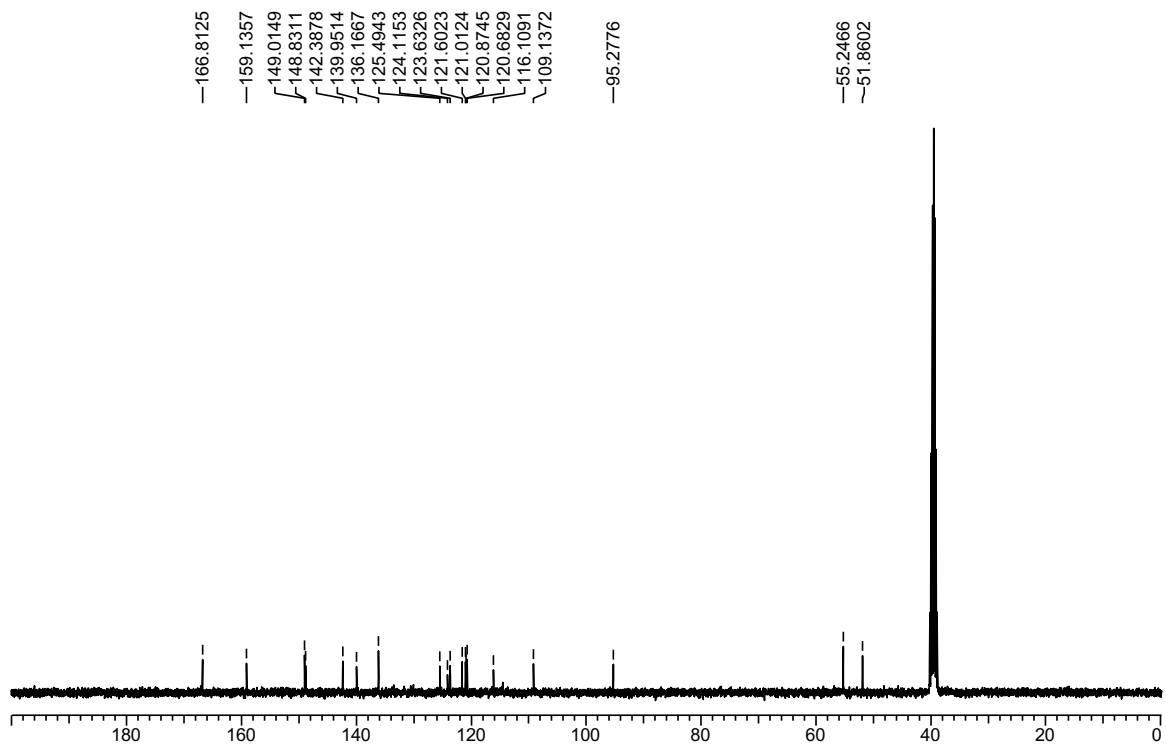


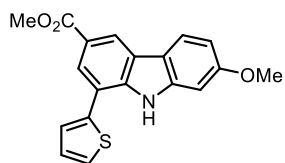




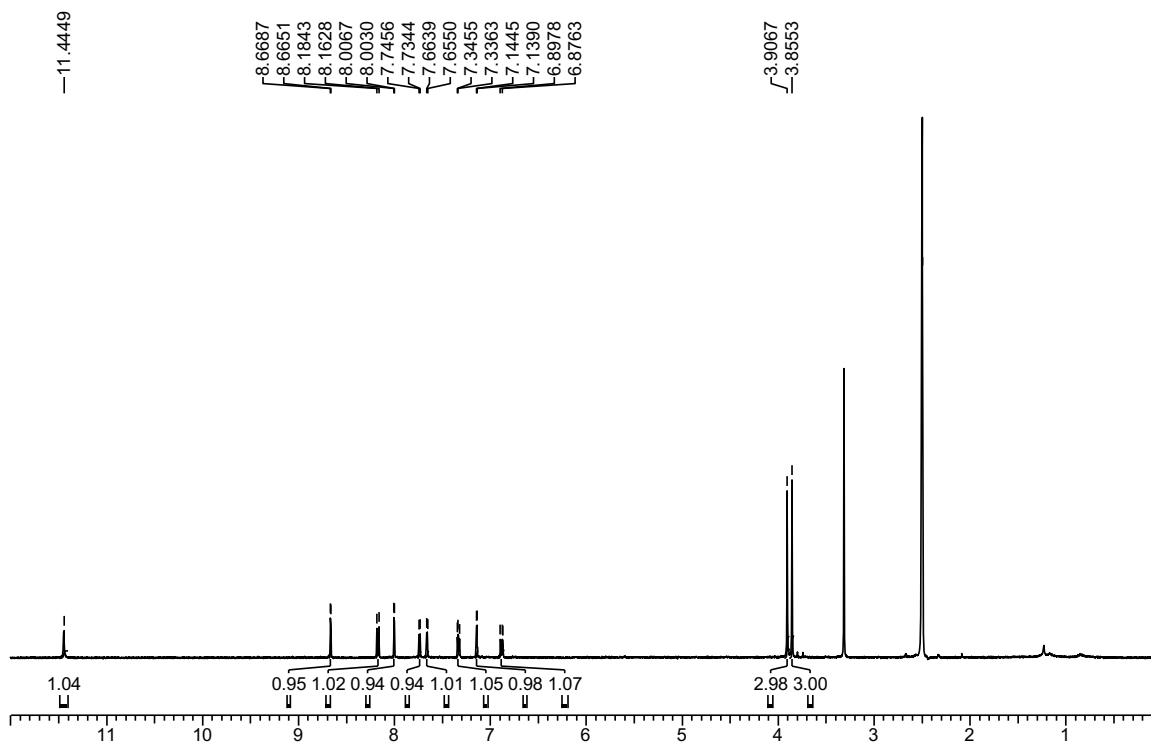




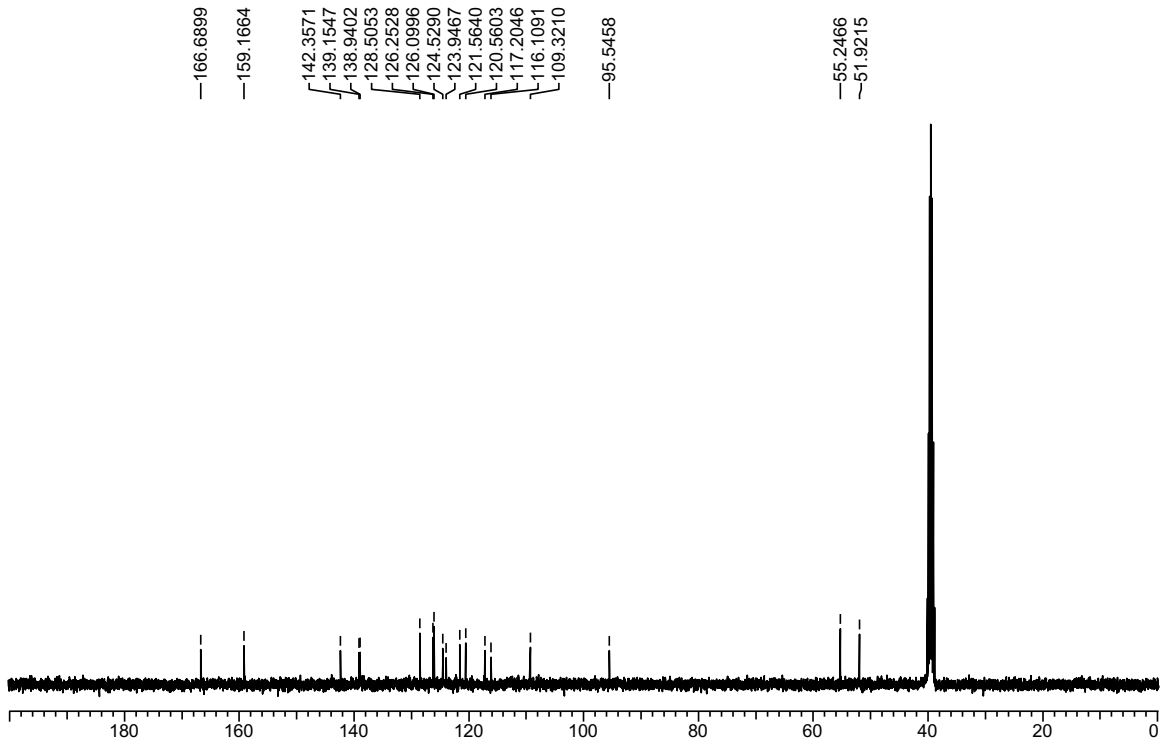


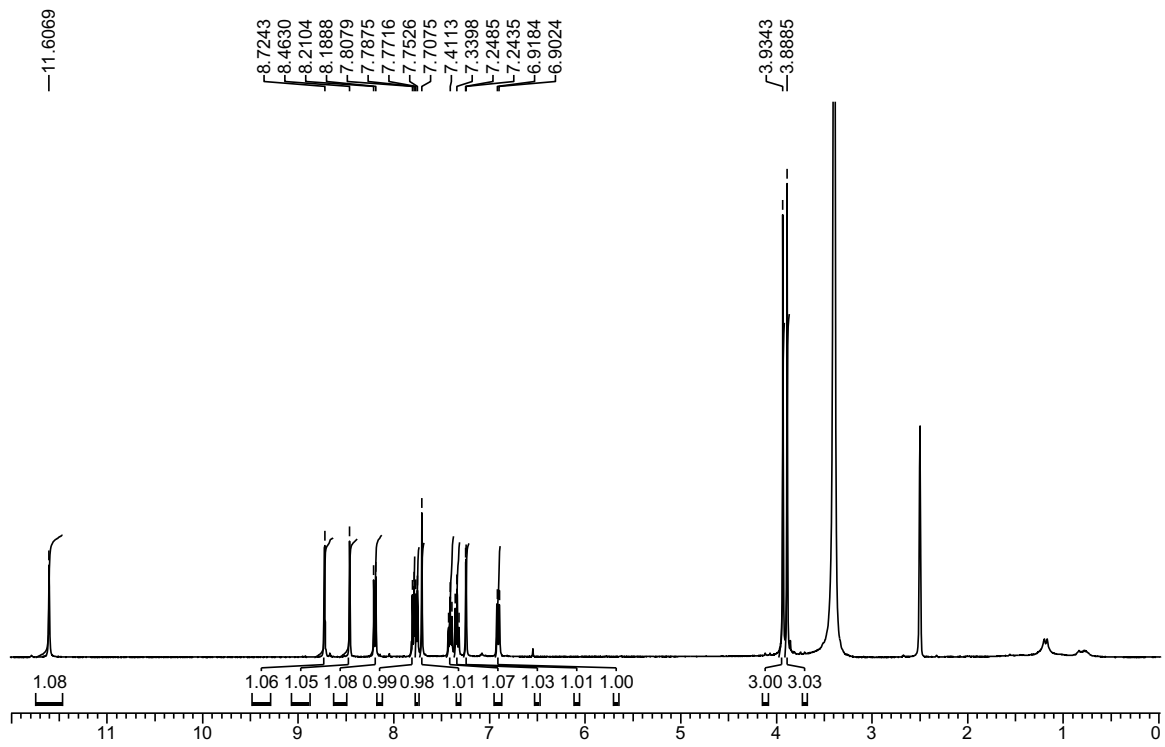
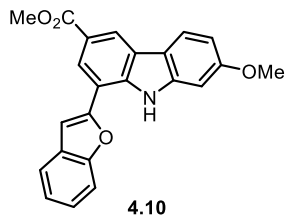


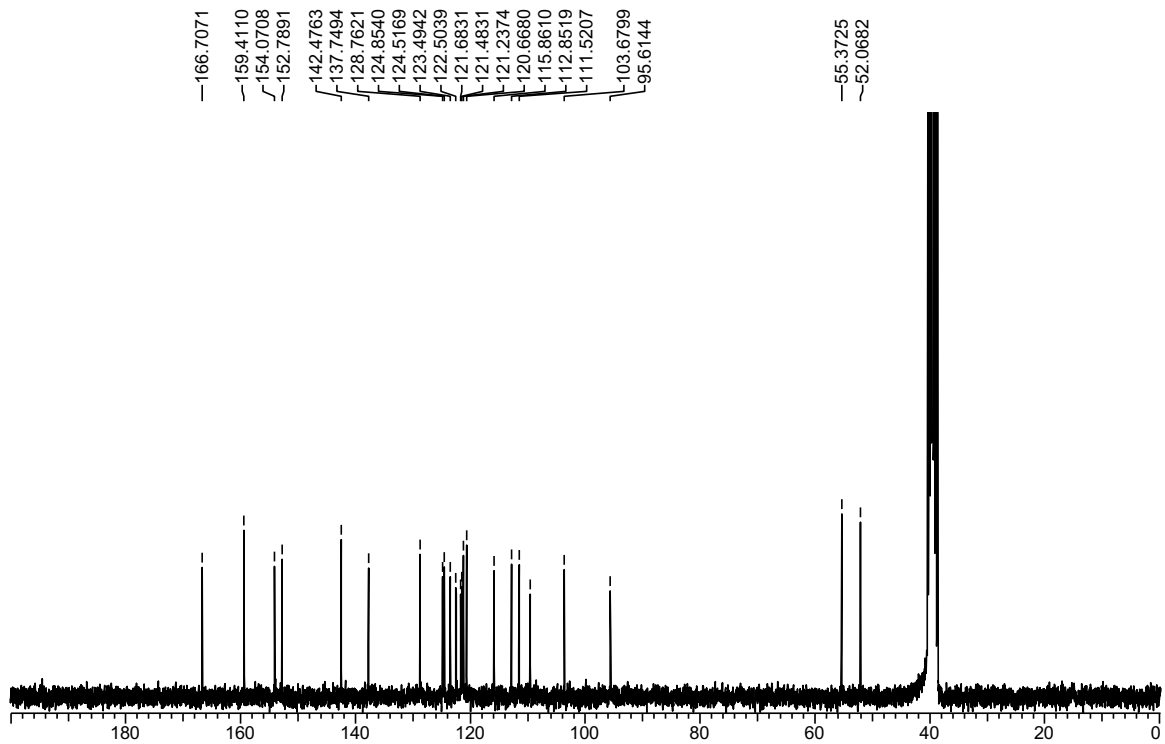
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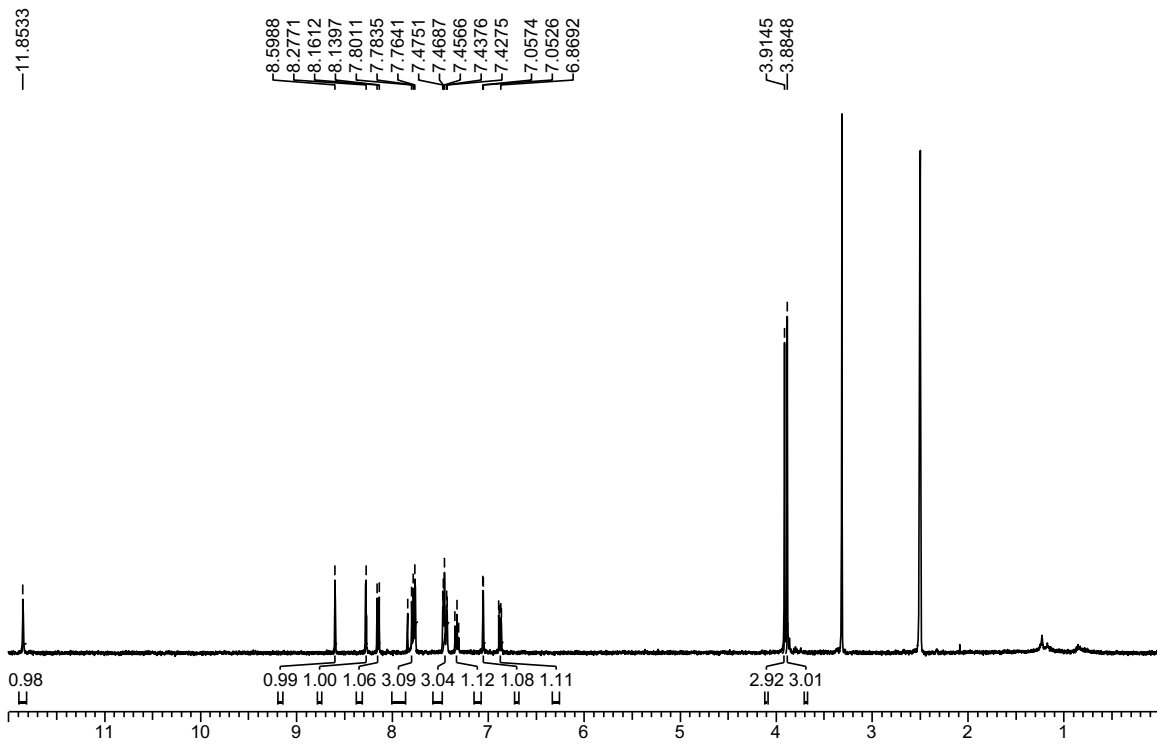
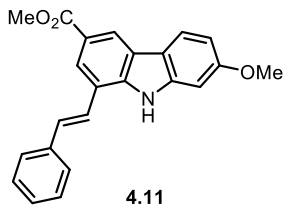


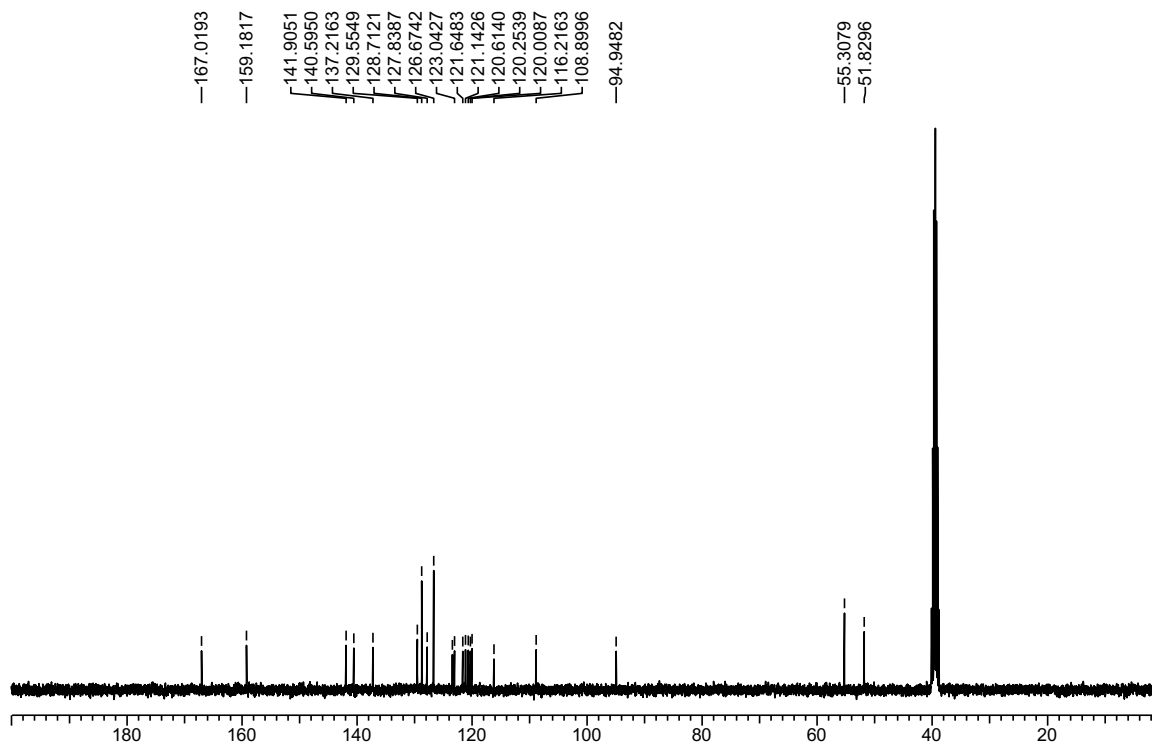


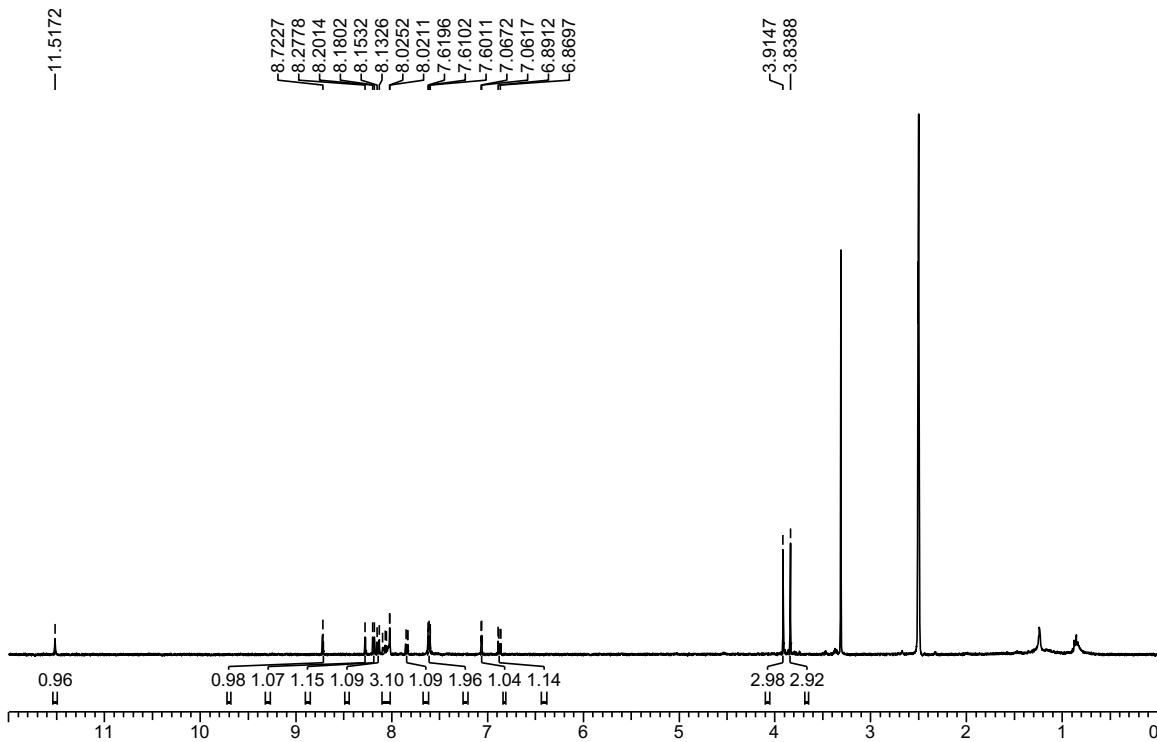
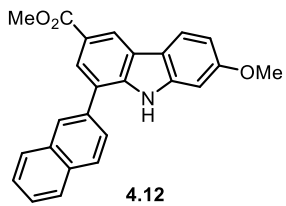


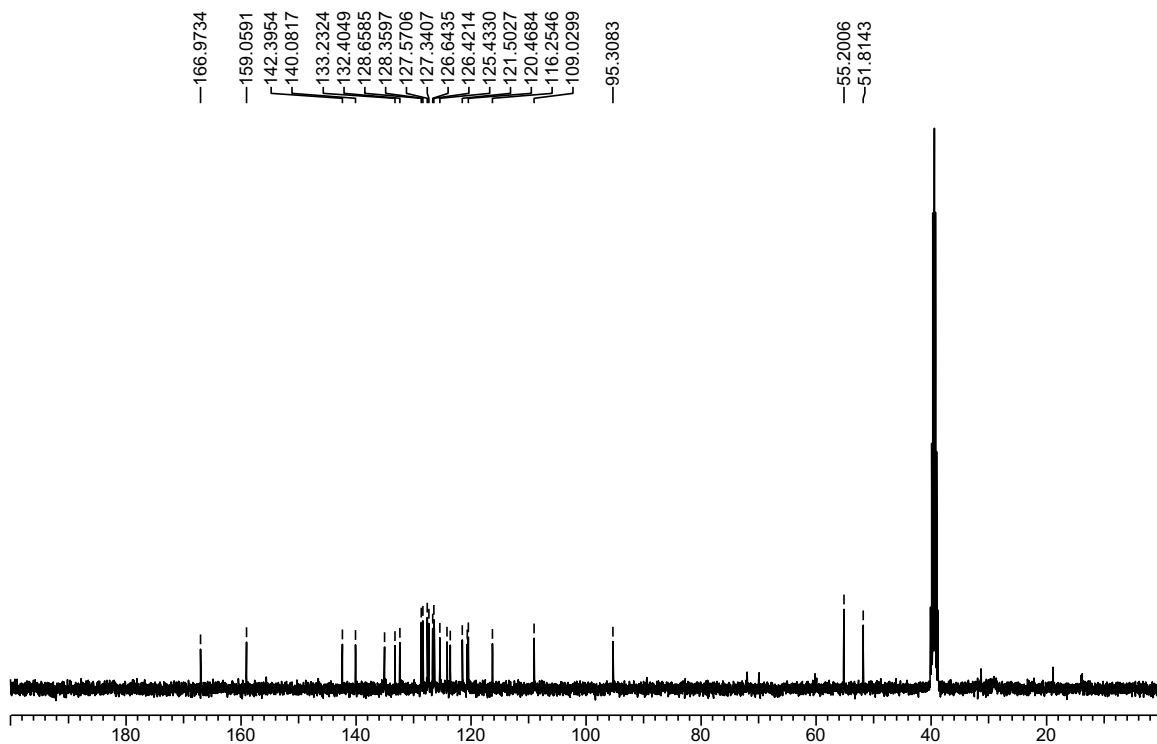


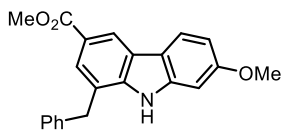




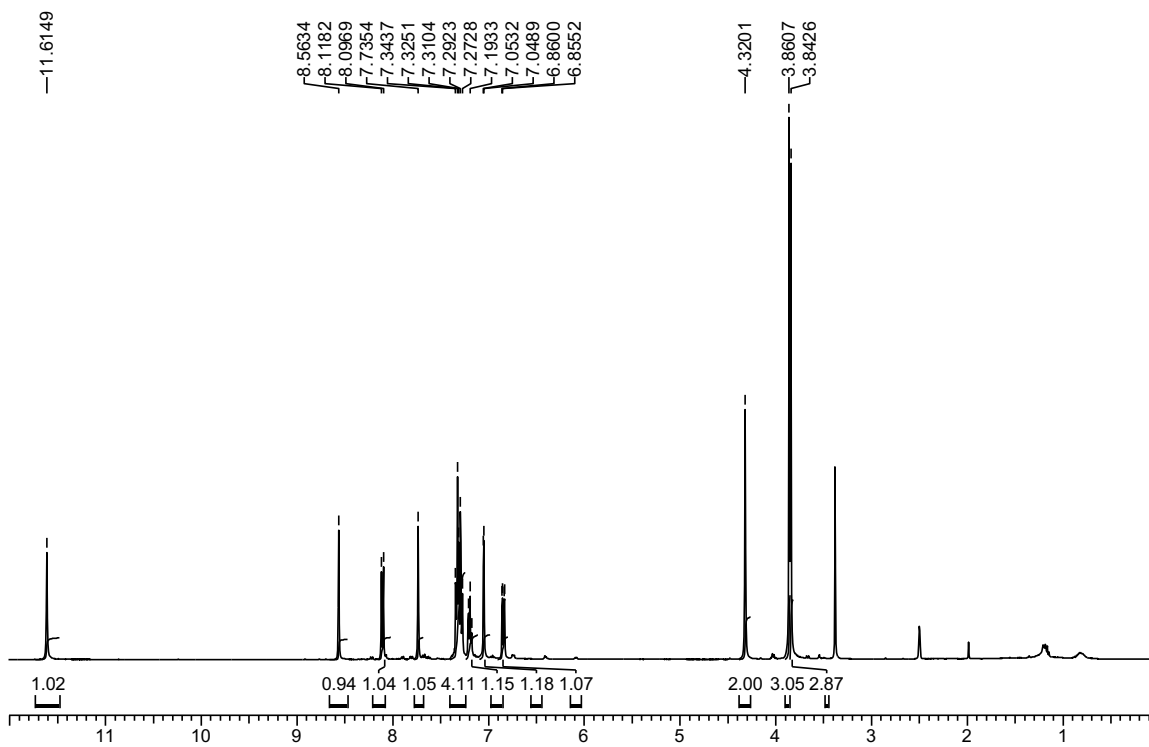




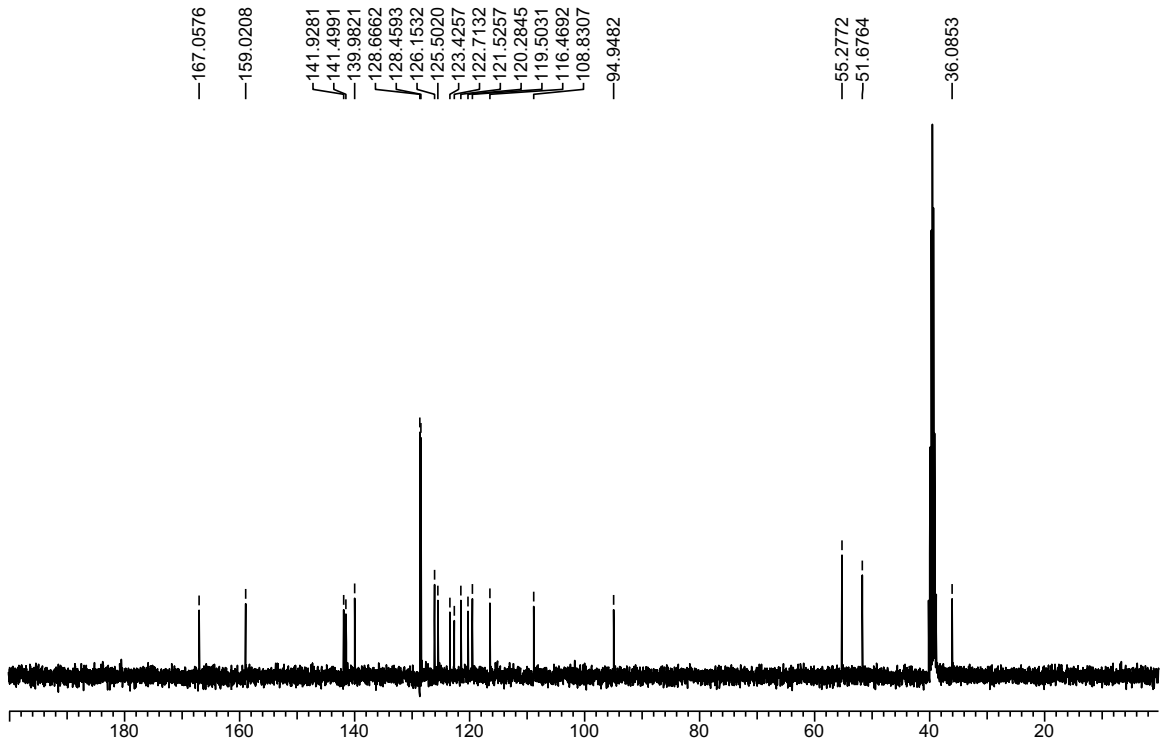




4.13







## 8.6 Bibliography

1. Shriver, D. F.; Drezdon, M. A., in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.
2. Still, W. C.; Kahn, M.; Mitra, A., Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.