universität wien

DISSERTATION / DOCTORAL THESIS

Titel der Dissertation /Title of the Doctoral Thesis

„I. The keteniminium ion: A Convenient Synthetic Intermediate

II. Redox reactions: Metal-Free Redox Transformations for C-C and C-N Bond Construction“

verfasst von / submitted by

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في الحياة.. لا تبحث عن البطولة.. ولكن قم بأداء دورك ببطولة

"بسام كوسا"

The greater the obstacle, the more glory in overcoming it

"Moliere"

The work presented in this doctoral thesis was conducted from October 2013 till September 2017 at the University of Vienna (Austria) under the supervision of Prof. Dr. Nuno Maulide.

Referees:

Prof. Dr. Paolo Melchiorre

Univ.-Prof. Dr. Kai Carsten Hultzsch

Herewith I would like to authenticate that I have written this thesis on my own.

I have not used other resources, tools or assistance than those reported in this thesis.

Saad Shaaban, November 2017

To my great parents...

لسّا مكملين.....

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My great parents, I know how much this moment means to you and I am very pleased to know that I made you proud of me... I overcame every weak moment in the last years by just thinking of you and remember your words...يا جبل البعيد

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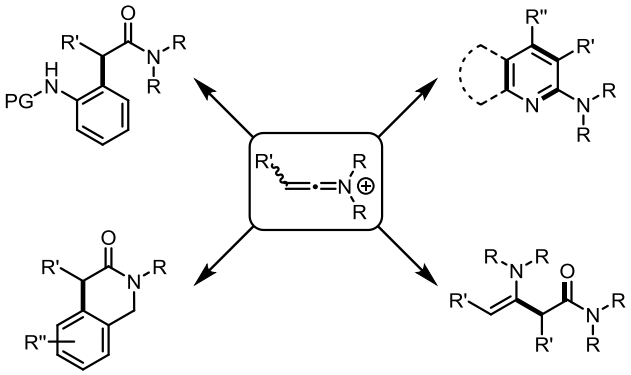
Table of Contents

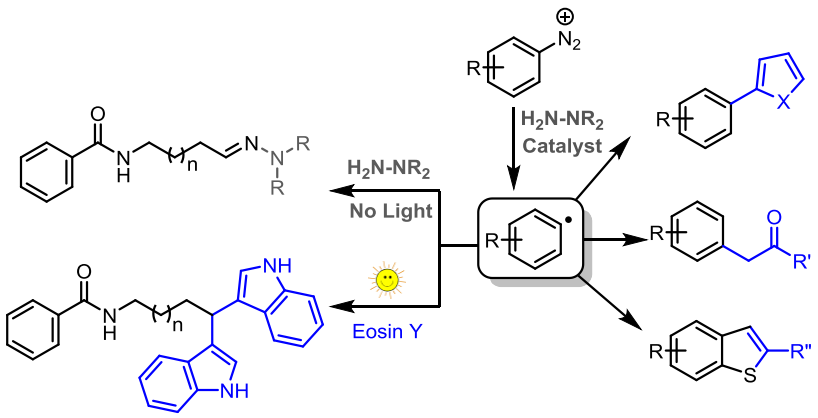
I. Abstract

Chapter I presents a brief discussion on keteniminium intermediates. These reactive intermediates, which are usually generated *in situ* from amides or ynamides have been successfully utilised in a range of reactions. The first example concerns the synthesis of penta-substituted pyridines by means of a [2+2+2] cycloaddition reaction of activated ynamides and cyanoalkanes. Also documented is the α-arylation of amides with hydroxamic acids via [3,3] sigmatropic rearrangements. Additionally, α-umpolung reactivity of amides and the hydrative dimerisation of ynamides is presented and discussed (Scheme I).



Scheme I. Reactions with keteniminium ion.

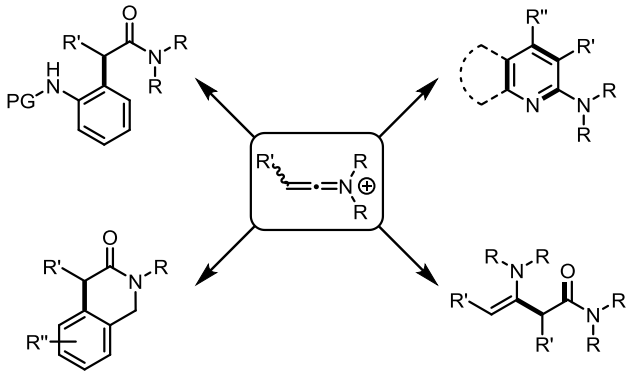
Chapter II summarises our recent redox reactions. The use of hydrazine derivatives to promote the reduction of diazonium salts into the corresponding aryl radicals and engaging them in a variety of transformations for C-C bond formation is presented. Hydrazines acted in dual role when used in stoichiometric quantities leading to the formation of hydrazone moieties. In addition, a visible light photo-catalysed formation of bis-indole derivatives *via* 1,5 hydrogen migration was also achieved (Scheme II).



Scheme II. Metal-free redox reactions for C-C and C-N bond formation.

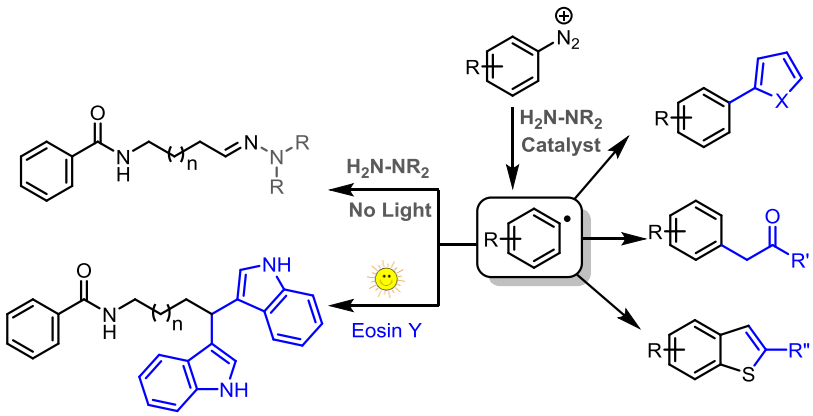
II. Kurzzusammenfassung

Kapitel I zeigt eine kurze Diskussion von Keteniminium-Intermediaten. Basierend auf diesen reaktiven Intermediaten, die *in situ* aus Amiden oder Inamiden hergestellt werden, wurden erfolgreich diverse Reaktionen entwickelt. Das erste Bespiel präsentiert die Herstellung von Pyridinderivaten durch eine hochselektive [2+2+2] Cycloaddition. Die α-Arylierung von Amiden mit Hydroxamsäuren durch eine [3,3] sigmatrope Umlagerung ist ebenso dokumentiert. Zusätzlich werden auch die α-Umpolung von Amiden und die Dimerisierung von Inamiden präsentiert und diskutiert (Schema I).



Schema I. Reaktionen mit Keteniminium-Intermediaten.

Kapitel II fasst unsere neuesten Redoxreaktionen zusammen. Hydrazine können die Reduktion von Diazoniumsalzen zu den entsprechenden Radikalen katalysieren. Die Radikale reagieren weiter und bilden neue C-C Bindungen aus. Bei stöchiometrischer Verwendung von Hydrazine wurden Hydrazone als Reaktionsprodukte erhalten. Außerdem konnten wir zeigen, dass ein Photokatalysator (Eoisn Y) die Herstellung von Bisindol-Derivaten erfolgerich orchestriert. Der Mechanismus dieser Reaktion verläuft über einen 1,5-Wasserstoff-Shift (Schema II).



Schema II. Metallfreie Redoxreaktionen für die Herstellung von neuen C-C und C-N Bindungen.

III. List of abbreviations

Ac	Acetyl
AcO	Acetate
Alk	Alkyl
Aliph	Aliphatic
Ar	Aryl, aromatic
aq.	Aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
Boc	*tert*-butyloxycarbonyl
n-Buli	*n*-Butyllithium
cat.	Catalyst/catalytic
Cy	Cyclo-
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
d.r.	Diastereomeric ratio
DMAP	Dimethyl amino pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
E	Electrophile
EDCI	1-ethyl-3-(3 dimethylamino-propyl)carbodiimide
EDG	Electron-donating group
ESI	Electrospray ionization
Et	Ethyl

EWG	Electron-withdrawing group
ee	Enantiomeric excess
Equiv	Equivalent(s)
e.r.	Enantiomeric ratio
h	Hour(s)
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass
LUMO	Lowest unoccupied molecular orbital
LDA	Lithium diisopropylamide
m	Multiplet
MTBE	Methyl *tert*-butyl ether
M_W	Molecular weight
m	Meta
M	Metal
[M]	Molar (concentration)
Me	Methyl
MeCN	Acetonitrile
MS	Molecular sieves
μ_w	Microwave radiation
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
Nu	Nucleophile
NIS	*N*-iodoosuccinimide
NEt_3	Triethylamine
n	Normal
nm	Nanometres
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
PC	Photocatalyst
PG	Protecting group

Ph	Phenyl
ppm	Part per million
Pr	Propyl
Py	Pyridine
Pr	Propyl
PMB	*p*-methoxybenzyl
q	Quadruplet
rac.	Racemic
r.t.	Room temperature
sat.	Saturated
SET	Single electron transfer
SOMO	Singly occupied molecular orbital
SN	Nucleophilic substitution
tert	Tertiary
t	Triplet
T	Temperature
TBAF	Tetrabutylammonium fluoride
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf_2O	Trifluoromethanesulfonic anhydride (triflic anhydride)
TfOH	Triflic acid
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Ts	Tosyl
TS	Transition state

Chapter I. The keteniminium ion: A convenient synthetic intermediate

Allene and hetero-allene moieties are very important building blocks in organic chemistry. Their unique structure with two adjacent, though non-conjugated, double bonds render them highly reactive partners; namely in nucleophilic additions and cycloaddition reactions. [1]

Neutral hetero-allenes; such as ketenes, proved to be particularly reactive species. However, their low stability and tendency to form oligomers has limited their use. In this regard, keteniminium salts have emerged as superior alternatives; their high reactivity in combination with their relatively good stability in comparison to ketenimines and ketenes make them an ideal choice for a range of reactions (Figure A).

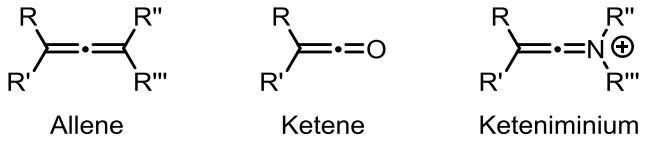


Figure A. Structures of allene, ketene and keteniminium salts.

Since the first preparation of a keteniminium salt by Viehe *et al.* in the early 1970's through to recent times, numerous transformations of this reactive species have been explored. [2]

Although several procedures for their preparation have been developed, ynamides and amides are the most common starting materials for this purpose. As seen in figure B, Brønsted acid activation of an ynamide or an activation of a tertiary amide with triflic anhydride (Tf_2O) and a pyridine base are both efficient routes for *in situ* generation of a keteniminiums ion (Figure B).

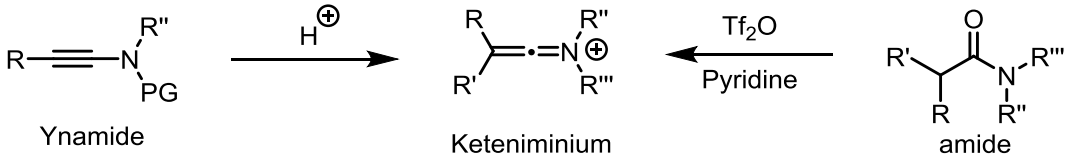


Figure B. Generation of keteniminiums from an amide or ynamide.

Reactions developed on keteniminium intermediates derived from ynamides or amides will be classified into two subchapters. The first chapter focuses on the chemistry of ynamides, whereas the second discusses amide activation processes.

1. Ynamides: From synthesis of heterocycles to dimerisation

1.1 Introduction

Alkynes are very important building blocks in organic chemistry, and their reactivity has been well-studied over the last decades. [3] Heteroatom-substituted alkynes probably represent the most versatile class of alkynes. In particular, nitrogen-substituted alkynes (*Ynamines*) have been utilised in numerous synthetic methods. Despite the difficulty in preparation, the electron-donating ability of the nitrogen atom strongly polarizes the triple bond, which allows for a high level of reactivity. [4] However, this high reactivity increased their instability and sensitivity toward hydrolysis (Figure 1.1 b). To overcome this problem, the addition of an electron-withdrawing group (carbonyl, sulfonyl or carbamate) at nitrogen made this reactive species more stable, and the resulting compounds (called *Ynamides*) are significantly easier to handle. [5]

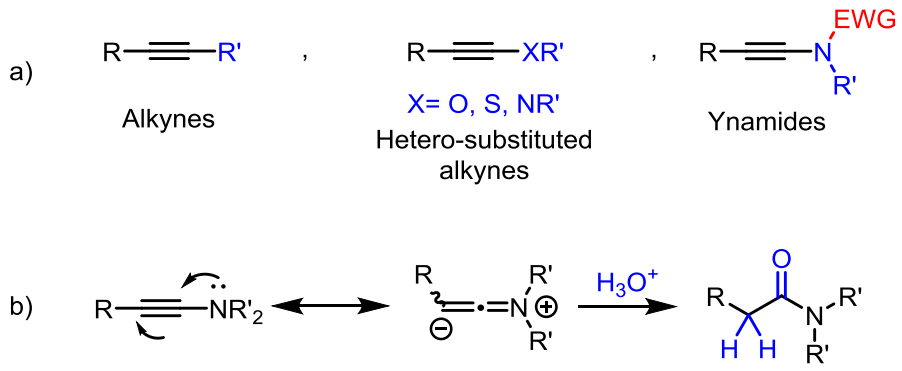
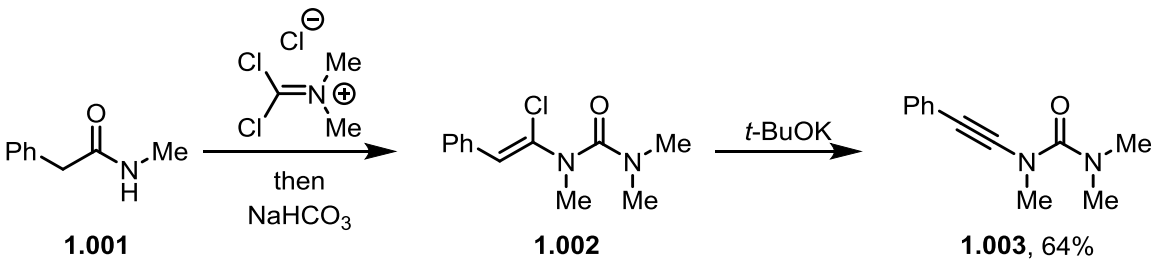


Figure 1.1. a) Structure of alkynes, hetero-substituted alkynes and ynamides. b) Sensitivity of ynamines toward hydrolysis.

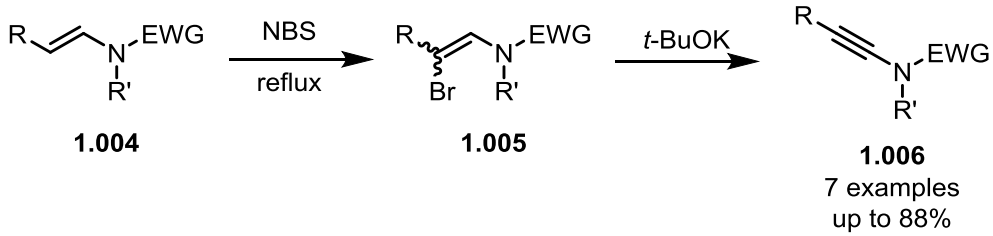
1.1.1 Synthesis of ynamides

Over the last 20 years, different synthetic methods for the efficient preparation of ynamides have been developed. The very first synthesis was achieved by Viehe *et al.* in 1972. [6] Reaction of secondary amide **1.001** with phosgeneimmonium chloride, followed by elimination of the α-halo-enamide **1.002**, led to the isolation of urea-ynamide **1.003** as the unique product (Scheme 1.1).



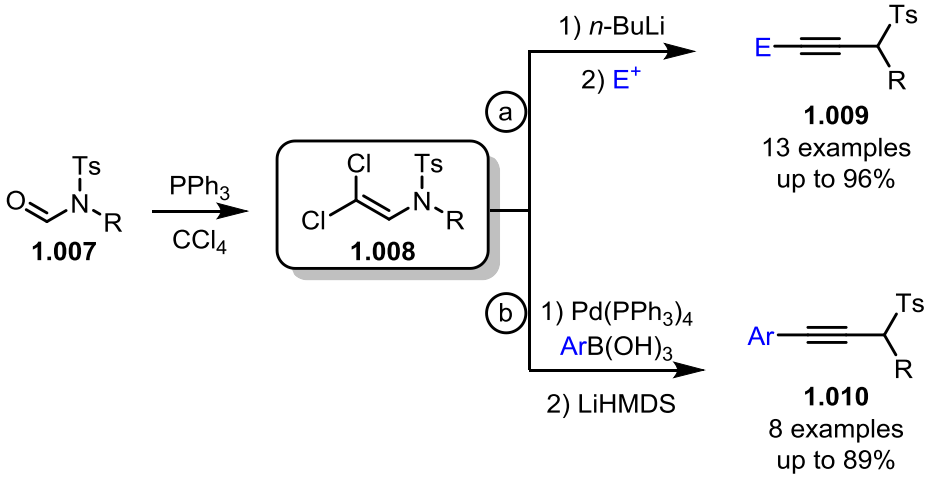
Scheme 1.1. The first synthesis of ynamide by Viehe in 1972.

Based on this reaction, Hsung *and* co-workers developed in 2001 a relatively milder method. [7] Bromination of enamides **1.004** followed by base-promoted elimination of β-bromo-enamides **1.005** lead to the formation of ynamides **1.006** in good yield but with poor functional group tolerance (Scheme 1.2).



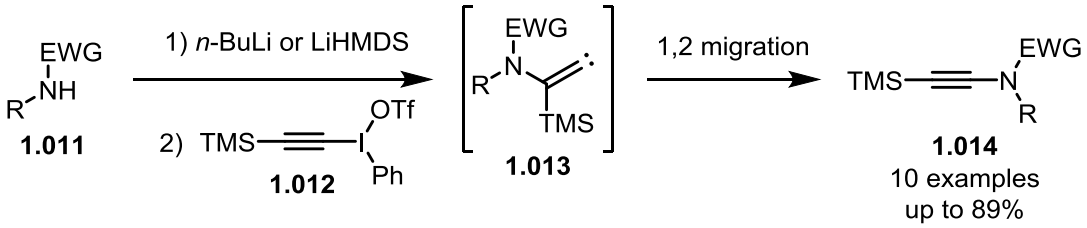
Scheme 1.2. Synthesis of ynamides via elimination of β-bromo-enamides.

Another approach for the synthesis of ynamides starting from β-β-dichloro-enamides was reported. β-β-dichloro-enamide **1.008** derived from *N*-formyltosyl amide **1.007** could be transformed into different ynamide products, either by an overall like Corey-Fuchs reaction followed by electrophilic capture (Scheme 1.3 a), [8] or by Suzuki-Miyaura cross-coupling followed by elimination (Scheme 1.3 b). [9]



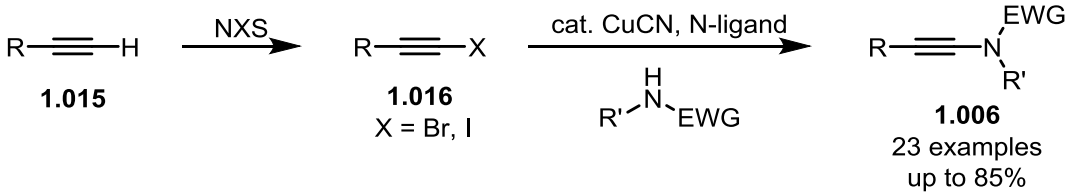
Scheme 1.3. Synthesis of ynamides from β-β-dichloro-enamides.

An alternative method was developed by Witulski and co-workers. [10] Deprotonation of the amide **1.011** followed by addition of trimethylsilylethynyliodonium triflate **1.012** gave the silylated ynamide **1.014**. In this reaction, the higher migration ability of the silyl group favours the formation of the ynamide as the exclusive product (Scheme 1.4).



Scheme 1.4. Synthesis of ynamides via reaction with iodonium alkynes.

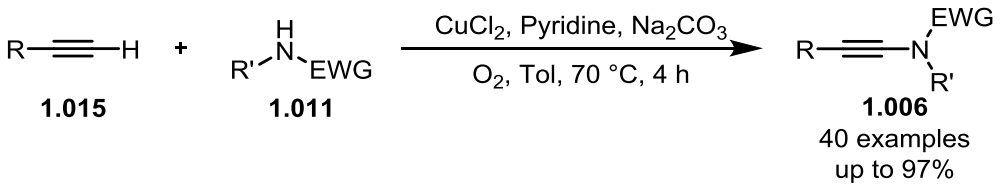
Although these methods can deliver ynamides in reasonably good yields, the long reaction sequence with relatively harsh conditions and the need for sensitive reagents leaves space for improvement. Thus, Hsung and co-workers developed in 2003 a copper-catalysed coupling of halo-alkynes **1.016** with amides. This two-step sequence starting from simple halogenation of terminal alkynes **1.015** followed by direct coupling with amides was successful with variety of alkynes as well as amide moieties (Scheme 1.5). [11]



Scheme 1.5. Cu-catalysed coupling of halo-alkynes with amides.

Several coupling reaction systems with halo-alkynes were further developed by Danheiser, [12] Skrydstrup, [13] Evano, [14] Anderson, [15] and Zhang. [16]

In 2008, Stahl and co-workers achieved a copper-catalysed direct C-H/N-H coupling of terminal alkynes with amides, using molecular oxygen as the terminal oxidant. [17] The reaction worked smoothly with a variety of alkynes and nitrogen partners. The only limitation for this reaction is the need to use an excess of the amide partner (5 equiv.) in order to suppress the alkyne homo-coupling side reaction (Scheme 1.6).



Scheme 1.6. Cu-catalysed coupling of terminal-alkyne with amide.

The ensemble of methods presented in this section provide a secure access to ynamides bearing a plethora of substituents and substitution patterns. In the following section, a discussion about the reactivity of ynamides and some important selected examples will be presented.

1.1.2 Reactivity of Ynamides

1.1.2.1 Addition of nucleophiles and electrophiles

The reactivity of ynamides toward nucleophiles and electrophiles is straightforward to predict, due to the electron-donating ability of the nitrogen atom (Figure 1.2). Conjugation to the triple bond means that electron density is concentrated on the β-carbon, with the α-centre behaving as the electrophilic position.

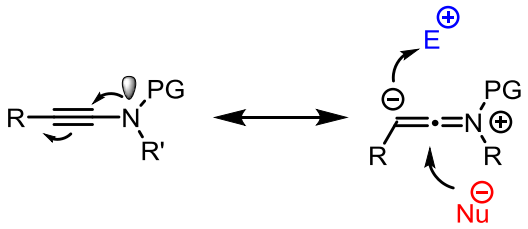
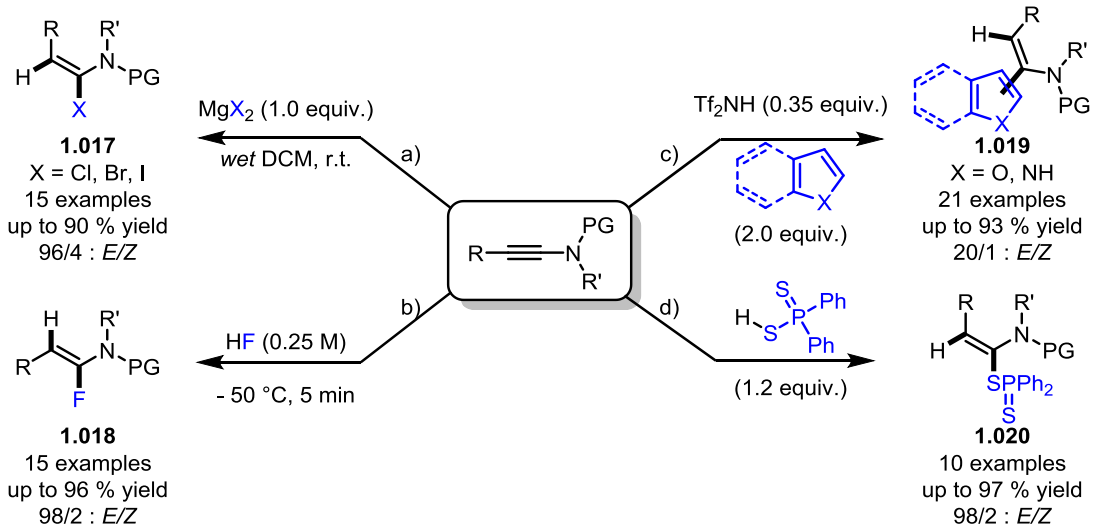


Figure 1.2. General reactivity of ynamides with nucleophiles and electrophiles.

1.1.2.1.1 Brønsted acid activation with nucleophilic addition

Activation of ynamides with Brønsted acids delivers a keteniminium intermediate. This intermediate can then be trapped with a plethora of nucleophiles as seen in scheme 1.7.



Scheme 1.7. Brønsted acid catalysed addition at the α-position of ynamides.

Hsung *et al.* developed a regioselective halogenation of ynamides using MgX_2. [18] It is crucial to work in *wet*-DCM since the reaction proceeds *via* formation of HX. This *in situ* generated acid activates the ynamide, followed by nucleophilic addition of X^- to deliver (*E*)-α-halo-enamides **1.017** (Scheme 1.7 a). The high stereoselectivety in this reaction suggests a *syn*-addition of HX.

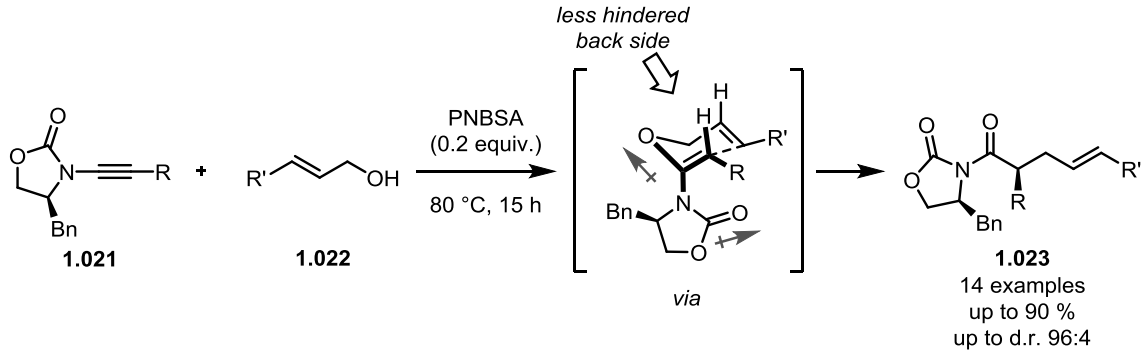
Similarly, hydrofluorination using hydrofluoric acid HF as a solvent furnished (*E*)-α-fluoro-enamides **1.018**, as reported by Evano and co-workers (Scheme 1.7 b). [19]

Carbon nucleophiles can also be incorporated in this chemistry. Zhang *et al.* showed the possibility of forming new C-C bonds via acid-catalysed ynamide activation using triflimide, followed by capture of the keteniminium intermediate with electron-rich arenes. [20] Different indoles, furans and pyrroles were efficient in this reaction in a stereoselective manner (formation of *E*-products). While indoles and furans gave the desired products **1.019** with high regioselectivity (C3- and C2-, respectively), pyrroles led to the formation of regioisomer mixtures (C2 and C3) (Scheme 1.7 c).

The α-thiolation of ynamides was reported by Yorimitsu and co-workers. [21] The use of diphenyldithiophosphinic acid in DME led exclusively to *E*-α-thio-enamides **1.020**. As expected, the bulky group on sulfur led to exclusive *syn*-addition (Scheme 1.7 d).

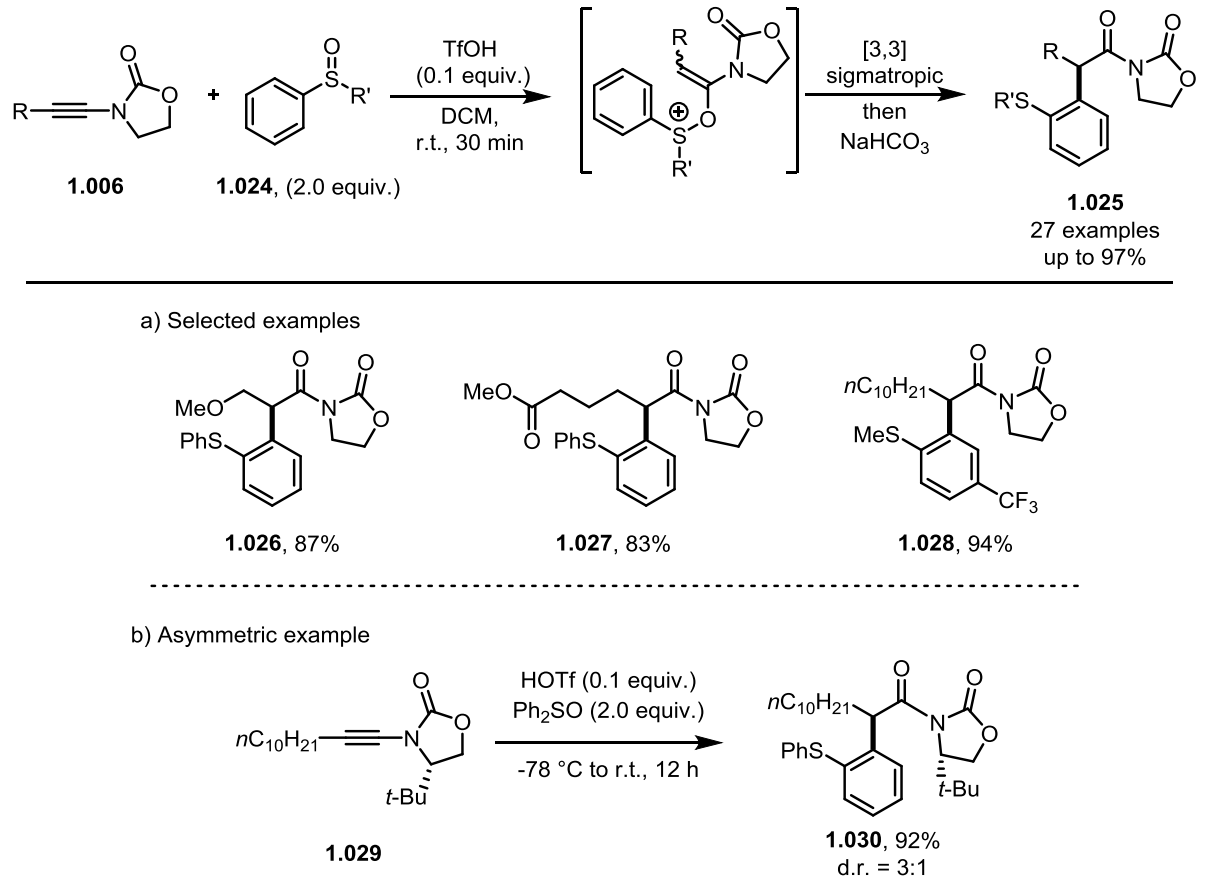
Allylic alcohols were also used as nucleophiles. Based on the pioneering work of Ficini *et al.* on the Claisen rearrangement of chiral ynamines and allylic alcohols in the late 1960s, [22] Hsung and co-workers developed an asymmetric version of this transformation. [23] Treatment

of chiral ynamides **1.021** with catalytic amounts of *p*-nitrobenzensulfonic acid (PNBSA) in the presence of allylic alcohols **1.022** under thermal conditions led to the formation of allyimide moieties **1.023** in high yields and very good diastereoselectivities (Scheme 1.8).



Scheme 1.8. Brønsted acid catalysed asymmetric Ficini-Claisen rearangment.

In 2014, our group has developed a redox-neutral α-arylation of ynamides using arylsulfoxides. [24] Activation of the ynamide with catalytic amounts of triflic acid (TfOH) formed the keteniminium intermediate. Nucleophilic addition of sulfoxides **1.024** followed by [3,3]-sigmatropic rearrangement delivered the α-arylated imide **1.025** in very high yield and short reaction time (Scheme 1.9). Different functional groups were tolerated in this transformation as seen in the selected examples (Scheme 1.9 a). Initial attempts towards an asymmetric version of this reaction using chiral ynamide **1.029** gave the corresponding imide **1.030** in high yield but with a moderate diastereoselectivity (3:1) (Scheme 1.9 b)

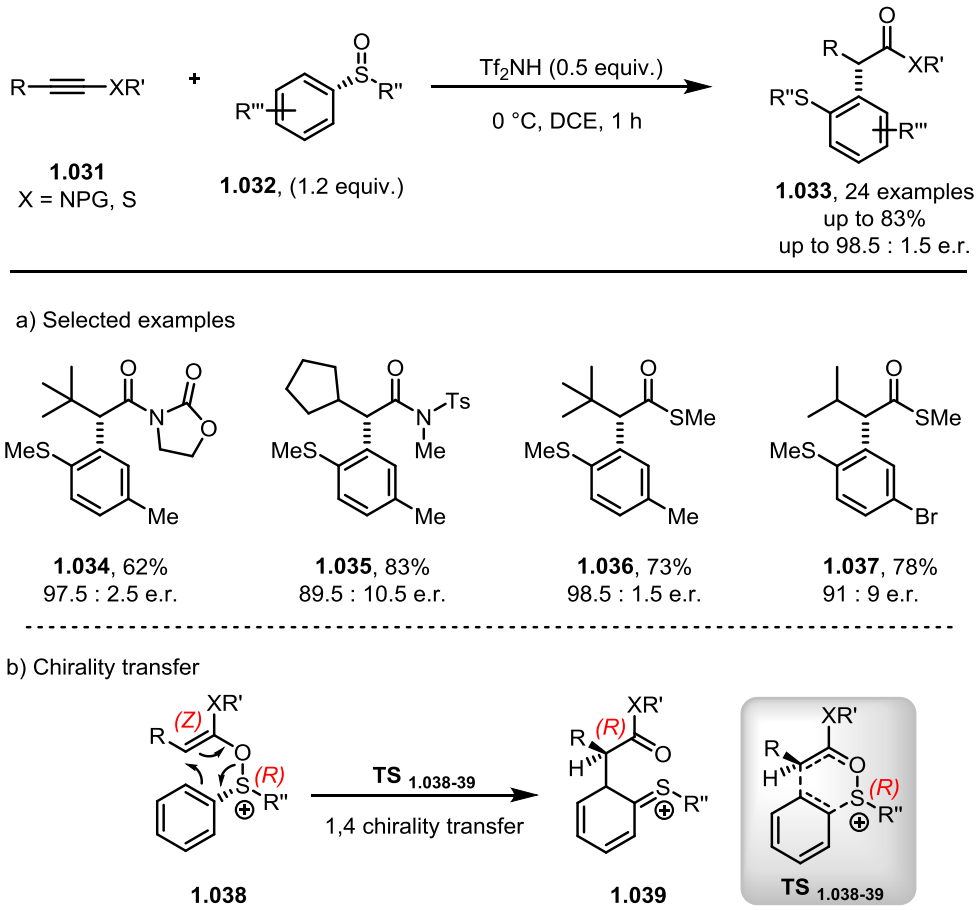


Scheme 1.9. Brønsted acid catalysed α-arylation of ynamides via [3,3]-sigmatropic rearrangement.

Recently, we also have achieved a direct chirality transfer from sulfur to carbon. [25] The use of chiral sulfoxides in the previous discussed reaction allowed the arylation to proceed in high enantioselectivity. Interestingly, thioalkynes were be also efficient in this enantioselective rearrangement, and the enantioselectivity increased with steric bulk of the ynamide (or thioalkyne) substituent (Scheme 1.10 a).

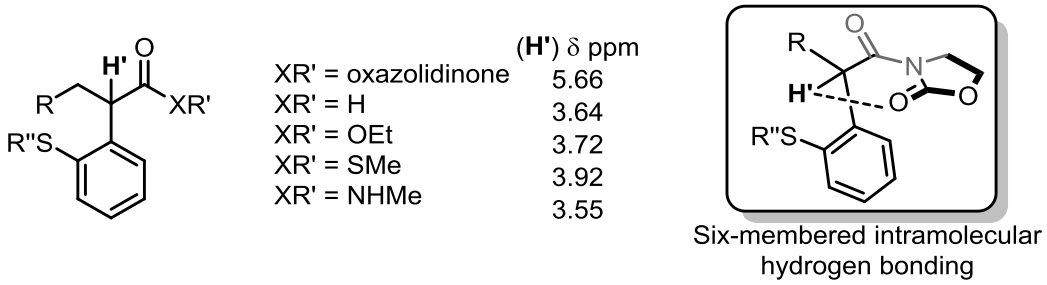
Computational analysis for intermediate **1.038** and the key transition state $\mathbf{TS_{1.038\text{-}39}}$ was carried out. Intermediate **1.038** has a double bond which leads to the existence of *Z* (*cis*) and *E* (*trans*) isomers. Both isomers can undergo conversion to the intermediate **1.039** and ultimately result in either an (*R*)- or (*S*)-configured chiral carbon atom. The barriers $\Delta G_{298}^{\#}$ for the four possible reaction pathways [*cis*-(*R*), *cis*-(*S*), *trans*-(*R*), and *trans*-(*S*)] were calculated. *Cis*-(*R*) pathway has the smallest barrier among all the pathways investigated. This explains the formation of (*R*)- products. Simultaneously, the use of (*R*)-configured sulfoxides led mainly to (*R*)-configured products, supporting the barriers calculated (Scheme 1.10 b). Importantly, further computation for the steric bulk effect revealed that, the gap between the

barriers for *cis*-(*R*) and *trans*-(*S*) is largest for the *tert*-butyl substituent and smallest for the Me group; this is also in accordance with the experimental results.



Scheme 1.10. Asymmetric arylation *via* chirality transfer from chiral sulfoxides.

In a recent study, [26] we explained the unusually high chemical shift of α-proton **H'** in the α-arylated products of this methodology, particularly in comparison to the chemical shift of other related carbonyl analogues. DFT calculations supported the existence of a six-membered intramolecular hydrogen bond with the carbamate carbonyl as the source of abovementioned "standard" chemical shift (Scheme 1.11).

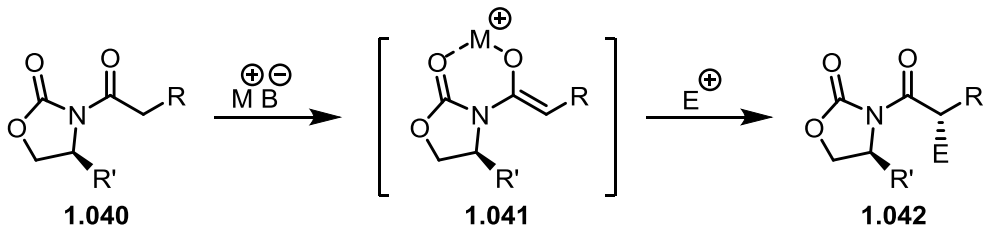


Scheme 1.11. Standard chemical shifts of α-H' in the products of redox-neutral α-arylation and computationally validated explanation.

1.1.2.1.2 Transition Metal-catalysed reactions with ynamide

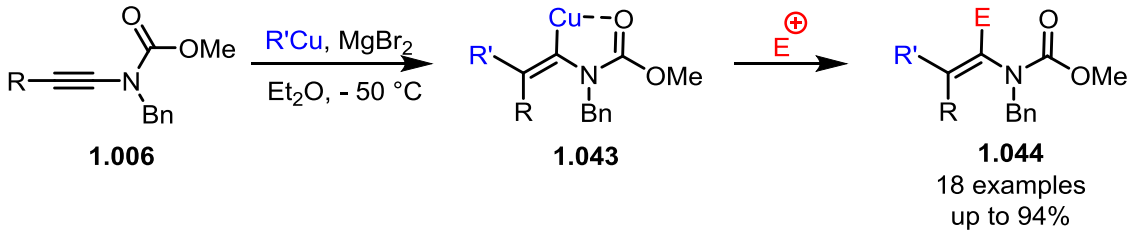
Carbamate as chelating group

Since the pioneering work of Evans on chiral *N*-acyl oxazolidinones, [27] these scaffolds have termed the basis for a plethora of novel enantioselective transformations including Aldol, alkylation and pericyclic reactions. [28] Upon treatment of the *N*-acyl-oxazolidinone **1.040** with organometallic base, it selectively forms the *Z*-enolate intermediate **1.041**. The later can further react with electrophiles furnishing the products **1.042** in high diastereoselectivity (Scheme 1.12).



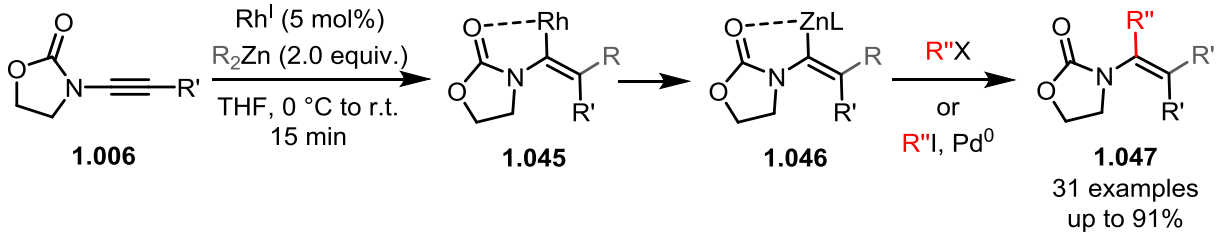
Scheme 1.12. General reactivity of *N*-acyl-oxazolidinones with electrophiles.

Ynamides where the nitrogen atom is embedded with an oxazolidinone residue soon emerged as valuable synthons for stereoselective reactions. In 2003, Marek and co-workers developed a regioselective carbometalation of ynamides. [29] Due to the chelating nature of the carbamate moiety, addition of the organocopper reagent selectively leads to intermediate **1.043**. Further addition of electrophiles selectively furnishes the enamide **1.044** (Scheme 1.13).



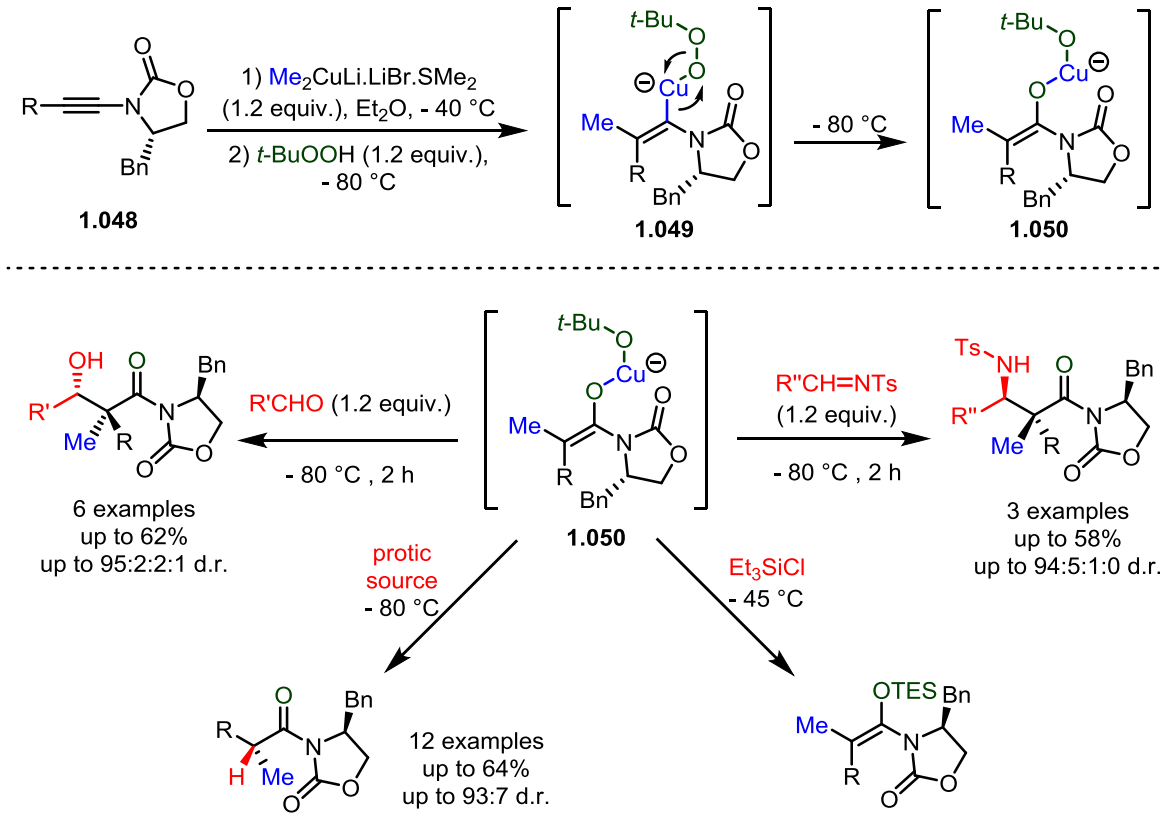
Scheme 1.13. Regioselective carbometalation of ynamides.

In 2008, Lam and co-workers achieved a regioselective rhodium-catalysed carbozincation of ynamides. [30] An organorhodium species would be generated from the reaction of Rh(cod)(acac) with the organozinc reagent. Carbonyl-directed *syn*-carbometalation of the ynamides **1.006** would provide alkenylrhodiums **1.045** with high regioselectivity. The later would then undergo transmetalation with organozinc species giving alkenylzinc species **1.046**. Protonation, electrophilic addition, or Negishi coupling furnished the highly substituted enamides **1.047** with high regioselectivities (Scheme 1.14).



Scheme 1.14. Regioselective carbozincation of carbamate ynamide.

The breakthrough on this chemistry was reported by Marek in 2012, who developed an alternative approach for the preparation of all-carbon quaternary stereocentres. [31] Carbocupration of chiral ynamides **1.048** followed by an addition of *tert*-butyl hydroperoxide led to the formation of stereodefined vinyl cuprate **1.049**. This species is known to undergo a 1,2-metalate rearrangement to form copper enolate **1.050**. [32] This can subsequently react with different electrophiles to give the products in very high diastereoselectivities (Scheme 1.15).



Scheme 1.15. Formation of all-carbon quaternary stereocentres from ynamides.

Activation of the triple bond by π-acids

As discussed earlier, the nitrogen atom within ynamide imposes an electronic bias onto the alkyne. This results in a high regioselective attack onto this polarized alkyne by a large variety of nucleophiles, leading directly to synthetically useful *N*-containing molecules (Figure. 1.3).

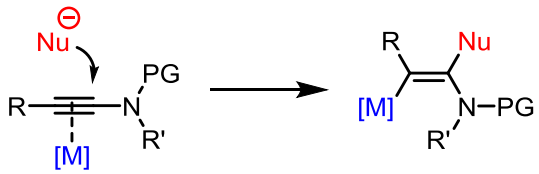
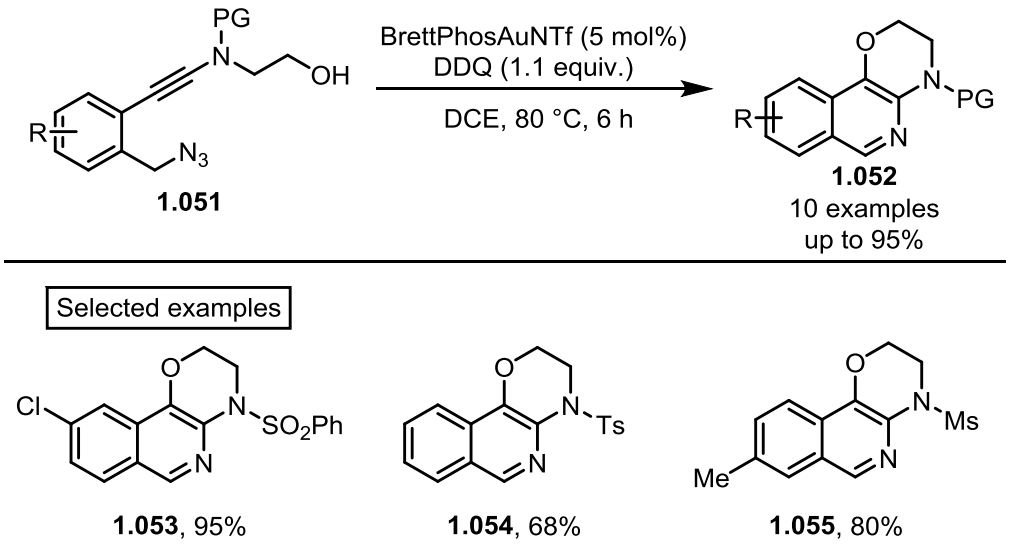


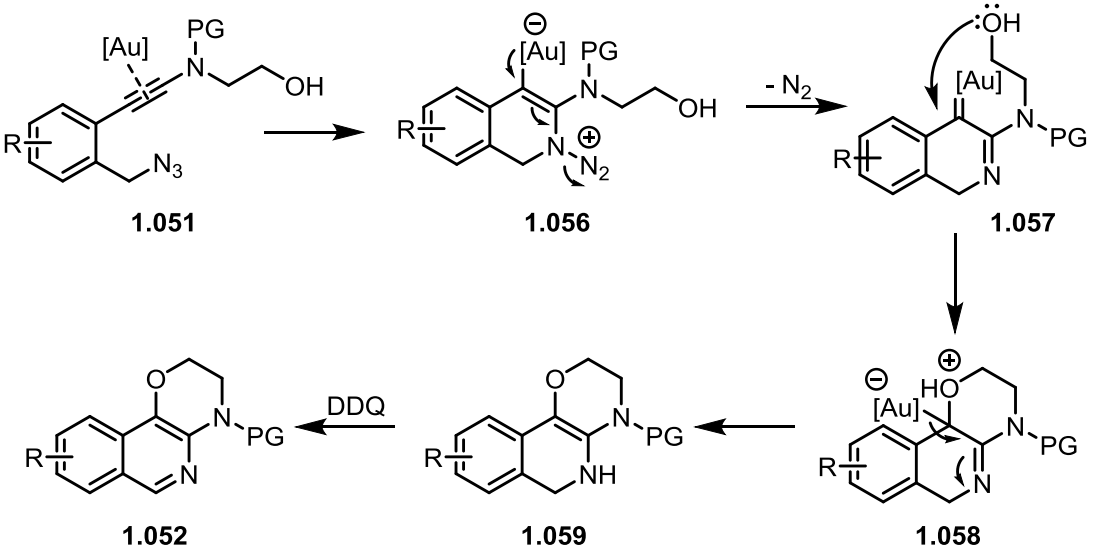
Figure 1.3. General reactivity of ynamides with π-acids.

Several methods that imply the activation of ynamide with π-acids (mainly gold catalysis) followed by inter- or intramolecular nucleophilic addition have been developed. [33] One of the examples is the work of Ye *et al.* in 2016, [34] where a gold-catalysed tandem ynamide amination/intramolecular O-H insertion was reported. As seen in scheme 1.17, cyclisation of 2-alkynylbenzyl azide **1.051** could be intercepted by an intramolecular oxygen nucleophile to furnish isoquinoline derivative **1.052**. Different amine protecting groups and functional groups on the aryl ring were tolerated in this reaction (Scheme 1.17).



Scheme 1.17. Gold-catalysed synthesis of fused isoquinolines from ynamides.

The reaction proceeds *via* nucleophilic addition of the azide nitrogen onto the alkyne moiety upon activation with gold to give intermediate **1.056**. Loss of nitrogen generates an α-imino gold carbene intermediate **1.057**. Subsequent intramolecular trapping of **1.057** with the hydroxyl group affords intermediate **1.058**. The later further undergoes proton transfer/deauration to give intermediate **1.059**. Finally, oxidation with DDQ delivers the targeted fused isoquinolines **1.052** (Scheme 1.18).

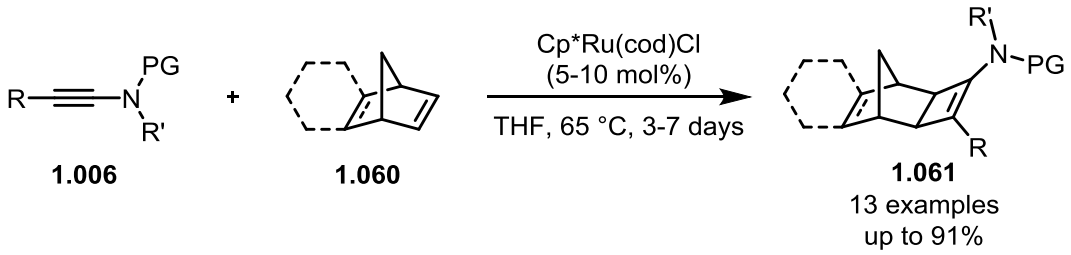


Scheme 1.18. Proposed reaction mechanism for the Au-catalysed Synthesis of fused isoquinolines from Ynamides.

1.1.2.2 Cycloaddition reactions of ynamides

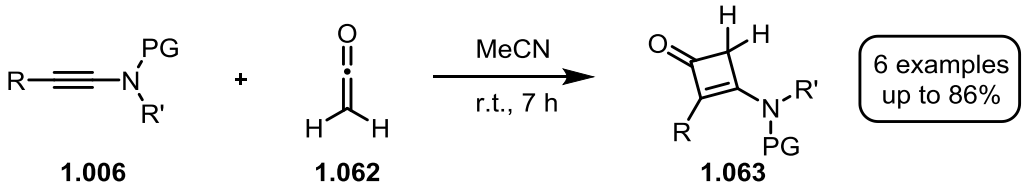
[2+2] cycloaddition reactions

In 2006, [35] Tam and co-workers reported a [2+2] cycloaddition reaction of ynamides **1.006** with bicyclic and tricyclic alkenes **1.060** under ruthenium catalysis (Scheme 1.19). Although the yields were good for most substrates, attempts toward asymmetric version of this reaction, through chirality transfer from the ynamide did not deliver the product in satisfactory diastereoselectivity.



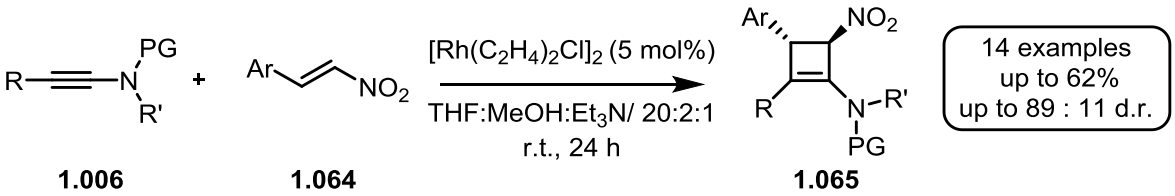
Scheme 1.19. Ru-catalysed [2+2] reaction with ynamide.

Danheiser and co-workers also reported a [2+2] cycloaddition of ynamides **1.006** with *in situ* generated ketene **1.062**, providing substituted 3-amidocyclobutenones **1.063** in good yields (Scheme 1.20). [36]



Scheme 1.20. [2+2] cycloaddition of ynamides with ketene.

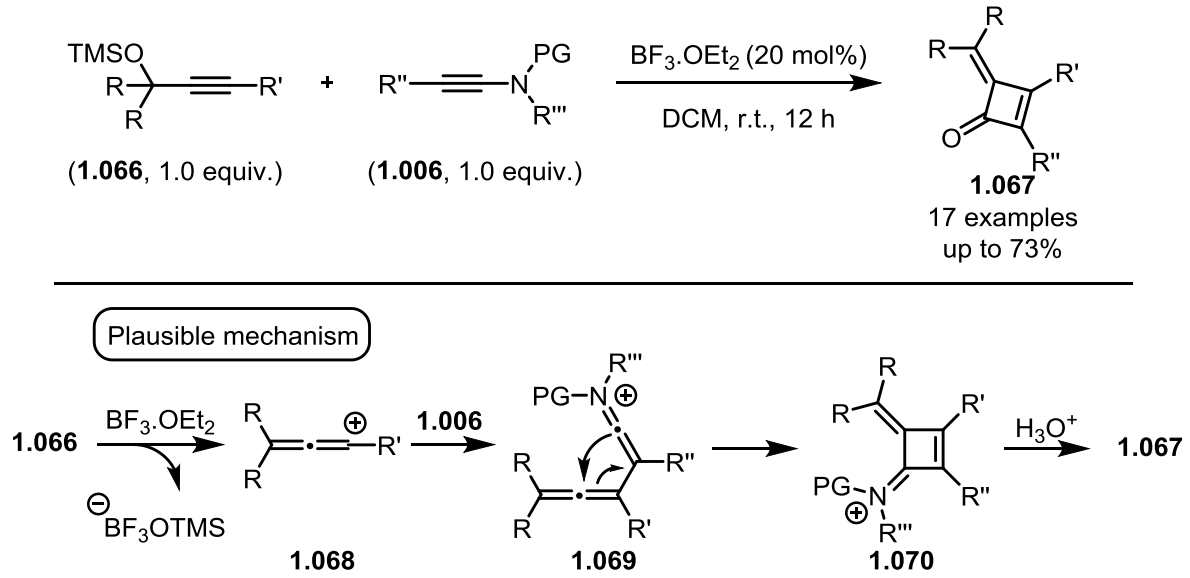
In 2012, Lam and co-workers disclosed a rhodium-catalysed [2+2] cycloaddition reaction of ynamides **1.006** with arylnitroalkenes **1.064** (Scheme 1.21). The reaction was promoted by an achiral rhodium complex, resulting in a range of cyclobutenamide products with poor to good diastereoselectivities. [37]



Scheme 1.21. Rh-catalysed [2+2] reaction of ynamides with nitroalkenes.

Recently, Xu and co-workers published a Lewis acid (LA) catalysed [2+2] cycloaddition reaction of ynamides **1.006** with propargyl silyl ethers **1.066** which provides a regioselective

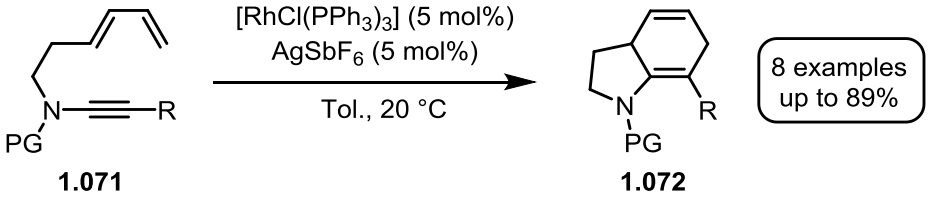
access to four-membered enones **1.067**. [38] The reaction proceeds *via* generation of allenyl cation **1.068** formed from propargyl silyl ether **1.066** upon treatment with BF_3OEt_2. Nucleophilic addition of ynamide **1.006** followed by 4π electrocyclisation provides the iminium ion **1.069** which upon hydrolysis delivers the enones **1.070** (Scheme 1.22).



Scheme 1.22. LA-catalysed [2+2] reaction of ynamides with propargyl silyl ethers.

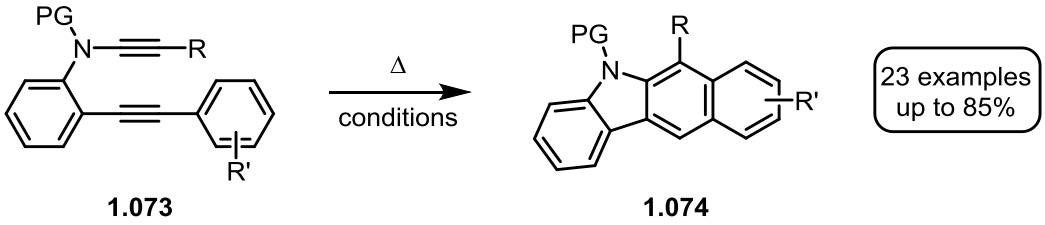
[4+2] cycloaddition

Witulski and co-workers reported in 2003 the first intramolecular [4+2] cycloaddition employing diene-ynamides **1.071**. [39] Their protocol provided an efficient and versatile access to functionalised dihydroindolines **1.072** employing a rhodium catalyst (Scheme 1.23).



Scheme 1.23. Rh-catalysed intramolecular [4+2] cycloaddition of ynamide.

An intramolecular dehydro-Diels-Alder reaction of ynamides **1.073** was reported by Saa´ and co-workers. [40] This approach proved to be an efficient method for the synthesis of carbazole skeletons **1.074** (Scheme 1.24). It is noteworthy that, depending on the substrate, various additives (including NEt_3, MeOH, and *i*-PrOH) were required to achieve optimal yields.

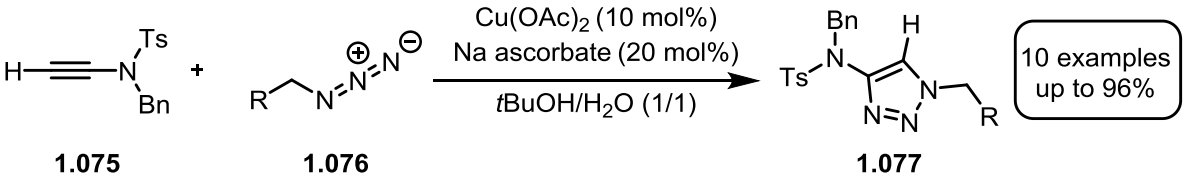


1.073 **1.074**

Scheme 1.24. Carbazoles synthesis *via* intramolecular [4+2] cycloaddition of ynamides.

[3+2] cycloaddition reactions

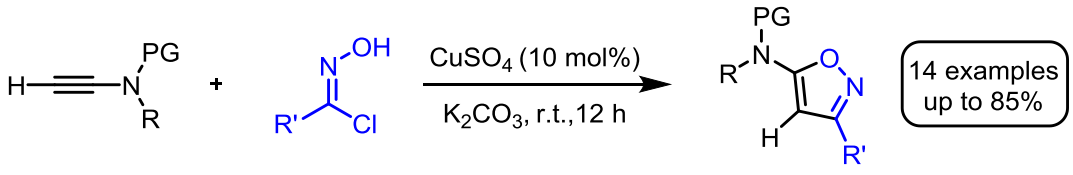
The first example of "click" chemistry employing ynamides was reported by Cintrat and co-workers in 2006. [41] *N*-tosyl *N*-benzyl ynamide **1.075** was reacted with a variety of alkyl azides **1.076** under copper catalysis to give 4-amino-1,2,3-triazoles **1.077** in high yields and with very high level of regioselectivity (Scheme 1.25).



1.075 **1.076** **1.077**

Scheme 1.25. 'Click chemistry' of *N*-benzyl *N*-tosyl ynamide with alkyl azides.

In 2007, Hsung and co-workers disclosed a highly regioselective copper-catalysed [3+2] cycloaddition between terminal ynamides **1.078** and *in situ* generated nitrile oxides from chloro oximes **1.079**. [42] This reaction led to a variety of 5-amido-isoxazoles **1.080** in very good yields and excellent regioselectivities (Scheme 1.26).

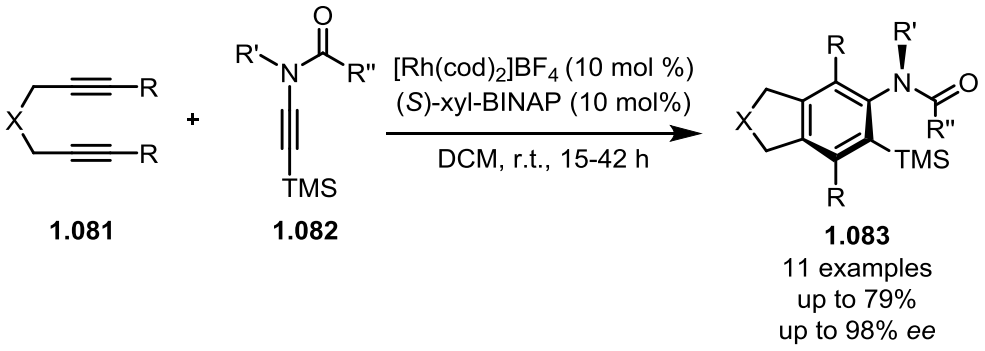


1.078 **1.079** **1.080**

Scheme 1.26. Synthesis of 5-amino-isoxazoles *via* [3+2] cycloaddition with ynamides.

[2+2+2] cycloaddition reactions

In 2006, Tanaka and co-workers reported an enantioselective rhodium-catalysed [2+2+2] cycloaddition of symmetrical diynes **1.081** with trimethylsilylynamides **1.082** for the synthesis of axially chiral anilides. [43] The combination of a rhodium(I) precatalyst and chiral *xyl*-BINAP ligand provided the amino-benzenes **1.083** with very good enantiomeric induction up to 98% *ee* (Scheme 1.27).



Scheme 1.27. Synthesis of axially chiral anilides *via* [2+2+2] cycloaddition reaction.

1.2 Results and discussion

Our work on ynamide chemistry is divided into two parts. In the first part, a discussion of metal-free [2+2+2] pyridine synthesis from ynamides will be presented. The second part will focus on Brønsted acid mediated dimerisation of ynamides.

1.2.1 Metal-free synthesis of pyridines *via* [2+2+2] cycloaddition reaction of ynamides and cyanoalkynes

This work was carried out in collaboration with Dr. Langui Xie and Dr. Xiangyu Chen. The results were reported in: *Angew. Chem. Int. Ed*. **2016**, *55*, 12864-12867. [44]

1.2.1.1 Introduction and background

Pyridine cores are among the most abundant and important *N*-heterocyclic motifs in nature. Their presence is not limited to nature, but includes drugs, materials and ligands for catalysis. (Figure 1.4)

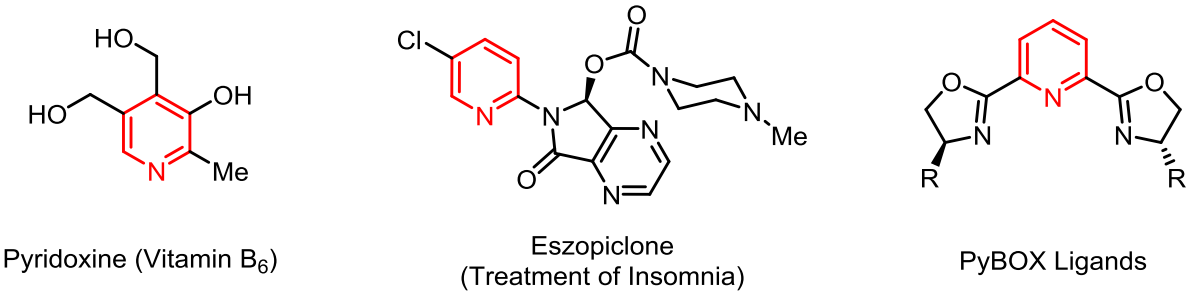


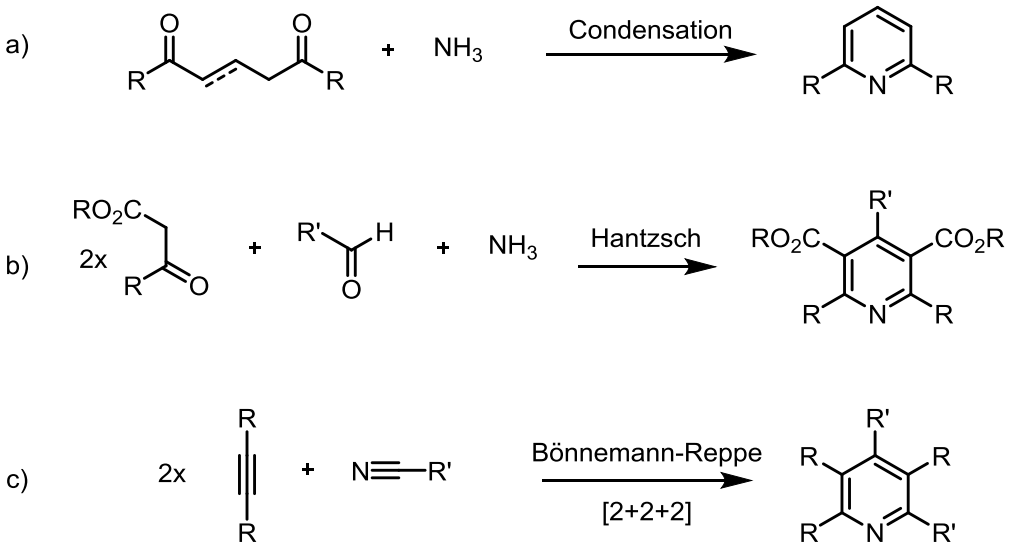
Figure 1.4. Selected examples of pyridine cores in biology, pharmaceuticals and catalysis.

Due to this central role of pyridines, several synthetic approaches have been developed over the last century. [45] Classically, a simple condensation reaction between 1,5-dicarbonyls and ammonia (or an ammonium equivalent) gives the pyridine core (Scheme 1.28 a). However, the need for preparing it and the limitations of the reaction scope hinder the use of this reaction.

Another approach is the multi component condensation reaction known as Hantzsch pyridine synthesis. The reaction involves condensation of 2 equivalents of a β-ketoester with an aldehyde and an ammonium salt (Scheme 1.28 b).

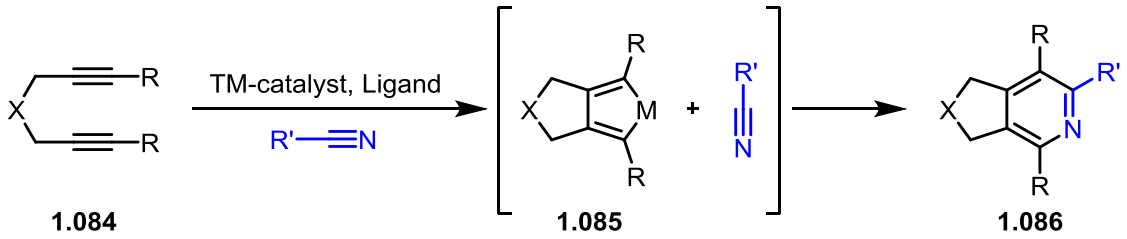
There are also a number of classical textbook reactions that rely on the combination of two or more components in which at least one contains carbonyl functionality. Examples include the Boger, Bohlmann-Rahtz and Kröhnke pyridine syntheses. [46]

The cobalt-catalysed cyclocondensation of a nitrile and two alkynes is called Bönnemann cyclisation (Scheme 1.28 c). This modification of the cobalt-catalysed Reppe alkyne trimerisation usually requires high pressures and temperatures. [47]



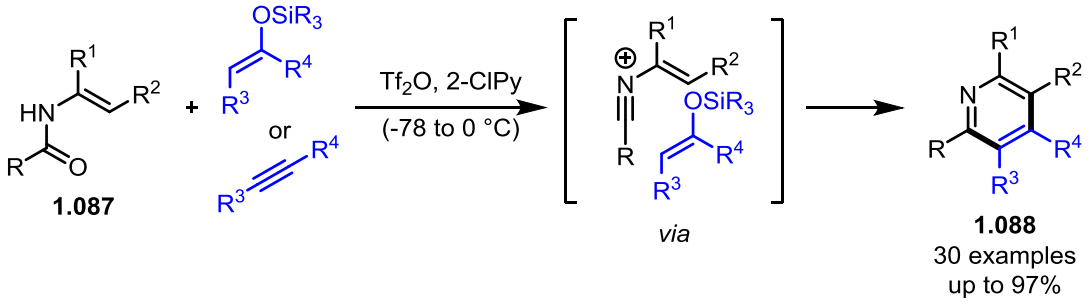
Scheme 1.28. Classical routes for the synthesis of pyridines.

Over the past years, several metal-catalysed versions of the [2+2+2] approaches have been developed. [48] The reaction usually proceeds as detailed in scheme 1.29. An oxidative addition into the diyne moiety **1.084** delivers the metallacyclopentadiene **1.085**. This further reacts with a nitrile to give the pyridine products **1.086** (Scheme 1.29) in an atom-economical manner. Although very low catalyst loadings can deliver the pyridine products in high yields, the sensitivity of the catalysts and the generally poor regioselectivity (mandating the use of symmetrical diynes) need to be taken in consideration.



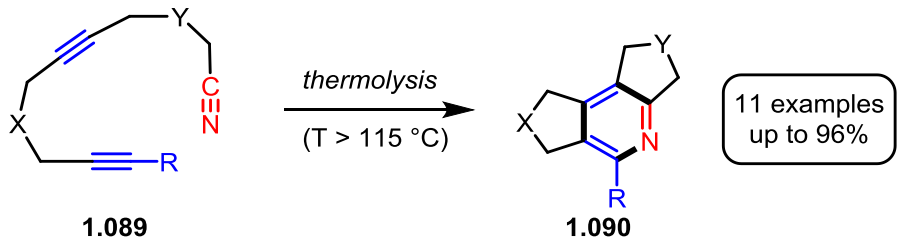
Scheme 1.29. General metal-catalysed [2+2+2] reaction of diynes and nitriles.

Alternative metal-free approaches for the synthesis of pyridines have also been developed. In 2006, Movassaghi and co-workers reported that upon activation of secondary enamides **1.087** with triflic anhydride (Tf_2O) and 2-chloropyridine, nitrilium species was formed. [49] Electron-rich alkynes or silyl enol ethers reacted subsequently with nitrilium species to deliver fully-substituted pyridines **1.088** (Scheme 1.30)



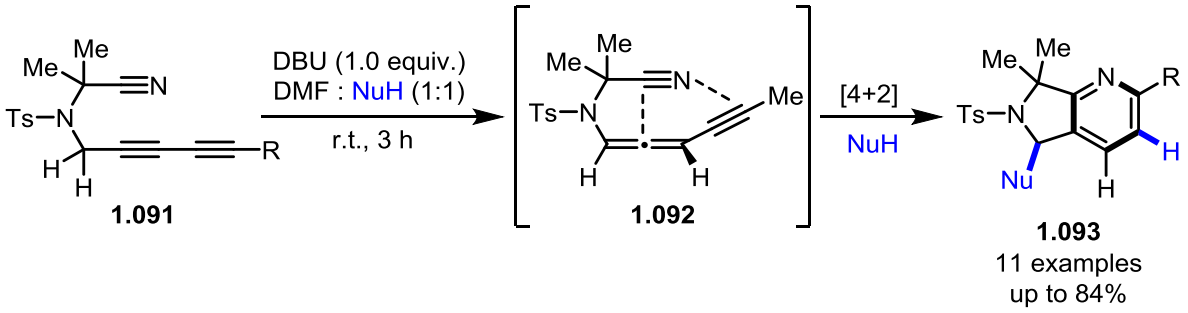
Scheme 1.30. Movassagi's approach for pyridine synthesis *via* activation of secondary amides.

In 2010, Danheiser and co-workers reported the first metal-free intramolecular [2+2+2] cycloaddition reaction of cyanodiynes **1.089** for the synthesis of the corresponding fused pyridines **1.090** (Scheme 1.31). [50] The reaction proceeds *via* a propargylic ene reaction followed by cyano-Diels Alder reaction to furnish the pyridine products. This transformation typically required high temperatures which limited the functional group tolerance.



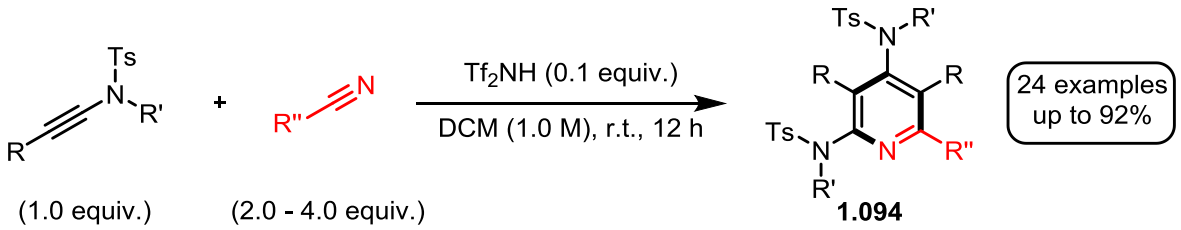
Scheme 1.31. Formal [2+2+2] cycloadditions via propargylic ene/cyano Diels-Alder reactions for the construction of fused pyridines.

In 2016, Hoye and co-workers disclosed a base-promoted pentadehydro-Diels-Alder reaction (PDDA) that led to the construction of pyridines. [51] Treatment of the cyanodiynes **1.091** with an organic base (DBU) promoted the generation of allenyl sulphonamides **1.092** which then underwent *aza*-PDDA cycloaddition reaction. A nucleophilic capture would finally take place to deliver the desired pyridine adducts **1.093** in good yields (Scheme 1.32).



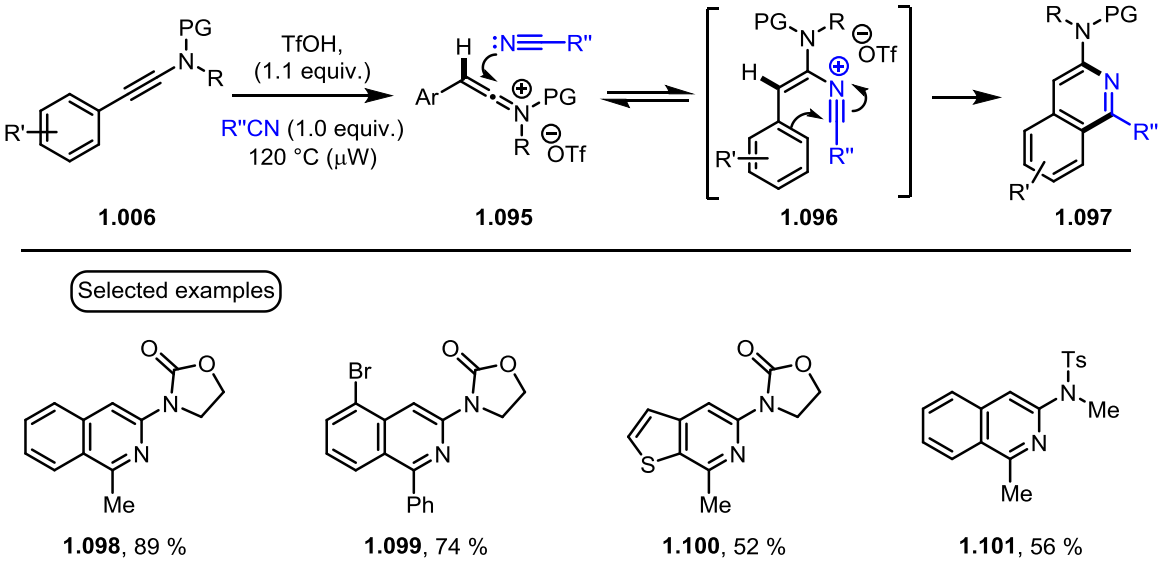
Scheme 1.32. Intramolecular cyclisation of cyanodiynes **1.091** in the *aza*-PDDA reaction.

In 2016, Sun and co-workers reported the first fully intermolecular [2+2+2] cycloaddition reaction of 2 equivalents of ynaimdes and a nitrile. [52] Catalytic amount of triflimide (Tf_2NH) promoted this transformation and led to the formation of pyridine products **1.094** in very good yields and with high level of regioselectivities (Scheme 1.33).



Scheme 1.33. Intermolecular [2+2+2] cycloaddition of ynamides and nitriles for the construction of pyridines.

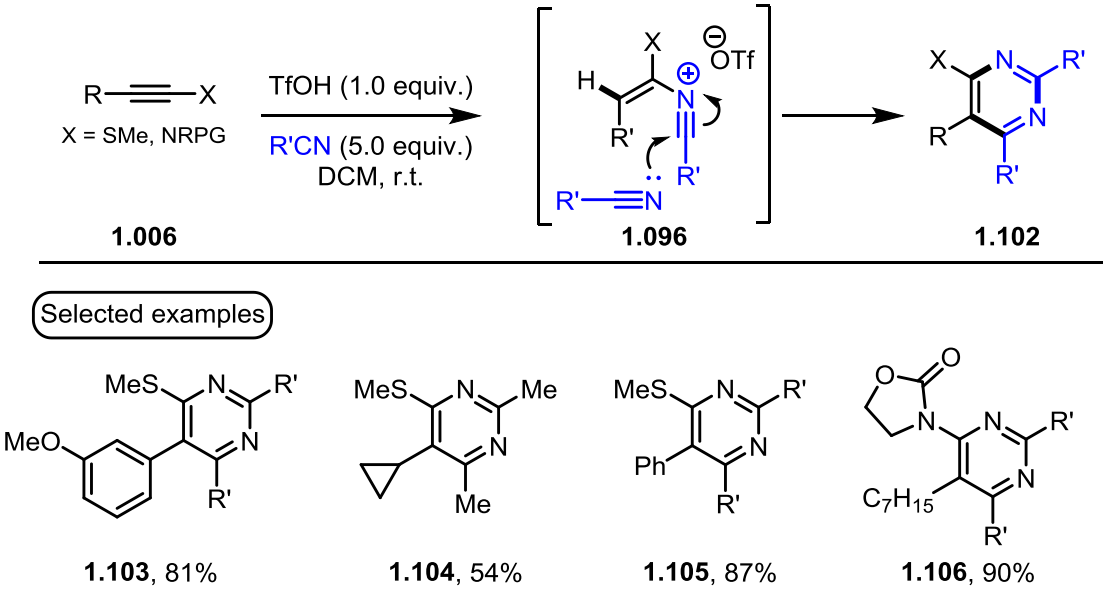
Our group has recently developed a metal-free approach for the synthesis of isoquinoline and pyrimidine rings. [53] Activation of aromatic ynamides **1.006** with triflic acid (TfOH) forms the keteniminium intermediate **1.095**, which undergoes nucleophilic addition by a nitrile to form nitrilium species **1.096**. Finally, ring closure affords the isoquinolines **1.097** in good yields as seen in the selected examples (Scheme 1.34).



Scheme 1.34. Maulide's approach for isoquinoline synthesis from ynamides.

Surprisingly, when running the reaction under milder temperatures and with an excess of nitrile (5.0 equiv.) the pyrimidine core **1.102** was formed as the major product. This can be explained at first glance by a second nucleophilic addition of the nitrile, component onto the nitrilium species **1.096**. DFT calculations revealed that this intermolecular nucleophilic addition is energetically favoured over the intramolecular ring closure seen previously, which

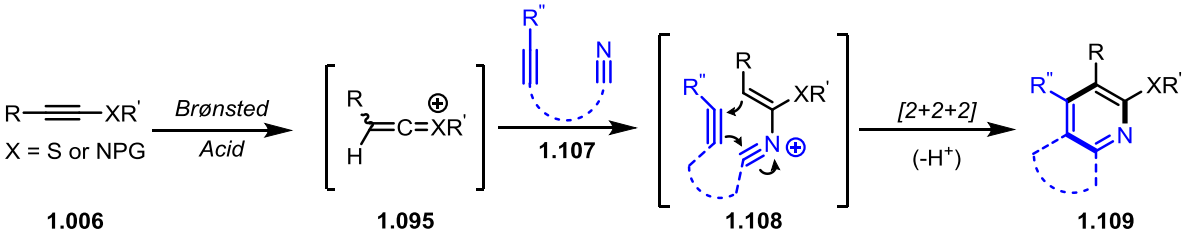
requires higher thermal activation. Interestingly, the use of thiolakynes was also successful and furnished 4-thio-pyrimidines as products in high yields (Scheme 1.35).



Scheme 1.35. Metal-free pyrimidine synthesis from ynamides or thioalkynes.

1.2.1.2 Aim of the project

The hypothesis of this project was to capture the generated keteniminium (or ketenthionium) species **1.095** generated from an ynamide (or a thioalkyne) with cyanoalkynes **1.107**. The resulting intermediate **1.108** might then undergo a formal [2+2+2] cycloaddition reaction to furnish penta-substituted pyridine cores **1.109** (Scheme 1.36).

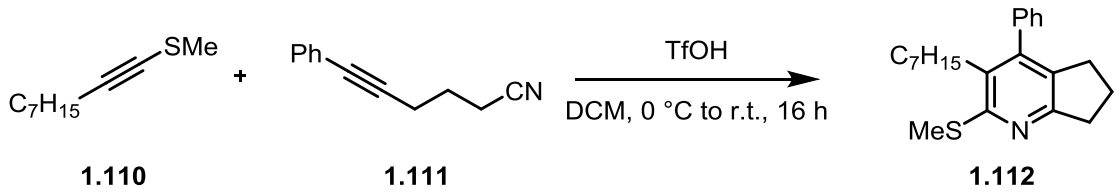


Scheme 1.36. Our approach for a metal-free synthesis of fused pyridines.

1.2.1.3 Optimisation of reaction conditions and scope of substrate

At the outset, we investigated the reaction of thioalkyne **1.110** with cyanoalkyne **1.111** in the presence of triflic acid (Table 1.1). Although our mechanistic hypothesis postulates the need for only catalytic amounts of acid, only traces of pyridine product were observed when using 0.2 equiv. of TfOH (entry 1). We reasoned the obvious preferential protonation of the basic pyridine product as an effective catalyst inhibition pathway. The use of stoichiometric amounts of acid afforded the desired pyridine product **1.112** in 72% and 70% yield (entry 2

and 3). The amount of thioalkyne and TfOH could be further lowered to 1.1 equiv., leading to even slightly better yields of **1.112** (entry 4). Notably, concentration plays an important role in this process. Performing the reaction at [0.1 M], led to a lower yield of the desired product and formation other by-products arose (entry 5).

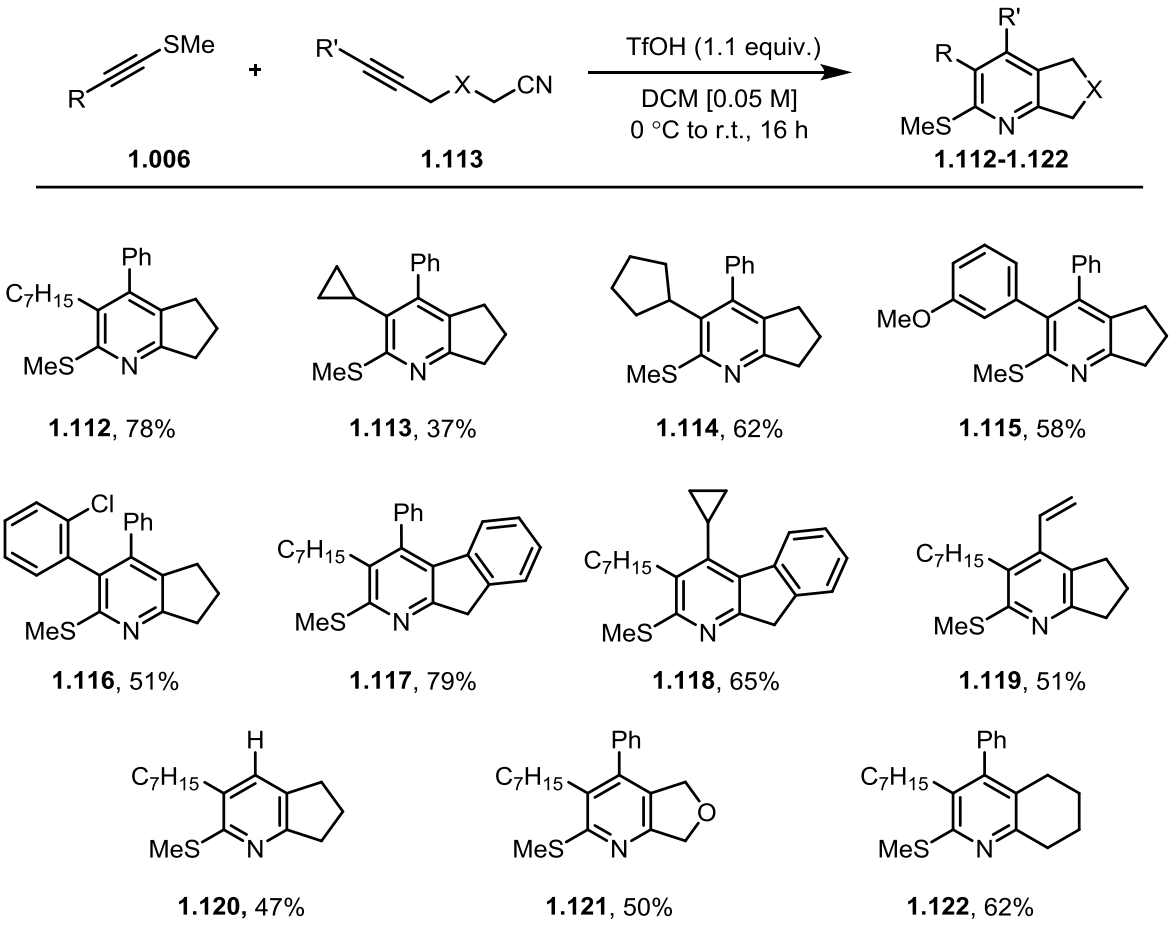


1.110 **1.111** **1.112**

Entry	Thio (eq.)	CN (eq.)	H^+ (eq.)	Concentration (M)	Yield (%)
1	1.1	1.0	0.2	0.05 M	Trace
2	1.5	1.0	1.5	0.05 M	72
3	1.1	1.0	1.5	0.05 M	70
4	1.1	1.0	1.1	0.05 M	78
5	1.1	1.0	1.1	0.1 M	62

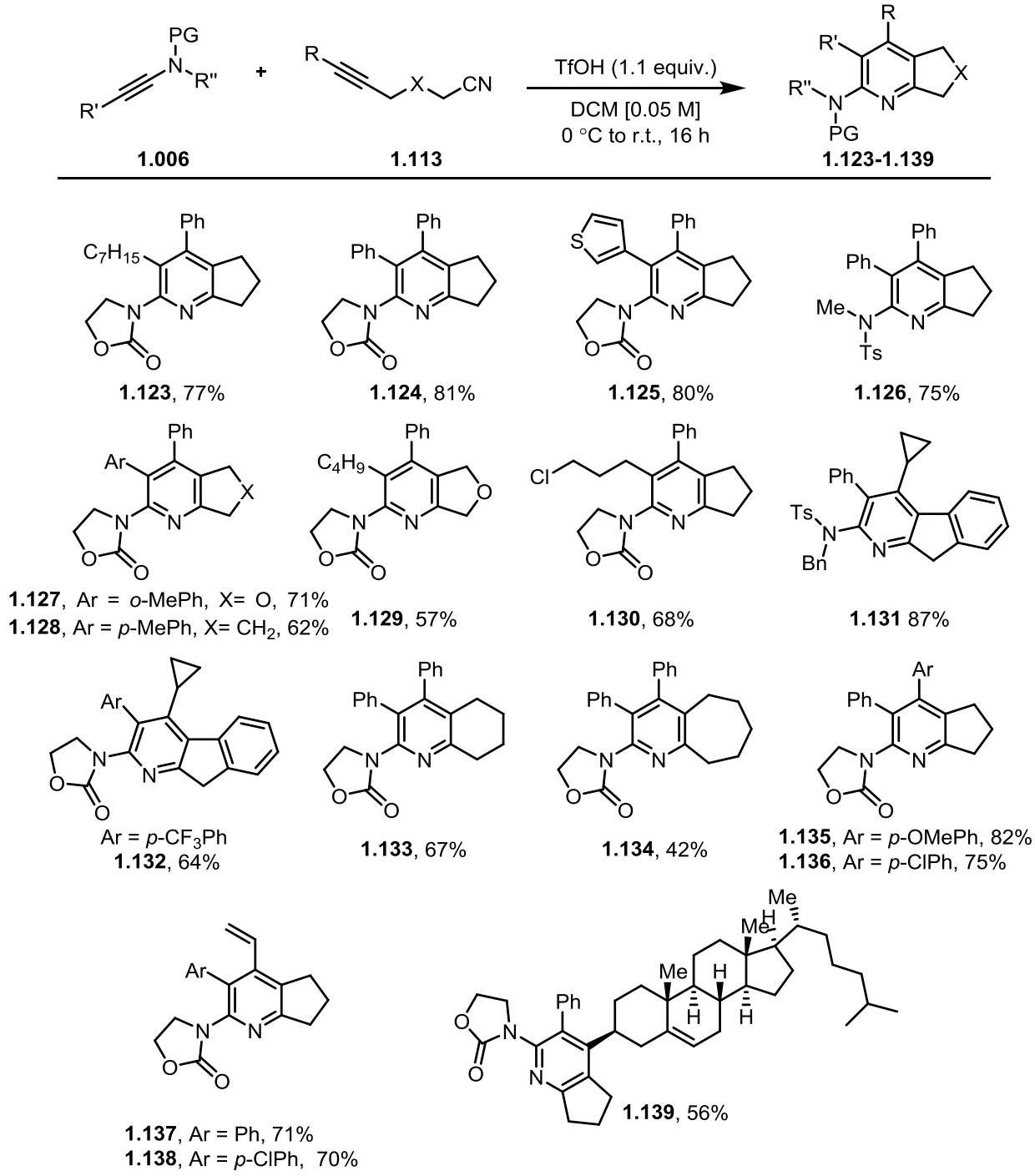
Table 1.1. Optimisation reaction conditions. [a] Reactions were performed on 0.2 mmol scale. [b] Yields of isolated products.

With the optimised reaction conditions in hand, we examined the scope of this transformation. As seen in Scheme 1.37, different thioalkynes **1.006** and cyanoalkynes **1.113** afforded the desired pyridine products in yields ranging from 37% to 79%.



Scheme 1.37. Substrate scope of pyridines from thioalkynes.

Cyclopropyl and cyclopentyl groups (**1.113** and **1.114**) could be incorporated into the pyridines with 37% and 62% yields. Other thioalkynes bearing aryl appendages with different substituents in varied positions were successfully tested (**1.115-1.116**). This methodology was also suitable for introducing an additional arene ring along the tether, resulting in tricyclic pyridines **1.117-1.118** in high yields.

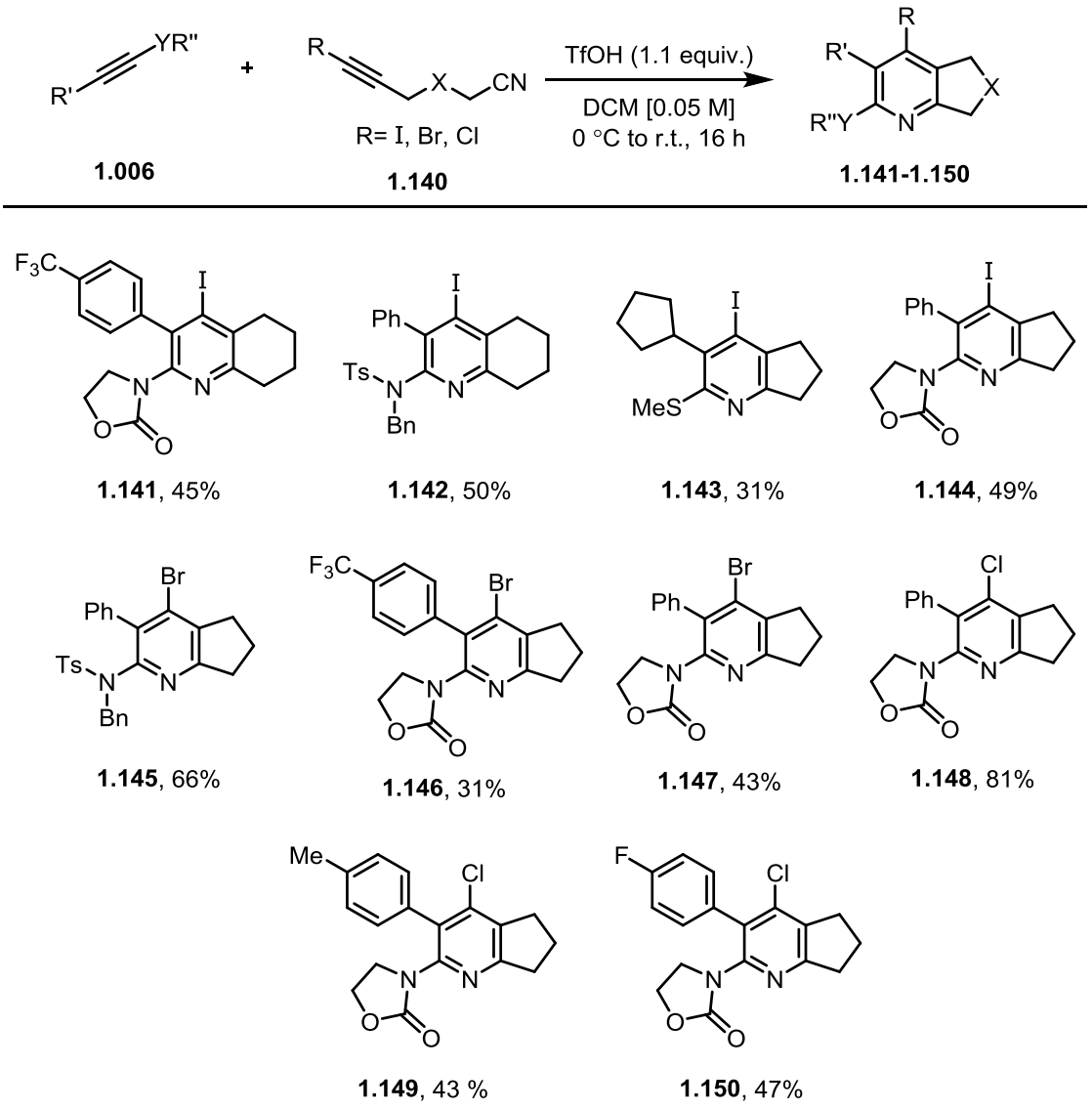


Scheme 1.38. Substrate scope of pyridines from ynamides.

A vinyl-substituted cyanoalkyne furnished the corresponding alkenylpyridine **1.119** in good yield. A terminal cyanoalkyne was also employed, affording the product **1.120** in 47% yield. Importantly, the reaction was also successful for other tethers, as shown by the six-membered ring fused pyridines **1.122**, as well as the ether-linked pyridine **1.121**.

Subsequently, a broad range of ynamides **1.006** were subjected to this formal cycloaddition reaction affording the 2-aminopyridine products in good to excellent yields (Scheme 1.38).

Alkyl- and (hetero)aryl-substituted ynamides furnished the heterocycles **1.123-1.125** in good to excellent yields. With a tosyl-protected ynamide, the reaction proceeded smoothly as well (**1.126** and **1.131**). Oxygen-tethered cyanoalkynes were also amenable to this transformation, leading to the furo-pyridines **1.127** and **1.129**. Importantly, 7-membered bicyclopyridine **1.134**, can also be prepared in moderate yield. Very good yields were observed for cyanoalkynes carrying aryl groups **1.135-1.136**, vinyl groups **1.137-1.138** as well as cholesterol derivative **1.139**.



Scheme 1.39. Substrate scope of 4-halopyridines.

Interestingly, the use of halogen-substituted cyanoalkynes **1.140** delivered 4-halopyridines. As seen in Scheme 1.39, different halogenated cyanoalkynes carrying I, Br or Cl reacted productively with different ynamides and thioalkynes to furnish pyridine moieties **1.141-1.152** in good to moderate yield. The lower yield can be explained by the relatively low stability of

halogenated cyanoalkynes in strong acidic media, as observed in control experiments. It is also important to mention that increasing the loading of the halogenated cyanoalkyne up to 2.0 equiv. did not lead to an improvement in yield. The structure of the halopyridine products was unambiguously confirmed by X-ray analysis of **1.141** (Figure 1.5).

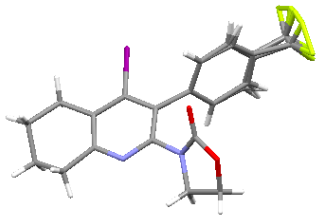
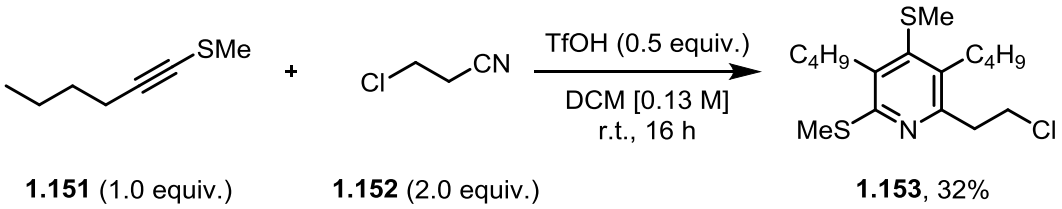


Figure 1.5. X-ray structure of **1.141**.

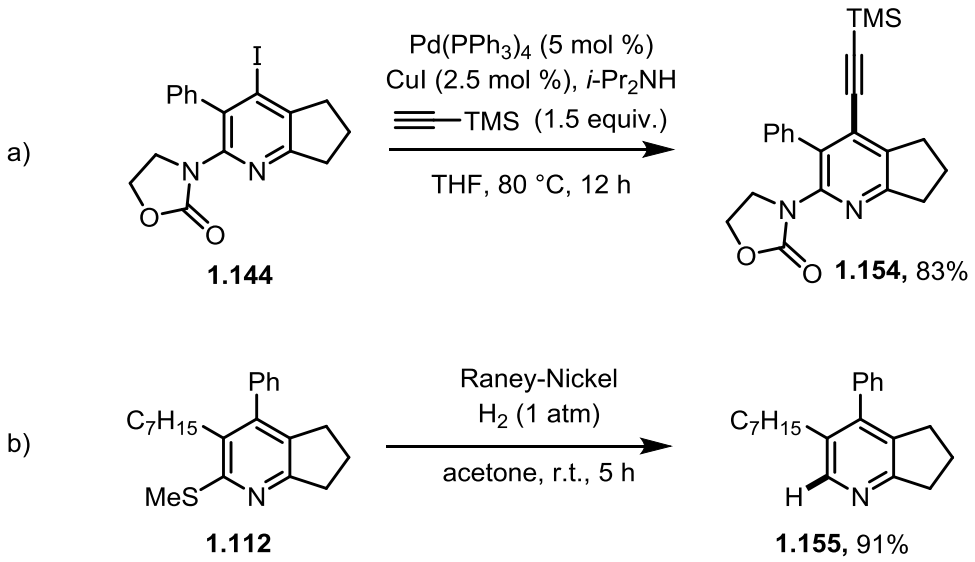
1.2.1.4 Intermolecular version and derivatisation on the products

A more challenging transformations is the fully intermolecular [2+2+2] combination of two non-tethered alkynes and a nitrile. Such a transformation is hardly possible in regioselective manner even under state-of-the-art transition metal catalysis. After several attempts, our best result was the formation of pyridine **1.153** in 32% yield by treating 1.0 equiv. of butyryl-thiolaklyne **1.151** and 2.0 equiv. 3-chloropropionitrile of **1.152** with 0.5 equiv. of TfOH at room temperature (Scheme 1.40).



Scheme 1.40. Fully intermolecular formal [2+2+2] cycloaddition for pyridine synthesis.

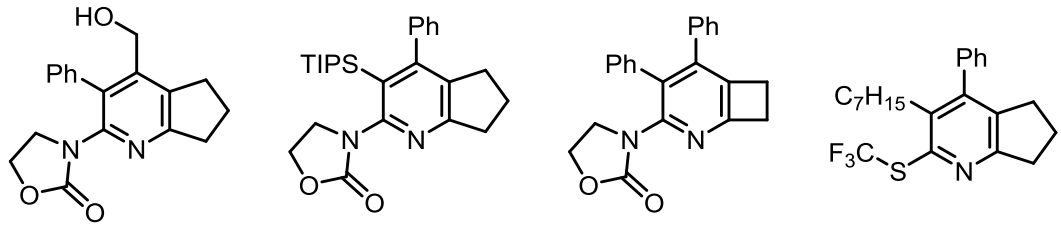
The prepared 4-halopyridines appear to be suitable partners for cross-coupling reactions. Sonogashira coupling of **1.144** furnished 4-alkynylpyridine **1.154** in 83% yield (Scheme 1.41 a). The (methylthio) moiety of pyridines such as **1.112** can also be readily hydrogenated in the presence of Raney-Nickel to give the tetra-substituted derivative **1.155** (Scheme 1.41 b).



Scheme 1.41. Derivatisation of the pyridine products.

1.2.1.5 Limitations of this method

During the course of this study, some substrates probed were not successful. As seen in scheme 1.42, cyanoalkyne with an alcohol residue did not deliver the predicted pyridine ring, probably due to its low stability under acidic conditions. Silylynamide was also not successful due to the silicon hyperconjugation (silyl β-stabilisation of carbocation). A four-membered ring formation, as well as the use of SCF_3 group did not give the expected product and only hydrolysed ynamide or decomposition product resulting from the corresponding thioalkyne were detected.



Scheme 1.42. Structure of pyridines that failed in this study.

The (methylthio) moiety of some pyridines suggested the possibility of engaging it in cross-coupling reactions. [54] However, several attempts following literature-known palladium-catalysed procedures failed in our case. We reasoned that the steric hindrance on the 3-position of the pyridine ring may prevent the metal insertion from taking place.

With the 2-oxazolidino-pyridine structure, we were intrigued by the possible hydrogenation of this one to the corresponding piperidine following the previously reported work of Glorious

et al. [55] However, several attempts involving variable amounts of Pd/C under 60 bar of H_2 and 150 °C for three days did not deliver the reduced product. Only starting material (pyridine) was recovered.

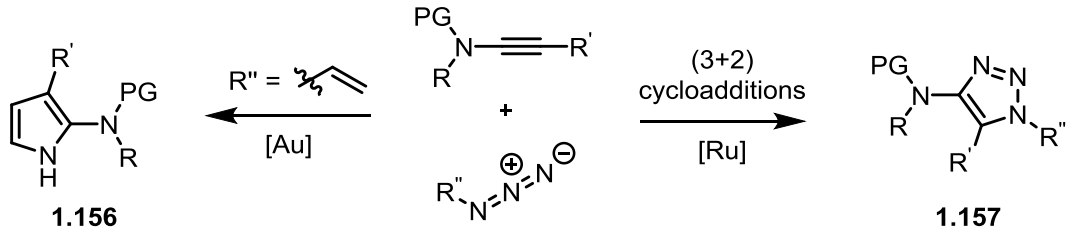
1.2.2 Combining ynamides with azides: from rearrangements to a metal-free dimerisation process

This work was carried out in collaboration with Msc. Veronica Tona, Dr. Stefan Ruider, Msc. Martin Berger, Dr. Mohan Padmanaban and Dr. Langui Xie. The results were reported in: Chem. Sci. **2016**, *7*, 6032-6040. [56]

My contribution to this project was mainly focused on the dimerisation reaction. However, a brief discussion about this work will take place, followed by more detailed discussion about the dimerisation.

1.2.2.1 Introduction

Organic azides have been used extensively in organic chemistry as versatile nitrogen reagents. Due to their high nucleophilicity and relative stability, several transformations have been reported. [57] In particular, ynamides and azides have been utilised for the synthesis of nitrogen containing heterocycles. Several gold-catalysed transformations were reported by Huang, [58] Ye [59] and Liu [60] which led to the formation of 2-amino pyrroles **1.156** (Scheme 1.43 left). On the other hand, azides are the typical reagents for the (3+2) cycloaddition reaction with alkyne. [61] As discussed earlier, the (3+2) click reaction of ynamides with azide was reported by Cintrat and co-workers in 2006. [41] A ruthenium-catalysed version was established and allowed access to a range of 4-aminotriazoles **1.157** (Scheme 1.43 right).

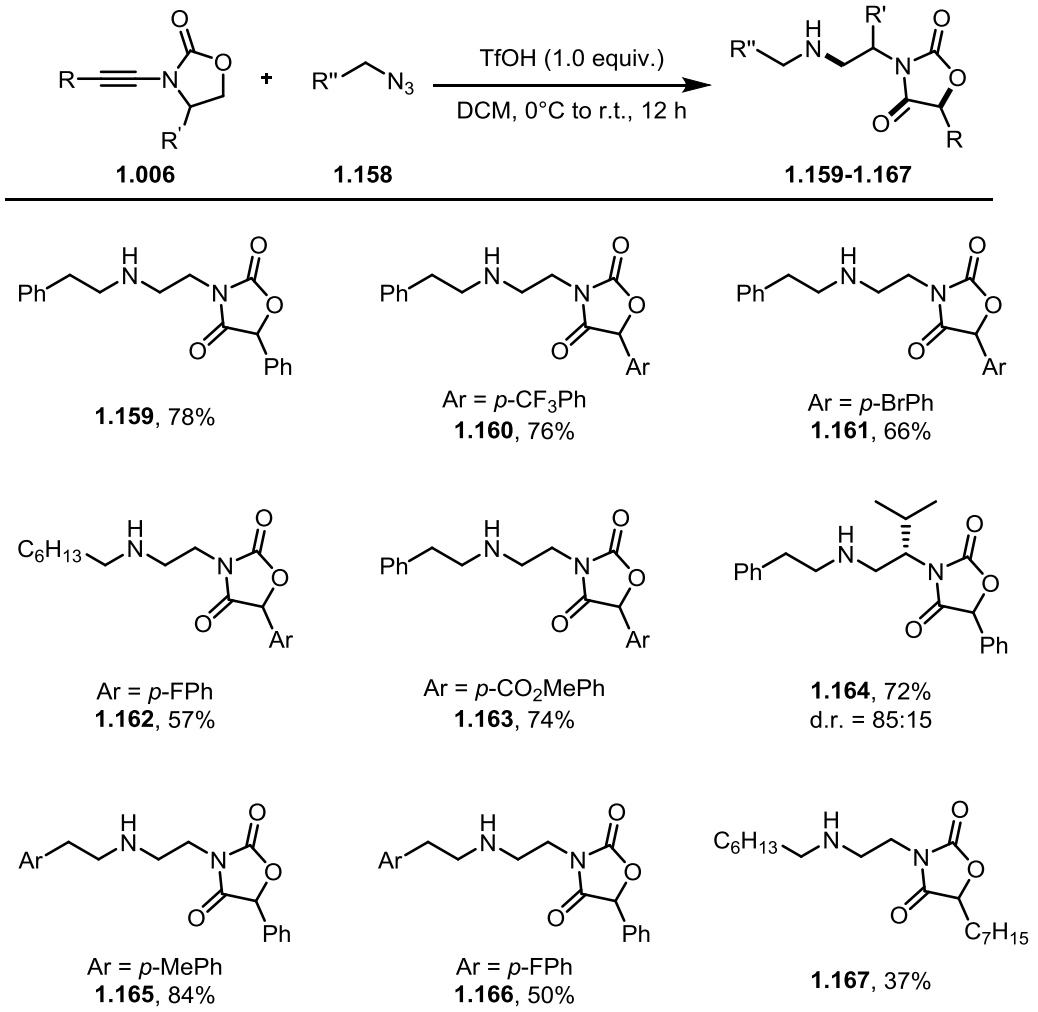


Scheme 1.43. Transition-metal-catalysed reactions of ynamide and azides for the construction of *N*-heterocycles.

1.2.2.2 Preliminary work and motivation

Our group has published an α-amination of amides using azides. This transformation, which proceeded *via* a keteniminium intermediate will be discussed in more detail in the next

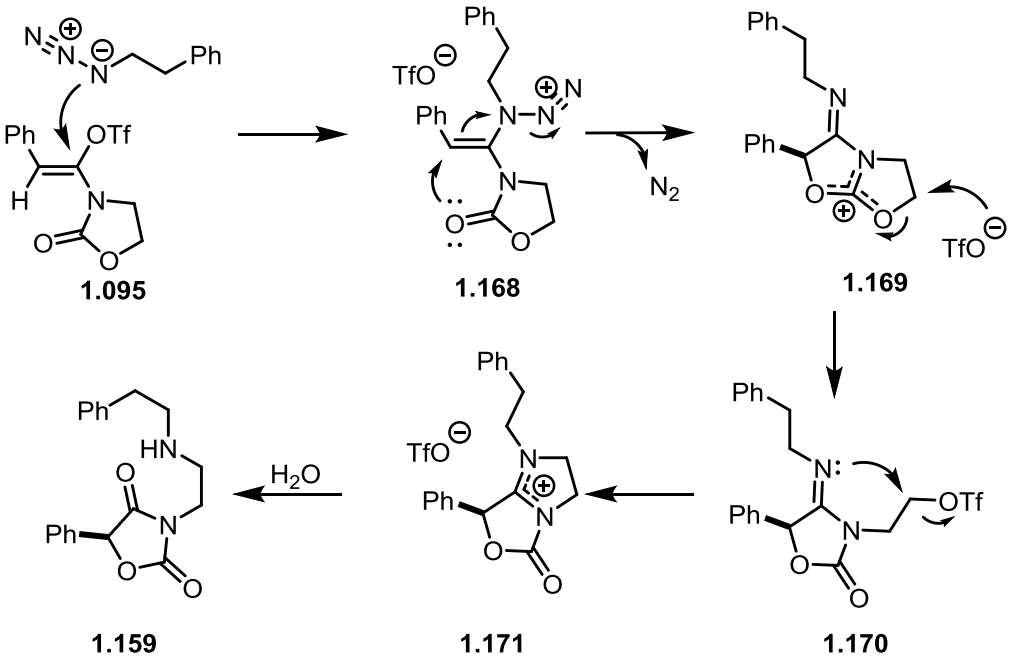
chapter. [62] When trying to evaluate this chemistry on keteniminium intermediate generated by Brønsted acid activation of ynamides, we have detected the formation of oxazolidine-2,4-diones **1.159-1.167** as the sole product. After optimising the reaction conditions, a wide scope of substrates was explored as seen in some selected examples (Scheme 1.44).



Scheme 1.44. Scope of coupling ynamides with azides for the formation of oxazolidine-2,4-diones.

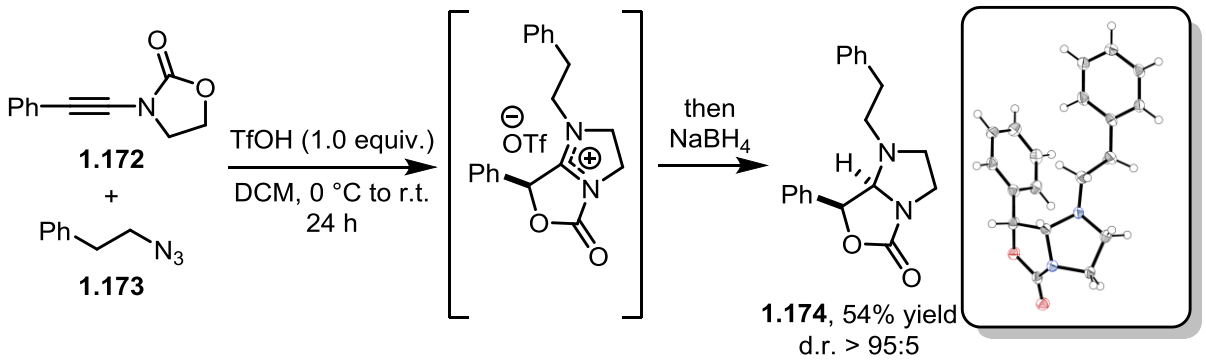
To further understand the mechanism of this transformation, a DFT study was carried out. A proposed mechanism for this rearrangement is depicted below. Nucleophilic addition from the azide onto the keteniminium intermediate generated species **1.168**. The latter is formally umpoled, opening the possibility of internal nucleophilic addition to give oxazolium moiety **1.169**. Triflate-mediated opening and recyclisation ultimately generated the amidinium triflate **1.170**. Straightforward aqueous basic hydrolysis of **1.171** delivered the observed oxazolidine-2,4-dione **1.159** (Scheme 1.45).

The calculations showed that all of the individual barriers towards the formation of oxazolium **1.169** were fairly small, and thus the reaction proceeded smoothly up to this point. The subsequent rearrangement of the bicycle **1.169** involves rather high barriers of activation. This suggests that triflate-mediated formation of amidinium **1.170** is the rate-limiting step.



Scheme 1.45. Proposed mechanism for the triflic acid-mediated rearrangement of azides with ynamides.

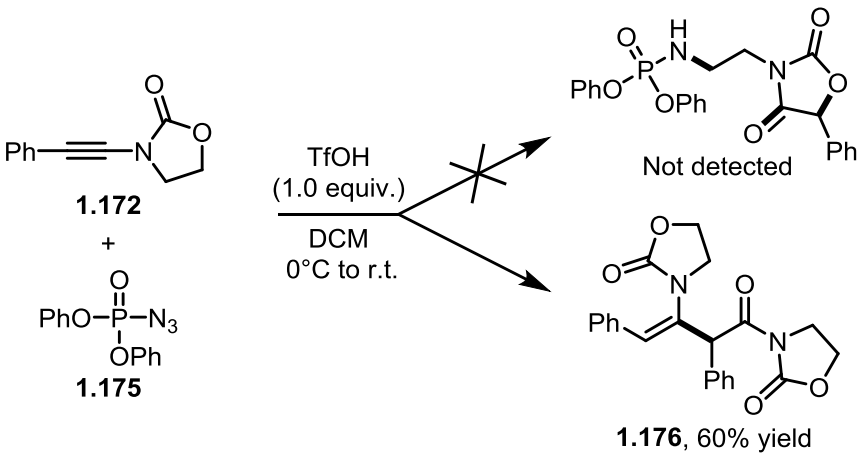
In further support of the proposed mechanism, treatment of the reaction mixture obtained by combining **1.172** and **1.173** under the optimised conditions followed by treatment with sodium borohydride before hydrolysis afforded *N*,*N*-acetal **1.174**. X-ray crystallographic analysis supported the expected NMR assignment. **1.174** was formed as a single trans-diastereoisomer (Scheme 1.46).



Scheme 1.46. Interception of amidinium intermediate by reduction with sodium borohydride.

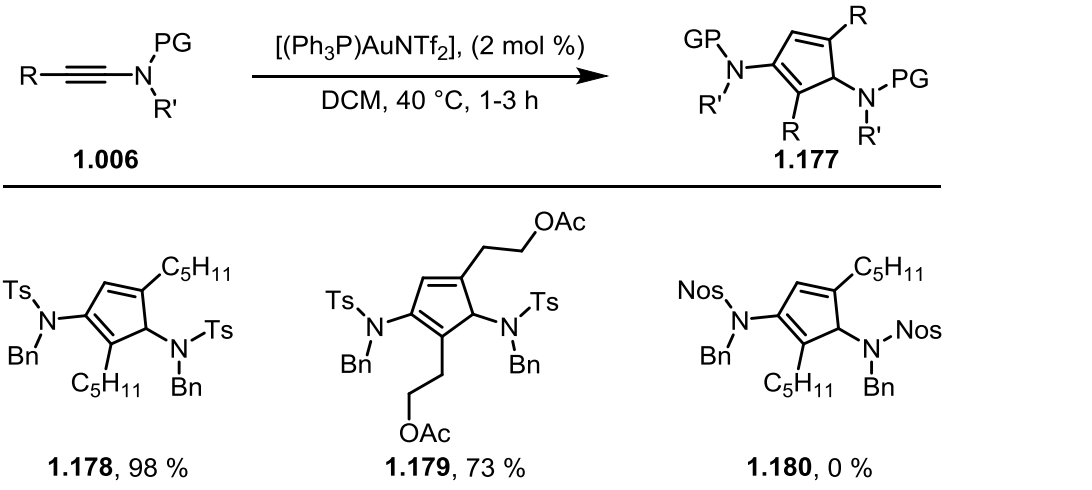
1.2.2.3 Metal-free hydrative dimerisation of ynamides

Interestingly, when screening different azides in the previous transformation, an unexpected result was observed. The use of diphenylphosphoryl azide (dppa) **1.175** under the same reaction conditions led to the formation of a dimer **1.176** resulting from the union of two ynamide reactant molecules (Scheme 1.47).



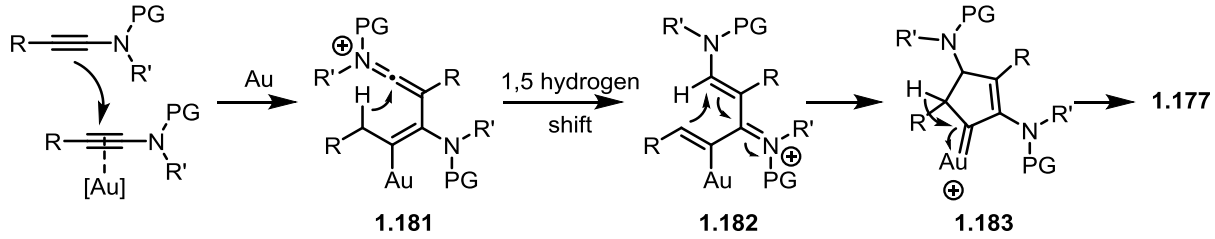
Scheme 1.47. Unexpected dimer formation upon reaction of ynamide **1.172** with dppa.

The direct dimerisation of alkynes is almost exclusively the domain of transition-metal catalysis. In 2011, Skrydstrup and co-workers have reported a dimerisation of ynamides that involves the use of a gold catalyst. [63] Upon treatment of electron-rich ynamides with an electrophilic gold(I) species, rapid homologation to the 1,3 diaminocyclopentadienes **1.177** was observed. As seen in the selected examples, the use of alkyl-substituted ynamides furnished the desired products in very good yield (**1.178** and **1.179**). However, the presence of a strongly electron-withdrawing group on the nitrogen atom (nosyl group) completely shut down the reaction (Scheme 1.48)



Scheme 1.48. Gold-catalysed dimerisation of ynamides.

The authors' mechanistic proposal starts with nucleophilic addition of the ynamide **1.006** to the gold-activated ynamide to form keteniminium intermediate **1.181**. A subsequent 1,5-hydrogen shift delivers intermediate **1.182**. Metalla-Nazarov reaction (formally a 4π-electrocyclisation) then takes place leading to gold carbene **1.183**. The cyclopentadiene **1.177** can then be obtained by a 1,2-hydride shift/gold catalyst regeneration (Scheme 1.49).



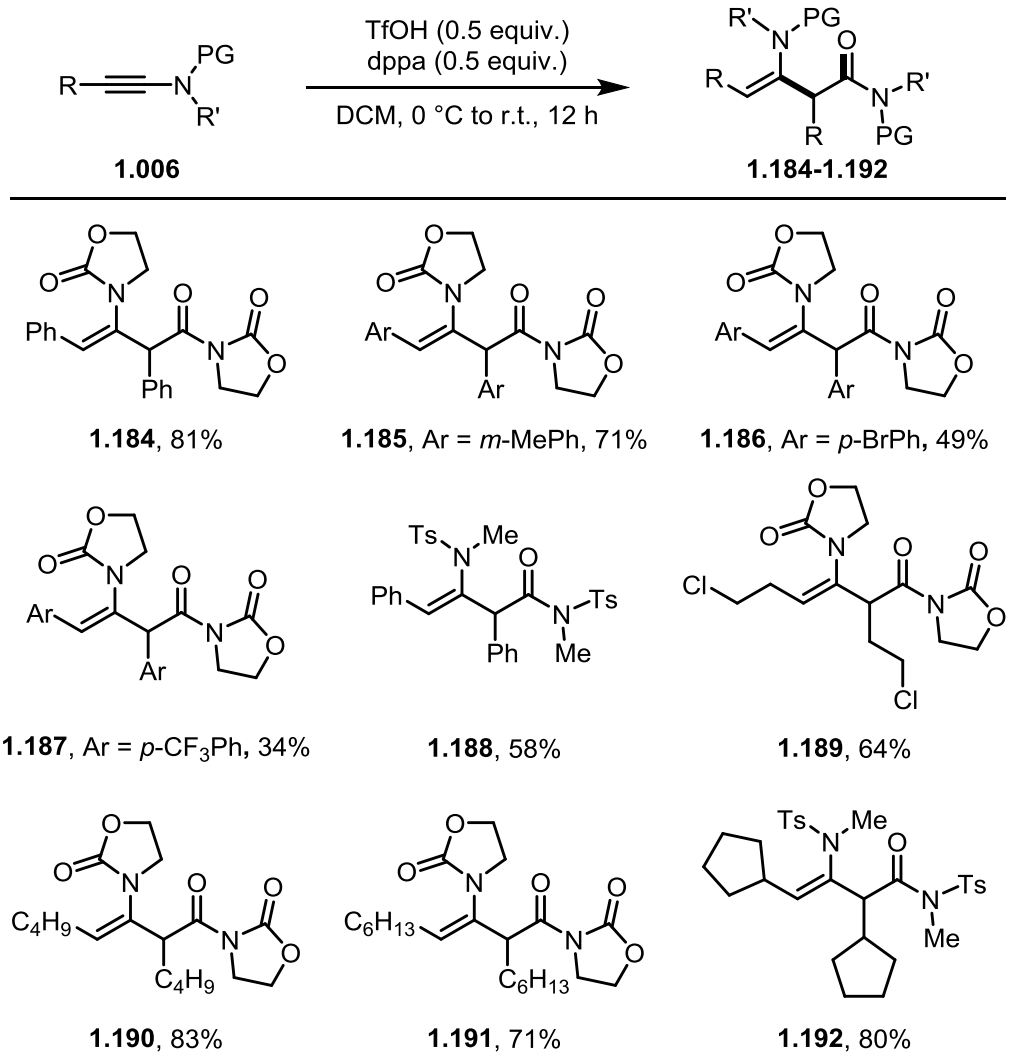
Scheme 1.49. Proposed mechanism for the Au-catalysed dimerization of ynamides.

Whilst this reaction is conceptually very interesting, it presents some limitations. The presence ynamides with either aromatic or cycloalkyl residue led to the formation of other products (not shown here). Therefore, a controlled dimerisation process under simple acidic conditions piqued our interest.

1.2.2.4 Optimisation, reaction scope and mechanistic considerations

Optimisation studies quickly showed that the presence of dppa **1.175** was crucial for this dimerisation process: in its absence, only the hydrolysed product was detected. Further optimisation enabled the generation of this ynamide dimer in 81% yield in the presence of only substoichiometric amounts of both TfOH and dppa (The use of lower amounts of either component led to lower yield of the desired product).

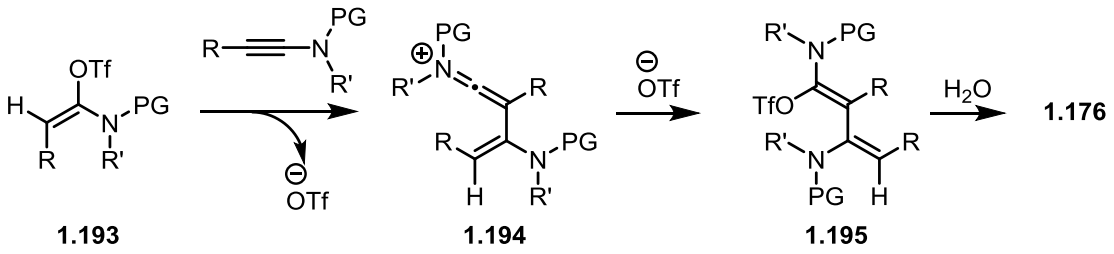
The scope of this transformation proved to be broad (Scheme 1.50). Hydrative dimerisation products of differently substituted aryl, alkyl, cycloalkyl ynamides were obtained in very good yields. The use of an arylynamide carrying a strongly electron-withdrawing CF_3 moiety led to lower yield (**1.187**). Notably, *N*-sulfonylynamides enabled dimerisation to take place in moderate yield (**1.188**).



Scheme 1.50. Substrate scope on ynamide dimerisation.

This reaction is believed to proceed *via* nucleophilic addition of the ynamide onto the keteniminium species to form intermediate **1.194** in analogue to the Skrydstrup report (Scheme 1.51). Computations showed that, in the presence of dppa, the barrier of activation of the ynamide to form **1.194** is remarkably low. Also, the energy of the transient keteniminium **1.194** is reduced in comparison to the previous intermediate **1.193**. This suggests that dppa plays an important role in stabilising intermediate **1.194**. Triflate addition

generates the *N,O*-ketene acetal **1.195**, aqueous workup of which furnishes the hydrative dimer **1.176**.



Scheme 1.51. Proposed mechanism for triflic acid-mediated dimerisation of ynamides.

2. Amide Activation: From α-arylation to α-Umpolung reactivity

1.2 Introduction

The amide functional group is perhaps the key chemical connection in life and is found in a plethora of organic molecules, such as peptides, proteins, polymers and scores of secondary metabolites. [64] Amides are considered as the most stable functional groups among carboxylic acid derivatives. This high stability comes from the delocalisation of the nitrogen lone pair to the carbonyl group (Figure 1.6).

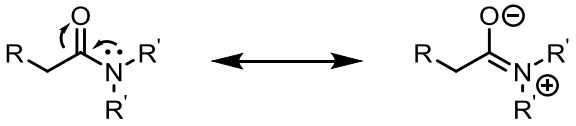


Figure 1.6. Delocalisation of the nitrogen lone pair in an amide bond.

The chemistry of amide bond formation is well established. Typical preparation of amides involves a coupling reaction between a carboxylic acid (or its chloride derivative) and an amine. [65] A multitude of activating reagents have been developed to enable so-called 'amide-' or 'peptide coupling' (Figure 1.7).

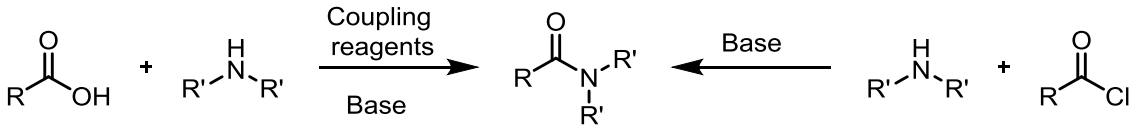


Figure 1.7. General routes for amide preparation.

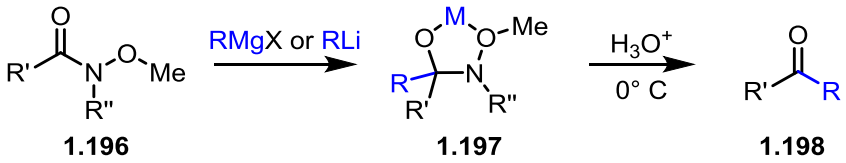
Although the amide bond is considered highly stable, some methods have emerged for its activation. We shall briefly review them in the following section.

1.2.2 Reactivity of amides

1.2.2.1 Metal-catalysed activation of amides

Amides are considered virtually inactive toward organometallic species due to the aforementioned delocalisation of the nitrogen lone pair. In the early 1980s, Weinreb and Nahm disclosed the possibility of converting an amide into ketone, in a report that eventually become textbook knowledge (Weinreb-Nahm ketone synthesis). [66] The presence of a methoxy group adjacent to the nitrogen atom increases the reactivity of the amide toward organometallic partners. Addition of different organomagnesium or organolithium species into these so-called

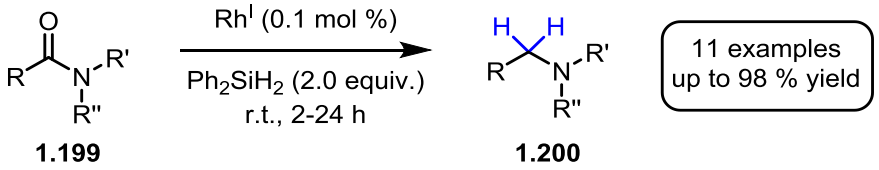
Weinreb amides **1.196** results in stable tetrahedral intermediates **1.197**, stabilised by the chelating nature of the oxygen atom. Hydrolysis of **1.197** at low temperature furnishes the corresponding ketones **1.198** without over-addition (Scheme 1.52).



Scheme 1.52. Weinreb-Nahm ketone synthesis.

However, this venerable reaction does not address chemoselectivity issues. In the presence of other reactive carbonyl functionality, such as esters, aldehydes or ketones, nucleophilic addition from the organometallic species on these moieties outcompetes addition to the Weinreb amide.

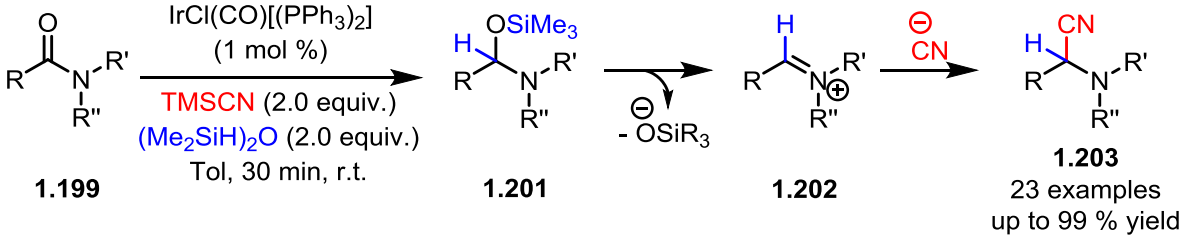
Numerous metal-catalysed reduction reactions of amides into the corresponding amines have been developed. In 1998, Ito and co-workers developed a rhodium-catalysed reduction of amides with hydrosilane. [67] The catalyst [RhH(CO)(PPh_3)$_3$] has been used with diphenylsilane to efficiently reduce a variety of tertiary amides and lactams **1.199** to the amines **1.200** in very high yields under mild reaction conditions (Scheme 1.53).



Scheme 1.53. Rh-catalysed reduction of amides with diphenylsilane.

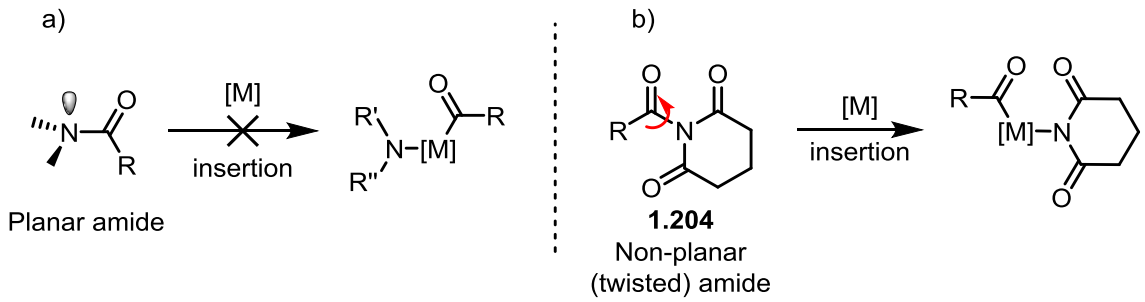
Other metal-catalysed approaches for the reduction of amides have been reported by Beller, [68] Adolfsson, [69] Brookhart [70] and Nagashima. [71]

In 2017, Dixon and co-workers reported a reductive Strecker reaction of amides leading to the formation of α-amino nitriles. [72] The use of an iridium catalyst (Vaska's complex) with amide and hydrosilane partners furnished the hemiaminal **1.201**, leading to the iminium **1.202** after elimination of the silyloxy moiety. The presence of trimethylsilyl cyanide prevented further reduction by the nucleophilic addition of the cyanide anion, delivering the α-amino nitrile derivatives **1.203** (Scheme 1.54). Whilst the reaction is broadly efficient with amides and lactams, chemoselectivity over other functional groups still remains a limitation for this process.



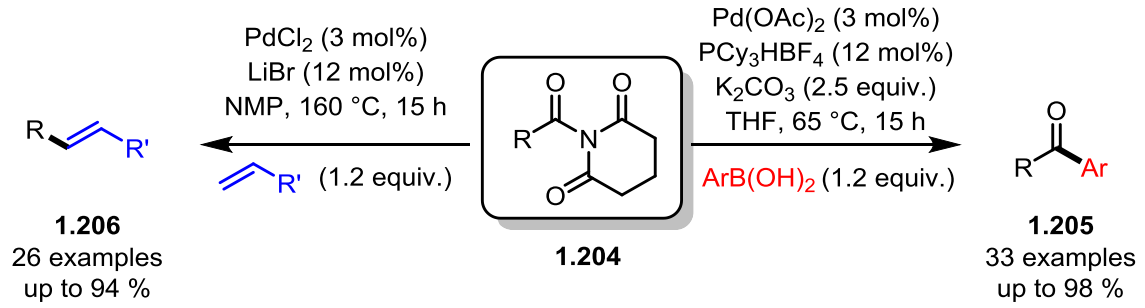
Scheme 1.54. Ir-catalysed reductive cyanation of amides.

Amides are usually unreactive toward metal-catalysed cross-coupling reactions, and metal insertion in the amide C-N bond is generally seen as not possible. To overcome this problem, Sozstak and co-workers used an imide (in particular piperidine-2,6-dione) which prevents delocalisation of the nitrogen lone pair due to twisting (Scheme 1.55). Thus, amide **1.204** is non-planar and metal insertion can take place successfully. [73]



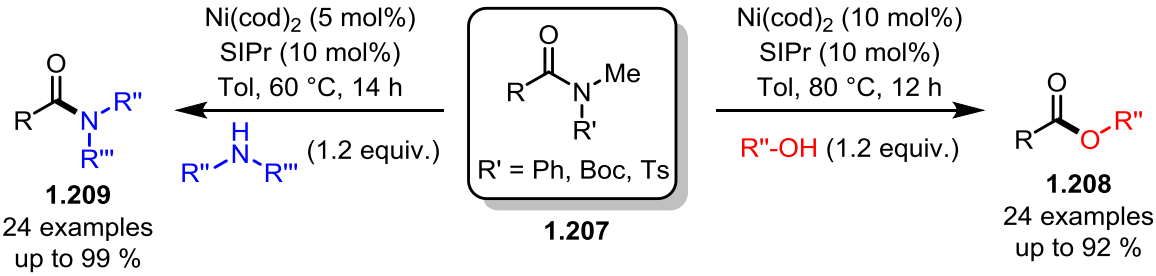
Scheme 1.55. Metal insertion into planar and twisted amides.

Palladium-catalysed Suzuki coupling of these twisted amides **1.204** with aryl boronic acids was smoothly achieved and furnished ketones **1.205** in very good yields (Scheme 1.56 right). A Heck-type reaction was also reported with electron-deficient alkenes. [74] The reaction proceeded with metal insertion concomitant with release of carbon monoxide (CO) to form the alkenes **1.206** in good yields (Scheme 1.56 left).



Scheme 1.56. Pd-catalysed Suzuki and Heck coupling with twisted amides.

In 2015, Garg and co-workers reported a nickel-catalysed transamidation and esterification of amides. After calculating the oxidative addition barriers for several amides using Ni/SIPr as the metal/ligand combination, it was clear that the presence of a ligand coordinating to the nitrogen central disrupts the ($n_N \rightarrow \pi^*_{CO}$) conjugation and makes the oxidative addition step more feasible (lower barrier). [75] As seen in scheme 1.57, amides carrying either *N*-Boc, *N*-Ph or *N*-Ts residue (**1.207**), readily allow metal insertion into the C-N bond to take place. In the presence of an alcohol, the corresponding esters **1.208** were obtained (Scheme 1,57 right), while with amines the secondary or tertiary amides **1.209** occurred (Scheme 1.57 left). [76] Both transesterification and transamidation proceeded under thermal conditions in very good yields.



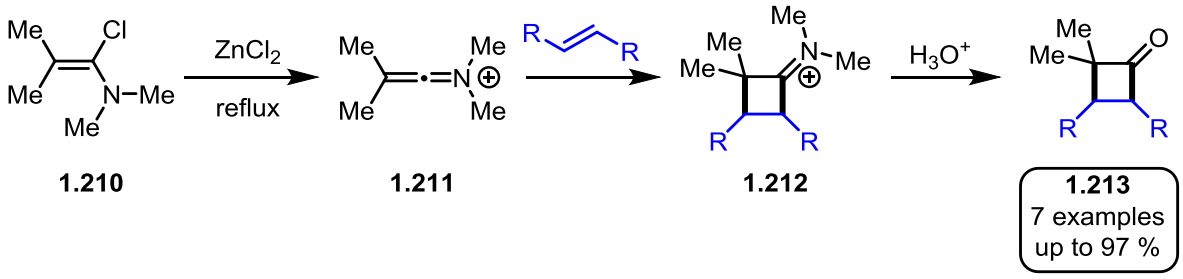
Scheme 1.57. Ni-catalysed transamidation and esterification of amides.

Other approaches by Zou, [77] Shi [78] and Chatani [79] for metal-catalysed activation of similar amides have also been reported.

1.2.2.2 Metal-free electrophilic activation of amides

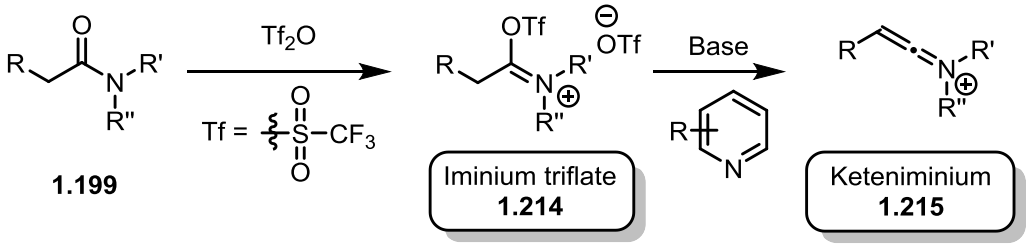
Activation of amides with electrophiles has been extensively documented. Various textbook transformations involve an electrophilic activation; namely, the Vilsmeier-Haack and Bischler-Napieralski reactions. Both reactions utilise phosphoryl chloride ($POCl_3$) for the activation.

In 1974, Ghosez and co-workers disclosed the [2+2] cycloaddition reaction between alkenes and keteniminiums generated *in situ* from *N*-*N*-dimethyl-α-chloroenamine **1.210** (Ghosez's reagent). [80] Activation of the α-chloroenamine with zinc chloride ($ZnCl_2$) as Lewis acid transiently generated the corresponding keteniminium ion **1.211**. The latter reacted further with symmetric alkenes to furnish cyclobutyl iminium salts **1.212**. Final hydrolysis delivered the cyclobutanones **1.213** in high yields (Scheme 1.58).



Scheme 1.58. Ghosez's first keteniminium [2+2] cycloaddition reaction with alkenes.

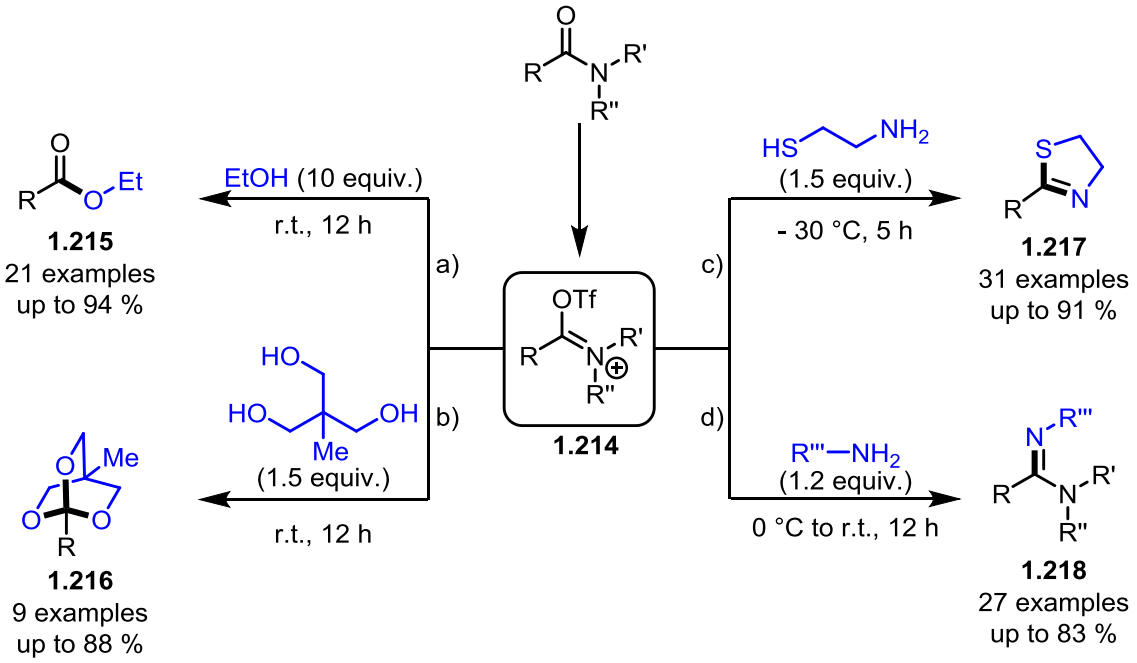
Later on, Ghosez reported the *in situ* generation of keteniminium salts from simple amides upon treatment with trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O) and collidine. [81] The reaction between amides **1.199** and triflic anhydride initially results in the formation of an iminium triflate **1.214**. The latter undergoes elimination to the keteniminium **1.215** in the presence of a pyridine base (Scheme 1.59).



Scheme 1.59. General pathway for activation of amides with triflic anhydride.

Since the pioneering work of Ghosez on the [2+2] cycloaddition reactions of keteniminium ions, the use of triflic anhydride (Tf_2O) in combination with amides led to considerable amount of new transformations. [82]

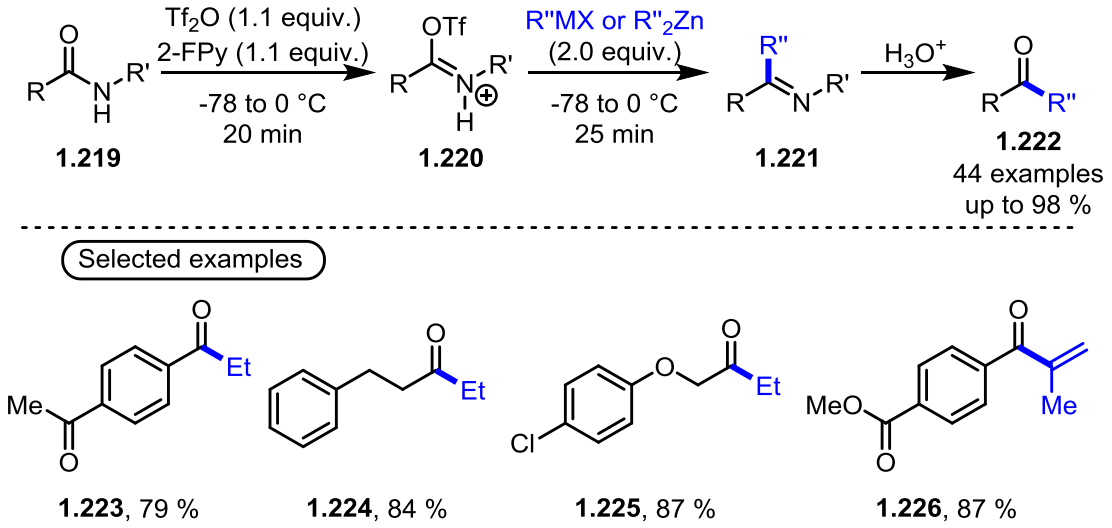
Charette and co-workers applied this method in multiple synthetically useful transformations. Several nucleophiles can intercept the iminium triflate **1.214** (Scheme 1.60). Upon addition of excess ethanol to **1.214**, an esterification reaction will take place. [83] This valuable reaction proceeded well with a diversity of secondary and tertiary amides (Scheme 1.60 a). The addition of a triol furnished the caged orthoesters **1.216**. [84] Orthoesters are somewhat underutilised protecting groups for carboxylic acids due to their stability towards strong bases and their lability towards mild acidic hydrolysis. This synthetic method delivered these orthoesters in very good yield with relatively mild reaction conditions (Scheme 1.60 b).



Scheme 1.60. Charette's nucleophilic additions to iminium triflates.

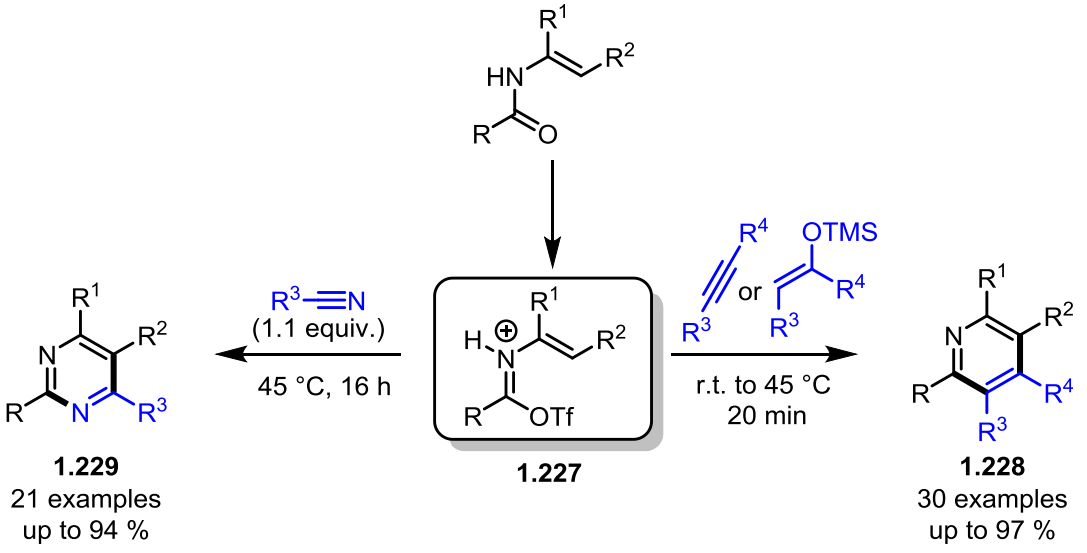
Treatment of **1.241** with 2-aminoethanethiol led to the formation of thiazolines **1.217** (Scheme 1.60 c), [85] while the addition of amines furnished the amidine derivatives **1.218** (Scheme 1.60 d). [86] Both interesting building blocks and useful synthons in the synthesis of various other heterocyclic compounds.

In 2012, Charette further developed an alternative method for the synthesis of ketones from amides. [87] Upon activation of secondary amides **1.219** with triflic anhydride and 2-fluoropyridine, followed by treatment of the iminium triflate **1.220** with organometallic species (Grignard reagents and organozinc species), imine moieties **1.221** were successfully formed. Subsequent hydrolysis delivered ketones **1.222** (Scheme 1.61). Different functional groups were compatible with the conditions of the reaction. Notably, the presence of an ester or ketone moiety did not affect the transformation and led to the formation of the desired ketones **1.223** and **1.226** in chemoselective fashion.



Scheme 1.61. Preparation of ketones from secondary amides.

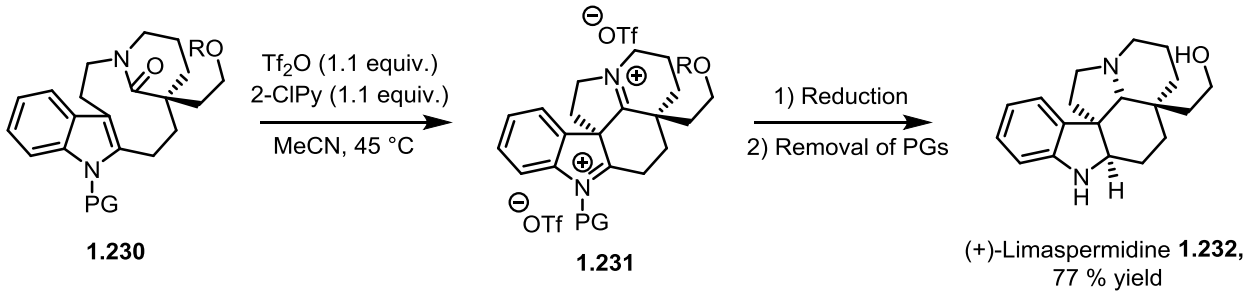
In 2007, Movassaghi and co-workers applied this strategy in the synthesis of heterocycles. [88] Treatment of secondary enamide with triflic anhydride and 2-chloropyridine yielded the iminium triflate **1.227**. This intermediate was further trapped either by electron-rich alkynes (as well as silyl enol ethers) and furnished the penta-substituted pyridines **1.228** (as mentioned earlier), or with different nitriles to give the pyrimidine derivatives **1.229** (Scheme 1.62). This methodology was very efficient and many alkynes and nitriles gave the desired heterocycles in very good yields.



Scheme 1.62. Synthesis of pyridines and pyrimidines form secondary amides.

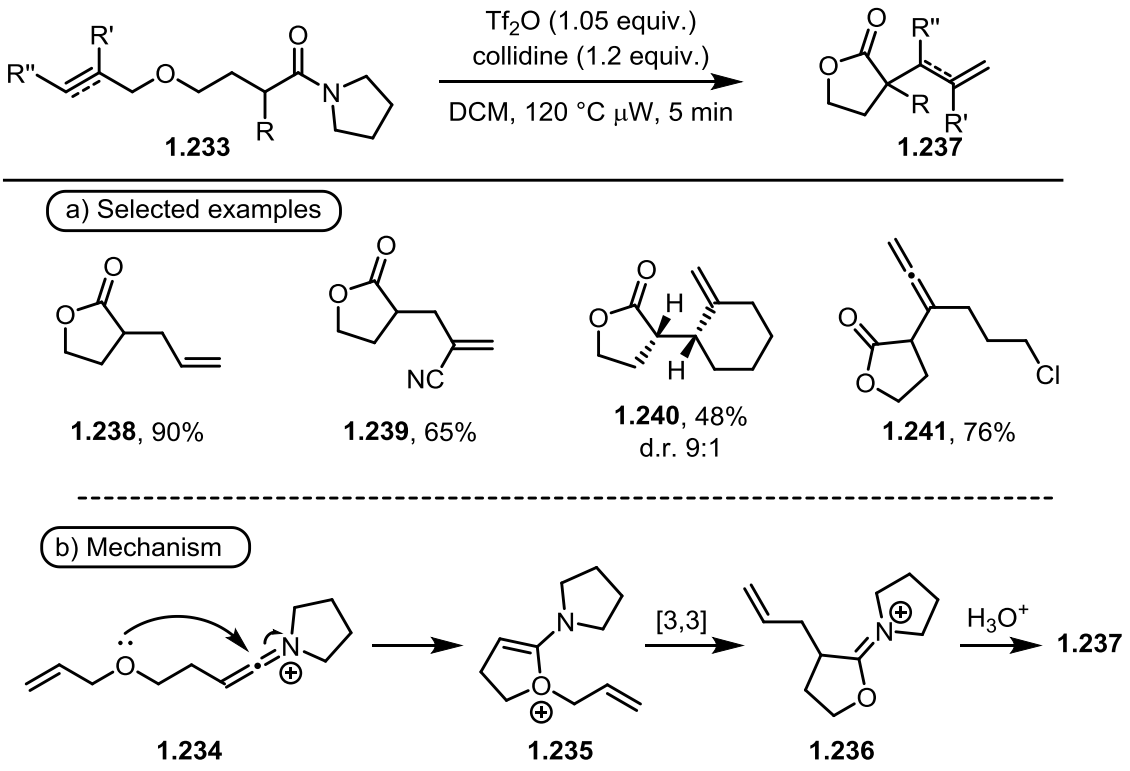
Movassaghi recently applied this method in the total synthesis of Aspidosperma alkaloids. [89] As seen in scheme 1.63, treatment of lactam **1.230** with triflic anhydride and 2-chloropyridine

triggered a nucleophilic addition of the indole, resulting in the diastereoselective formation of diiminium ion **1.231**. Further reduction and removal of protecting groups delivered (+)-Limaspermidine **1.232**.



Scheme 1.63. Amide activation in the total synthesis of Aspidosperma alkaloids.

In 2010, our group has developed a method for the synthesis of α-allyl lactones derived from γ-allyloxy amides *via* activation with triflic anhydride. [90] Treatment of amides **1.233** with triflic anhydride and collidine, followed by microwave irradiation in for 5 min and subsequent hydrolysis delivered lactones **1.237** in high yields (Scheme 1.64). The reaction proceeds *via* formation of the keteniminium intermediate **1.234**, which does not undergo [2+2] cycloaddition reaction (as seen before in Ghosez's work). A nucleophilic attack from the oxygen moiety instead delivers intermediate **1.235**, poised for [3,3] sigmatropic rearrangement towards the iminium ion **1.236**. Finally, hydrolysis furnishes the products **1.237** (Scheme 1.64 b). Different functional groups were tolerated in this transformation (nitrile, ester and halides). Lactones such as **1.240**, bearing branched allyl substituents in the α-position were generated in very good diastereoselectivities. Importantly, propargyl ether derivatives led to the formation of the corresponding α-allenyl lactones (such as **1.241**) in very good yield (Scheme 1.64 a).



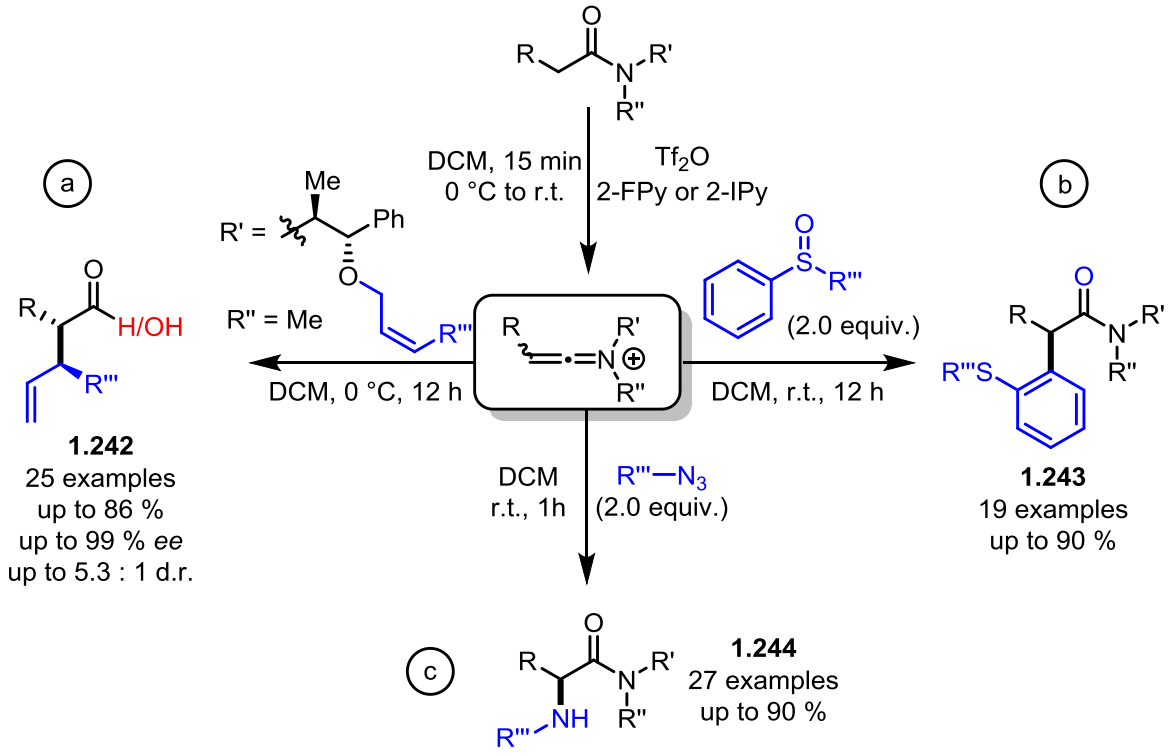
Scheme 1.64. Lactone formation *via* electrophilic rearrangement of amides.

Our group has developed multiple important transformations based on this initial report (Scheme 1.65). An asymmetric Claisen rearrangement triggered by an electrophilic activation of chiral amides was also achieved. [91] Chiral pseudoephedrine amides bearing an allyl residue were activated and underwent [3,3] sigmatropic rearrangement. Subsequent reduction or hydrolysis of the resulting iminium ions provided enantioenriched α-allylic aldehydes or carboxylic acids **1.242** (Scheme 1.65 a). The substrate scope of this transformation was broad. A variety of common functional groups were tolerant (ketones, esters, ethers, cyanides and halides).

Treatment of the keteniminium intermediate with aryl sulfoxides led to the development of a highly chemoselective α-arylation of amides. [92] The reaction also proceeds via [3,3] sigmatropic rearrangement to deliver the α-arylated products under relatively mild reaction conditions. Once again, a variety of functional groups tolerated this transformation and gave the desired arylation products **1.243** in very good yields. (Scheme 1.65 b).

In addition, a stereoselective α-amination of amides was reported. [62] Upon treatment of the keteniminium intermediate with simple azides, a formal 2π-electrocyclisation with loss of N_2 delivered an azirinium (not shown), the hydrolysis of which resulted in the observed product **1.244** (Scheme 1.65 c). The reaction was fully chemoselective for amides over other carbonyl

groups (esters or ketones). In the event, the use of a chiral amide led to successfully preparation of optically enriched products.



Scheme 1.65. Our developed transformations on electrophilic amide activation.

Other approaches developed by Huang on amide reduction [93] and on trapping the iminium with organometallic species [94] were also reported. De Mesmaeker and co-workers also reported a [2+2] cycloadditions with keteniminium ions. [95]

1.2 Results and discussion

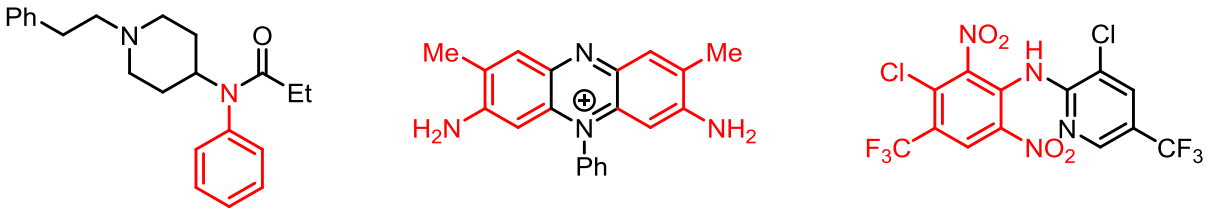
The work on amide activation is divided in two parts. In the first part, a discussion about an *ortho*-amino arylation with hydroxamic acids will take place. The second part will focus on the Umpolung of amides followed by brief discussion on the synthesis of oxazoles.

1.2.1 Hydroxamic acids as regioselective aminoarylating reagents.

This work was carried out in collaboration with Msc. Veronica Tona and Dr. Bo Peng. The results were reported in: *Angew. Chem. Int. Ed.* **2017**, *56*, 10938-10941. [96]

1.2.1.1 Introduction

Aniline is the parent molecule of a vast family of aromatic amines. Since its discovery in 1826 by Otto Unverdorben, it has become one of the most important building blocks in chemistry. Aniline derivatives are used in many different fields of applications, such as pharmaceuticals, polymers, pigments and agrochemicals (Figure 1.8). [97]



Fentanyl
(Opioid analgesic)

Safranin
(*Organic Dye*)

Fluazinam
(*Fungicide*)

Figure 1.8. Examples of industrial compounds containing an aniline core.

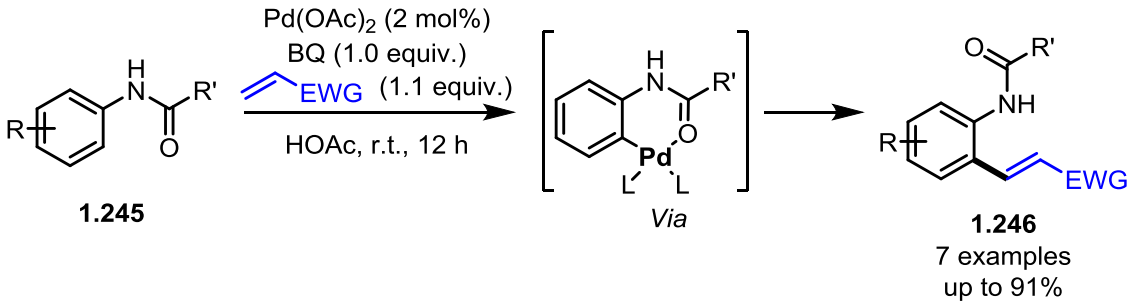
Due to their importance, several preparation methods have been developed, such as reduction of nitro, reductive amination, copper-catalysed coupling at high temperatures, addition to benzyne intermediates, direct nucleophilic substitution on aromatic or heteroaromatic halides and more recent, palladium-catalysed coupling reactions of amines with aryl halides. [98]

1.2.1.2 Aim of the project

Building on our group's previously discussed work in amide activation, we were intrigued by a new approach for the direct *ortho*-functionalisation of anilines *via* sigmatropic rearrangement.

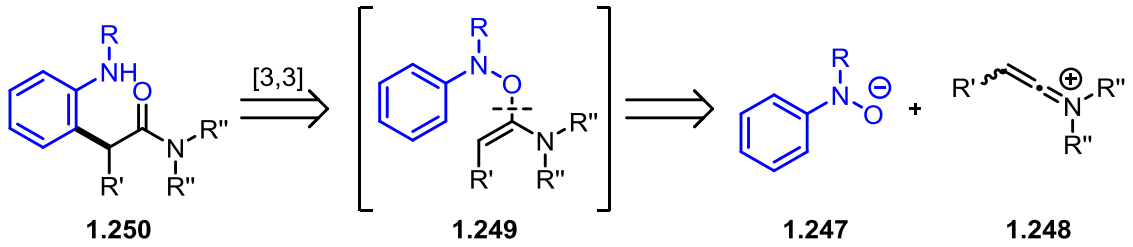
Anilide derivatives are well known to act as *ortho*-directing groups for transition metal-catalysed C-H functionalisation; namely an oxidative Heck-type reaction. In 2002, Van

Leeuwen and co-workers reported a mild method for functionalising anilides **1.245** with electron-deficient alkenes using palladium acetate as a catalyst together with benzoquinone (BQ) as an oxidant (Scheme 1.66). [99]



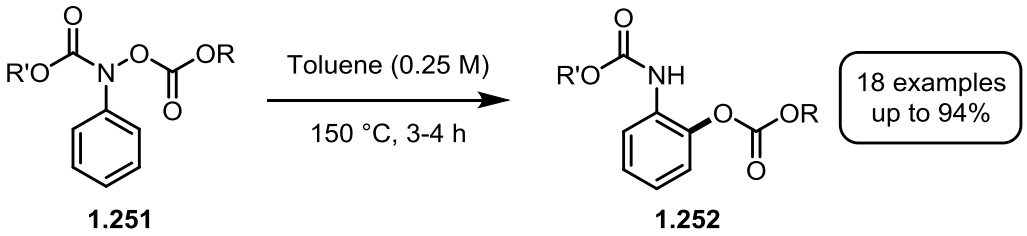
Scheme 1.66. Pd-catalysed *ortho*-functionalisation of anilides with alkenes.

Our hypothesis was to use an *N*-O-aryl moiety **1.247** to trap the keteniminium intermediate **1.248**. Such a reaction could result in the formation of intermediate **1.249**, which can undergo [3,3] sigmatropic rearrangement to furnish the *ortho*-functionalised anilines **1.250** (Scheme 1.67). This methodology would provide a metal-free approach for direct C-C bond formation between simple amides and anilines in a regioselective manner.



Scheme 1.67. Our approach for *ortho*-functionalisation of *N*-hydroxyanilines.

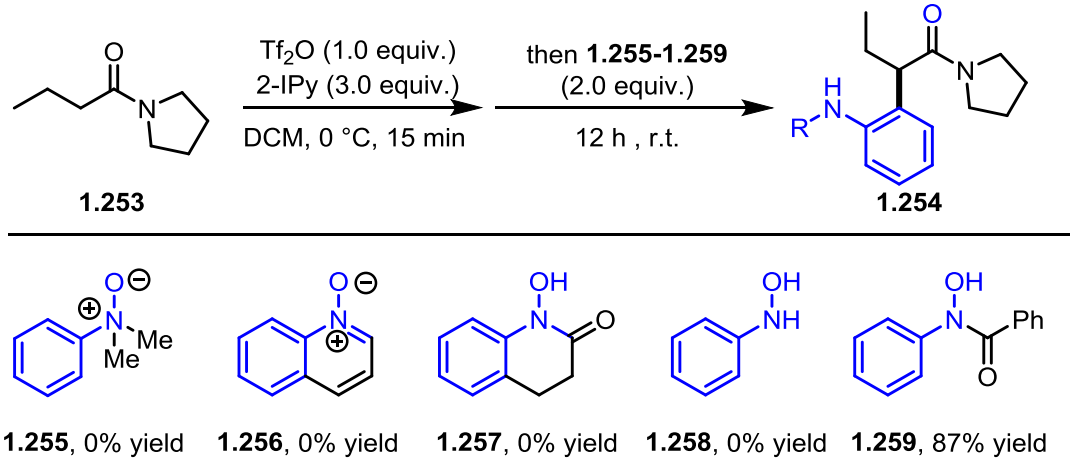
Related variants of this transformation have been well reported by Tomkinson [100] and Shudo. [101] Different aromatic *N*-*O*-hydroxylamine derivatives generated *in situ* proved to undergo a [3,3] rearrangement with N-O bond cleavage. One selected example reported by Tomkinson in 2010 is depicted in scheme 1.68. [102] The reaction usually requires high temperature and results in high yield.



Scheme 1.68. Thermal intramolecular [3,3] rearrangement of *N*-arylhydroxylamines.

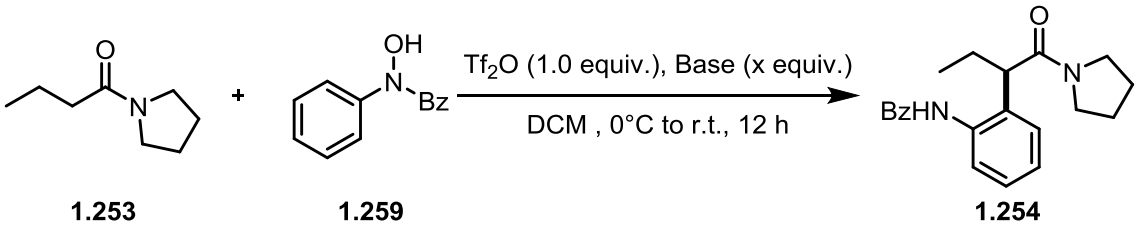
1.2.1.3 Screening of *N*-O nucleophiles and optimising reaction conditions

At the outset, we screened different *N*-*O*-aryl moieties with the activated amide **1.253** (Scheme 1.69). Surprisingly, *N*,*N*-dimethylaniline-*N*-oxide **1.255**, which was originally expected to be the suitable candidate for this transformation, led to no observable reaction. The use of quinolin *N*-oxides **1.256** did not deliver the desired product. Only formation of the α-ketoamide in low yield was observed by a mechanism akin to our group's prior report. [103] The use of *N*-phenylhydroxylamine **1.258** led to no observable products, probably due to the competitive nucleophilicity of the aniline nitrogen. In this case, only starting material was recovered after hydrolysis. Cyclic hydroxamic acid **1.257** was also unsuccessful; however, its acyclic variant **1.259** delivered the desired product **1.254** in high isolated yield (87%).



Scheme 1.69. Screening of different *N*-*O*-aryls.

Further screening of conditions was carried out. As seen in table 1.2, the use of 2-fluoropyridine led to lower yield (Entry 2). Pyridine prevented the formation of the desired product (Entry 3). This can be rationalised by the formation of a high stable pyridinium intermediate. [104] Further decrease of the amount of base and hydroxamic acid led to lower yields (Entry 4 and 5).



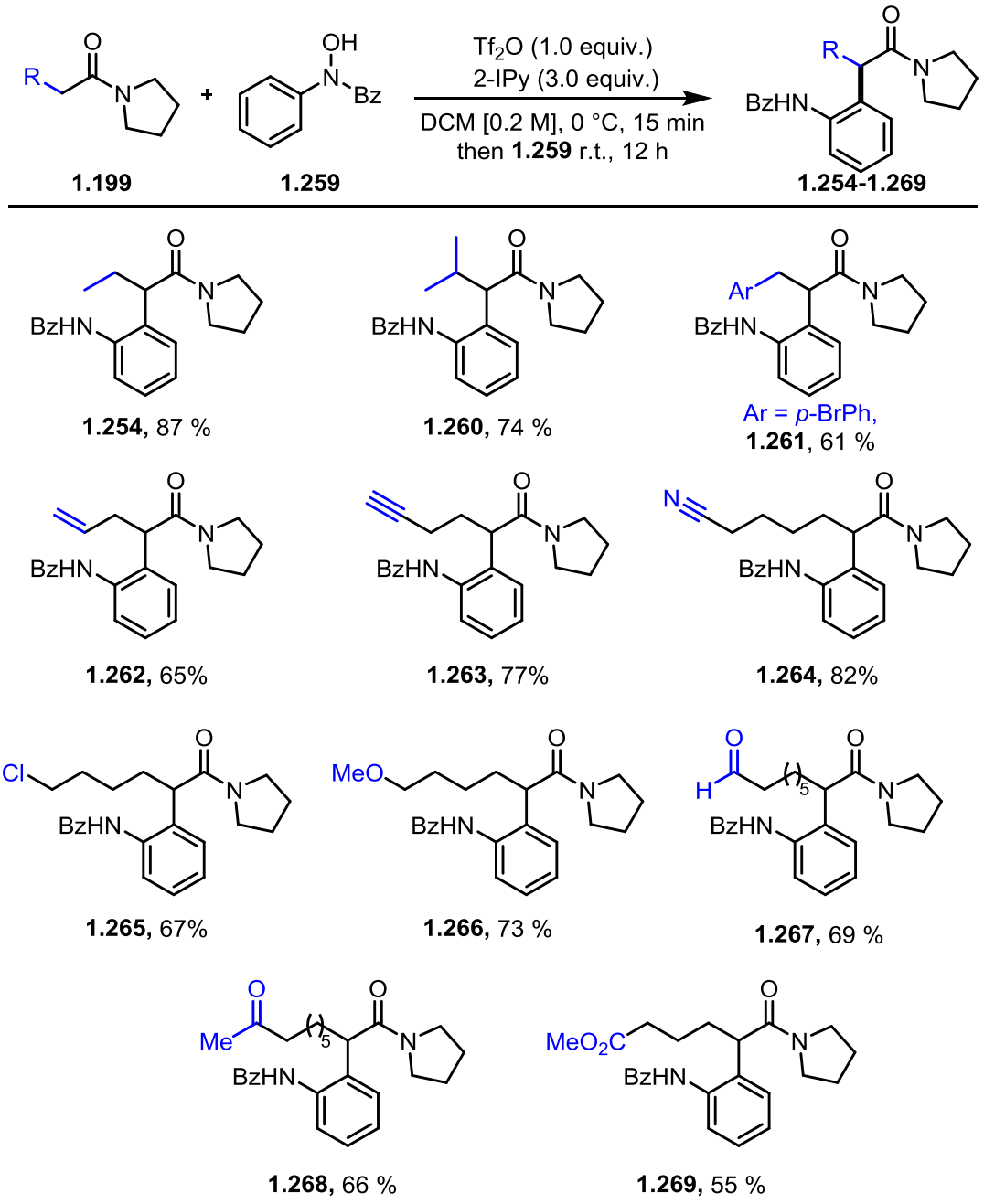
1.253 **1.259** **1.254**

Entry	Base	Py (eq.)	1.259 (eq.)	Yield[a] (%)
1	2-Iodopyridine	3.0	2.0 eq.	87%
2	2-Fluoropyridine	3.0	2.0 eq.	50%
3	Pyridine	3.0	2.0 eq.	0%
4	2-Iodopyridine	2.0	2.0 eq.	60%
5	2-Iodopyridine	3.0	1.2 eq.	50%

Table 1.2. Optimisation of reaction conditions. [a] Isolated yield. [b] Reactions were performed at [0.2 M].

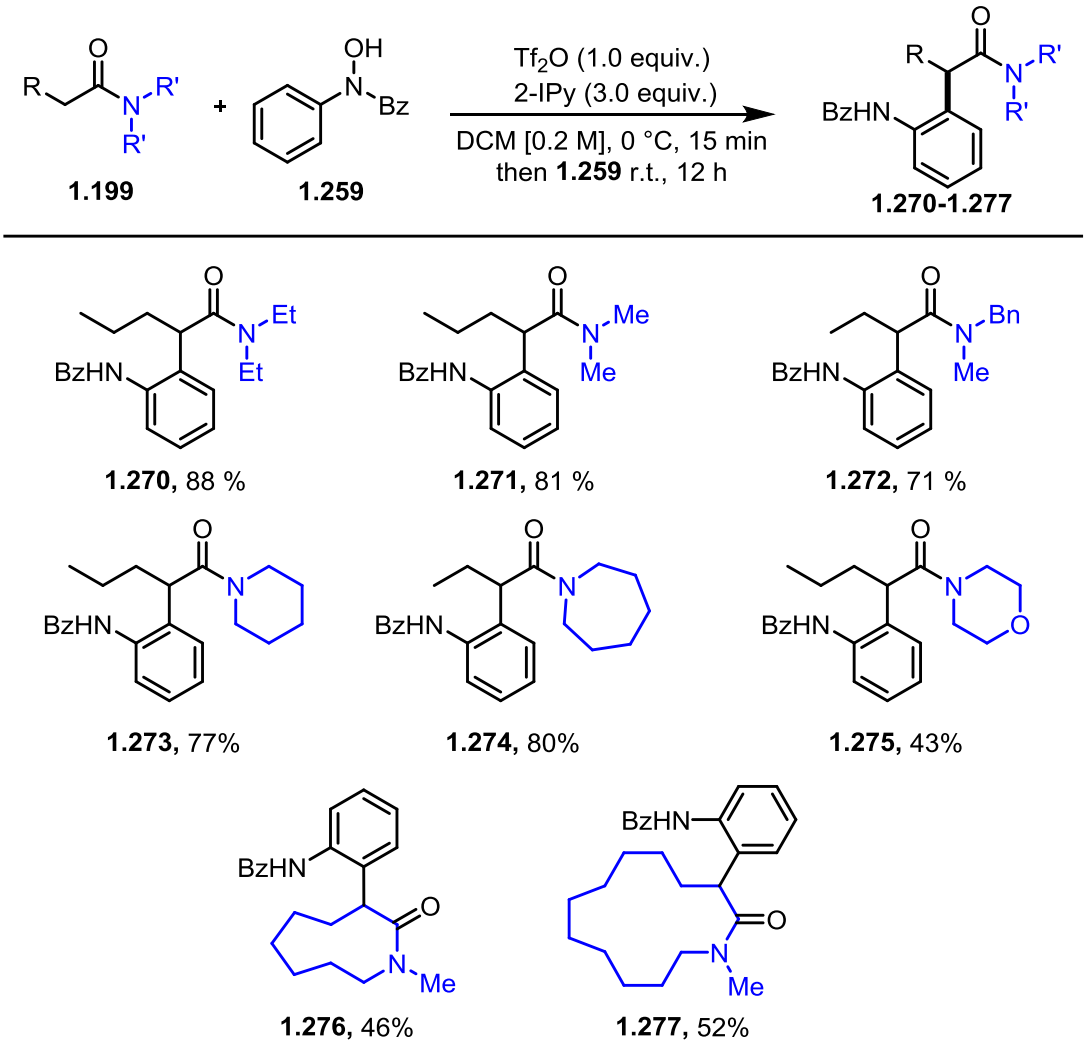
1.2.1.4 Substrate scope

With the optimised reaction conditions in hand, we studied the scope of this transformation.



Scheme 1.70. Scope of amides in the arylation with hydroxamic acid **1.259**.

As seen in scheme 1.70, different functional groups were tolerated this reaction. Alkyl, branched alkyl and aryl chains afforded the desired products in good yields (**1.254, 1.260** and **1.261**). Other functional groups such as alkene (**1.262**), alkyne (**1.263**), ether (**1.266**), nitrile (**1.264**) or alkyl chloride (**1.265**) were also smoothly converted into their arylated variants. Notably, an ester, a ketone and even a terminal aldehyde were tolerated and activation took place selectively on the amide carbonyl furnishing the desired products in chemoselective fashion and good yields (**1.267-1.269**).

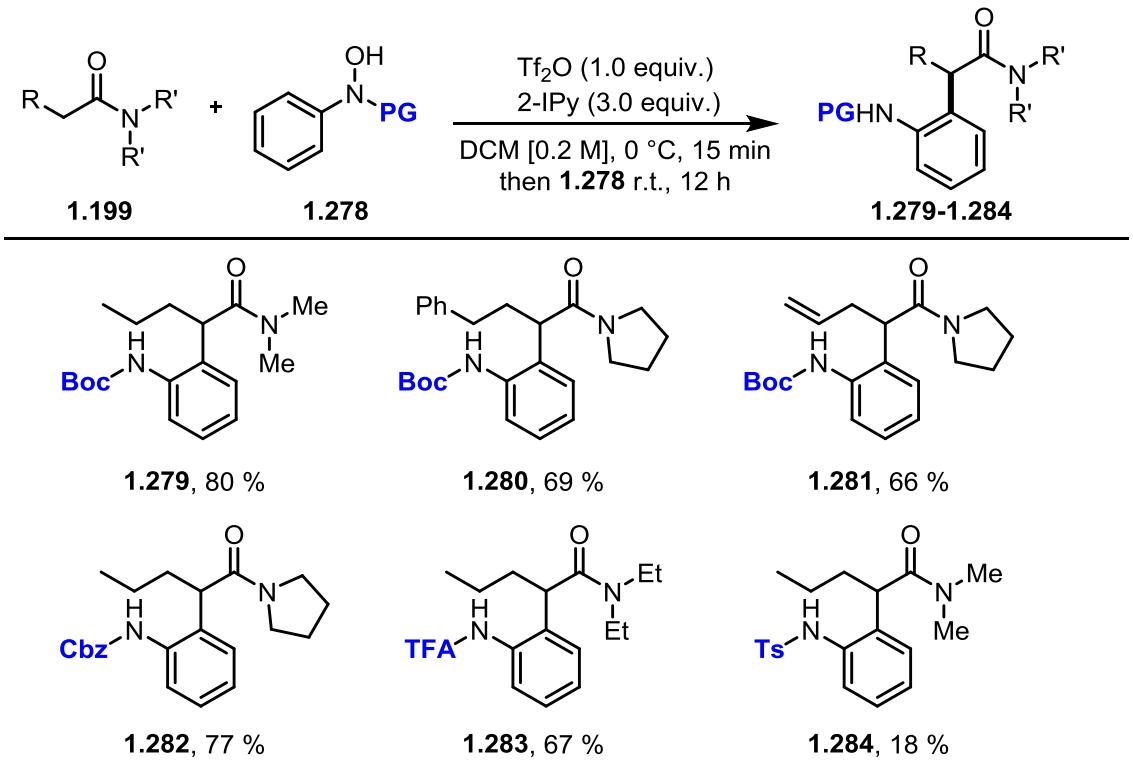


Scheme 1.71. Substrate scope of amine residues.

Then we tested different amide nitrogen residues in this transformation. As seen in scheme 1.71, several *N*-alicyclic (piperidine **1.273** and azepane **1.274**) and *N*-aliphatic amides successfully underwent aminoarylation (**1.270-1.272**). Morpholine **1.275**, a less electron-donating moiety, delivered the desired product in lower yield as might be expected. Interestingly, 8- and 12-membered-ring lactams were smoothly α-arylated in acceptable yields (**1.276** and **1.277** respectively).

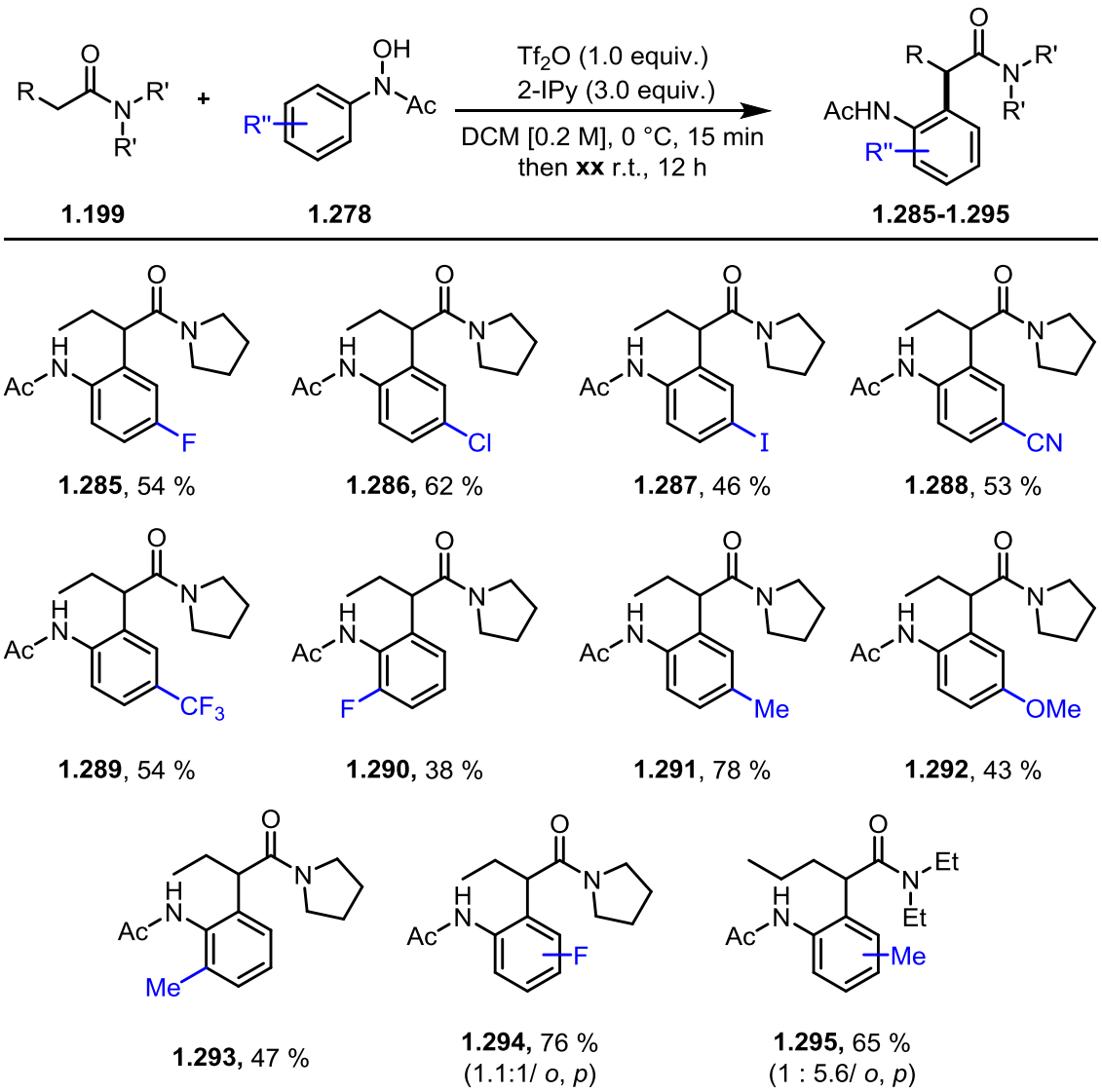
Different protecting groups on the hydroxamic acid partners were also investigated. Remarkably, Boc-protected hydroxamic acid products (with a more convenient functionality for post-reaction deprotection) furnished the expected products in very good yields (**1.279-1.281**). The Cbz- and TFA-protected hydroxamic acids were also tolerated and delivered products (**1.282** and **1.283** respectively) in good yields. Finally, a Ts-protected hydroxamic

acid gave the desired product **1.284** in lower yield due to its poor nucleophilicity (Scheme 1.72).



Scheme 1.72. Substrate scope of other protecting groups on the hydroxamic acids.

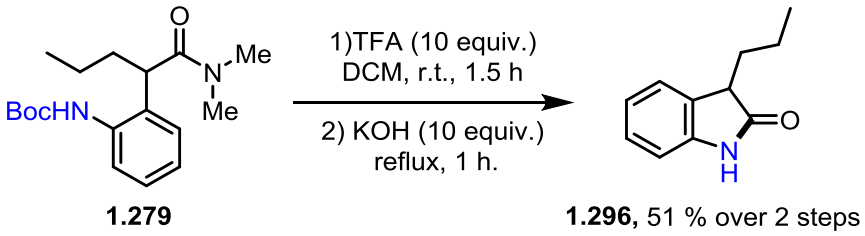
Different aryl moieties were also examined. A variety of substituted-hydroxamic acids **1.278** were converted to the desired aminoarylated variants in moderate to good yields (Scheme 1.73). Notably, electron donating as well as electron withdrawing groups were tolerated and gave the desired products in good yield (**1.285-1.295)**. The presence of an aryl halide moiety gives a possibility for further elaboration of the final products. Interestingly, whilst a *meta*-fluoro derivative led to 1.1:1 mixture of regioisomers, *meta*-methyl-substituted hydroxamic acid favoured the *ortho* product in 5.6:1 ratio (**1.294** and **1.295** respectively). This can be rationalised by the enhanced steric bulk of the methyl group in comparison to a fluorine atom.



Scheme 1.73. Substrate scope of substituted-hydroxamic acids.

1.2.1.5 Derivatisation of the products

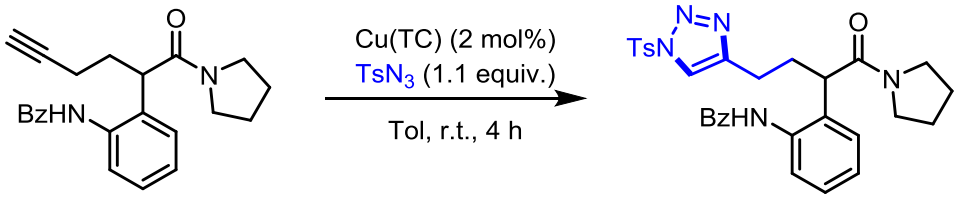
The presence of an aniline moiety in the final products offers multiple synthetic advantages. Upon deprotection of the Boc group of the amide **1.279**, condensation reaction under basic conditions delivered the 3-butyryl-oxindole **1.296** in good yield (Scheme 1.74). This pathway opens up a simple route for synthesising 3-substituted-oxindoles, a family of compounds that has several interesting biological activities.



1.279 **1.296,** 51 % over 2 steps

Scheme 1.74. Synthesis of 3-butyryl-oxindole from aniline **1.279**.

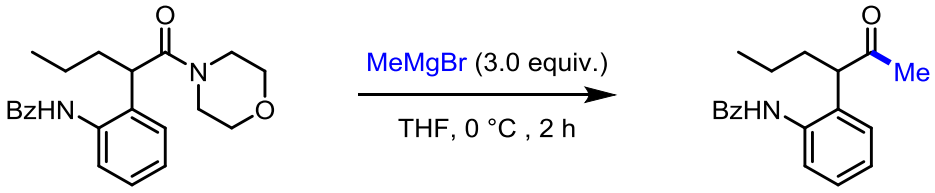
The presence of an alkyne moiety in the product **1.263** suggested the possibility to do a (3+2) cycloaddition reaction. A copper-catalysed click reaction with tosylazide took place smoothly and furnished 1,2,3-triazole **1.297** in high yield (Scheme 1.75).



1.263 **1.297,** 91 %

Scheme 1.75. (3+2) cycloaddition of aniline **1.263** with TsN_3.

Finally, in the case of the morpholine amide **1.275**, the direct conversion into its corresponding ketone was also possible upon treatment with a Grignard reagent. Addition of methylmagnesium bromide to **1.275** furnished α-arylated ketone **1.298** in very good yield (Scheme 1.76). The importance of this chemistry hinges on the usual difficulty in the regioselective preparation of α-aminoarylated-ketones.

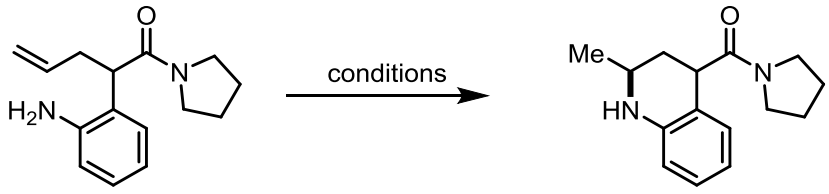


1.275 **1.298,** 73 %

Scheme 1.76. Synthesis of α-aminoarylated-ketone **1.298** via Gringard addition.

1.2.1.6 Unsuccessful attempts on the intermolecular hydroamination of the products

Further attempts to derivatise the product were carried out. Intramolecular hydroamination on product **1.299** looked feasible. However, after Boc-deprotection, no desired product **1.300** was observed when using palladium catalyst under thermal conditions (Table 1.3). Starting material was recovered with some degradation of the aniline reactant **1.299**.

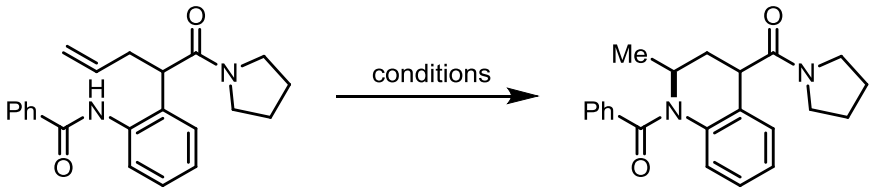


1.299 **1.300**

Entry	Time	Catalyst	Temp(°C)	Base	Yield (%)
1	14 h	$PdCl_2(MeCN)_2$ (5 mol%)	66	Et_3N (1.0 eq.)	0%
2	14 h	$PdCl_2(MeCN)_2$ (5 mol%)	66	___	0%

Table 1.3. Attempts toward hydramiantion with aniline derivative **1.299**.

Then we tried to perform this reaction on the anilidine product **1.262**. As seen in Table 1.4, no desired product **1.301** was observed when using palladium or gold catalyst and starting material was recovered after aqueous work up (entry 1 and 2). Notably, the use of even stoichiometric amount of the catalyst combined with higher temperature and longer reaction time (entry 3) did not give the desired product and only degradation of the starting material took place. We reasoned that the presence of the amide moiety is more favoured in the chelation with the metal catalyst over the alkene moiety.



1.262 **1.301**

Entry	Time	Catalyst	Temp (°C)	Base	Yield (%)
1	14 h	$PdCl_2(MeCN)_2$ (5 mol%)	66	Et_3N (1.0 eq.)	0%
2	14 h	$Au(MeCN)SbF_6$ (5 mol%)	80	___	0%
3	36 h	$Pd(OAc)_2$ (100 mol%)	80	___	0%

Table 1.4. Attempts toward hydroamination with anilidine derivative **1.262**.

1.2.2 Umpolung of amide: an enolate-like intermediate enables intramolecular C-C coupling reaction

This work was carried out in collaboration with Msc. Daniel Kaiser and Dr. Aurélien de la Torre. The results were reported in: *Angew. Chem. Int. Ed.* **2017**, *56*, 5921-5925. [105]

1.2.2.1 Introduction

Umpolung is a German word used internationally in organic chemistry and broadly meaning "polarity inversion". This term was introduced by Corey and Seebach in the late 1960s. [106] The majority of important organic molecules contain heteroatoms that polarise carbon atoms depending on their electronegativity. In polar organic reactions, new bonds are classically formed between atoms of opposite polarity. This can be considered to be the "normal reactivity" (Figure 1.9).

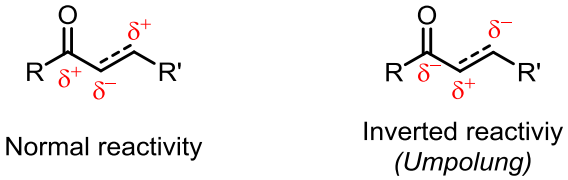
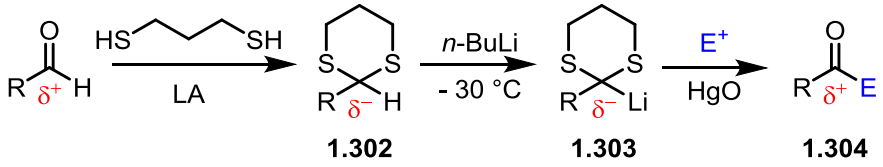


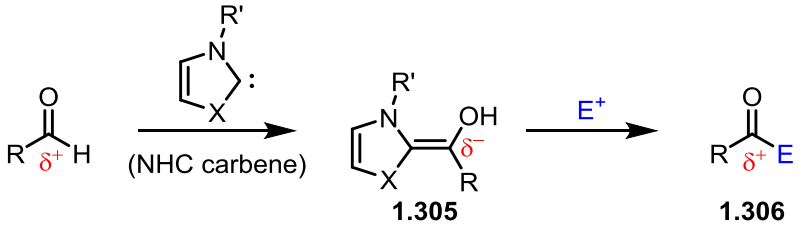
Figure 1.9. Inversion of reactivity on carbonyl groups.

The acyl anion is the most known "umpoled" synthon. The inversion in reactivity makes the usually electrophilic carbonyl carbon behaves as a nucleophile. Acyl anion equivalents can be generated classically using thioacetals, a textbook reaction (Corey-Seebach reaction). [107] Conversion of aldehydes into its thioacetal derivatives **1.302** (1,3-dithianes are most popular) inverts the reactivity of the carbon centre. The acidity difference of the C-H bond in both compounds is caused by the greater polarisability of sulfur and the longer C-S bond. Treatment of thioacetal **1.302** with *n*-BuLi (or other strong bases) at low temperatures delivers lithio-derivatives **1.303**. The latter can then react with different electrophiles (aldehydes, ketones, epoxides, acid derivatives and alkyl halides) followed by irreversible thioacetal deprotection with mercury (II) salts to give adducts **1.304** (Scheme 1.77)



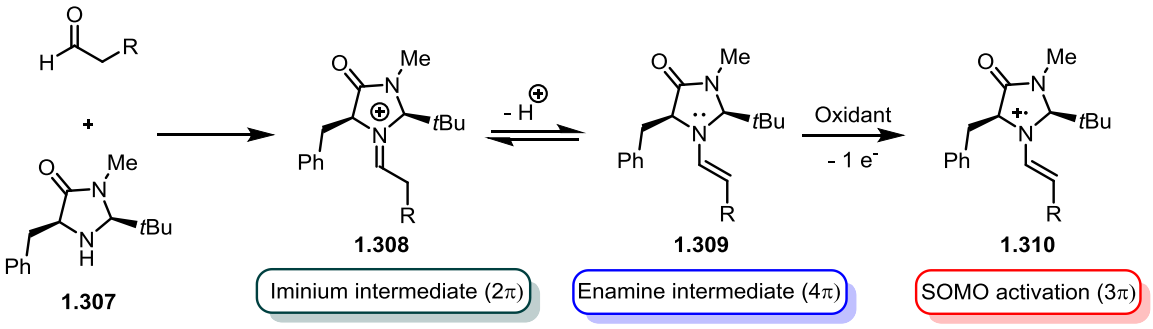
Scheme 1.77. Corey-Seebach Umpolung reaction of aldehydes.

N-heterocyclic carbenes (NHCs) have also been implicated in the chemistry of acyl anion equivalents. [108] Their unusual chemical ambivalence allows them to trigger Umpolung behaviour as they classically react with aldehydes to afford an enamine type intermediates **1.305** (termed "Breslow intermediate"). Thus, the originally electrophilic carbon atom of the aldehyde has acquired nucleophilic character. It can then attack various electrophiles to furnish products **1.306** (Scheme 1.78).



Scheme 1.78. NHC-mediated Umpolung of aldehydes.

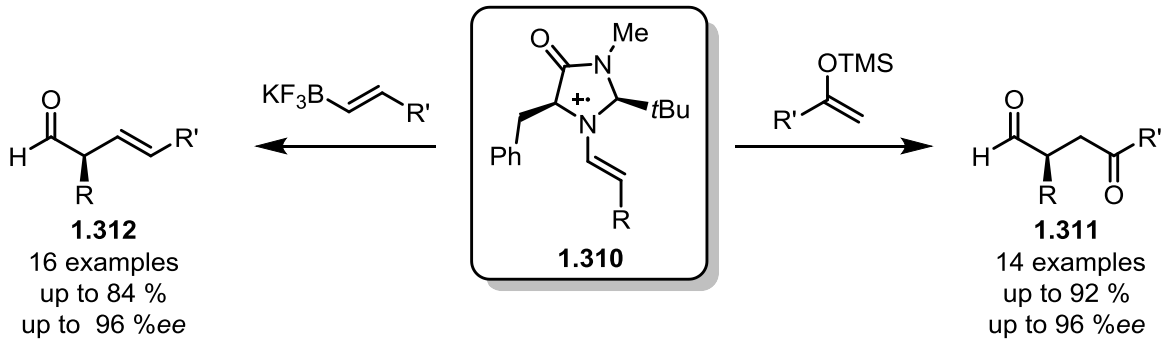
However, polarity reversal at the α-position of a carbonyl (a usual nucleophilic centre by virtue of enolisation) is less common. This problem was only recently addressed by MacMillan and co-workers by merging organocatalysis and SOMO (singly occupied molecular orbital) activation. [109] It is well known that enamines and iminium ions can rapidly interconvert by proton transfer. As seen in scheme 1.79, when mixing chiral amine **1.307** with simple aliphatic aldehyde, the reaction results in the formation of iminium intermediate **1.308** in equilibrium with the enamine **1.309**. Selective oxidation led to the formation of the aminoradical cation **1.310**, a SOMO activated species.



Scheme 1.79. SOMO catalysis *via* single-electron oxidation of enamines.

Thus, inversion of polarity on the α-position of the carbonyl group took place and the SOMO activated intermediate **1.310** can further be trapped with π-rich somophiles. As seen in scheme 1.80, the use of silyl enol ethers led to the formation of γ-ketoaldehydes **1.311** in very good yields and high enantioselectivity (Scheme 1.80 right). [110]

An asymmetric α-vinylation of aldehydes using vinyl trifluoroborate salts was also reported. [111] The reaction resulted in the formation of β,γ-unsaturated aldehydes **1.312** in very good yields and high enantioselectivity (Scheme 1.80 left).

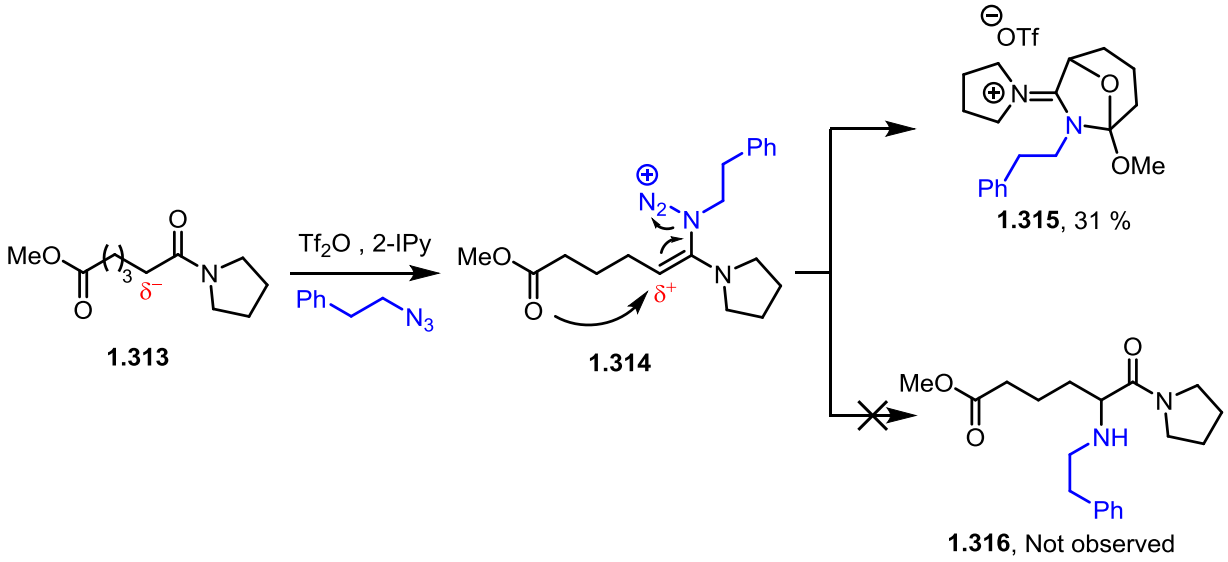


Scheme 1.80. Capture of SOMO activated intermediate **1.310** with π-rich somophiles.

Other approaches applied to invert the polarity at α-position of carbonyls using iodonium salts, [112] oxime derivatives [113] and isoxazolidines [114], were also reported.

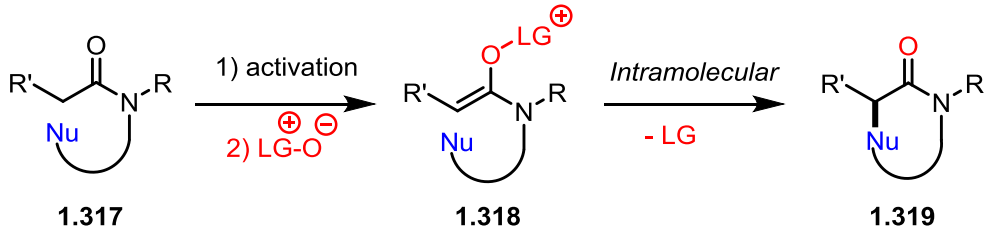
1.2.2.2 Aim of the project

During our previously discussed α-amination reaction of amides, an unexpected result was observed. [62] When using an amide bearing an ester moiety **1.313** within suitable distance of the amide α-position, a tricyclic product **1.315** was observed instead of the expected aminated one **1.316** (Scheme 1.81). This suggested that intermediate **1.314** was trapped by nucleophilic attack of the ester carbonyl. Thus, intermediate **1.314** behaved as a partially electrophilic (and thus "umpoled") enamine.



Scheme 1.81. Unexpected formation of bicyclic product **1.315** when performing the α-amination on amide **1.313**.

Thus, we speculated that an enolate-like intermediate **1.318** could arise from reaction between an activated amide **1.317** and a suitable *O*-nucleophile bearing a leaving group. Intermediate **1.318** can then by interrupted intramolecularly in a C-C bond formation process to yield lactams **1.319** (Scheme 1.82).

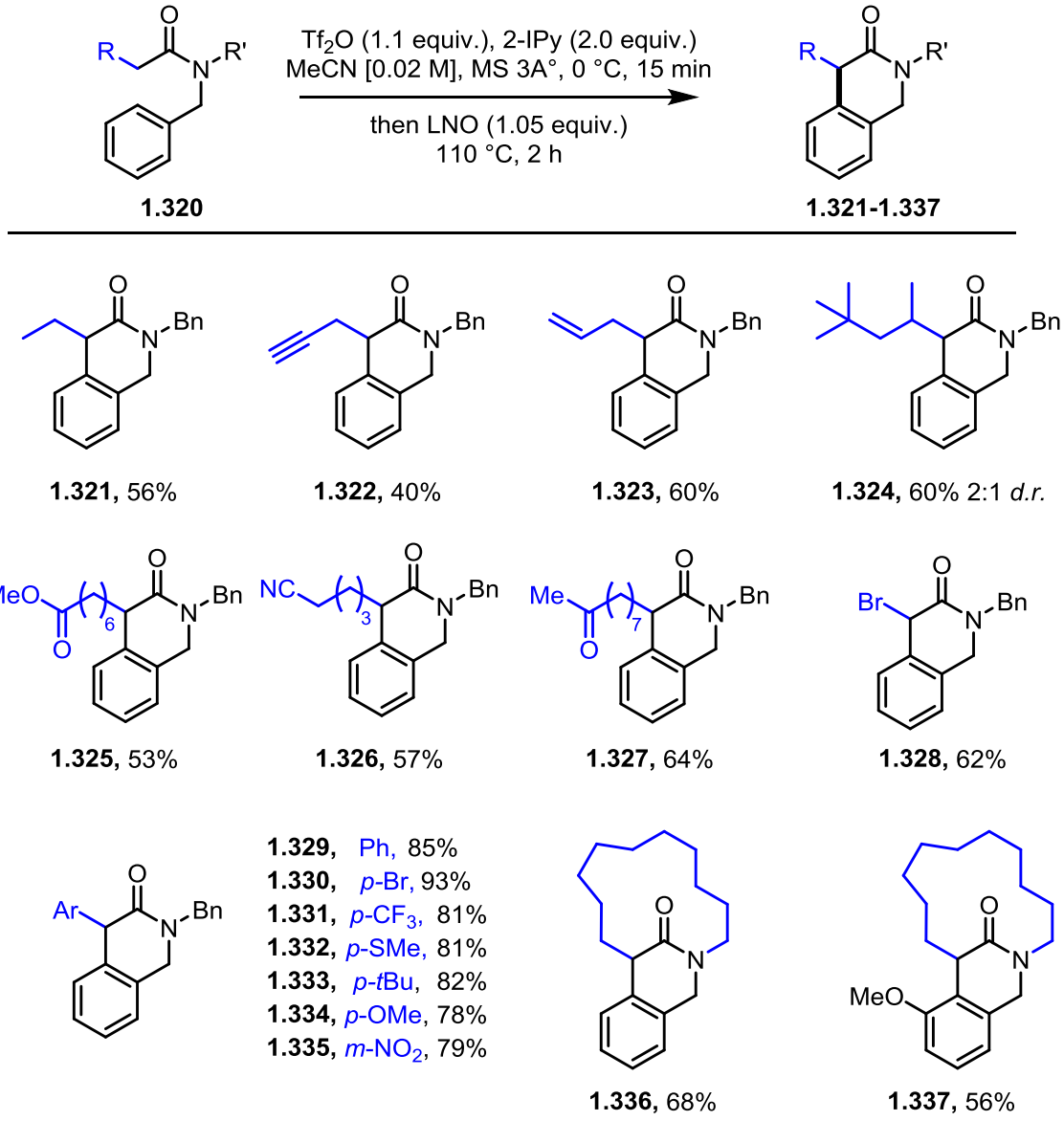


Scheme 1.82. Our proposed approach for the Umpolung of the α-position of amides.

1.2.2.3 Substrate scope

We chose a dibenzylamide as a substrate model expecting a nucleophilic capture from the aryl group to take place and to afford dihydroisoquinolinone adduct **1.321** (optimisation not shown here). After optimisation, we found out that 2,6-lutidine *N*-oxide (LNO) and 2-iodopyridine afforded the best result for this transformation. Thermal conditions were applied after the addition of LNO for 2 hours. The use of molecular sieves was necessary to avoid hydrolysis of the keteniminium intermediate. With these suitable conditions, we further explored the scope of this transformation. As seen in scheme 1.83, varied alkyl, alkenyl, alkynyl and β-branched alkyl gave the desired products in good yields (**1.321**-**1.324**). Other carbonyl functions (ester and ketone) and cyano were smoothly converted to their

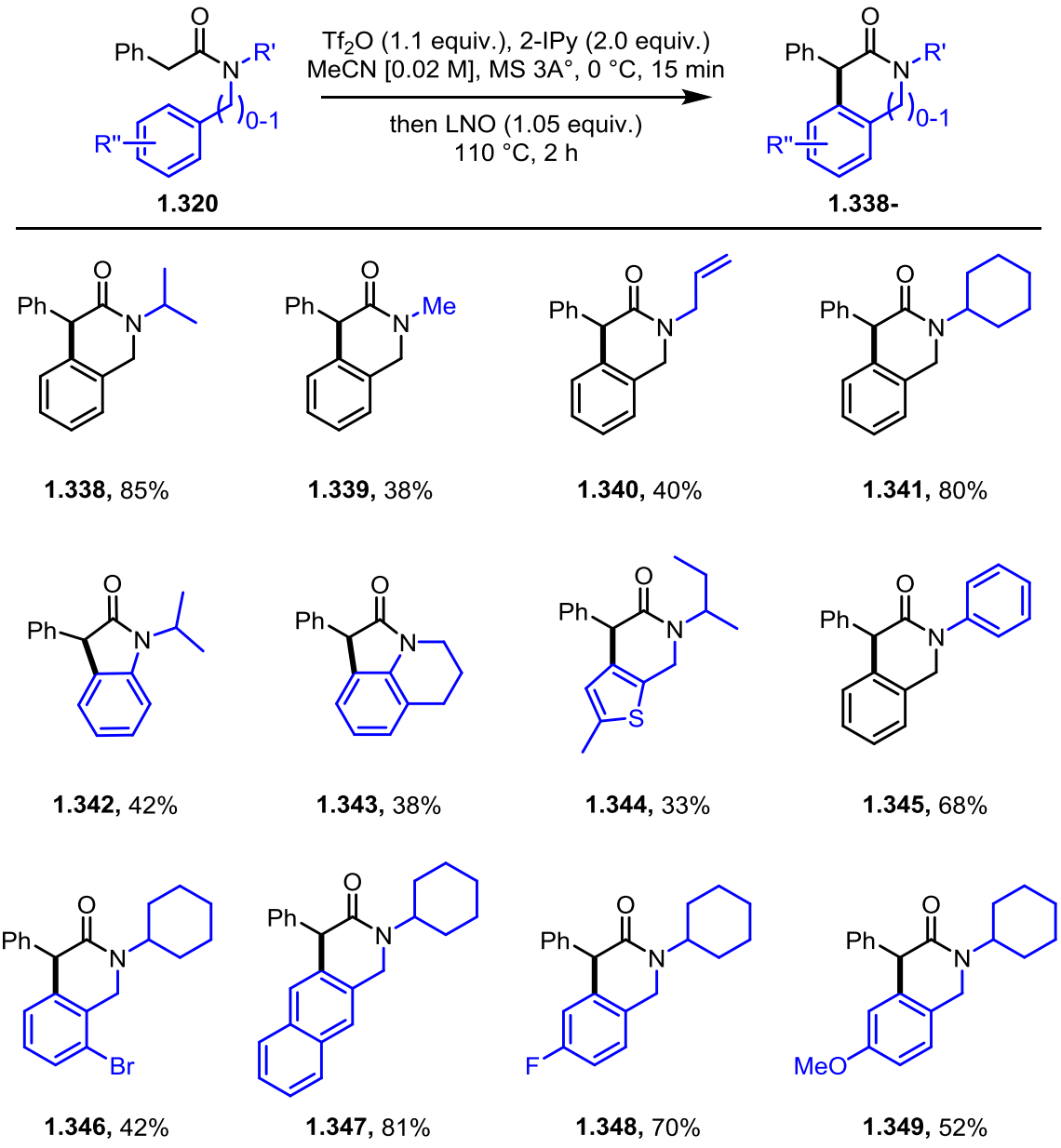
dihydroisoquinolinone derivatives (**1.325-1.327**) in a chemoselective fashion. In general, α-arylamides were the most efficient substrates and the expected products **1.329-1.335** were obtained in very good yields. We believe that this is due to the stability overlap of the π-system of the aromatic with the LUMO of the enolate-like intermediate. The observation with α-bromoamide **1.328** confirmed this hypothesis. Interestingly, benzylmacrolactams were also tolerated and gave the dihydroisoquinolinone derivatives in good yields (**1.336** and **1.337**).



Scheme 1.83. Substrate scope of various benzylamides for the Umpolung arylation.

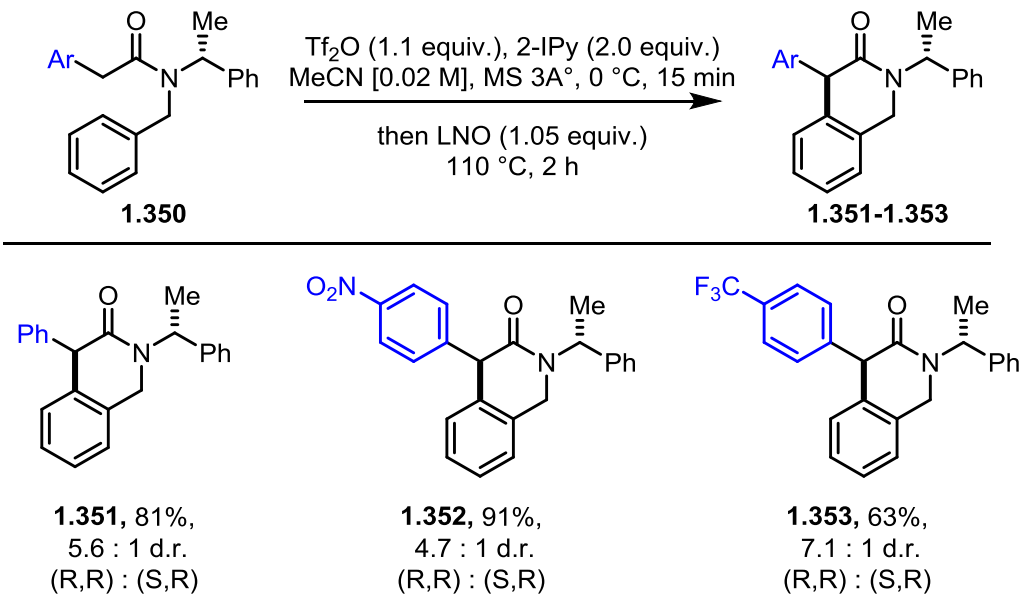
We then turned our attention to the use of unsymmetrical tertiary amides (Scheme 1.84). In the event, increasing steric bulk around the nitrogen atom facilitated the desired cyclisation by likely promoting the necessary orientation of the corresponding nucleophilic moiety *via* Thorpe-Ingold effect (**1.338-1.341**). Importantly, it was possible to convert *N*-phenyl amides

into their oxindole derivatives in good yields (**1.342** and **1.343)** via *5-endo-trig* cyclisation. However, *N*-phenyl-*N*-benzyl amide was converted into the dihydroisoquinolinone **1.345** exclusively, and the oxindole partner was not observed. *N*-heteroaryl and *N*-benzyl groups with varied substituents differing both in position and electronic properties afforded the expected products in good yields **1.346**-**1.349**.



Scheme 1.84. Substrate scope of unsymmetrical amides.

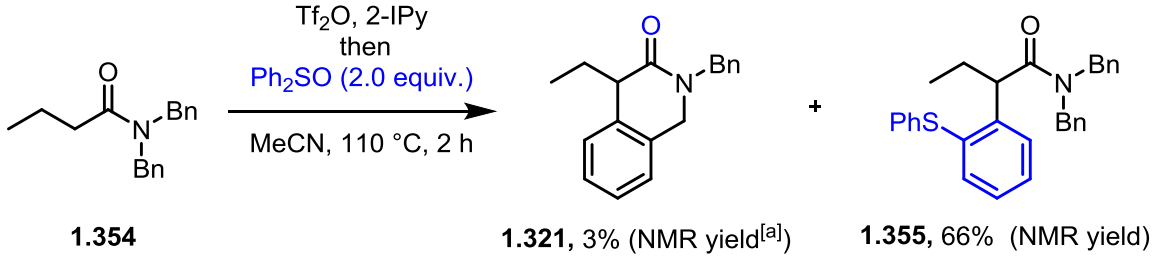
Finally, we explored the possibility of performing this transformation in a diastereoselective fashion. Upon using chiral amides, a diastereoselective cyclisation took place furnishing products **1.351**-**1.353** in good yields and moderate to good diastereoselectivities (Scheme 1.85).



Scheme 1.85. Diastereoselective C-C coupling.

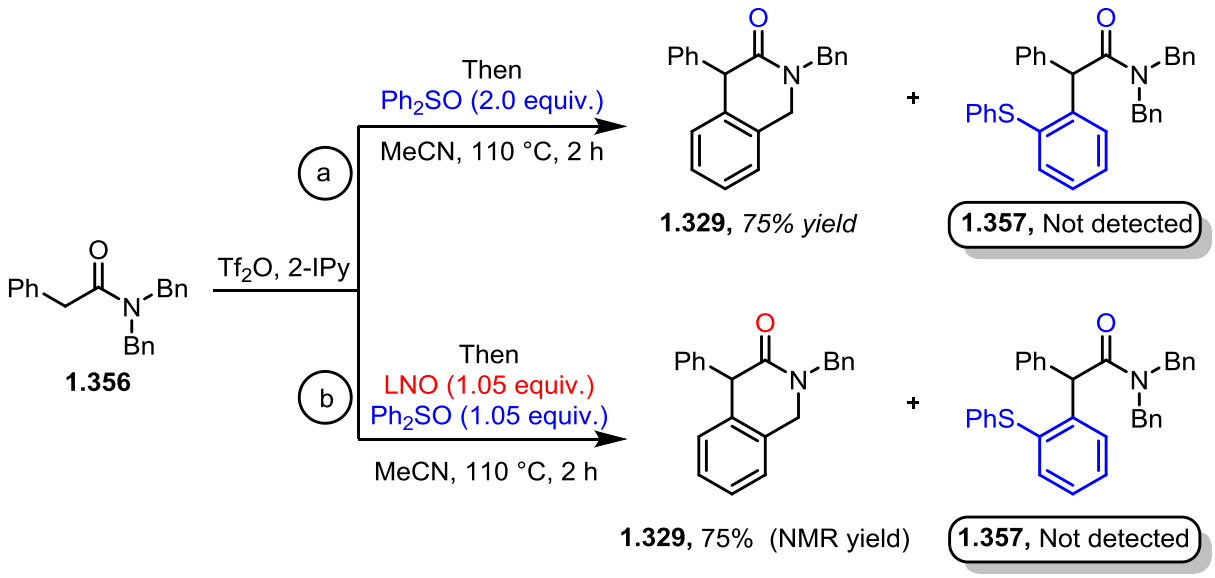
1.2.2.4 Mechanistic considerations

We were then interested in investigating if diphenylsulfoxide (Ph_2SO) could promote this reaction. Utilising Ph_2SO under our optimised conditions on aliphatic amide **1.354** instead of LNO nearly shut down the umpolung reactivity. Instead, the arylation product **1.355** was observed as the major product (the reaction that was mentioned before). [92] Only traces of the umpolung product **1.321** were detected (Scheme 1.86).



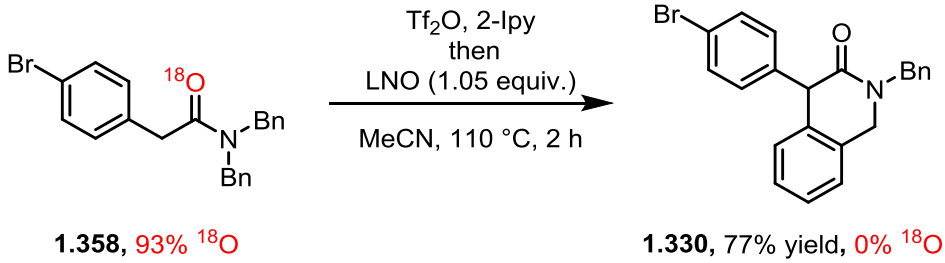
Scheme 1.86. Attempts toward promoting the reaction with Ph_2SO. [a] CH_3I was used as internal standard.

However, in the case of α-phenyl amide **1.356**, diphenylsulfoxide was able to promote the umpolung reactivity and no arylation product **1.357** was detected (Scheme 1.87 a). When using a (1:1) mixture of LNO and Ph_2SO, the umpolung product was the solely observed product. No traces of **1.357** were detected (Scheme 1.87 b). More importantly, no diphenylsulfide was observed which implies that LNO was more reactive in promoting this transformation.



Scheme 1.87. Comparison between LNO and Ph_2SO in promoting this reaction on amide **1.356**.

Finally, an ^{18}O labelled amide **1.358** (with 93% ^{18}O) was set to the reaction conditions. This led to the formation of a product **1.330** with complete loss of the ^{18}O label in support of our hypothesised mechanism (Scheme 1.88).



Scheme 1.88. ^{18}O-labeling experiment.

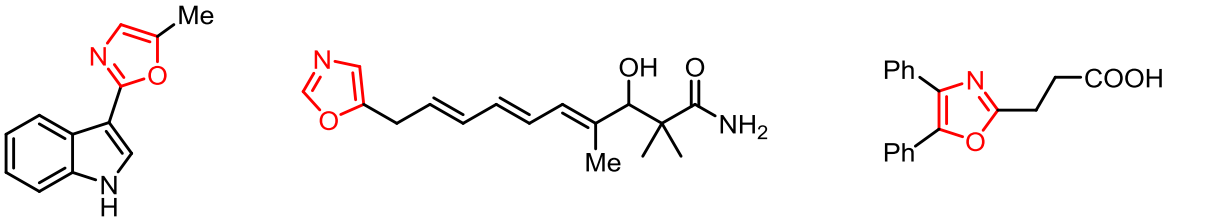
1.2.3 Metal-free oxazoles synthesis *via* activation of amides

This work was carried out in collaboration with Msc. Giovani De Mauro, Dr. Boris Maryasin and Msc. Daniel Kaiser. The results were reported in; *Org. Lett.* **2017**, *19*, 3815-3818. [115]

My contribution to this project was on the oxazole synthesis.

1.2.3.1 Introduction

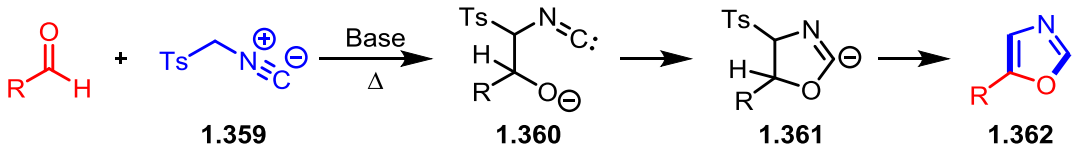
Oxazoles are a very important class of aromatic heterocycles. Several natural products as well as useful industrial compounds contain oxazole core (Figure 1.10). [116]



Pimprinine *(Natural product)* | Inthomycin C *(Natural Product)* | Oxaprozin *(Nonsteroidal anti-inflammatory)*

Figure 1.10. Selected examples of oxazole derivatives.

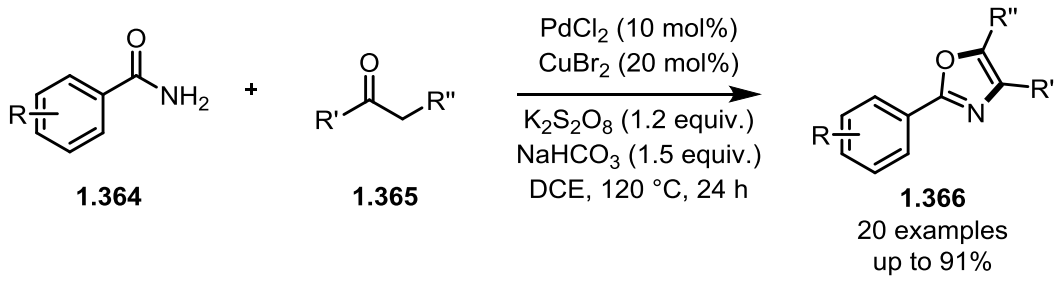
Oxazoles are usually prepared *via* condensation of aldehydes with tosylmethyl isocyanide **1.359**, a reaction developed by Van Leusen in the early 1970s. [117] Addition of the deprotonated tosylmethyl isocyanide **1.359** to the aldehyde delivers intermediate **1.360**. A ring closure takes place and results in a formation of an oxazoline intermediate **1.361**. Elimination then furnishes the oxazole products **1.362** (Scheme 1.89).



1.359 **1.360** **1.361** **1.362**

Scheme 1.89. Van Leusen oxazole synthesis.

A palladium-catalysed approach for the synthesis of oxazoles from aryl amides **1.363** and ketones **1.364** was developed by Jiang and co-workers in 2014. [118] The reaction proceeded through a condensation to form an imine followed by a C-O bond formation closing the ring under thermal conditions and delivering a variety of 2-aryl oxazoles **1.365** in very good yields (Scheme 1.90).

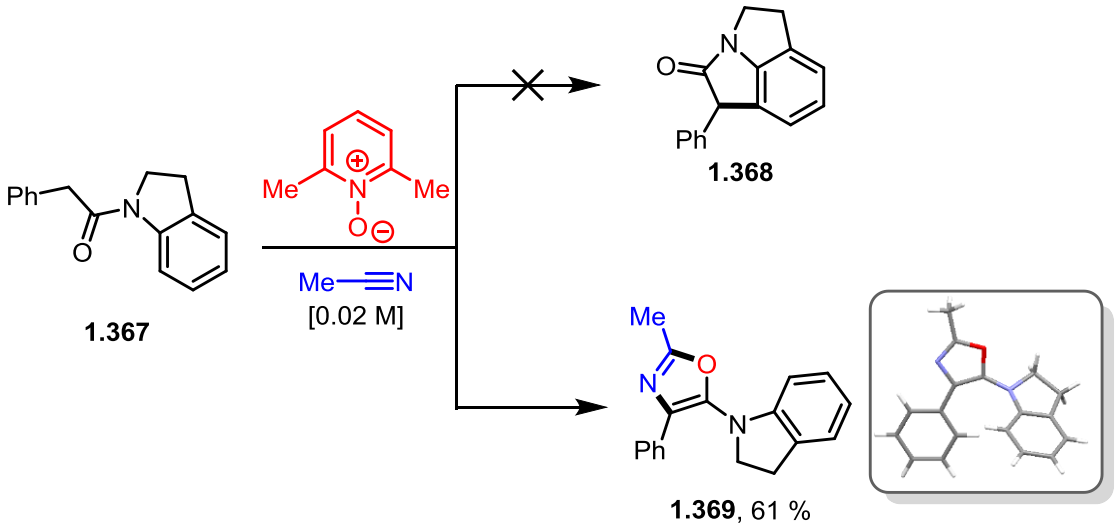


Scheme 1.90. Pd-catalysed synthesis of oxazoles from aryl amides and ketones.

Several other approaches and synthetic methods including condensation of carbonyl derivatives, cycloisomerisations and [3+2] cycloaddition reactions, were reported over the last years. [119]

1.2.3.2 Aim of the project

In the course of studies on our umpolung transformations, an unexpected by-product was observed upon carrying out the reaction on indoline amide moiety **1.367**. The reaction did not give the expected tricyclic product **1.368**, but led to the formation of the oxazole **1.369** in 61% isolated yield, a structure that was further confirmed by X-ray analysis (Scheme 1.91).



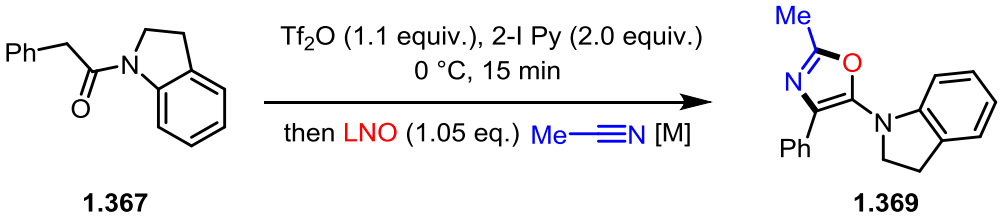
Scheme 1.91. Unexpected observation *via* reaction of **1.367** with LNO in MeCN.

Noticing the incorporation of acetonitrile in the product, we became interested in exploring what effectively amount to a metal-free synthesis of 5-amino-oxazoles using readily available nitriles and amides.

1.2.3.3 Optimisation of reaction conditions

Although the unexpected observation gave the desired oxazole in acceptable yield, further optimisation to reduce the nitrile loading (i.e. increase concentration or avoid the use of nitrile

as solvent altogether) and to lower the temperature were carried out. As seen in table 1.5, performing the reaction at ambient temperature led to lower yield (entry 2). Attempts using dichloromethane as solvent followed by addition of acetonitrile at different temperatures and reaction time led to significantly lower yields (entries 3, 4 and 5). Finally, increasing the concentration in combination with lower temperature and reaction time delivered the desired adduct in roughly similar yields (entry 6).



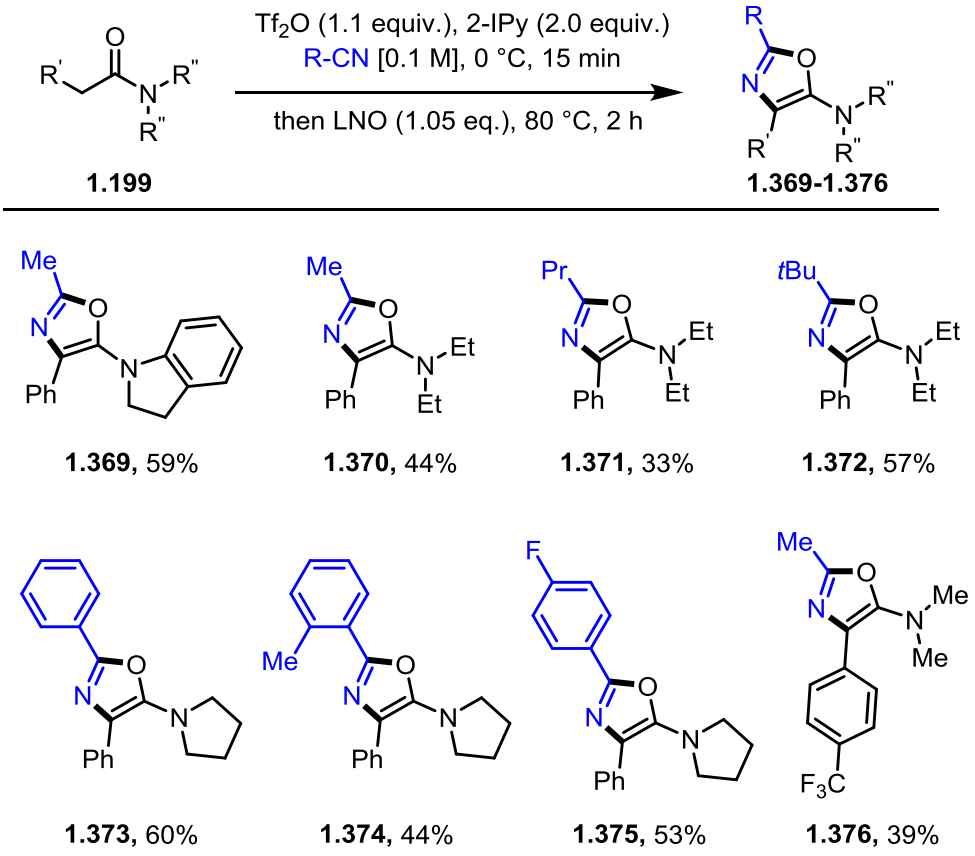
1.367 **1.369**

Entry	Solvent	Time (h)	Temp (°C)	Conc. [M]	Nitrile (eq.)	Yield[a] (%)
1	MeCN	2 h	110 °C	0.02 M	solvent	61%[b]
2	MeCN	12 h	r.t.	0.02 M	solvent	27%
3	DCM	12 h	r.t.	0.02 M	20 eq.	14%
4	DCM	2 h	40 °C	0.1 M	20 eq.	14%
5	DCM	2 h	40 °C	0.1 M	40 eq.	26%
6	MeCN	2 h	80 °C	0.1 M	solvent	59%[b]

Table 1.5. Optimisation of reaction conditions. [a] NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] isolated yield.

1.2.3.4 Scope of substrates

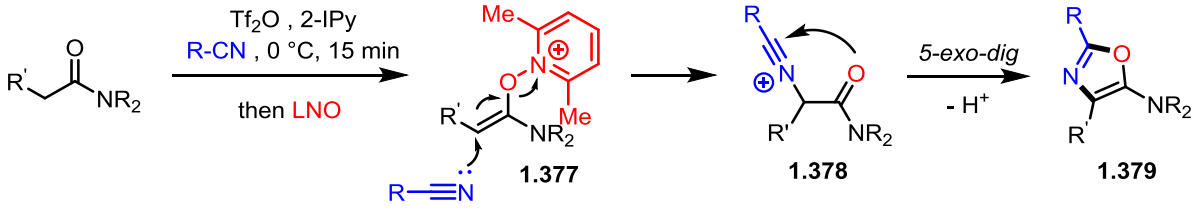
With suitable reaction conditions in hand, the scope of this transformation was further explored. Varied amides were tolerated and the use of diverse commercially available nitriles (aliphatic and aromatic) afforded the desired compounds **1.369-1.376** in good to moderate yields (Scheme 1.92). As expected, the possible substituents on the amide backbone were limited to aromatics. This can be once again explained by the LUMO stabilisation of the lutidinium intermediate by the aryl moiety.



Scheme 1.92. Scope of 5-amino-oxazoles *via* reaction of nitriles with amides.

1.2.3.5 Plausible mechanism

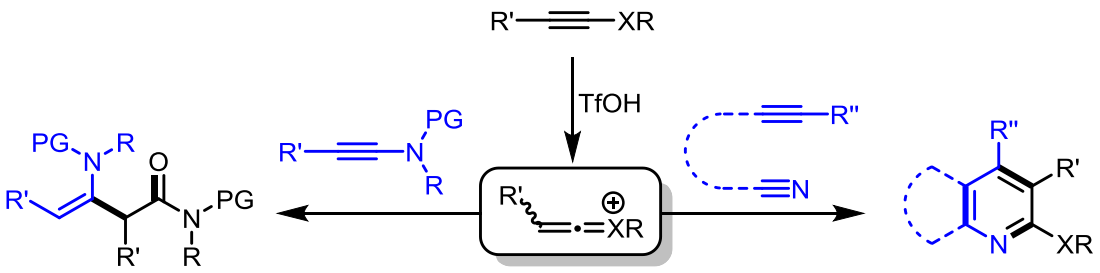
The reaction proceeds *via* an addition of 2,6-lutidine *N*-oxide (LNO) to the keteniminium ion forming an α-electrophilic intermediate **1.377**. An intermolecular addition of the nitrile forms nitrilium intermediate **1.378**. Subsequent *5-endo-dig* cyclisation of the amide onto the formed nitrilium ion will furnish oxazole rings **1.379** (Scheme 1.93).



Scheme 1.93. Proposed reaction mechanism for the oxazoles formation.

1.3 Conclusion

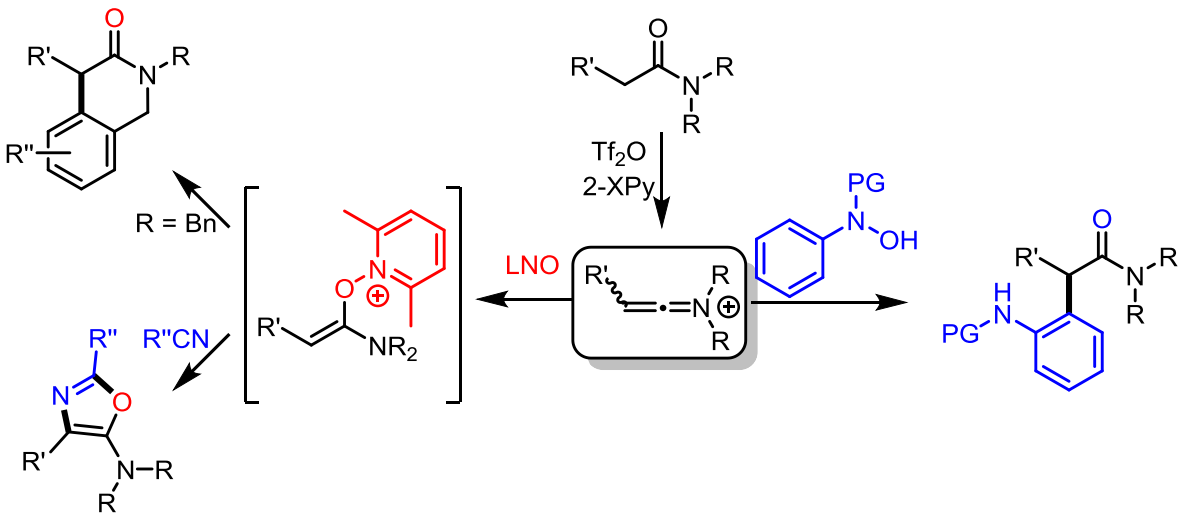
In conclusion we have demonstrated the utility of the keteniminium intermediates in a variety of synthetically and conceptually useful transformations. These reactive intermediates can be generated *in situ* from amides or ynamides. Activation of ynamides (or thioalkynes) with triflic anhydride followed by treatment of the generated keteniminium (or ketenthionium) intermediate with cyanoalkyne derivatives led to the formation of penta-substituted pyridine rings. This reaction represents a metal-free highly regioselective [2+2+2] cycloaddition reaction. The reaction tolerated a variety of functional group (Scheme 1.94 right). In particular, the formation of 4-halo pyridines was demonstrated which opens up the possibility for further elaboration. The hydrative dimerisation of ynamides in the presence of dppa was also achieved (Scheme 1.94 left). Activating the ynamides with triflic acid in the presence of (dppa) led to the formation of the dimerisation product. This reaction is conceptually very interesting from as it represents a controlled dimerisation process under simple acidic conditions. The reaction proceeded well with ynamides bearing varied alkyl-, aryl- and cycloaliphatic residues.



Scheme 1.94. *In situ* generation of keteniminium intermediates for the synthesis of fully-substituted pyridines and the hydrative dimerisation of ynamides.

The keteniminium intermediates could also be generated from simple amides via activation with triflic anhydride and pyridine derivatives. This intermediate was trapped by hydroxamic acids which led to the formation of α-arylated amide with aniline residue (Scheme 1.95). The reaction proceeded *via* [3,3] sigmatropic rearrangements and tolerated a variety of functional group. In particular, the presence of other carbonyl groups (aldehyde, ketone and ester) did not affect the reaction and the arylation took place smoothly in chemoselective fashion.

When trapping the keteniminium intermediate with lutidine-*N*-oxide, an enolate-like intermediate was formed. This Intermediate can then be interrupted intramolecularly in a C-C bond formation process delivering lactams (Scheme 1.95 right). A nucleophilic capture from nitrile solvents can also take place and furnish oxazole derivatives.



Scheme 1.95. *In situ* generation of keteniminium intermediates in the rearrangement with hydroxamic acid and the generation of enolate-like intermediate for new C-C bond formation.

Chapter II. Redox reactions: Metal-Free Redox Transformations for C-C and C-N Bond Construction

2.1 Introduction

The term redox reaction (reduction-oxidation reaction) is an abbreviation for a reaction that involves changes in oxidation states of the reactants, in other words, a reaction that involves transfer of electrons between two chemical species. Thus, reduction-oxidation reactions are a combination of two processes: oxidation, in which electrons are lost, and reduction, in which electrons are gained. These two processes occur simultaneously. [120]

Redox reactions have recently become conceptually appealing transformations in organic synthesis. The importance of these processes in organic chemistry stems from their atom economy. In the recent literatures, various initiators/catalysts have been utilised, such as transition-metal catalysts, Lewis and Brønsted acids and more recently visible-light photocatalysts. [121] We will focus our attention on the latter.

2.1.1 Visible-light photochemistry

2.1.1.1 Introduction

Visible light-induced transformations have long intrigued chemists, since they take advantage the most abundant energy source in the planet, namely sunlight. [122] The majority of organic molecules tend to absorb photons only in the ultraviolet (UV) region, which has limited the development of large-scale industrial photochemical synthesis. Importantly, UV photons are quite high in energy, and can cause considerable unproductive decomposition reactions. Therefore, the use of catalysts or initiators that can absorb visible light and transfer their energy after absorption into other organic molecules, enabling them to get involved in further transformations, is what is nowadays termed as 'photoredox catalysis'. [123]

As seen in figure 2.1, the general photocatalytic cycle starts with the photocatalyst (**PC**) absorbing a photon in the visible range and being promoted to an excited state (**PC***). This state is both a stronger oxidant and a stronger reductant than its corresponding ground state (**PC**). Depending on the nature of the reactants, (**PC***) can react in two different pathways. The first of these involves the delivery of an electron to species **B** in a single-electron transfer (SET) process furnishing the reduced species $\mathbf{B}^{\bullet -}$ and oxidised photocatalyst $\mathbf{PC}^{\bullet +}$, followed by reduction of $\mathbf{PC}^{\bullet +}$ to **PC**, through interaction with compound **A**, termed a reductive scavenger. This pathway is known as a reductive pathway, whereas an oxidative pathway

involves initial oxidation of a suitable reaction partner **C** into $\mathbf{C}^{\cdot+}$ generating the reduced species of the photocatalyst $\mathbf{PC}^{\cdot-}$. A second SET completes the catalytic cycle.

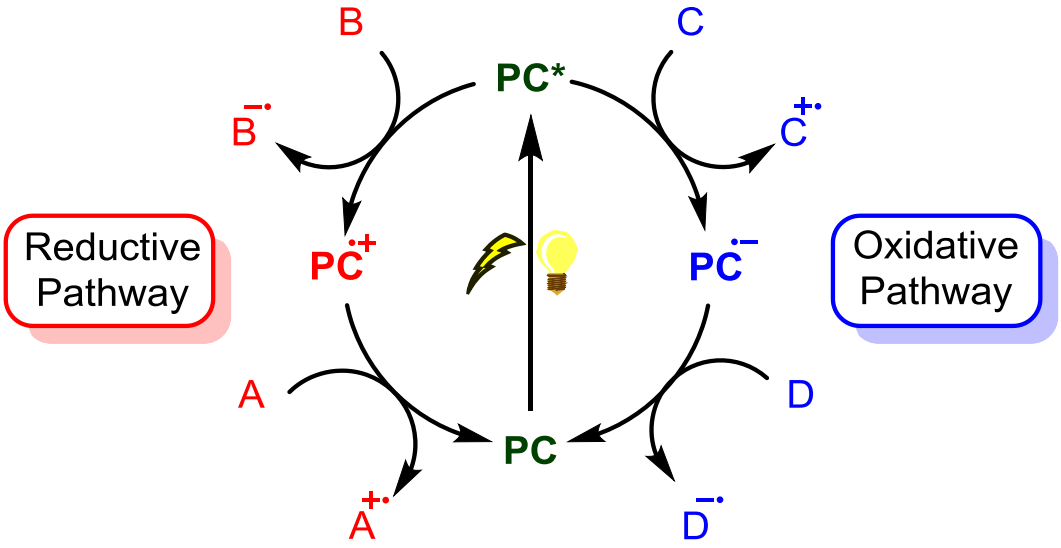
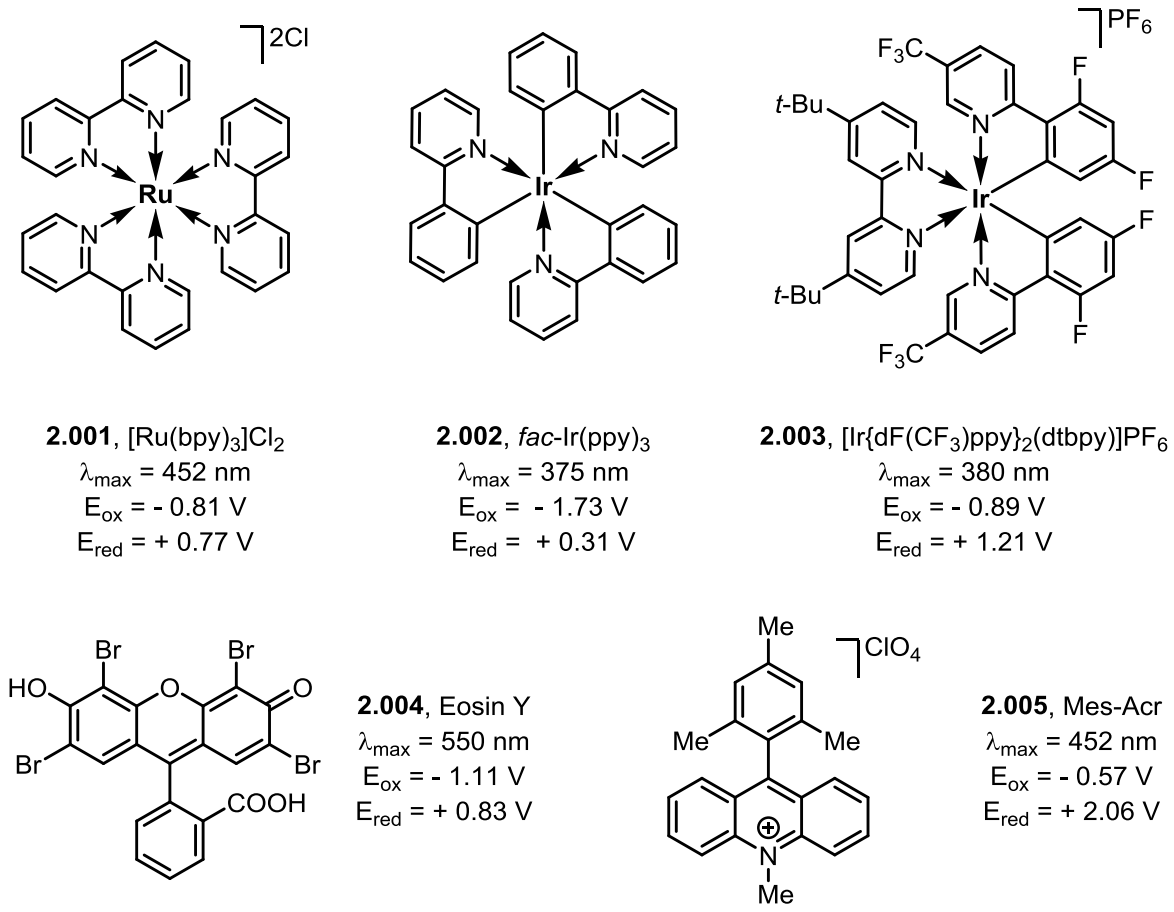


Figure 2.1. General photoredox catalytic cycle.

Recently, several transition metal complexes (primarily ruthenium and iridium complexes) as well as organic dyes (e.g. Eosin Y **2.004** and mesityl Acridinium salts **2.005**) have proven to be efficient in mediating such visible-light-promoted transformations (Scheme 2.1). [124]



2.001, $[Ru(bpy)_3]Cl_2$
λ_{max} = 452 nm
E_{ox} = - 0.81 V
E_{red} = + 0.77 V

2.002, *fac*-$Ir(ppy)_3$
λ_{max} = 375 nm
E_{ox} = - 1.73 V
E_{red} = + 0.31 V

2.003, $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$
λ_{max} = 380 nm
E_{ox} = - 0.89 V
E_{red} = + 1.21 V

2.004, Eosin Y
λ_{max} = 550 nm
E_{ox} = - 1.11 V
E_{red} = + 0.83 V

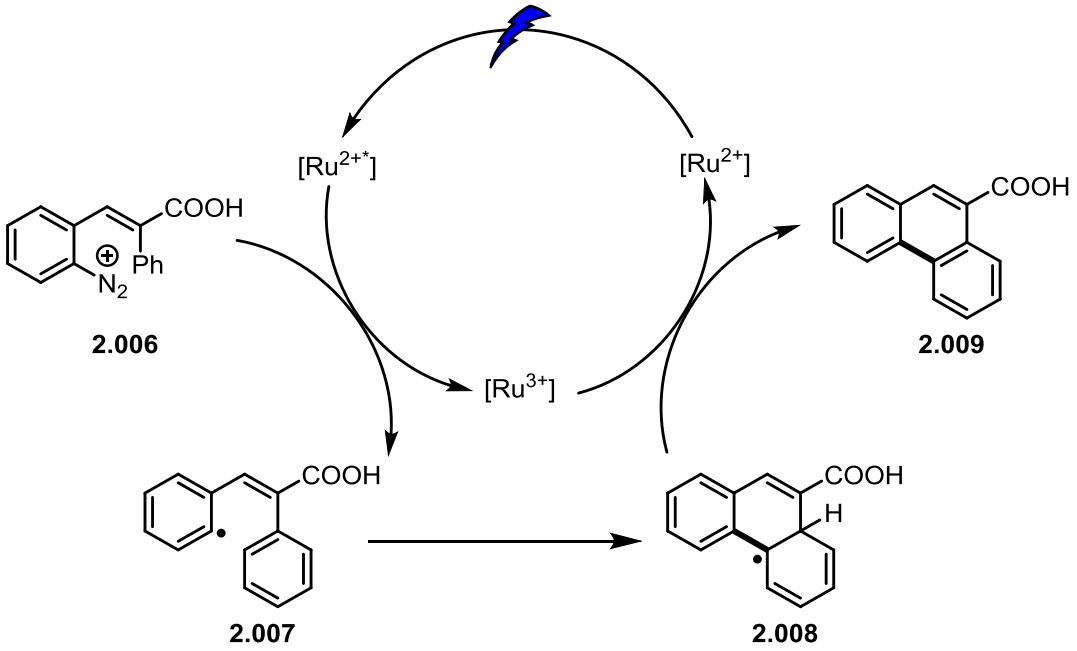
2.005, Mes-Acr
λ_{max} = 452 nm
E_{ox} = - 0.57 V
E_{red} = + 2.06 V

Scheme 2.1. Chemical structures of some common photoredox catalysts.

2.1.1.2 Photocatalysts as sole catalysts

Reductive pathways

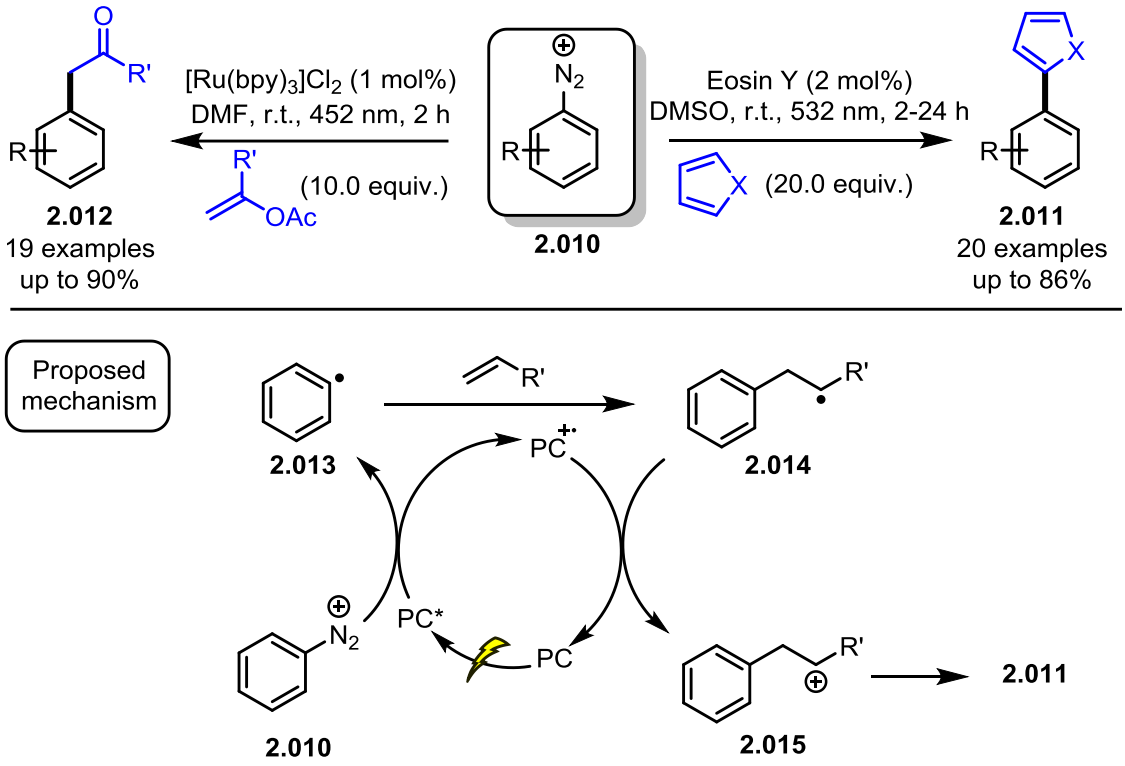
Although the idea of using visible-light to promote organic transformations has been long discussed, the first successful example was reported in 1984 by Deronzier and co-workers. [125] They reported the use of $[Ru(bpy)_3]Cl_2$ in combination with visible light to achieve a photocatalytic Pschorr cyclisation. The Pschorr reaction involves an intramolecular arylation upon reduction of a diazonium salt, classically by a transition-metal salt. [126] Upon treatment of stilbene diazonium salt **2.006** with the photocatalyst under visible light irradiation, phenanthrene carboxylic acid **2.009** was generated in a quantitative yield (Scheme 2.2). Excitation of $[Ru^{2+}]$ by visible light generates $[Ru^{2+*}]$ which transfers an electron to **2.006,** generating aryl radical **2.007** through loss of N_2. Intramolecular radical arylation furnishes radical **2.008**. Oxidation by $[Ru^{3+}]$ and subsequent deprotonation delivers phenanthrene **2.009** and regenerates the photocatalyst $[Ru^{2+}]$ (Scheme 2.2).



Scheme 2.2. Proposed mechanism for the photocatalytic Pschorr cyclisation.

König and co-workers have also developed several photo-catalysed transformations of diazonium salts. [127] The ability of various photocatalysts, upon excitation with the appropriate light source, to reduce diazonium salts into their aryl radical variants was the key step in these transformations. A direct intermolecular C-H arylation of heteroarenes with aryl diazonium salts **2.010** using Eosin Y as the photoredox catalyst with green light irradiation was successfully reported in 2012. [128] Aryl diazonium salts bearing both electron-donating and electron-withdrawing groups were smoothly coupled with a range of electron-rich heteroarenes (furans, thiophenes and pyrroles) to furnish the cross-coupling products **2.011** (Scheme 2.3 right). Notably, by using an organic photoredox catalyst, this method is a rare example of a metal-free cross-coupling reaction and can proceed under mild temperatures.

Extending this concept further, the synthesis of α-aryl carbonyl derivatives **2.012** under photoredox catalysis with aryl diazonium salts as the radical source and enol acetates as coupling partners was achieved in 2012. [129] $[Ru(bpy)_3]Cl_2$ proved to be the best photocatalyst in this case. Diazonium salts containing electron withdrawing or neutral groups with variety of terminal enol acetates were successfully subjected into the reaction conditions and delivered the corresponding α-aryl ketones **2.012** in good yields (Scheme 2.3 left).

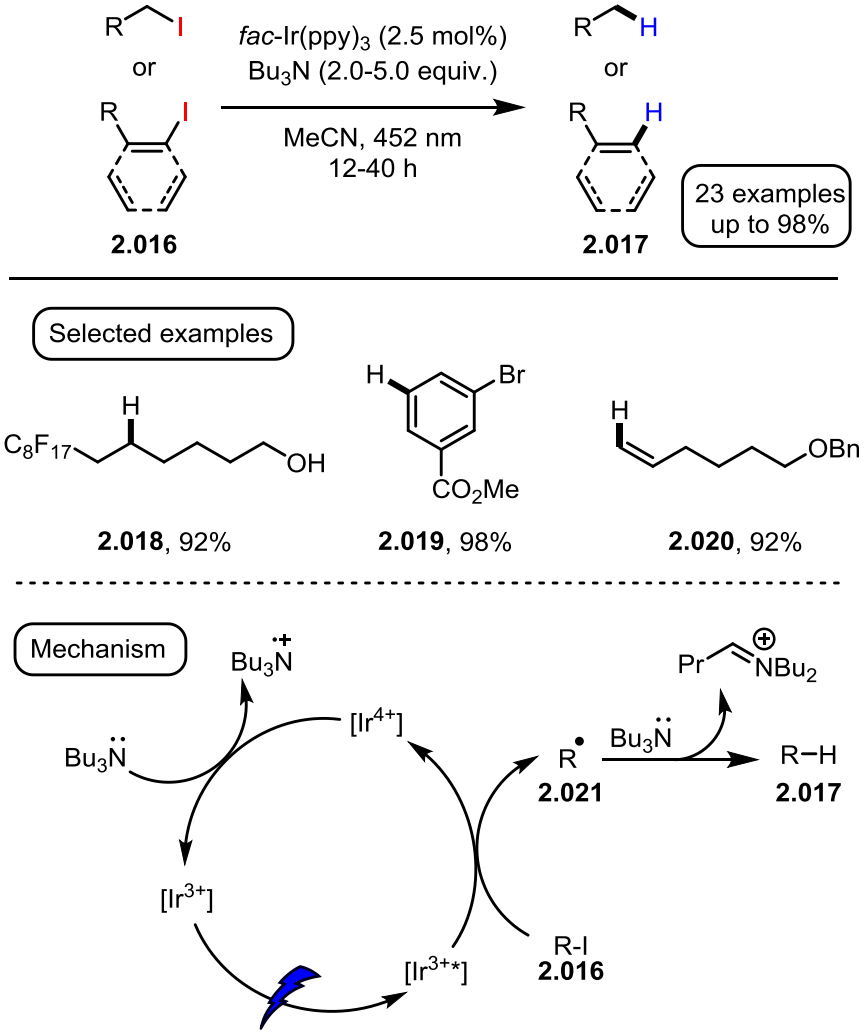


Scheme 2.3. Photo-catalysed Meerwein reaction with diazonium salts.

The suggested mechanism of these Meerwein-type reactions is depicted in Scheme 2.3. First, visible-light irradiation of the photocatalyst PC initiates a single-electron transfer to aryl diazonium salt **2.010** producing aryl radical **2.013** and the oxidised catalyst $PC^{\cdot+}$. Aryl radical **2.013** adds to the alkene or arene moiety to give a stabilised radical intermediate **2.014**. The latter is then reoxidised by $PC^{\cdot+}$ to produce the carbocation intermediate **2.015**, regenerating the photocatalyst. Deprotonation of carbocation intermediate **2.015** (in the case of cross coupling reaction) or loss of an acyl cation (in the case of α-aryl carbonyl synthesis) furnishes the desired products.

In 2012, Stephenson and co-workers disclosed a photo-catalysed reduction of organohalides. [130] Organohalides have long been considered an important source for the generation of radical species; however, this process usually requires a stoichiometric amount of reagents such as toxic tin hydrides, or relatively harsh reaction conditions. [131] In their work, they achieved such a reduction using an iridium photocatalyst (*fac*-$Ir(ppy)_3$ **2.002**) in combination with visible light to form radicals from inactivated alkyl, alkenyl and aryl iodides **2.016**. The radicals thus generated undergo reduction via hydrogen atom abstraction from the tertiary amine co-reactant (Scheme 2.4). The reaction conditions are relatively mild and display

interesting functional group tolerance; as seen in the selected examples, carbonyl functionality is tolerated under these reduction conditions.

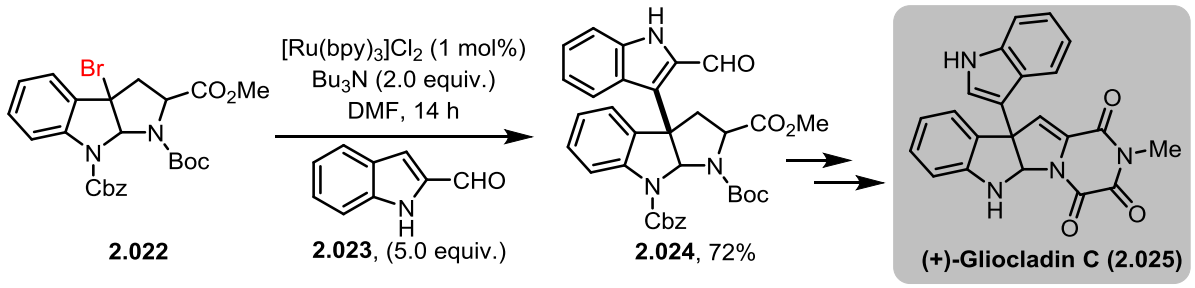


Scheme 2.4. Photo-catalysed reduction of organiodides.

Notably, the reduction of aryl and alkyl iodides took place chemoselectively over the corresponding bromides. It is, however, noteworthy that extending the reaction time in those cases did eventually lead to reduction of the C-Br bond.

The visible light-promoted reduction of haloalkanes was applied in the total synthesis of (+)-Gliocladin C. [132] (+)-Gliocladin C **2.025** belongs to the family of hexahydropyrroloindoline alkaloids and is cytotoxic against P-388 lymphocytic leukaemia cell lines. Several approaches toward the synthesis of this family of compounds have been reported. [133] In the key step of Stephenson's synthesis, reduction of bromopyrroloindoline **2.022** could be coupled to interception with indole-2-carboxaldehyde **2.023**, directly affording the indolopyrroloindoline **2.024** in 72% yield (Scheme 2.5). It is also important to mention that the use of other indole

derivatives (bearing electron-donating or withdrawing-groups) led to the formation of the corresponding products in good yields.

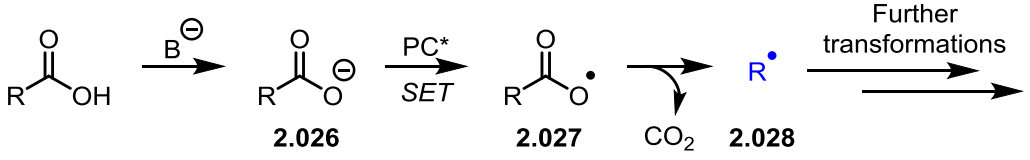


Scheme 2.5. Photo-catalysed coupling of bromopyrroloindoline **2.022** with indole **2.023** toward the synthesis of (+)-Gliocladin C.

Oxidative pathways

Decarboxylative reactions are well-documented synthetic methods that rely on the extrusion of CO_2, an entropically favourable process. Decarboxylation is of fundamental biological importance. Beside the biological enzyme-mediated decarboxylations in nature, various other decarboxylative technologies were developed with protocols such as the Kolbe, Hunsdiecker, Kochi and Barton decarboxylations. Recently, metal-catalysed decarboxylative cross coupling reactions were also reported. [134] As broad ranging as these methods are, achieving milder reaction conditions is still a key goal.

The group of MacMillan accomplished a photocatalytic decarboxylative reaction of alkyl carboxylic acids. This strategy relies on the stabilisation of the generated radical by an α-heteroatom. Upon treatment of a variety of carboxylic acids with inorganic bases, the generated anion **2.026** could undergo a SET oxidation in the presence of a suitable photocatalyst generating carboxyl radical **2.027**. Rapid extrusion of CO_2 then takes place forming alkyl radical **2.028** (Scheme 2.6). In some cases, secondary alkyl carboxylic acids were also efficiently oxidised into the corresponding radicals.



Scheme 2.6. General pathway for the photo-catalysed decarboxylation.

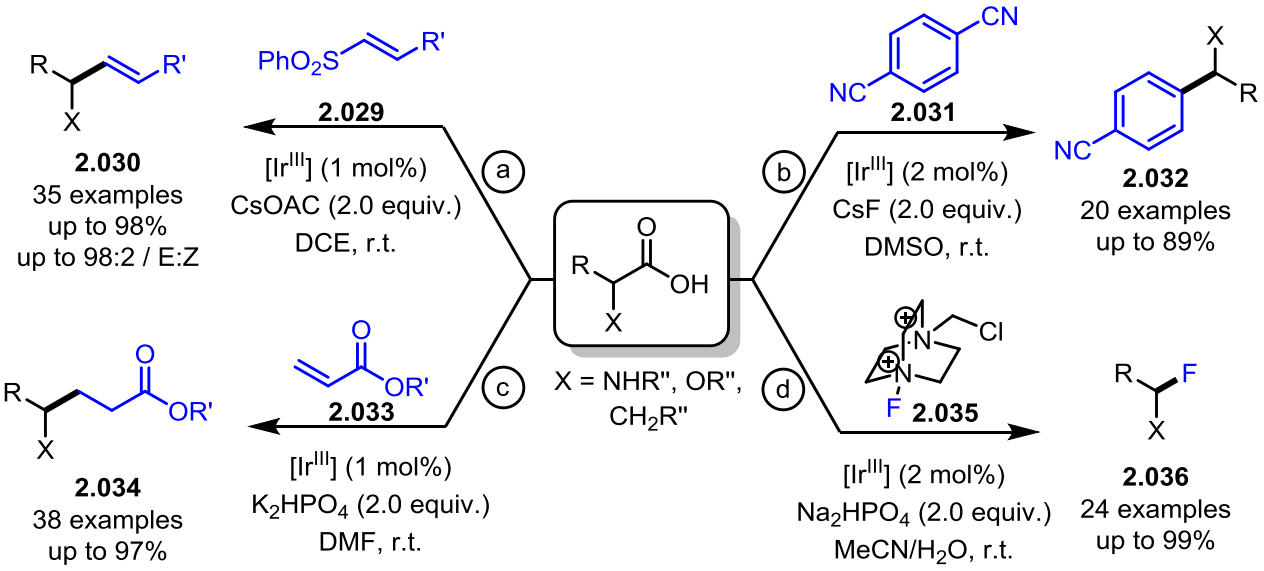
There have been numerous applications of decarboxylative radical formation with diverse reaction partners. One such protocol involves the union of vinyl sulfones **2.029** with

photoredox-generated α-amino radicals to provide allylic amines **2.030**. [135] Addition of the nucleophilic radical to the electron poor olefin generates β-sulfonyl radicals that are able to undergo elimination of a sulfinyl radical, affording the products **2.030** (Scheme 2.7 a). The resultant C-H decarboxylative vinylation of *N*-Boc α-amino acids proceeds in high yields and with excellent olefin geometry control (up to 98:2 *E*/*Z* in most of the cases).

The direct decarboxylative arylation of α-amino acids via visible light-mediated photoredox catalysis was also achieved. [136] Trapping the radical generated from α-amino or α-oxa acids with 1,4 dicyanobenzene **2.031** furnished the corresponding benzylic amines or ethers **2.032** in very good yields (Scheme 2.7 b). The reaction proceeds under mild conditions, which tolerate an array of sensitive functional groups, including esters, amides, carbamates, ethers and which tends to be oxidised under such conditions.

This strategy was also successfully used in a radical Michael addition process. [137] Photo-catalysed oxidation of a similar range of carboxylic acids was investigated as in the previous studies, provided versatile Michael donors. A variety of Michael acceptors **2.033** were amenable to this conjugate addition strategy and furnished the desired products **2.034** in very good yield (Scheme 2.7 c). This method provided a mild process for C-C bond formation without the need for any organometallic species.

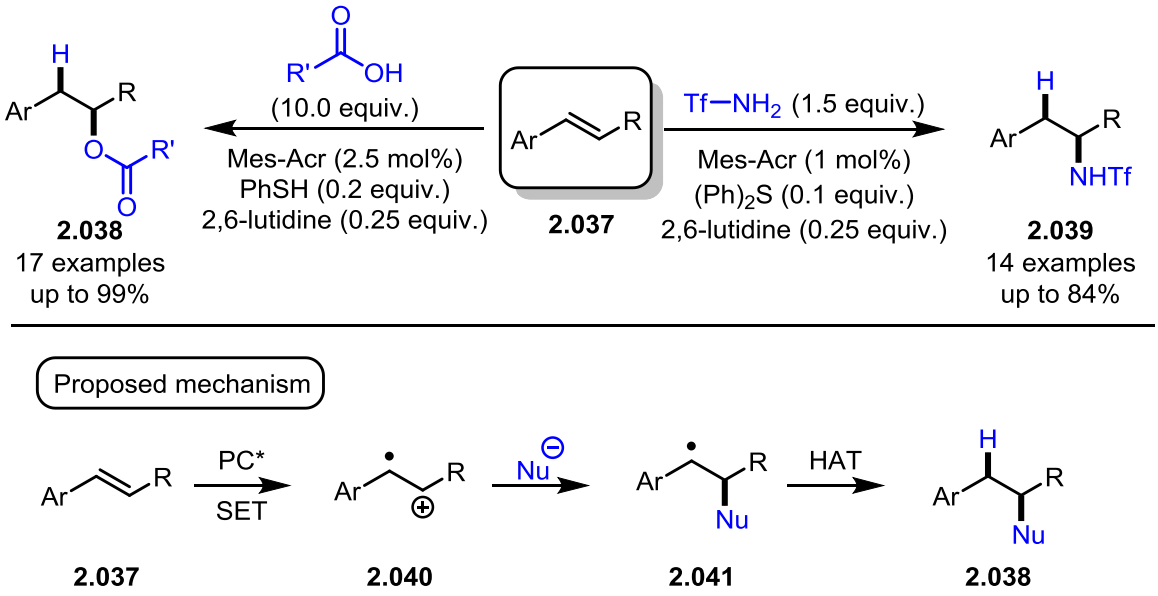
Finally, a direct conversion of simple aliphatic carboxylic acids to the corresponding alkyl fluorides was reported, in which the generated alkyl radical can abstract a F atom from Selecfluor **2.035**. [138] A variety of alkyl carboxylic acids were smoothly transformed into the corresponding fluoroalkanes **2.036** with high efficiency (Scheme 2.7 d). This process offers the use of inexpensive and easily available starting materials for the synthesis of fluorine-containing compounds.



Scheme 2.7. Macmillan's photo-catalysed decarboxylative transformations.

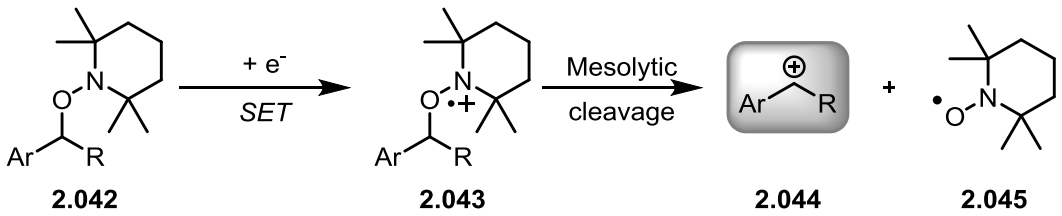
A different family of reaction was developed by Nicewicz and co-workers. A direct catalytic anti-Markovnikov addition of carboxylic acids to alkenes was reported. [139] The reaction was performed using mesityl acridinium salt **2.005** as a photooxidant with catalytic amounts of thiophenol (PhSH) as a hydrogen-atom donor. The combination of easily oxidisable styrene derivatives **2.037** with a variety of carboxylic acids afforded exclusively the anti-Markovnikov addition adducts **2.038** (Scheme 2.8 left). An intermolecular photo-catalysed anti-Markovnikov hydroamination of alkenes using a similar catalytic system was also achieved, in which an electron-poor sulfonamide was used as the nucleophile. [140] A variety of homobenzylic sulfonamides **2.039** were synthesised in this way in good yields (Scheme 2.8 right).

The proposed mechanism of this family of reactions begins with an oxidation of the alkene **2.037** by the excited state of the photocatalyst (PC*) resulting in the formation of an alkene cation radical **2.040**. Addition of the nucleophile to the radical cation provides radical intermediate **2.041**. A hydrogen-atom transfer step (HAT) from the accompanying thiol then takes place to deliver the desired products **2.038** or **2.039** (Scheme 2.8).



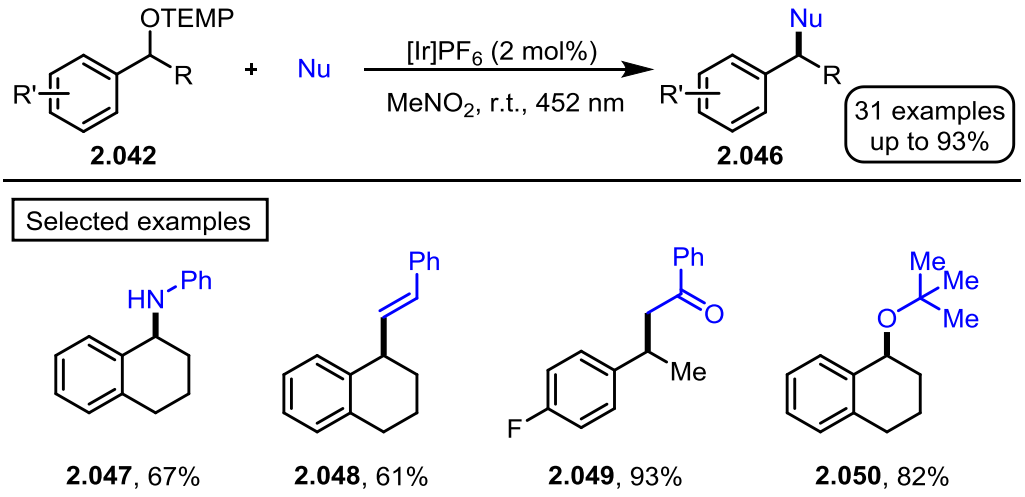
Scheme 2.8. Photo-catalysed anti-Markovnikov addition of carboxylic acids or amines to styrenes.

A particularly interesting example of the oxidation ability of these photocatalysts was reported by Knowels and co-workers in 2016. [141] Oxidation of TEMPO-derived alkoxyamine **2.042** with a suitable photocatalyst led to the formation of a radical cation **2.043** with a remarkably weak C-O bond. Species **2.043** can then undergo mesolytic fragmentation delivering stable nitroxyl radical TEMPO **2.045** and a reactive carbocation intermediate **2.044** (Scheme 2.9).



Scheme 2.9. Photo-catalysed *in situ* generation of carbocations *via* mesolytic cleavage.

After screening different conditions, the use of $[Ir(dF(CF_3)ppy)_2(d(CF_3)bpy)]PF_6$ **2.003** in combination with blue light efficiently delivered the desired carbocation **2.044**. This, *in situ* generated, carbocation could be intercepted by a wide range of nucleophiles. The use of nucleophiles such as aniline, a vinyl trifluoroborate salt, a silyl enol ether and *tert*-butanol was well tolerated by the reaction, generating a diverse range of products in very good yields (Scheme 2.10). This process occurs under neutral conditions, enabling catalytic cation generation in the presence of both acid sensitive and easily oxidisable nucleophilic partners.



Scheme 2.10. Nucleophilic capture of *in situ*, photocatalytically generated carbocations.

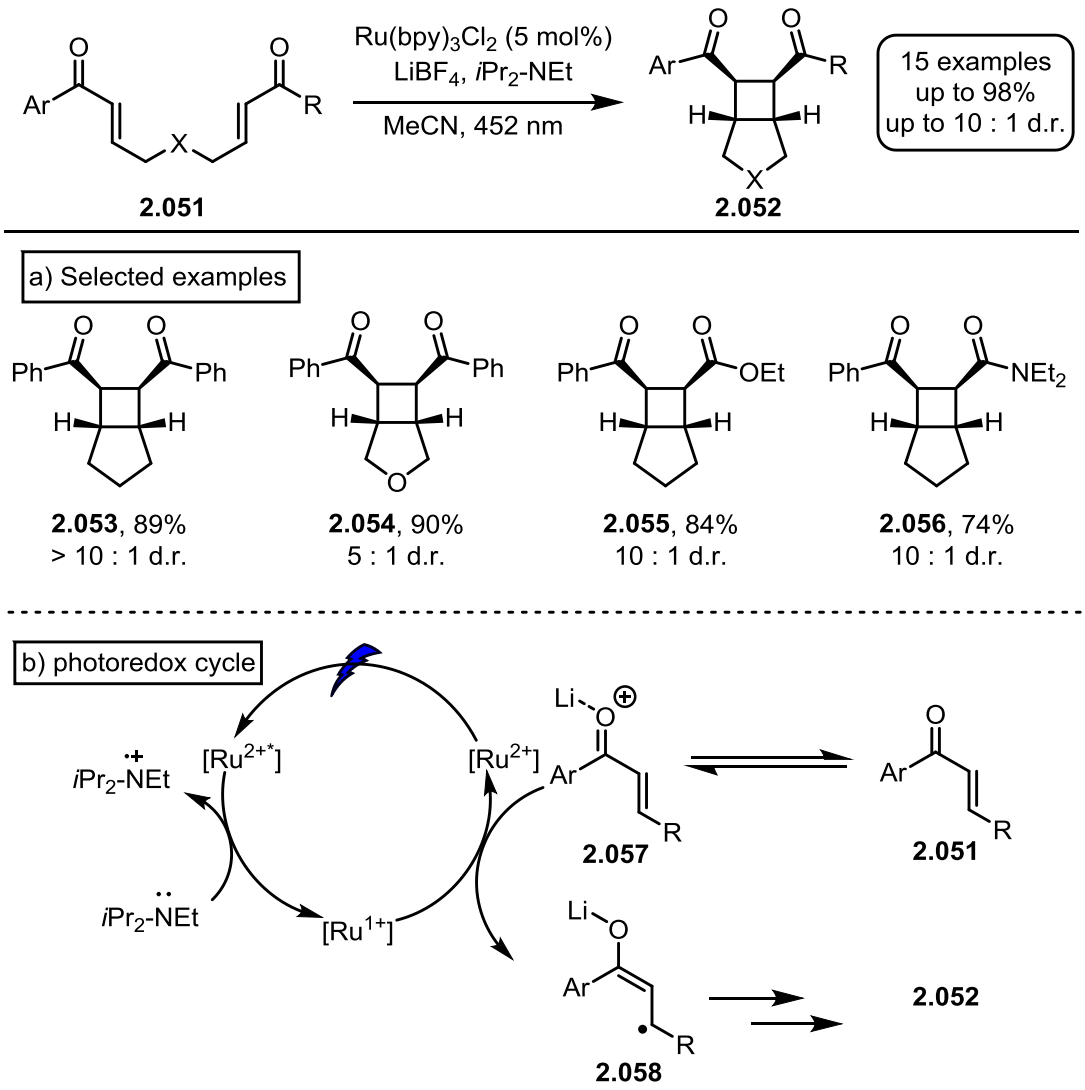
2.1.1.3 Photocatalysis in dual catalytic process

Whilst photoredox catalysis has already proven to be a powerful method in its own right, the combination of a visible-light-activated photoredox catalyst and another catalytic cycle has greatly advanced the field. In the dual catalytic variant, one of the SET events is an essential mechanistic step in a second catalytic cycle, whether the cycle is organocatalytic or organometallic. [142]

Lewis acid activation with photocatalysis

In 2008, Yoon and co-workers reported the highly diastereoselective photoredox-mediated intramolecular [2+2] cycloaddition of enones **2.051**. [143] The ability of enones to form radical anion intermediates in the presence of an SET reductant made them suitable substrates for photoredox reactions. Activation of **2.051** with a Lewis acid facilitates the reduction event. Thus, irradiation of an aryl dienone **2.051** with visible light and $[Ru(bpy)_3]Cl_2$ in the presence of Hünig's base (*i*-Pr_2NEt) and Lewis acid ($LiBF_4$) in acetonitrile furnished the desired intramolecular [2+2] cycloadducts **2.052** in high yield and high diastereomeric ratio (Scheme 2.11). Several functional groups were tolerated by these reaction conditions redundant (Scheme 2.11 a). Notably, all the cycloadducts were obtained preferentially as *cis*-cyclobutanes. The absence of *i*-Pr_2NEt led to no product formation. This suggests that the cycloaddition is initiated by $[Ru^{1+}]$, which results from a reductive quenching of $[Ru^{2+*}]$ by *i*-Pr_2NEt. Therefore, the reaction proceeds via reduction of the pre-activated enone **2.057** by the reduced photocatalyst species. The radical anion **2.058** will then undergo 5-*exo-trig* cyclisation. Further oxidation delivers the bicyclic products **2.052** (Scheme 2.11 b). A

limitation of this method is that one of the cycloaddition partners for this reaction must be an aryl enone to initiate the single electron reduction.



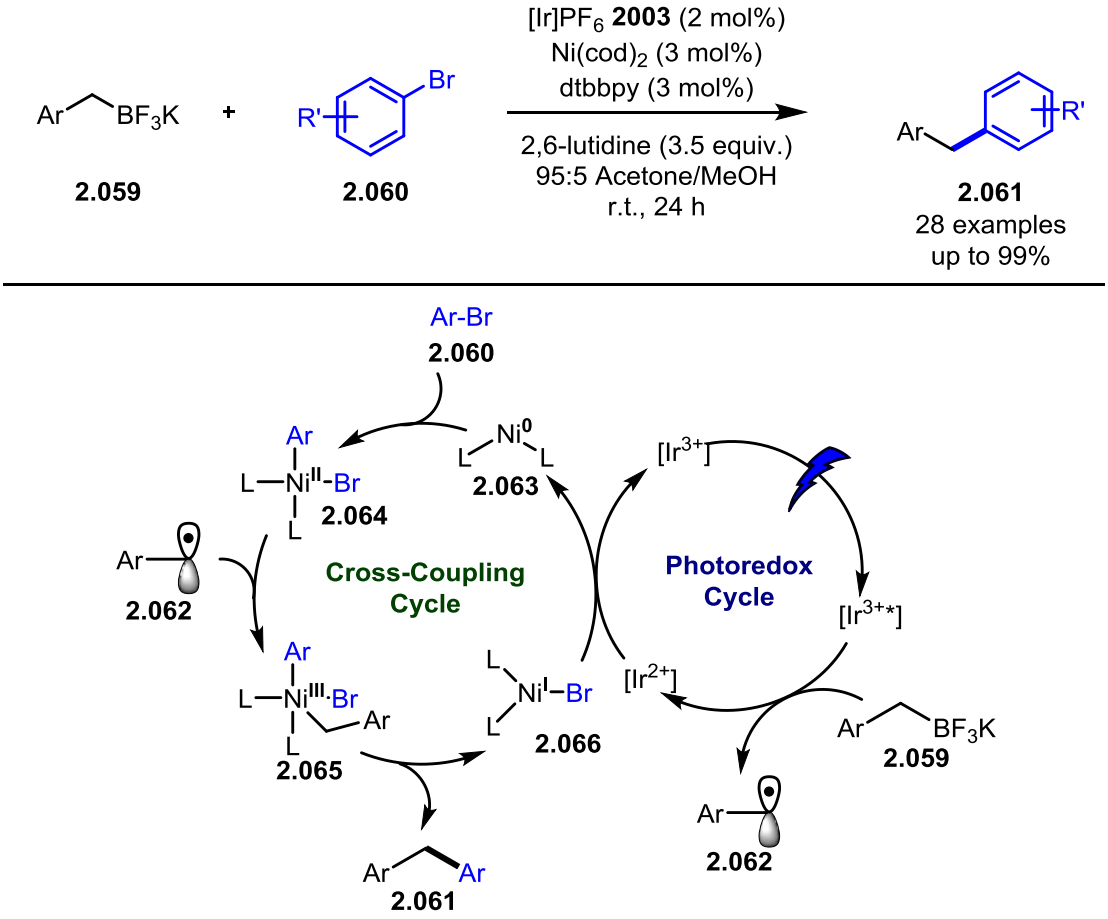
Scheme 2.11. Photo-catalysed [2+2] cycloaddition reaction of enones.

They subsequently expanded the scope of this transformation to encompass intermolecular [2+2] [144] and [4+2] [145] cycloadditions, an intramolecular [3+2] cycloaddition [146], and recently an enantioselective intramolecular version using a chiral Lewis acid. [147]

Transition Metal-catalysts with photocatalysts

The combination of transition-metal catalysis with visible-light photoredox catalysis has recently emerged as a versatile platform for the development of new and highly efficient synthetic methodology. Both powerful in their own right, these two fields can, when combined, allow for the use of non-traditional nucleophiles in cross-coupling processes. [148]

In 2014, Molander and co-workers reported a mechanistically unique single-electron transfer-based strategy for the activation of organoboron reagents toward transmetalation. [149] Transmetalation is usually the rate-limiting step, and accelerating the rate of transmetalation of Csp^3-hybridised boronic acids has proven particularly difficult. In most cases, excess base and high temperatures are used, thereby limiting functional group tolerance and leading to side reactions. [150] The development of an activation mode based on (SET) chemistry would therefore be an efficient strategy for engaging this class of reagents. Application of an iridium photoredox catalyst in tandem with a nickel catalyst effects the cross-coupling of potassium benzyltrifluoroborates **2.059** with a variety of aryl bromides **2.060** under mild conditions (visible light, ambient temperature, no strong base) furnishing the cross-coupling adducts **2.061** in excellent yields (Scheme 2.12).



Scheme 2.12. Photo-catalysed/nickel-catalysed cross coupling reaction with organoborones.

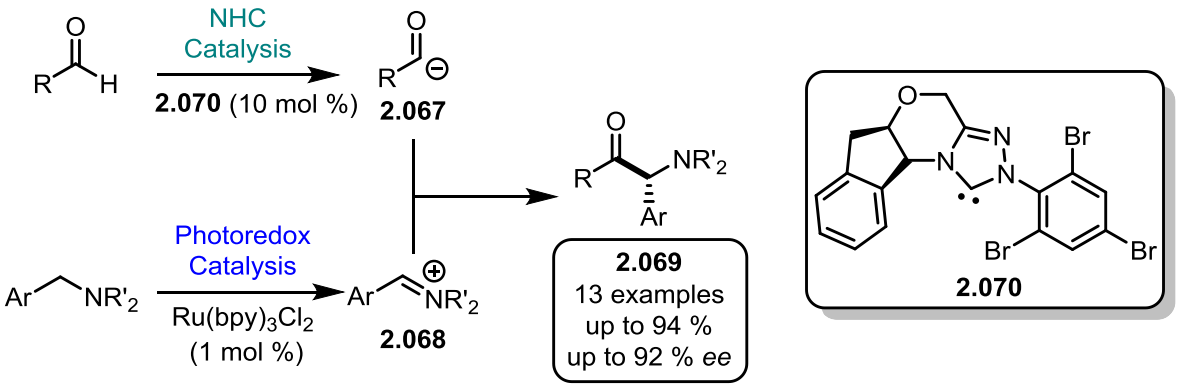
As seen in the proposed mechanism, the photocatalyst generates a benzylic radical **2.062** via SET oxidation of **2.059**. After oxidative addition into aryl bromides by Ni^0, a subsequent capture of the benzyl radical at Ni^{II} would yield high-valent Ni^{III} intermediate **2.065**. This

rapidly undergoes reductive elimination to generate the desired cross-coupling product **2.061** and Ni^{I} complex **2.066**. The photocatalyst can then regenerate the active nickel catalyst via SET reduction. Chiral ligands on the Ni catalyst were used to extend this transformation to the stereoconvergent cross-coupling of a racemic secondary benzyltrifluoroborate, which afforded the diarylethane product in a promising enantiomeric ratio of 75:25.

Other diverse methodologies involving the use of photocatalysts with transition-metal catalysts in dual catalytic systems have been reported by MacMillan, [151] Toste, [152] Sanford [153] and Wang [154].

Organocatalysts with photocatalysts

In 2012, Rovis and co-workers reported a catalytic asymmetric α-acylation of tertiary amines with aldehydes facilitated by a combination of chiral *N*-heterocyclic carbene (NHC) catalysis and photoredox catalysis. [155] The generation of an "acyl anion equivalent" (known as the Breslow intermediate) from an aldehyde is a well-established strategy in NHC catalysis. It is also well established that tertiary amines can be oxidised through photoredox catalysis. Thus, the acyl anion equivalents **2.067** generated from aldehydes were capable of undergoing coupling with iminium ions **2.068** generated from by oxidation of benzylic tertiary amines to form the α-amino ketones **2.069** in high yields and good enantioselectivities (Scheme 2.13). This method connects readily available substrates under mild conditions in an asymmetric manner.



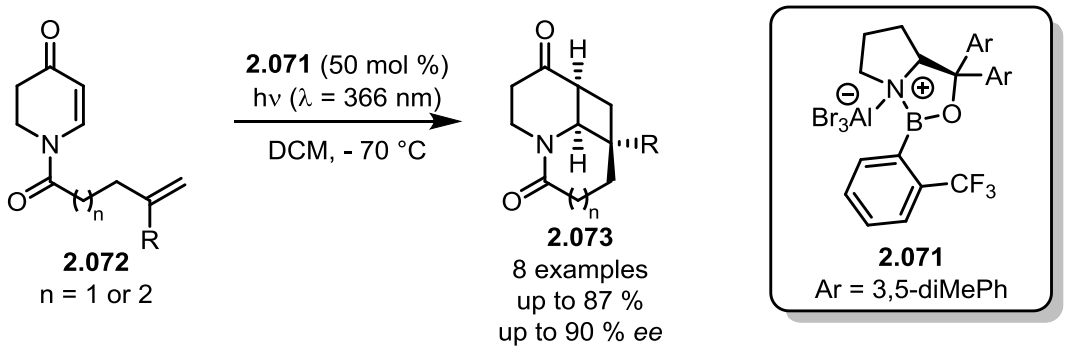
Scheme 2.13. NHC/photo-catalysed α-acylation of benzylic tertiary amines.

Another organocatalysed approach by Knowles and co-workers involved the merger of photoredox catalysis with Brønsted acid catalysis in the reductive cyclisation of alkenyl-substituted aryl ketones. [156] Early on, the group of MacMillan has also applied enamine organocatalysis together with photocatalysis for radical coupling reactions. [157]

2.1.1.4 Photochemical activity of donor-acceptor complexes

As discussed earlier, the majority of organic molecules do not absorb light in the visible region. In a number of cases, however, complexation of the organic substrate (quite often with Lewis acids) affects the absorption wavelength, sometimes even bringing it into the visible region of the spectrum. Termed a bathochromic shift, this effect has been exploited to great effect in photocatalysis as an alternative strategy for radical generation. Often, the catalyst used in this approach works as both a chiral catalyst and photosensitiser. [158]

In 2013, Bach and co-workers developed a light-driven enantioselective organocatalysed [2+2] cycloaddition reaction using chiral Lewis acid **2.071**. [159] The general photochemical [2+2] cycloaddition reaction of enones occurs on the triplet state of the enone, which can be reached via photoexcitation (UV irradiation). The key intermediate is the lowest-lying triplet state of the enone, which has π→π* character and to which another olefin can add, leading via a 1,4-diradical to cyclobutane rings, by its nature an achiral process. [160] Asymmetric catalysis of photochemical cycloadditions has been limited by the challenge of suppressing the unselective background reaction. Upon treatment with chiral Lewis acid **2.071**, 5,6-dihydro-4-pyridones **2.072**, a versatile class of enone substrates, undergo significant bathochromic absorption shift enabling their excitation at near visible light region (366 nm). Thus, an enantioselective intramolecular [2+2] photocycloaddition of **2.072** could take place to furnish the tricyclic [2+2] adducts **2.073** in good yield and enantiomeric excess (Scheme 2.14).

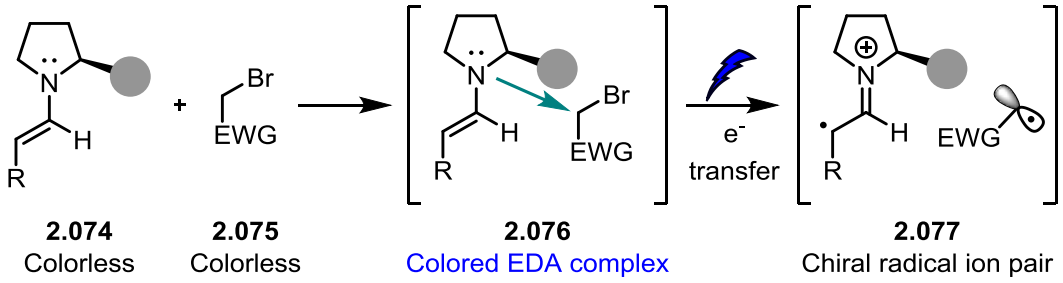


Scheme 2.14. Enantioselective LA-photo-catalysed intramolecular [2+2] cycloaddition reaction.

This method was also applied to the enantioselective intramolecular [2+2] cycloaddition of coumarin derivatives. [161]

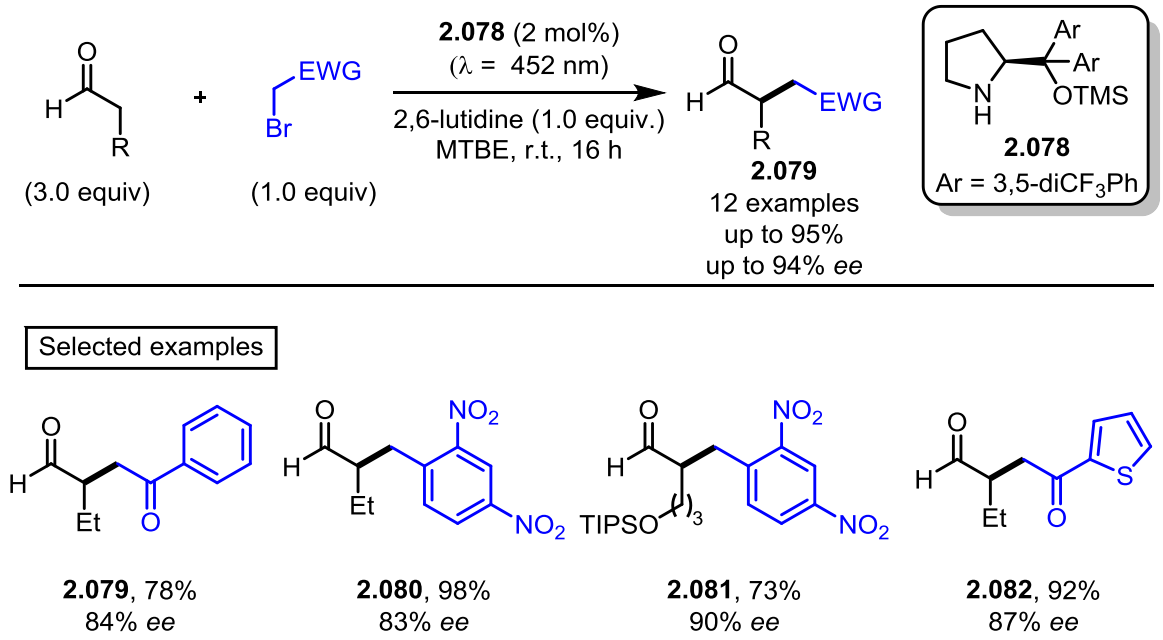
The group of Melchiorre developed a photo-catalysed stereoselective α-alkylation of aldehydes based on the formation of electron donor-acceptor (EDA) complexes. [162] In these cases, the catalysts do not act as photocatalysts but rather guide the photoactivation of the

substrates by inducing the transient formation of photon-absorbing chiral EDA complexes. [163]. The authors hypothesised that the lone pair of the pyrrolidine ring in the enamine **2.074**, generated through condensation of the chiral amine catalyst and the aldehyde starting material, could be engaged in the formation of EDA complexes with electron-accepting molecules such as **2.075**. The choice of partner **2.075** is guided by the fact that it should have a low enough reduction potential to enable the generation of the corresponding radical under these conditions. In the event, upon mixing the colourless enamine **2.074** with colourless **2.075**, a direct colour change occurred, which was ascribed to the formation of an EDA complex **2.076** (n→π* interactions, cf. Scheme 2.15). The colour change suggests a large bathochromic shift into the visible-light region. Shining visible light onto the reaction mixture induces an electron transfer to occur, affording a chiral radical-ion pair **2.077**.



Scheme 2.15. Proposed formation of an EDA complex for enantioselective C-C bond formation.

Application of this strategy using alkyl aldehydes and chiral amine catalyst **2.078** in combination with electron deficient benzyl and phenacyl bromides led to the formation of photon-absorbing electron donor-acceptor (EDA) complexes. A radical combination followed by hydrolysis furnished adducts **2.079** in good yield and high enantioselectivity (Scheme 2.16). This method thus presents a valuable method in the asymmetric intermolecular α-alkylation of aldehydes, a challenging transformation.



Scheme 2.16. Photo-catalysed stereoselective α-alkylation of aldehydes.

Later on, this method was successfully applied in the enantioselective alkylation of aldehydes with bromomalonates [164] and α-iodosulfones. [165]

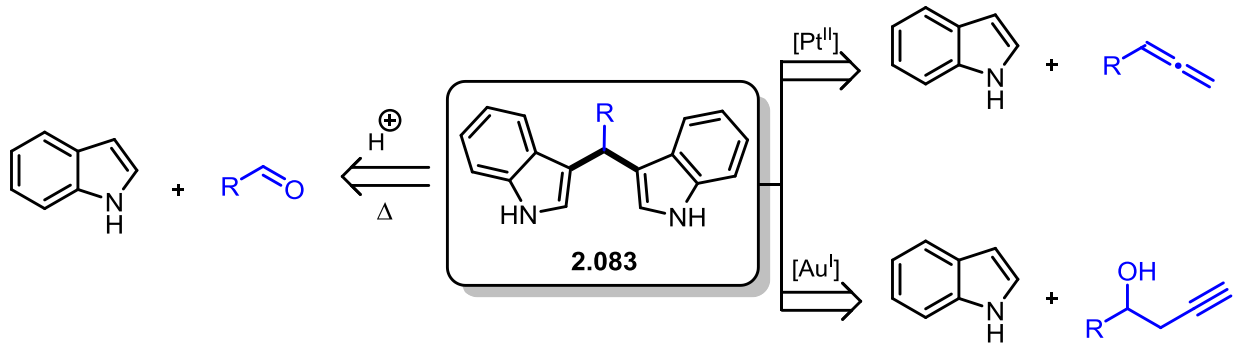
2.2 Results and discussion

2.2.1 Visible-light promoted α-amino C(sp^3)-H functionalisation via 1,5-hydrogen migration for the synthesis of bis-indole derivatives

The results in this chapter were reported in *Eur. J. Org. Chem.* **2015**, 7643-7647. [166]

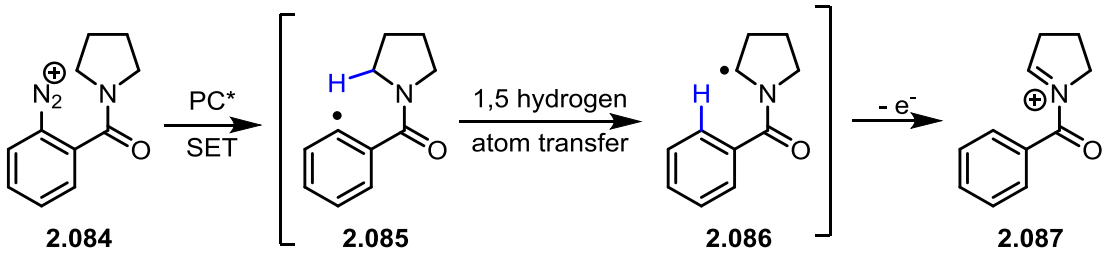
2.1.1.1 Introduction and Background

Indoles are very important subunits in organic synthesis. Several natural products and bioactive compounds contain indole cores. Bis(indolyl)alkanes **2.083** are also present in a large variety of natural products isolated from various marine natural sources. Recent interest in this family of compounds stems from their interesting biological activities. [167] Classical synthetic approaches to bis-indoles typically involve condensation of two equivalents of indole with an aldehyde under Brønsted acid catalysis (Scheme 2.17 left). [168] Another successful approach is the metal-catalysed addition of indoles to allenes or homopropargyl alcohols (Scheme 2.17 right). [169]



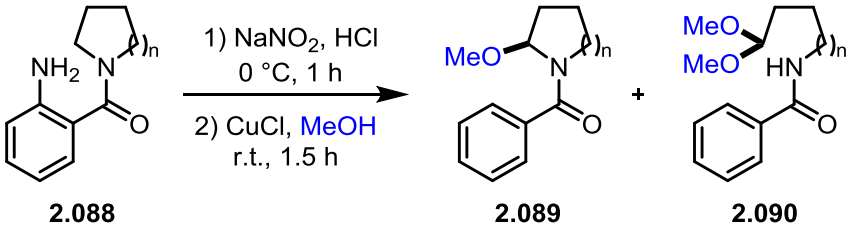
Scheme 2.17. General routes for the synthesis of bis-indolyl alkanes.

Our synthetic approach was based on *o*-diazobenzamides **2.084**. We envisaged that under photoredox conditions, diazonium salt **2.084** could be reduced to the corresponding aryl radical **2.085**. This intermediate is anticipated to undergo a radical translocation (1,5-hydrogen migration) to **2.086**, the subsequent oxidation of which will generate *N*-acyliminium intermediate **2.087** (Scheme 2.18). Nucleophilic capture of this azacarbenium intermediate should finally deliver a variety of α-functionalised amino derivatives.



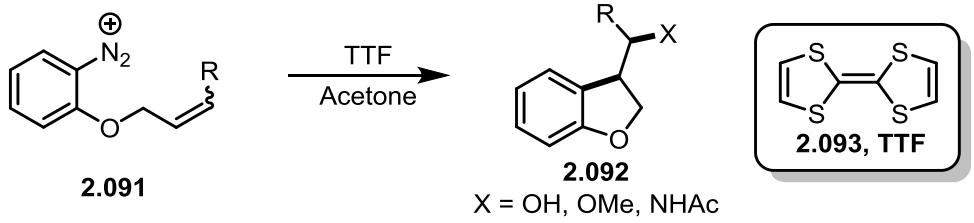
Scheme 2.18. Proposed remote C-H activation of diazonium salt **2.084** by visible-light photoredox catalysis.

We were encouraged by the work of Weinreb, which had achieved a related copper catalysed α-amino C-O bond formation starting from amide **2.088**. [170] Upon treating aniline derivatives **2.088** with sodium nitrite and hydrochloric acid, *in situ* formation of the corresponding diazonium salt took place. Addition of a copper (I) salt in methanol led to the formation of two major products (Scheme 2.19). As discussed earlier in in scheme 2.18, the reaction proceeds via SET from Cu(I) generating the aryl radical. The final azacarbenium intermediate was trapped with methanol to give α-methoxy amino compound **2.089**. However, this intermediate is not stable. A spontaneous ring opening followed by a second nucleophilic addition will take place furnishing acetals **2.090**. In most of the cases, the acetal was the major product. By careful control of the reaction time, it was possible to stop the reaction at a point (approximately one hour) where **2.089** was the major product, but at the expense of reduced conversion. For reactions left for 24 hours, acetal **2.090** was observed as the only product.



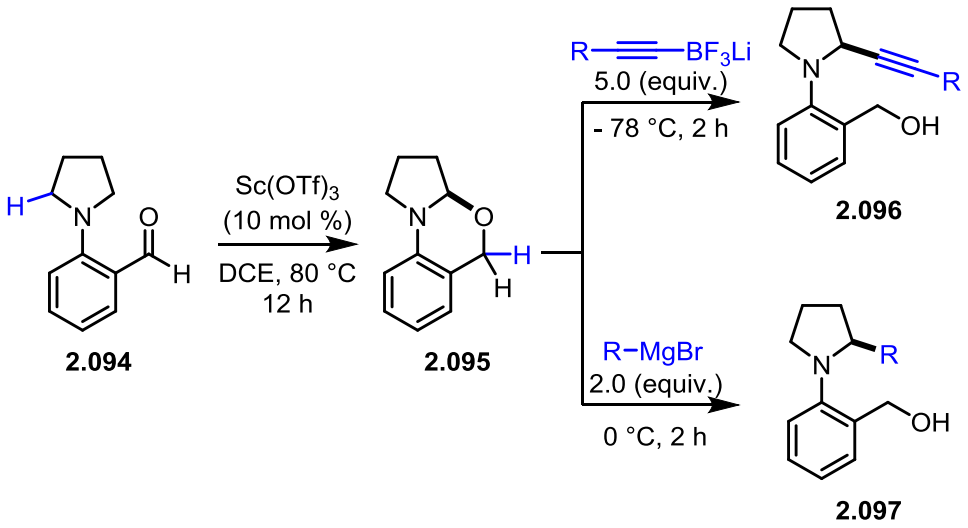
Scheme 2.19. Weinreb's copper-catalysed α-amino C-O bond formation.

The group of Murphy has similarly reported that diazonium salts **2.091** can react with tetrathiafulvalene (TTF) **2.093** in acetone to give the corresponding dihydrobenzofuran derivatives **2.092**. [171] They concluded that the reaction proceeds via electron transfer, dediazonisation and free radical cyclisation. Capture of the cyclic intermediate by nucleophilic solvents furnished the final products **2.092** (Scheme 2.20).



Scheme 2.20. Murphy's TTF-catalysed generation of aryl radicals from diazonium salts.

On the other hand, a remote, redox-neutral transformation for α-amino functionalisation *via* hydride transfer was reported by our group. [172] Lewis-acid activation of *o*-aminobenzaldehydes **2.094** promoted a redox isomerisation to deliver benzoxazines **2.095**. Subsequent nucleophilic addition with either lithium alkynyltrifluoroborates or Grignard reagents provided α-amino functionalised products **2.096** and **2.097**, respectively (Scheme 2.21).

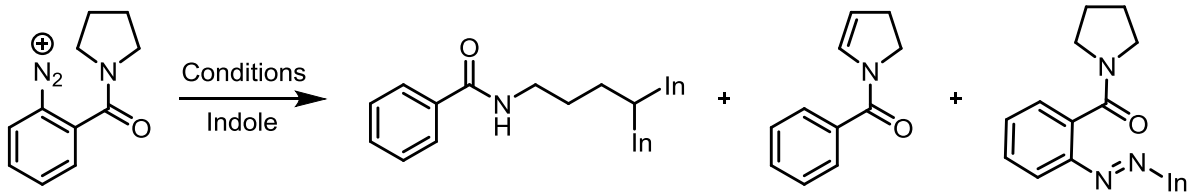


Scheme 2.21. An internal redox-triggered C-H functionalisation via 1,5 hydride transfer.

2.2.1.2 Optimisation of reaction conditions

At the outset, we chose indole as the nucleophile for the capture of azacarbenium intermediate **2.087**. As summarised in table 2.1, only 2 mol% of Eosin Y in DMSO was enough to promote full consumption of the starting material in the reaction of diazonium salt **2.098** with two equivalents of indole (Entry 1). However, the main product of this reaction was the bis(indolyl) derivative **2.099**, accompanied by small amounts of enamide **2.100**, the product of proton loss from *N*-acyliminium **2.087**. Rose Bengal led to a lower yield when used as a photocatalyst (Entry 2). Increasing the stoichiometry of the indole to 2.5 equivalents led to an improvement in yield (71%, Entry 3); whereas a further increase (to three equivalents) offered no additional improvement (Entry 4). In the absence of photocatalyst (Entry 5), the azo-

coupling product **2.101** was exclusively observed. In the absence of indole (Entry 6), elimination product **2.100** dominated the reaction mixture. Other common solvents (Entry 7 and 8) led to lower yields of the desired product. Finally, when the reaction was performed in the absence of light (Entry 9) no desired product was detected, but instead only **2.101**. A revealing observation was that bis(indolyl)adduct **2.099** was the only indole-containing product observed even when only a single equivalent of indole was utilised.



2.098 **2.099** **2.100** **2.101**

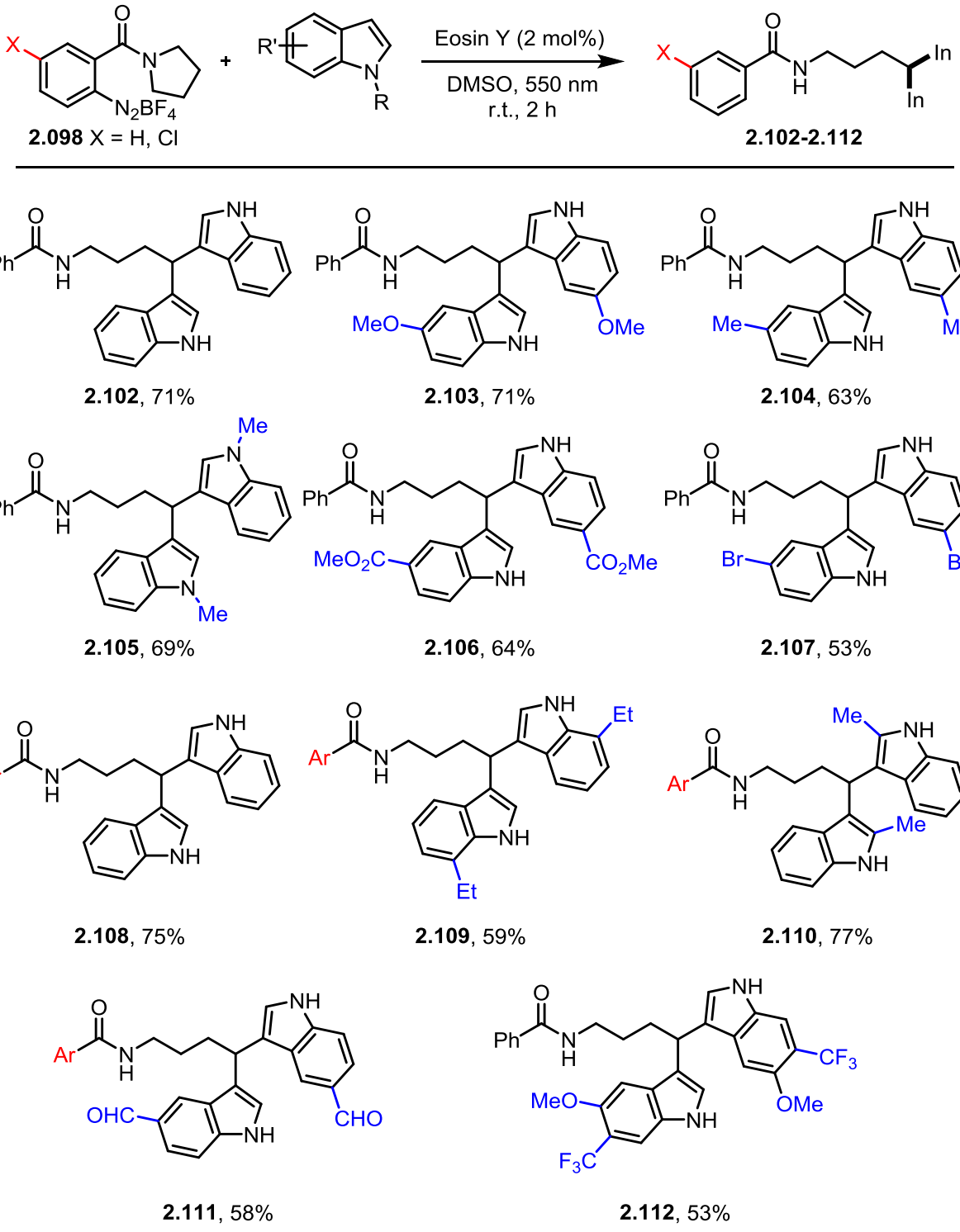
Entry	PC[a]	In[b] equiv.	Solvent	Yield 2.099/2.100/2.101
1	Eosin Y	2.0	DMSO	63/10/-
2	Rose Bengal	2.0	DMSO	34/20/-
3	Eosin Y	2.5	DMSO	71/5/-
4	Eosin Y	3.0	DMSO	71/5/-
5	___	2.5	DMSO	-/-/78
6	Eosin Y	__	DMSO	-/45/-
7	Eosin Y	2.5	DMF	54/14/15
8	Eosin Y	2.5	CH_3CN	-/15/56
9[c]	Eosin Y	2.5	DMSO	-/-/55

Table 2.1. Optimisation of reaction conditions. All the reactions where irradiated at 550 nm (green light) for 2 hours, at room temperature and [0.2 M] concentration. [a] PC: photocatalyst (2 mol%). [b] In: Indole. [c] In the dark.

2.2.1.3 Scope of Substrates

With the optimised reaction conditions in hand, we proceeded to study the scope of this transformation. As expected, electron rich-indoles were successful reaction partners and delivered the desired products in good yields (**2.102**-**2.105**). Conversely, indoles bearing

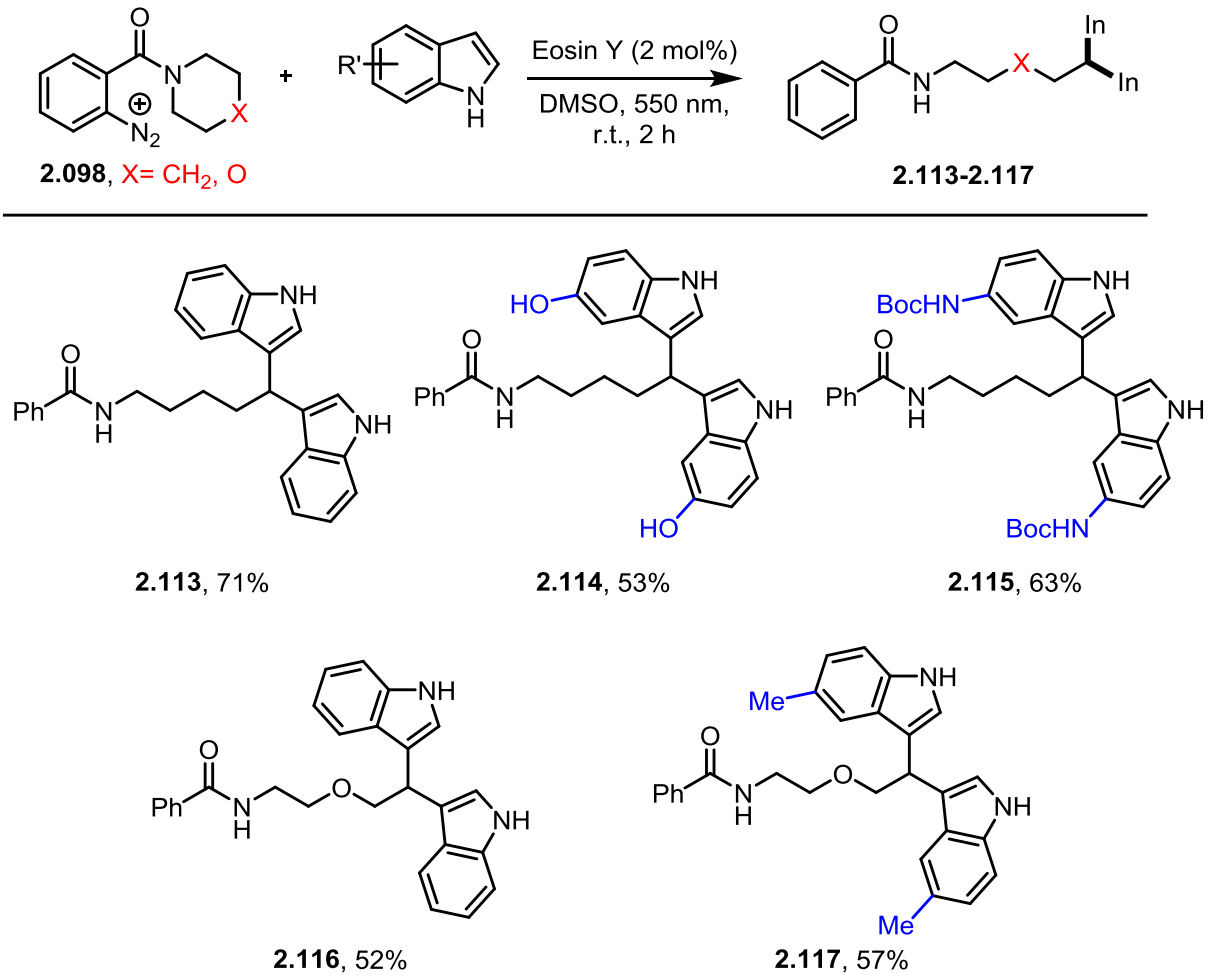
electron-withdrawing groups furnished the desired products in slightly lower yields (**2.106**-**2.107** and **2.112)**. Chlorinated aryldiazonium salt was also a suitable starting material (**2.108**-**2.111**). The presence of the aryl chloride functionality should allow further functionalisation of the products. Interestingly, this reaction tolerated a number of functional groups that are often reactive under photocatalytic conditions, e.g. aldehyde **2.111**, ester **2.106** and haloaryl **2.107** (Scheme 2.22).



Scheme 2.22. Substrate scope of bis(indolyl)alkanes.

Notably, not just pyrrolidine-derived amides could be used, but amides based on alternative cyclic amines were also tolerated in this transformation. Activation of the piperidine and morpholine analogues of **2.098** was successfully achieved under the optimised reaction conditions and led to the formation of adducts **2.113**-**2.117** in good to moderate yield (Scheme

2.23). Once again, indoles bearing electron-donating and withdrawing functionality smoothly underwent nucleophilic addition to afford bis-indolyl derivatives.



Scheme 2.23. Scope of substrates with six-membered ring amino-diazonium salts.

X-ray diffraction analysis of **2.110** proved unambiguously structure elucidation (Figure 2.2).

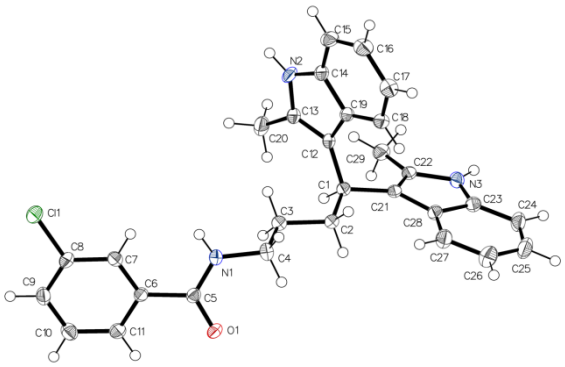
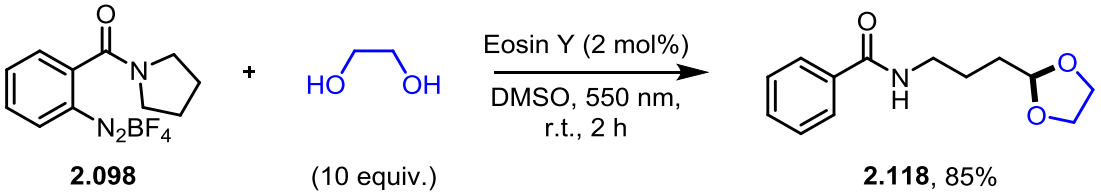


Figure 2.2. X-ray structure of product **2.110**.

Finally, we wanted to investigate the possibility of intercepting *N*-acyliminium intermediate with alcohols to form the corresponding acetals, similar to the previously discussed work of Weinreb. Upon treatment of diazonium salt **2.098** with ethylene glycol under the optimised reaction conditions, the corresponding masked aldehyde **2.118** was obtained in 85 % isolated yield (Scheme 2.24).



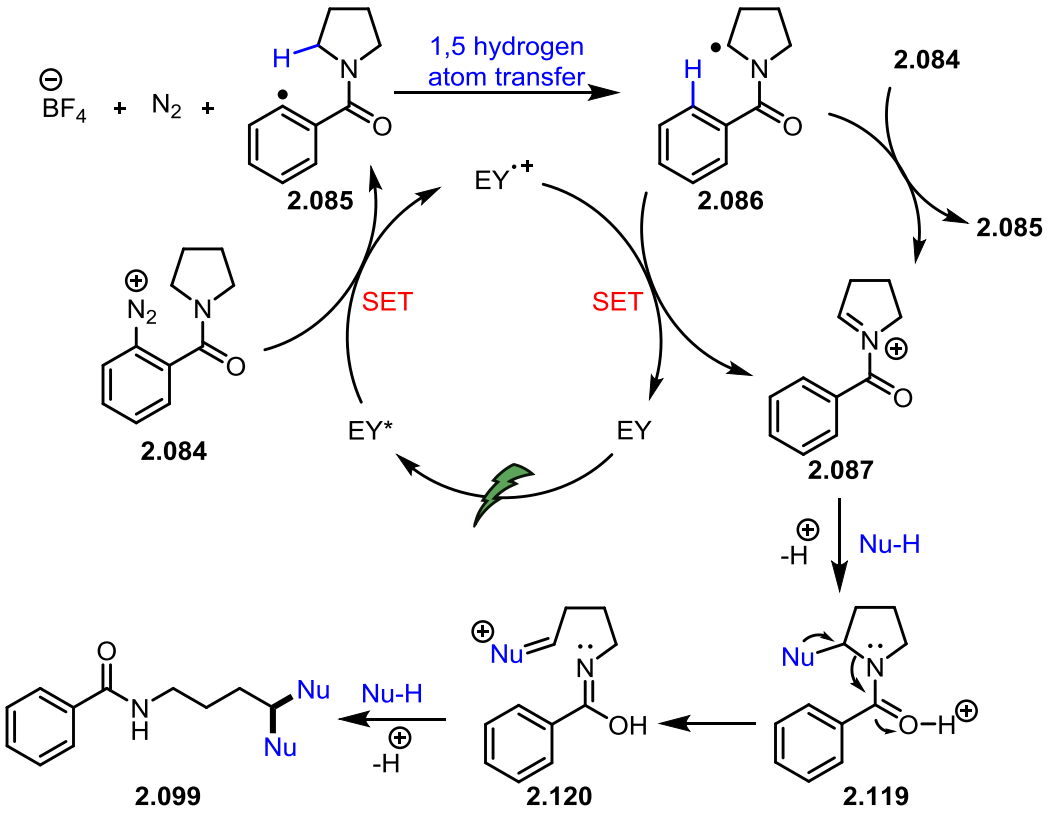
2.098 (10 equiv.) **2.118**, 85%

Scheme 2.24. Ethylene glycol as a nucleophile for the acetal formation.

2.2.1.4 Proposed mechanism

Based on previous studies, we were able to propose a plausible mechanism for this transformation (Scheme 2.25). Excitation of the photocatalyst (EY) with visible light enables a single-electron transfer (SET) to diazonium salt **2.084** furnishing the corresponding aryl radical **2.085** (with loss of nitrogen gas). Aryl radical **2.085** undergoes 1,5-hydrogen atom transfer to deliver α-amino radical intermediate **2.086**. Subsequent oxidation of this intermediate by the photocatalyst gives azacarbenium **2.087**. This oxidation can also take place *via* radical propagation from diazonium salt **2.084** itself. Nucleophilic attack of either the indole or alcoholic solvent on **2.087** furnishes intermediate **2.119**. Activation of this intermediate by H^+ (generated through nucleophilic capture) triggers a ring-opening process and affords stabilised carbenium **2.120**. A subsequent, second nucleophilic attack delivers the doubly functionalised product **2.099**.

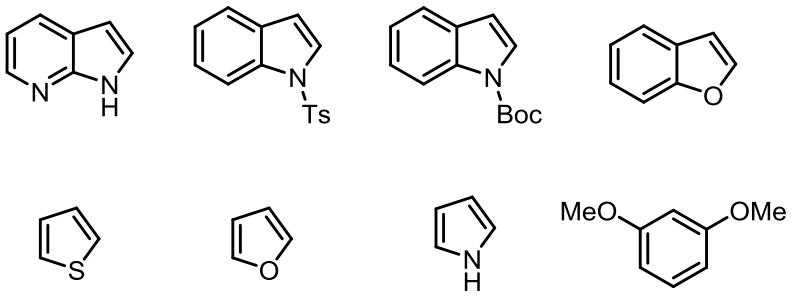
It is important to mention that the use of various inorganic or organic bases as additives was unfruitful to prevent the acid-promoted ring-opening event. It was never possible to observe mono-adduct **2.119**.



Scheme 2.25. Proposed reaction mechanism for the photo-catalysed formation of bis(indolyl)alkanes.

2.2.1.5 Reaction limitations

During the course of the investigations, a number of substrates failed to deliver the desired products, and have been summarised in scheme 2.26. 7-Aza indole, *N*-Boc and *N*-Ts indole failed to deliver the desired products and only enamide product **2.100** was observed. The use of other electron-rich (hetero)aromatic derivatives, such as benzofuran, thiophene, furan, pyrrole, and 1,3-dimethoxybenzene did not lead to the products of nucleophilic-capture. In these cases, a mixture of the azo-coupling product and the enamide product **2.101** was obtained.



Scheme 2.26. Failed substrates for the nucleophilic capture of azacarbenium ion.

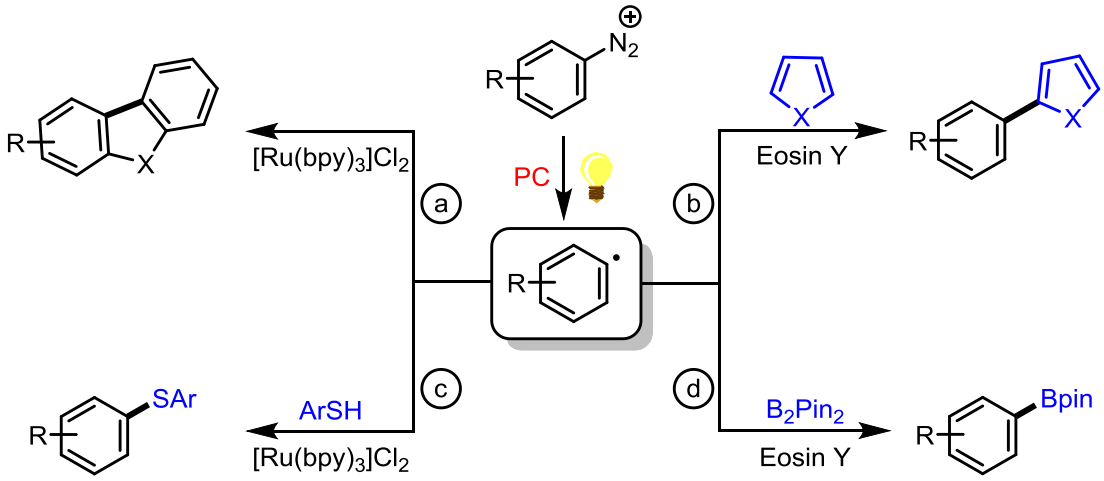
2.2.2 A family of low molecular-weight, organic catalysts for reductive C-C and C-N bond formation

This work was carried out in collaboration with Dr. Anais Jolit and Dr. Desislava Petkova. The results in this chapter were reported in: *Chem. Commun*. **2015**, *51*, 13902-13905 [173] and *Org. Lett.* **2016**, *18*, 345-347. [174]

2.2.2.1 Hydrazines as reductive catalysts for Diazonium salts in C-C bond formation

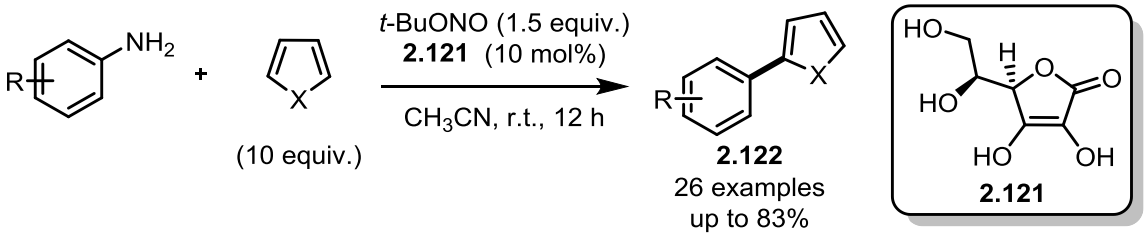
2.2.2.1.1 Introduction and Background

Diazonium salts have long been employed in organic synthesis due to their high reactivity and ease of preparation in large quantities from available starting materials (aniline derivatives). In addition to their applications in the synthesis of dyes, diazonium salts have also been utilised in organic transformations as aryl radical precursors, as we have seen in the previous section. Their ability to be reduced in SET processes by a variety of transition metal catalysts enables them to engage in several important transformations (e.g.; Meerwein arylation, Sandmeyer reaction or Pschorr cyclisation). [175] As discussed earlier, visible light photocatalysis has recently emerged as an alternative, milder strategy for the development of novel transformations with diazonium salts. Since the early work of Deronzier and co-workers on photo-catalysed Pschorr cyclisations (Scheme 2.27 a), [125] a plethora of other methods have been achieved. As mentioned earlier in this section, in 2012, König and co-workers has developed an Eosin Y-catalysed direct C-H bond arylation of aryl diazonium salts with heteroarenes (Scheme 2.27 b). [128] A one-pot Stadler-Ziegler process facilitated by photoredox catalysis for the preparation of a variety of diaryl sulfides from diazonium salts and aryl thiols was reported by Nöel *et al.* in 2013 (Scheme 2.27 c). [176] In 2012, Yan and co-workers demonstrated that the borylation of diazonium salts could be achieved in a photocatalytic manner. [177] Preparation of a variety of arylboronates was successfully achieved under mild reaction conditions (Scheme 2.27 d).



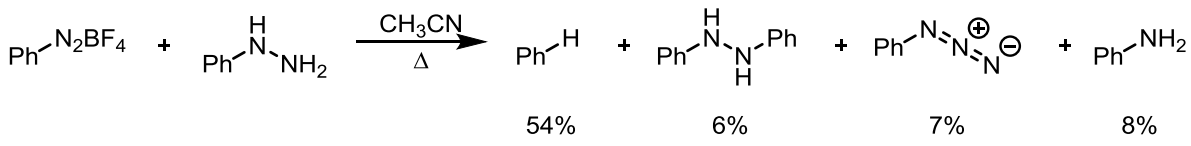
Scheme 2.27. Photo-catalysed reactions of diazonium salts for C-C, C-B and C-S bond formation.

In 2014, Carrillo and co-workers described the use of ascorbic acid (Vitamin C) as an initiator for the C-H arylation of anilines (Scheme 2.28). [178] Diazonium salts generated *in situ* from aniline derivatives were successfully reduced by vitamin C **2.121** to the corresponding aryl radicals, which underwent a homolytic coupling with (hetero)arenes furnishing the cross-coupling adducts **2.122** in good yields.



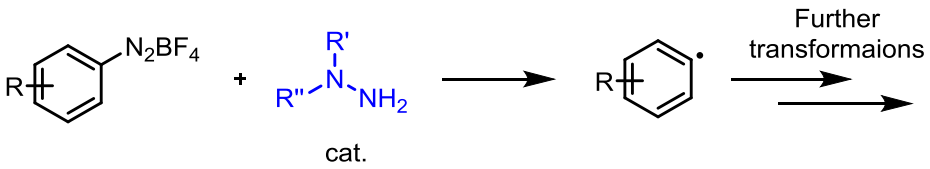
Scheme 2.28. Ascorbic acid **2.121** as a radical initiator for the arylation of diazonium salts.

In 1979, the group of Shevlin demonstrated the formation of an aryl radical when they reacted phenyldiazonium tetrafluoroborate with phenylhydrazine. [179] Instead of the expected tetrazine, the authors observed a mixture of compounds (Scheme 2.29). Benzene was observed as the major product, accompanied by minor by-products. The formation of benzene in this reaction was attributed to the intermediacy of a free phenyl radical, as supported by chemically induced dynamic nuclear polarisation (CIDNP) spectroscopic studies.



Scheme 2.29. Reaction of phenyldiazonium salt with phenylhydrazine under thermal conditions.

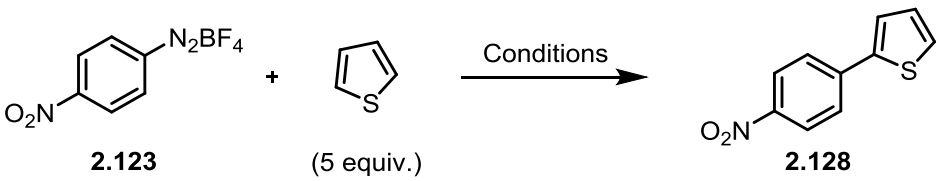
Inspired by this precedent, we were eager to investigate whether a catalytic amount of hydrazine derivatives could promote such a reduction of diazonium salts and engage the generated aryl radicals in further transformations (Scheme 2.30). This would provide a mild process that does not require light or heat and relies on readily available, low-molecular weight organic molecules.



Scheme 2.30. Hypothesised radical generation from hydrazines with diazonium salts.

2.2.2.1.2 Hydrazine screening and optimising reaction conditions

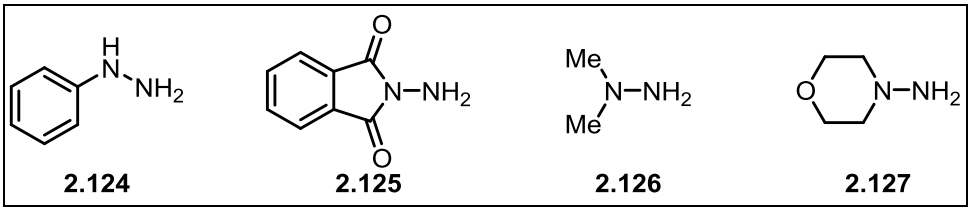
We chose *p*-nitrophenyl diazonium salt **2.123** and thiophene as model substrates. After screening different commercial available hydrazines, we were pleased to find that hydrazines indeed have the potential to function as catalysts in such a coupling transformation (Table 2.2). In the event, addition of a catalytic amount of *N*-phenylhydrazine **2.124** to the reaction mixture led to the formation of coupling product **2.128** in 30% yield (Entry 1). Electron poor *N*-aminophtalimide **2.125** gave the desired product in only 5% yield (Entry 2). However, *N*,*N*-disubstituted hydrazines, such as *N*,*N*-dimethylhydrazine **2.126** and 4-aminomorpholine **2.127**, afforded **2.128** in yields of 35% and 34%, respectively (Entries 3 and 4). More importantly the reaction was equally efficient when carried out in the dark, suggesting that visible light plays no appreciable role in this transformation (Entry 5).



2.123 (5 equiv.) **2.128**

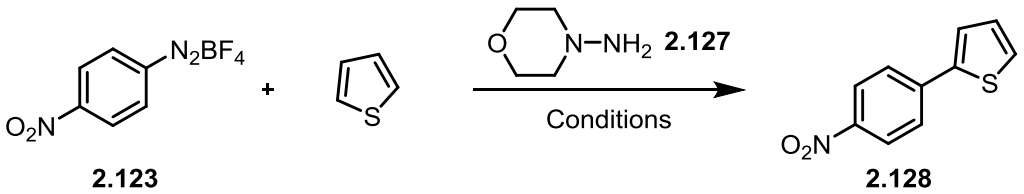
Entry	Hydrazine	Cat. loading	Yield of 2.128 [a]
1	2.124	10 mol%	30
2	2.125	10 mol%	5
3	2.126	10 mol%	35
4	2.127	10 mol%	34
5[b]	2.127	10 mol%	34

Table 2.2. Reactions were performed using (1 equiv.) of diazonium salt **2.123** with 5 equiv. thiophene and 10 mol% catalyst for 2 h at r.t. [a] Yields of the isolated product. [b] Reaction was performed in the dark.



2.124 **2.125** **2.126** **2.127**

We chose 4-aminomorpholine **2.127** for our studies due to both practical considerations (when performing the reactions on 0.1 mmol scales, the use of *N*,*N*-dimethylhydrazine **2.126** will require a less than 1 μl of the catalyst) and its low cost. At the outset, we attempted to increase the stoichiometry of the radical acceptor. Whilst ten equivalents of thiophene led to an improvement of the yield (Entries 1 and 2), the use of twenty equivalents afforded the desired product in 75% in just ten minutes (Entry 3). Screening other solvents did not improve the yield of the desired adduct (Entries 4-8). It was possible to reduce the catalyst loading to 5 mol% without much effect (Entry 9), but longer reaction times were needed when using 2.5 or 1 mol% (Entries 10 and 11). A control reaction (Entry 12) showed that the reaction proceeded negligibly in the absence of catalyst (Entry 12). Finally, performing the reaction under argon atmosphere did not offer any improvement (Entry 13), enabling these experiments to be carried out under simple and convenient aerobic conditions. In each case, vigorous and rapid evolution of nitrogen gas was detected as soon as the hydrazine catalyst was added into the reaction mixture.



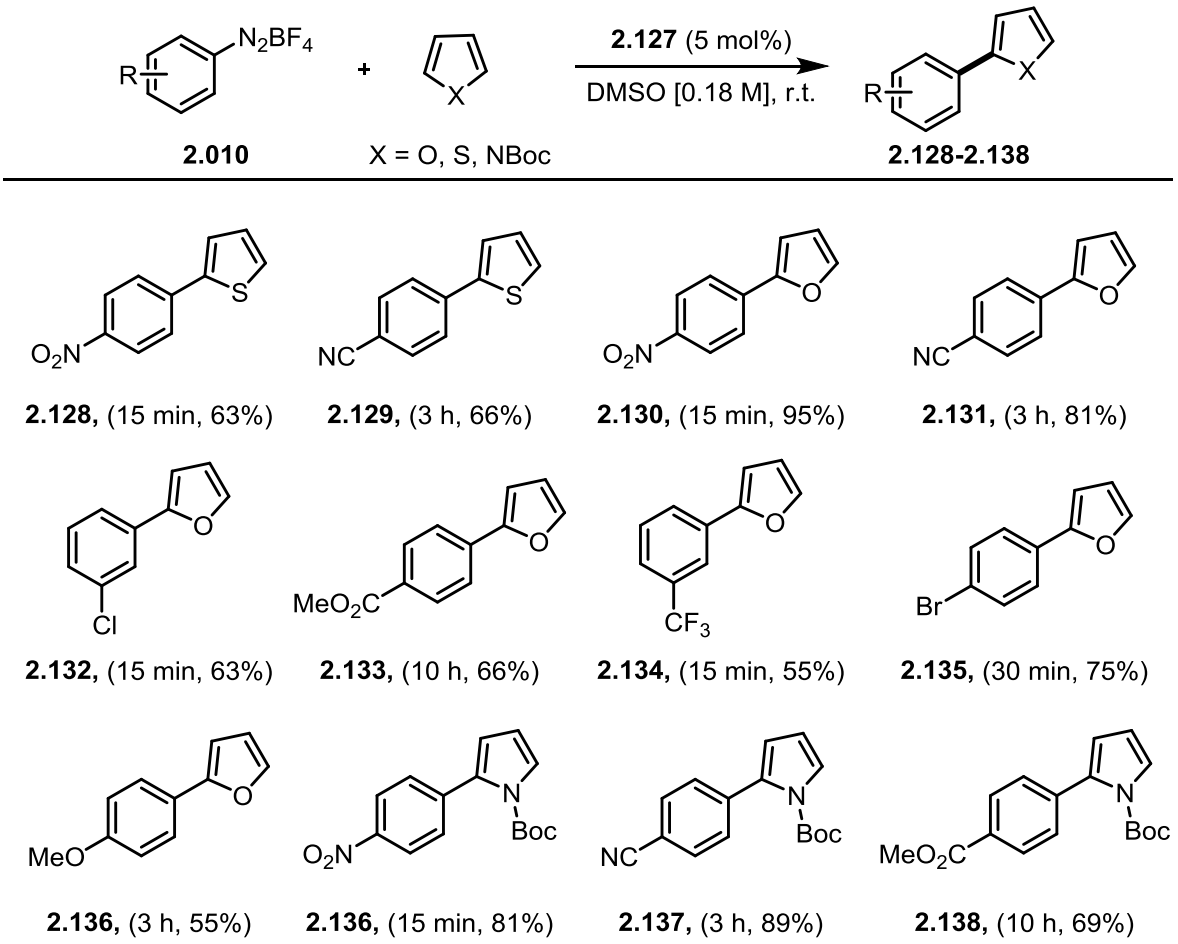
Entry	Solvent	thiophene (equiv.)	2.127 (mol%)	Time (min)	Yield of 2.128[a]
1	DMSO	5	10	120	34
2	DMSO	10	10	120	55
3	DMSO	20	10	10	75
4	CH_3CN	20	10	120	63
5	DCM	20	10	120	5
6	acetone	20	10	120	40
7	MeOH	20	10	120	60
8	DMF	20	10	20	57
9	DMSO	20	5	15	75
10	DMSO	20	2.5	60	73
11	DMSO	20	1	120	75
12	DMSO	20	—	15	5
13[b]	DMSO	20	5	80	70

Table 2.3. Optimisation conditions. Reactions were performed with **2.123** (0.11 mmol) in 0.6 ml Solvent [0.18 M] at r.t. [a] NMR yield. [b] The reaction was performed under argon atmosphere.

2.2.2.1.3 Scope of substrates for the hydrazine-catalysed Meerwein arylation

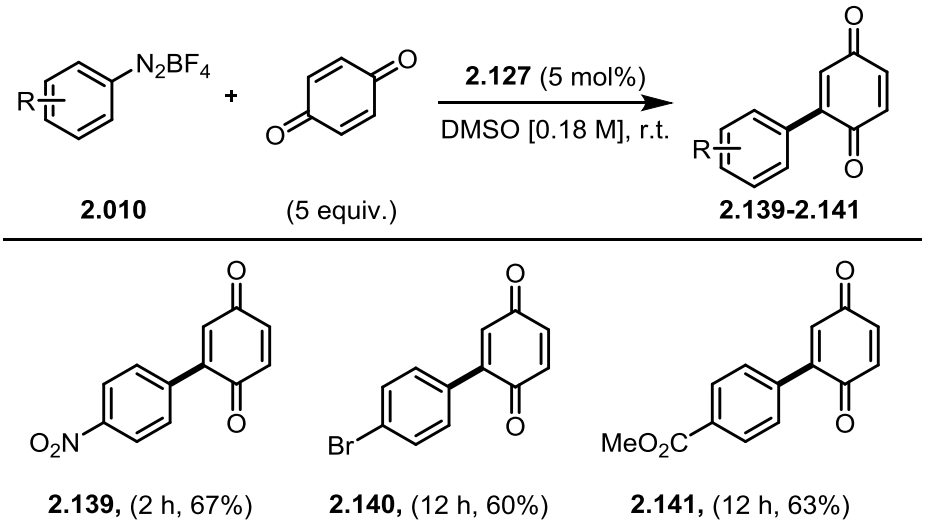
After optimising the reaction conditions, we wanted to test the substrate scope of this transformation. As shown in scheme 2.31, a range of functional groups, such as nitro, cyano, ester, and trifluoromethane were compatible with the reaction conditions. It became clear that the substituent on the aryl ring plays a vital role in the reaction time. While the reaction with nitro derivatives furnishes the products within 15 minutes, the presence of an ester group led to a longer reaction time (12 hours). This suggests that the electrophilicity of the diazonium

reagent impacts the rate of formation of the tetrazine. On the other hand, it also affects the radical propagation step due to their lower oxidation ability. Electron rich, 5-membered heteroarenes participated efficiently as coupling partners in this transformation leading to the cross-coupling products in good yields. Whilst electron-donating functionality had the effect of slowing the reaction down considerably, it was still possible to isolate product **2.136** in a 55% yield if the reaction was left for an extended period. Notably, the C-halogen bonds in **2.132** and **2.135** were not affected.



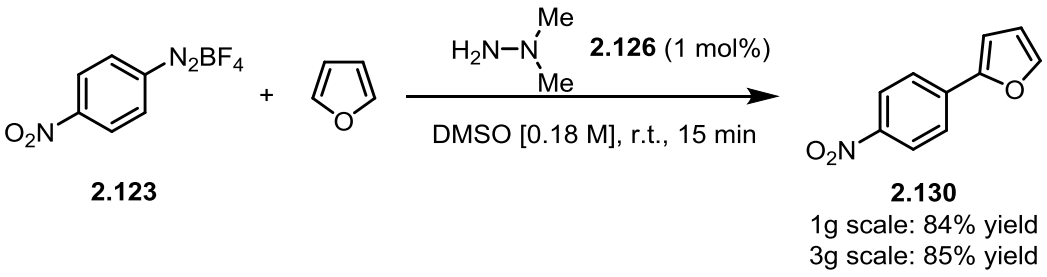
Scheme 2.31. Substrate scope of hydrazine-catalysed Meerwein arylation.

The arylation of quinones with diazonium salts is an interesting transformation due to the important role of functionalised quinones in medicinal chemistry. [180] Applying our optimised conditions using quinone as the coupling partner led to formation of the desired products **2.139-2.141** in good yields (Scheme 2.32). Notably, five equivalents of quinone were sufficient to afford the title compounds. The reaction time was notably longer than for the previously described reactions.



Scheme 2.32. Hydrazine-catalysed C-H arylation of quinones.

One of the strengths of this reaction is the low molecular weight of the catalysts, meaning that in larger scale reactions, a low weight of catalyst is still sufficient to achieve the transformation. This advantage was demonstrated in the scale up reaction between nitrobenzene diazonium salt **2.123** and furan. 1 mol% of *N*-Dimethylhydrazine **2.126** was used to achieve this coupling process yielding **2.130** in 85% yield in 15 minutes. This reaction shows the practicality of this method in achieving large scale reactions using very low-molecular weight catalysts (Only 7.6 mg (1 mol%) of the catalyst was used for 3 g scale reaction).



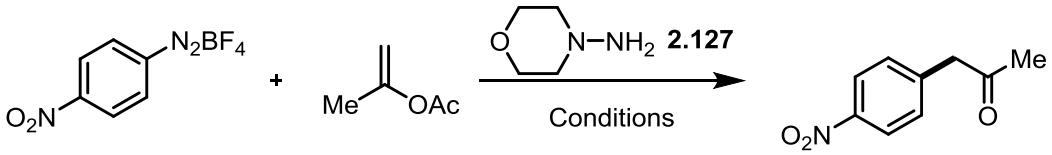
Scheme 2.33. Scale up reaction for Meerwein arylation with a low-molecular weight hydrazine catalyst.

2.2.2.1.4 Hydrazine-catalysed synthesis of α-aryl ketones

Given the scalable practicality of our developed catalytic system, we were eager to explore alternative reactions in which it could be employed. One example is the synthesis of α-aryl ketones from diazonium salts and enol acetate derivatives, a synthetically interesting transformation due to the importance of these motifs. This reaction has been achieved using copper catalyst by Raucher in 1983. [181] A photo-catalysed variant of this transformation was reported by König in 2012. [129] In both cases the reaction requires metal catalysts and

relatively harsh conditions, thus developing milder conditions would advantage this synthetic process.

For the optimisation of this process, we selected *p*-nitrophenyl diazonium salt **2.123** and isopropenyl acetate as model substrates (Table 2.4). When performing the reaction using five equivalents of isopropenyl acetate and with 20 mol% catalyst, the desired product **2.142** was delivered in 38% yield (Entry 1). Increasing the alkene loading and lowering the catalyst loading led to the formation of the desired product in 70% yield (Entry 2). Increasing the stoichiometry of the enol acetate further did not help, and lower yields were observed for reactions in which shorter and longer reaction times were used (Entries 3-5). Finally, screening other aprotic solvents did not improve the yield of the desired product (Entries 6-8).

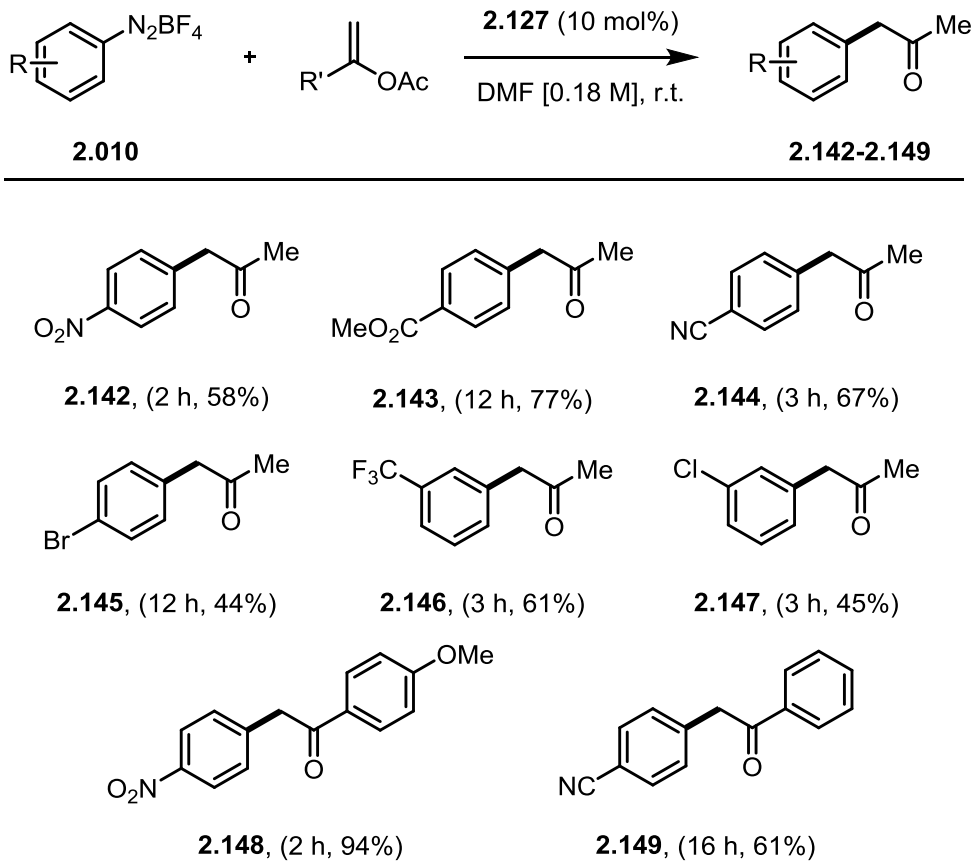


2.123 **2.142**

Entry	Solvent	Isopropenyl acetate equiv.	2.127 (mol%)	Time (h)	Yield of 2.142[a]
1	DMF	5	20	2	38
2	DMF	10	10	2	70
3	DMF	20	10	0.5	52
4	DMF	10	10	0.5	48
5	DMF	10	10	16	62
6	CH_3CN	10	10	2	30
7	DMSO	10	10	2	42
8	DMF/H_2O (1/1)	10	10	2	50

Table 2.4. Optimisation conditions. Reactions were performed with **2.123** (0.11 mmol) in 0.6 ml Solvent [0.18 M] at r.t. [a] NMR yield.

Under the optimised reaction conditions, several aryl diazonium salts were transformed into their α-aryl ketones when treated with alkenyl acetates (Scheme 2.34). A series of α-aryl ketones were synthesised in moderate to good yield. The reaction again tolerated several functional groups, such as nitro, ester and cyano groups. Mechanistically, this transformation hinges on the loss of an acylium cation following the aryl radical addition.



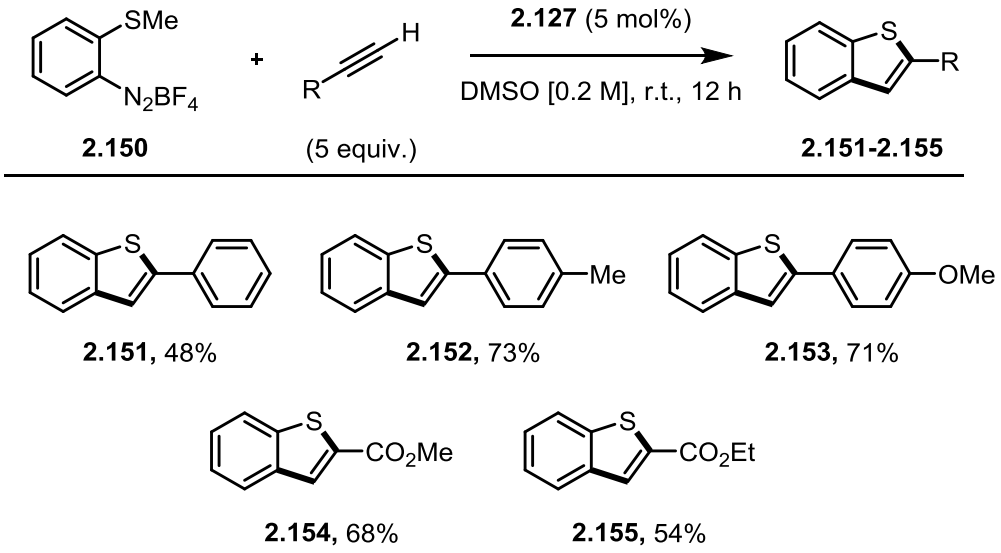
Scheme 2.34. Hydrazine-catalysed synthesis of α-aryl ketones from diazonium salts.

2.2.2.1.5 Hydrazine-catalysed synthesis of 2-substituted benzothiophenes

As a further example of the applicability of our system, we decided to investigate the synthesis of benzothiophene derivatives, which has attracted much attention in recent years due to their wide application in a range of fields of chemistry, for example medicinal chemistry. The use of 2-thiomethyl-diazonium salt **2.150** with terminal alkynes for the synthesis of 2-substituted thiophenes using transition metal catalyst has been previously reported by the groups of Zanardi in 1985. [182] In 2012, the group of König has achieved this transformation employing photocatalysis. [183]

Extensive optimisation of this process was not required, as 4-aminomorpholine **2.127** was at once able to catalyse this transformation furnishing the corresponding benzothiophenes in

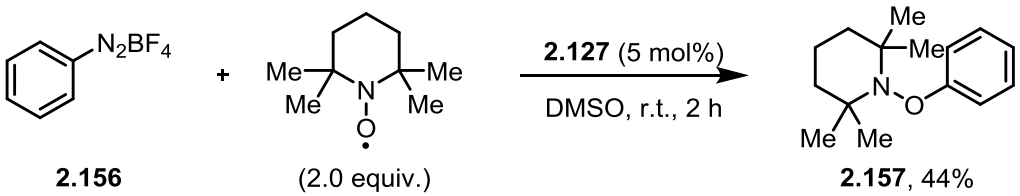
good to moderate yields from the very first attempts (Scheme 2.35). A number of terminal alkynes tolerated the reaction conditions leading to the formation of the benzothiophenes in a regioselective manner. The fact that this reaction proceeds with high regioselectivity stems from the preferred addition of the aryl radical onto the less hindered end of the alkyne.



Scheme 2.35. Hydrazine-catalysed synthesis of benzophenones from diazonium salts.

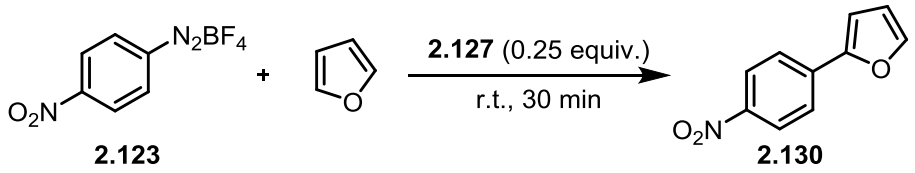
2.2.2.1.6 Mechanistic considerations

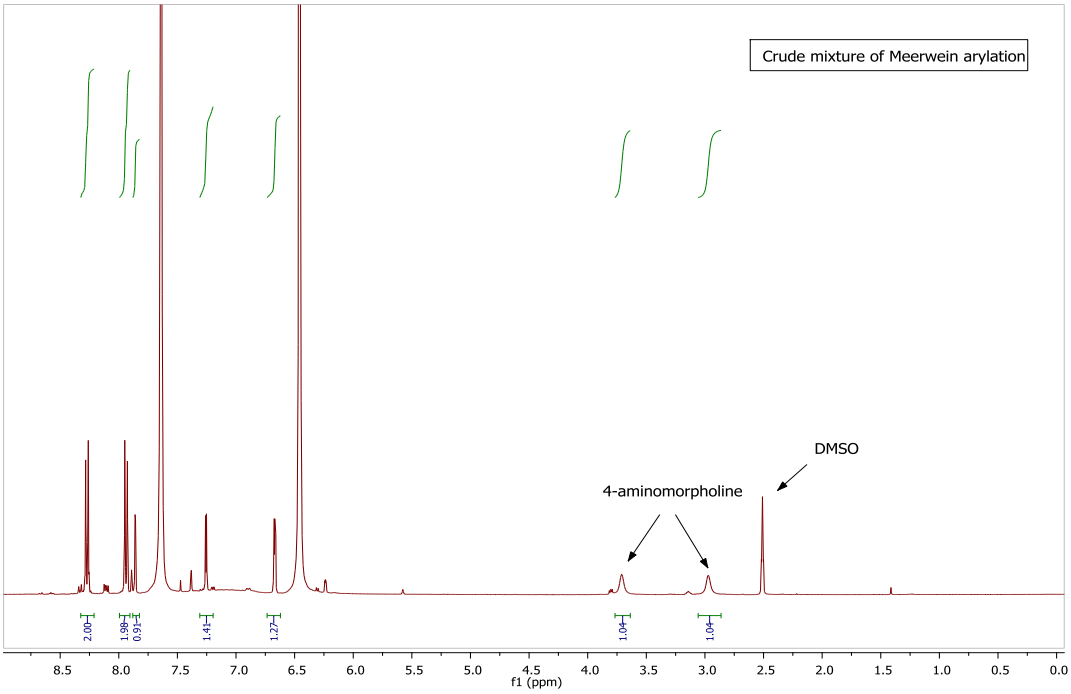
Several experiments for investigating the reaction mechanism were carried out. First, we wanted to validate the generation of an aryl radical intermediate. Exposing phenyldiazonium salt **2.156** to catalytic amounts of 4-aminomorpholine **2.127** and two equivalents of TEMPO (Scheme 2.36) resulted in a covalent adduct, 2,2,6,6-tetramethyl-1-phenoxypiperidine **2.157**, in 44% yield. This product appears to result from the trapping of the purported phenyl radical with TEMPO in a radical-radical coupling reaction.

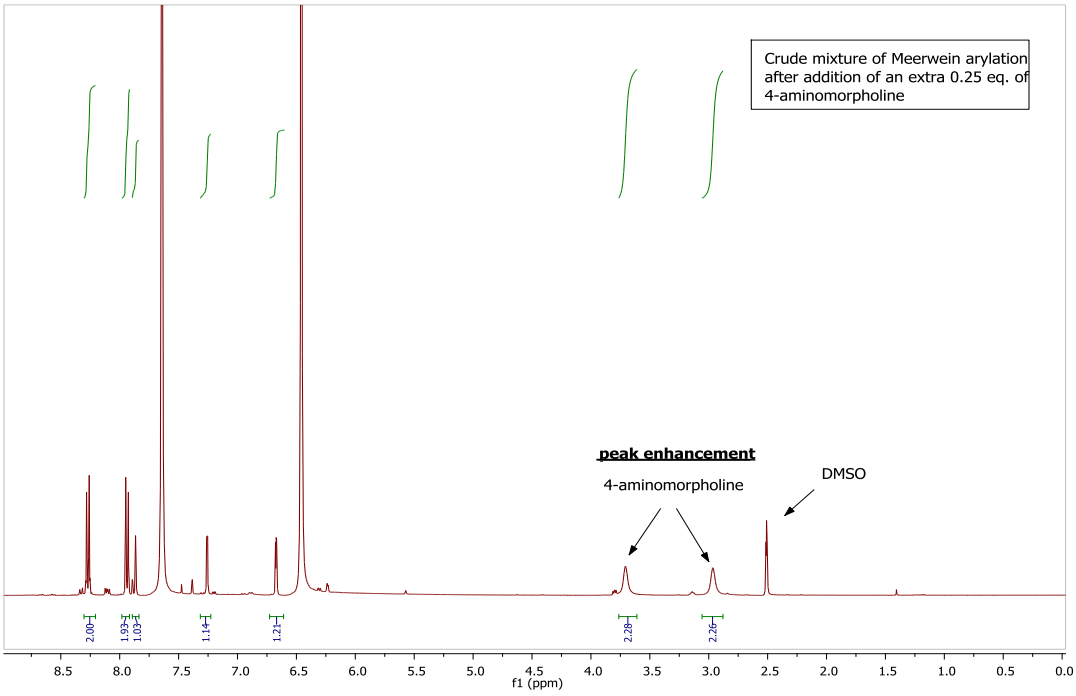


Scheme 2.36. Trapping the phenyl radical intermediate with TEMPO.

Further experiments to demonstrate the catalytic nature of the hydrazine were performed. Standard reaction with *p*-nitrophenyl diazonium salt **2.123** and furan in d_6-DMSO using (0.25 equiv.) of 4-aminomorpholine **2.127** was performed. After stirring for 30 min at room temperature, the NMR of the reaction mixture was recorded (Scheme 2.37 a).





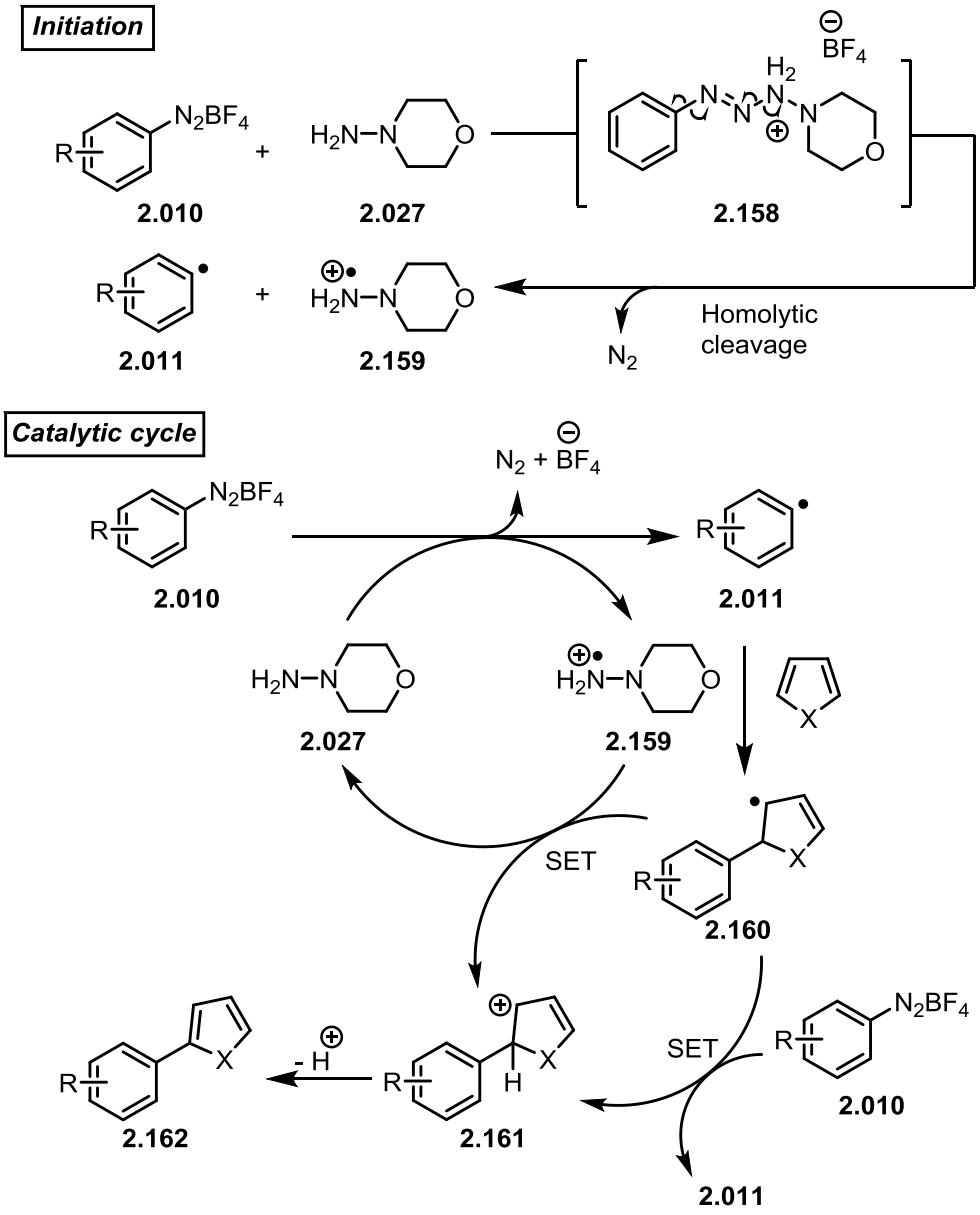


Scheme 2.37. ^{1}H-NMR spectra of the crude reaction mixture with: a) (0.25 equiv.) of **2.127** for 30 min. b) Addition of extra (0.25 equiv.) of **2.127**.

An extra 0.25 equivalents of **2.127** was then added to the reaction mixture and a second NMR was recorded (Scheme 2.37 b). The presence of 4-aminomorpholine **2.127** was confirmed by ^{1}H-NMR by two peak enhancements at 2.97 and 3.71 ppm after addition of an extra 0.25 equivalents of **2.127**.

The presence of 4-aminomorpholine **2.127** following completion of the reaction was further confirmed through LC-MS analysis of the crude reaction mixture.

Based on our experiments and the previous studies, we propose the following mechanism for this transformation (Scheme 2.38). The catalytic cycle is initiated via reduction of diazonium salt **2.010** by the hydrazine catalyst **2.127**, presumably through the homolytic decomposition of a rather unstable, positively charged tetrazene **2.158**. This cleavage leads to the generation of both aryl radical **2.011** and amine radical cation **2.159** accompanied by release of nitrogen gas. Radical **2.011** is then trapped by the radical acceptor, to form radical adduct **2.160**. Subsequent oxidation of **2.160** to the corresponding carbocation **2.161** can proceed by two possible pathways: either via reduction of aryl diazonium salt **2.010** to aryl radical **2.011** or a back single-electron-transfer to **2.159**. The presence of the hydrazine catalyst at the end of the reaction can be considered to support the second possibility. These pathways allow the regeneration of the hydrazine catalyst **2.127** and aryl radical **2.011**, enabling turnover. Finally, deprotonation of intermediate **2.161** furnishes adducts **2.162**.



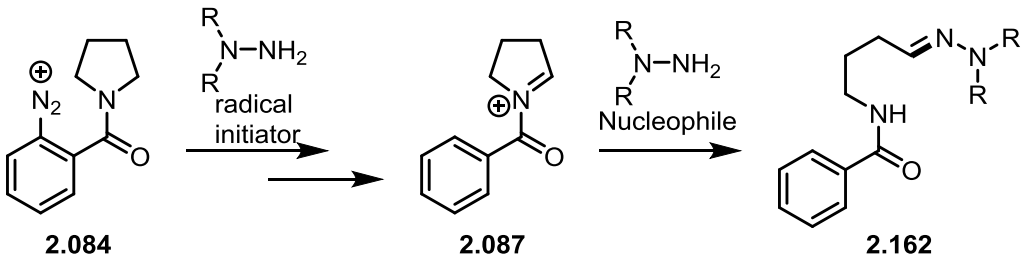
Scheme 2.38. Proposed mechanism for hydrazine-catalysed Meerwein reaction.

2.2.2.2 Metal-free, hydrazine catalysed α-amino C-H functionalisation: when the catalyst is also the nucleophile.

2.2.2.2.1 Introduction and aim of the project

The construction of C-N bonds is of significant importance in organic chemistry, given the wide presence of nitrogen in biologically relevant compounds. A variety of amination methods have been developed over the last years. In particular, hydrazines constitute useful compounds for the formation of C-N and C=N bonds, through processes ranging from classical condensation reactions with carbonyl derivatives to transition metal-catalysed transformations. [184]

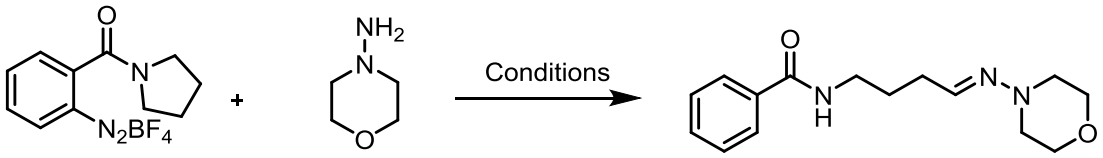
Given our prior success in the use of hydrazines as reductive catalysts for diazonium salts and on hydrogen migration in aryl radicals, we aimed to merge the two concepts (Scheme 2.39). It was postulated that the use of a stoichiometric quantity of hydrazine in conjunction with aryl diazonium salt **2.084** should promote the generation of *N*-acyl-iminium ion **2.087** which could be subsequently trapped by the hydrazine to furnish hydrazone adducts **2.162**. This process would provide a mechanistically interesting approach to C-N bond construction, utilising the hydrazine in a dual role as both the catalyst and the nucleophile.



Scheme 2.39. Proposed strategy for radical-initiated C-N bond formation with hydrazines.

2.2.2.2.2 Optimising reaction conditions

For our new investigations, we again selected diazonium salt **2.084** and 4-aminomorpholine **2.127** as model substrates (Table 2.5). When performing the reaction using one equivalent of 4-aminomorpholine **2.127** with diazonium salt **2.084** in DMSO, the desired hydrazone **2.162** was observed in moderate yield (Entry 1). Screening of other solvents showed an improvement in yield in the case of acetonitrile, while dioxane and heptane led to no detectable product (Entries 2-5). Increasing the hydrazine loading to 1.3 equivalents led to the formation of the desired product in 76% isolated yield after just 30 minutes (Entry 6). Extending the reaction time or further increasing the hydrazine loading (Entries 7 and 8) did not lead to better results.



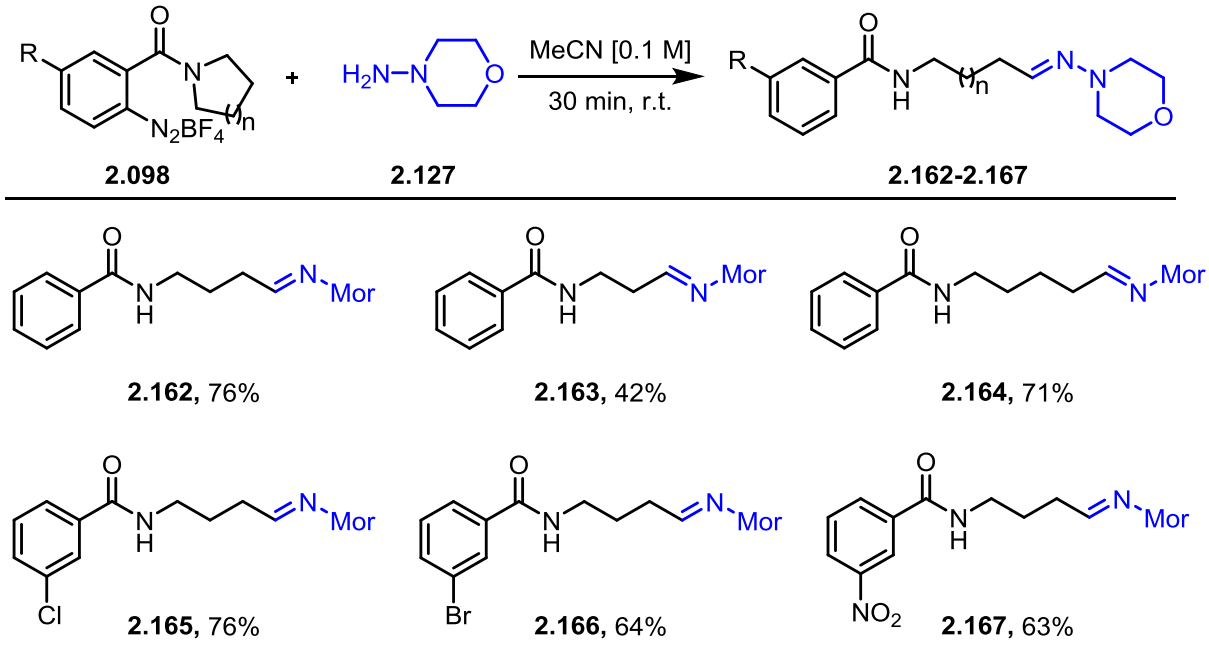
2.084 **2.127** **2.162**

Entry	Solvent	2.127 (equiv.)	Time (h)	Yield of 2.162 [a]
1	DMSO	1.0	2	30
2	DMF	1.0	2	22
3	CH_3CN	1.0	2	61
4	dioxane	1.0	2	0
5	hexane	1.0	2	0
6	CH_3CN	1.3	0.5	76[b]
7	CH_3CN	1.3	1	75
8	CH_3CN	2.0	0.5	76

Table 2.5. Optimisation of reaction conditions. Reactions were performed at [0.1 M] at r.t. [a] NMR yield. [b] isolated yield.

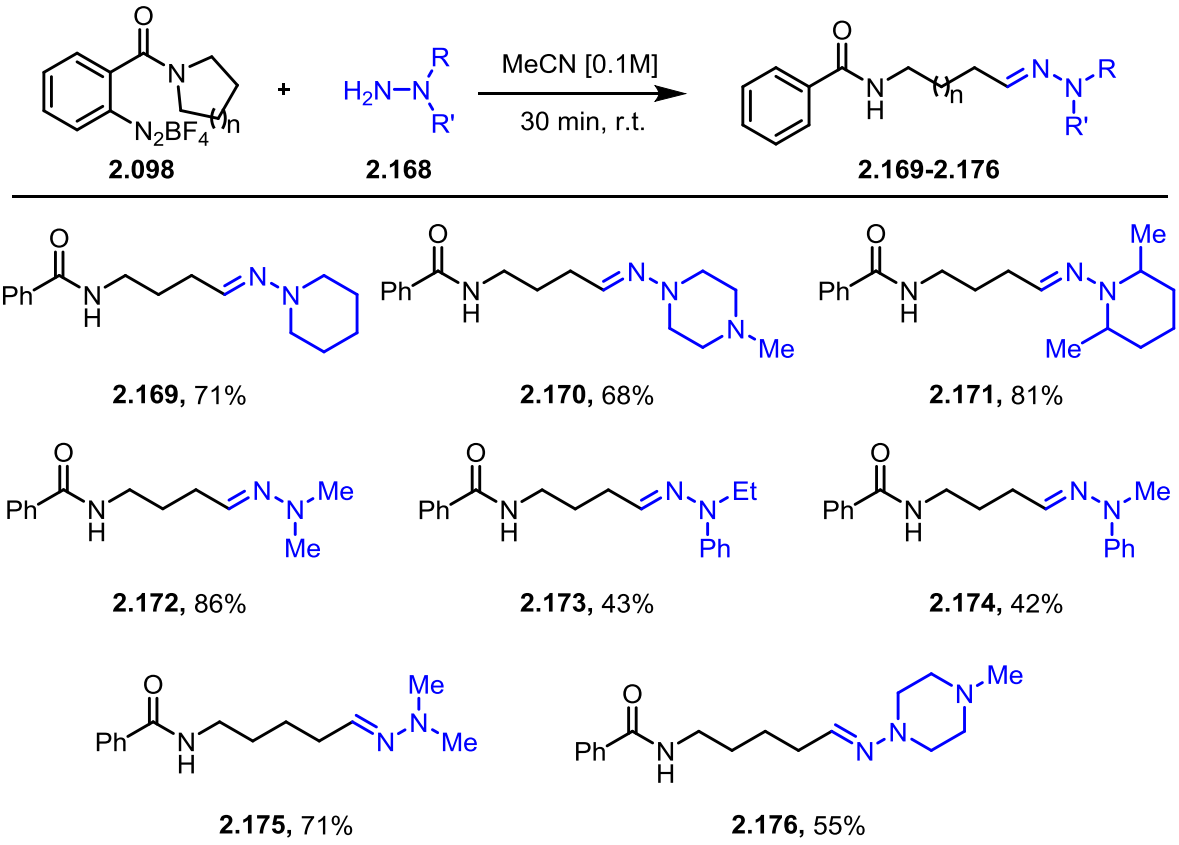
2.2.2.2.3 Scope of substrates and derivatisation of the hydrazones

With suitable reaction conditions in hand, we studied the scope of this transformation. As seen in scheme 2.40, different cyclic amines (pyrrolidine, azetidine and piperidine) were suitable substrates for this reaction and led the formation of the expected hydrazones in moderate to good yields (**2.162**-**2.164**). Notably, the small ring size resulted in a reduction in yield, but the product could still be isolated in a synthetically acceptable 42% yield. Substrates containing functional groups on the aromatic ring, affording opportunities for further synthetic elaboration, were smoothly activated and gave the desired adducts in good yields (**2.165**-**2.167**).



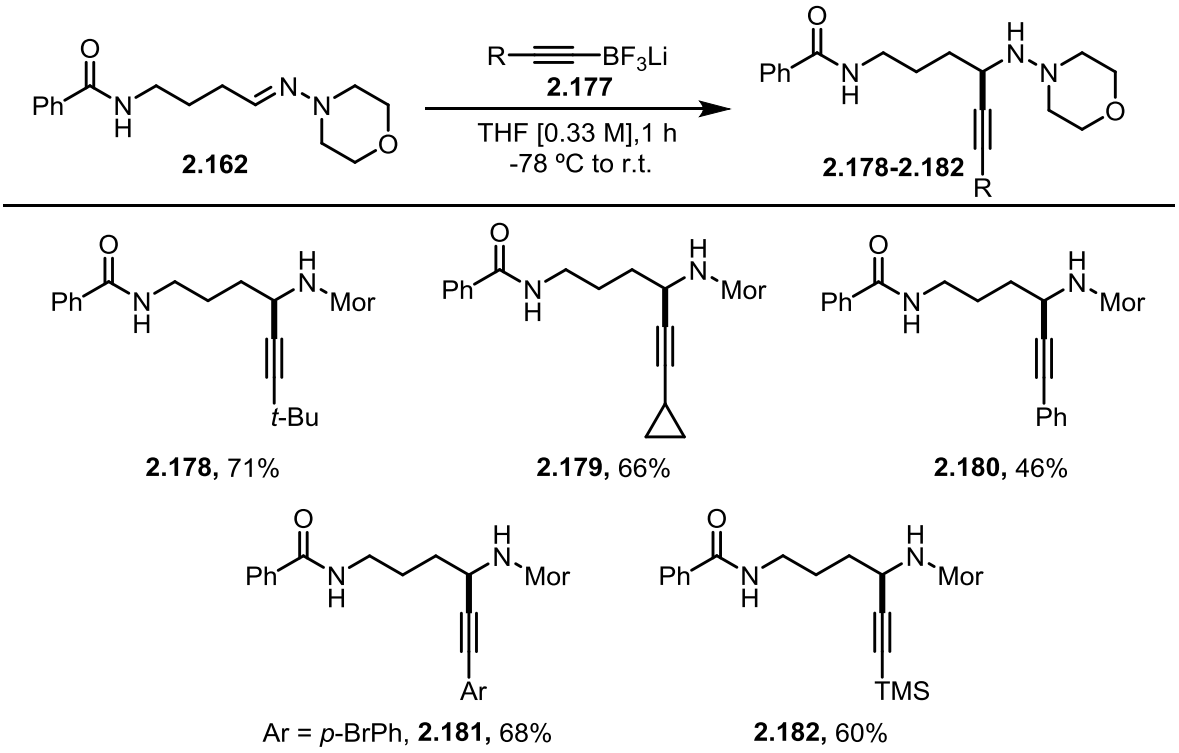
Scheme 2.40. Scope of substrates on cyclic amines.

Differentially substituted hydrazines also worked well in this transformation (Scheme 2.41). Hydrazines bearing piperidine, *N*-methyl pyrazine and more sterically demanding 2,6-dimethylpiperidine residues were tolerated and delivered the desired products in good yields (**2.169-2.171**). Dimethyl hydrazine and arylated hydrazines also led to the expected products in moderate to high yield (**2.172-2.174**). As demonstrated in Scheme 2.41, the piperidine-derived diazonium salt also underwent the transformation in similar yields to the pyrrolidine analogue (**2.175** and **2.176**).



Scheme 2.41. Scope of substrates on hydrazine moieties.

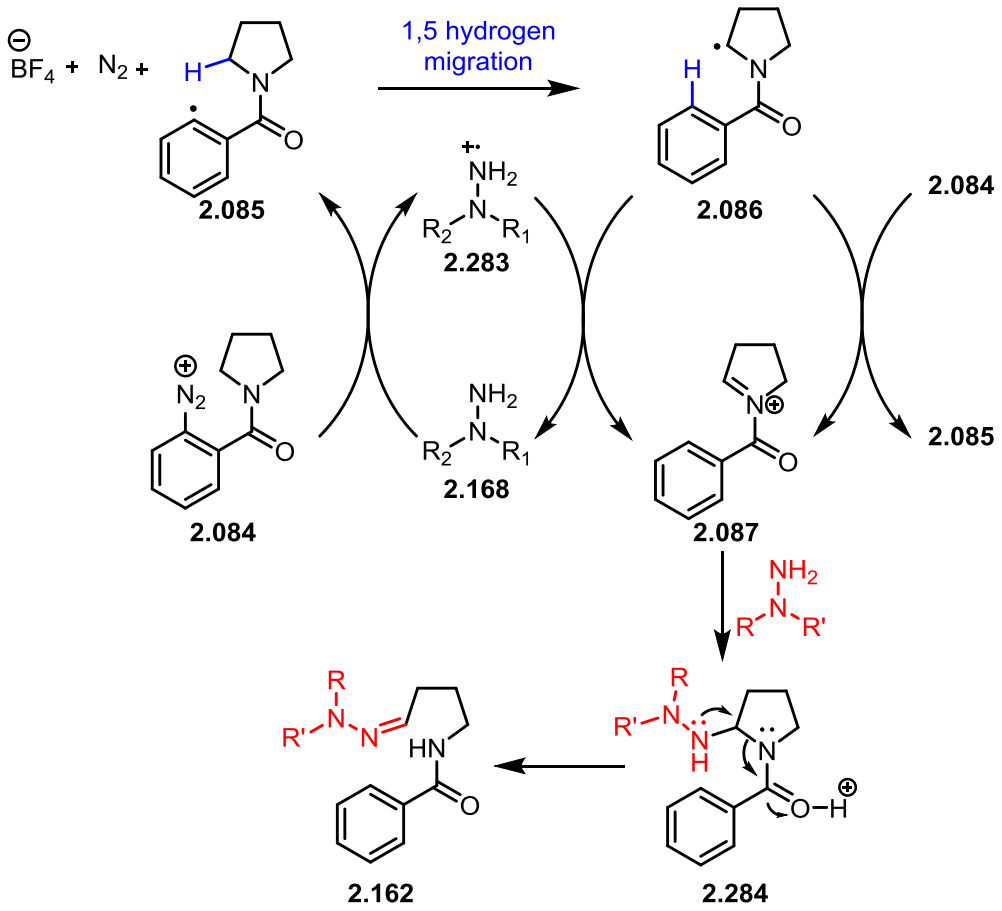
The presence of a hydrazone moiety in the products of these reactions suggests opportunities for further functionalisation. Treatment of the hydrazones **2.162** with alkynyltrifluoroborate nucleophiles **2.177** led to the products of nucleophilic addition **2.178-2.182** (Scheme 2.42). A variety of alkynes participated efficiently in this C-C bond formation. Aliphatic **2.178**, cyclic **2.179**, arylated **2.180** and **2.181** and silylated **2.182** alkynes were smoothly introduced. This functionalisation led to the formation of protected 1,4 diamines, a family of compounds with multiple interesting biological properties.



Scheme 2.42. Scope of alkynes for C-C bond formation.

2.2.2.2.4 Mechanism of this transformation

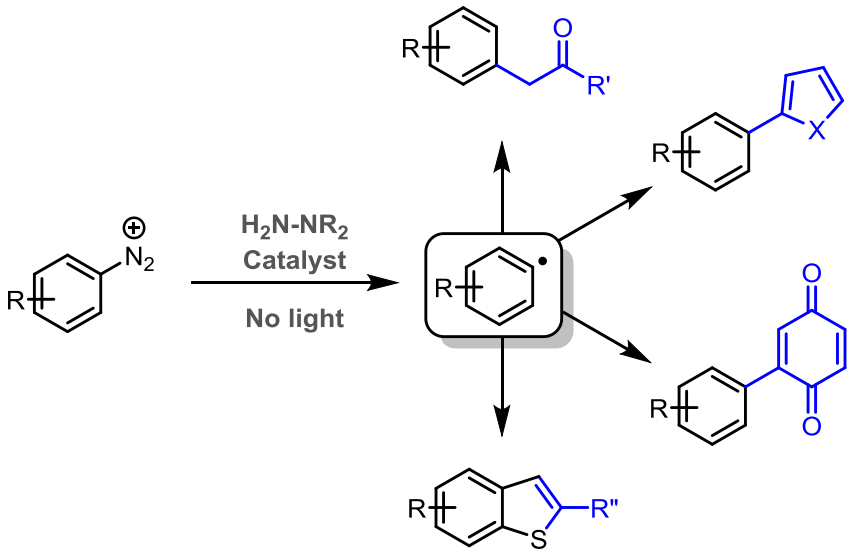
Based on previous studies, a possible mechanism for this transformation was proposed (Scheme 2.43). As discussed earlier, the reaction between hydrazine **2.168** and diazonium salt **2.084** is believed to lead to a tetrazene intermediate, which spontaneously fragments to generate aryl radical **2.085** with loss of N_2. Aryl radical **2.085** undergoes 1,5-hydrogen atom transfer furnishing α-amino radical intermediate **2.086**. The latter undergoes a subsequent oxidation, either by the amine radical carbocation **2.283** furnishing intermediate **2.087** and regenerating hydrazine **2.168**, or by a chain propagation, reacting with diazonium salt **2.084** and releasing again aryl radical **2.085**. A nucleophilic capture of hydrazine **2.168** by intermediate **2.087** will then form **2.284**. Finally, as stoichiometric acid is generated as a by-product of the reaction, intermediate **2.284** will undergo ring opening delivering hydrazone **2.162**. It is important to mention that radical- radical coupling between **2.087** and **2.283** is not expected to happen, in accordance with our unfruitful attempts to trap the α-amino radical **2.087**.



Scheme 2.43. Plausible mechanism for the hydrazones formation.

2.3. Conclusion

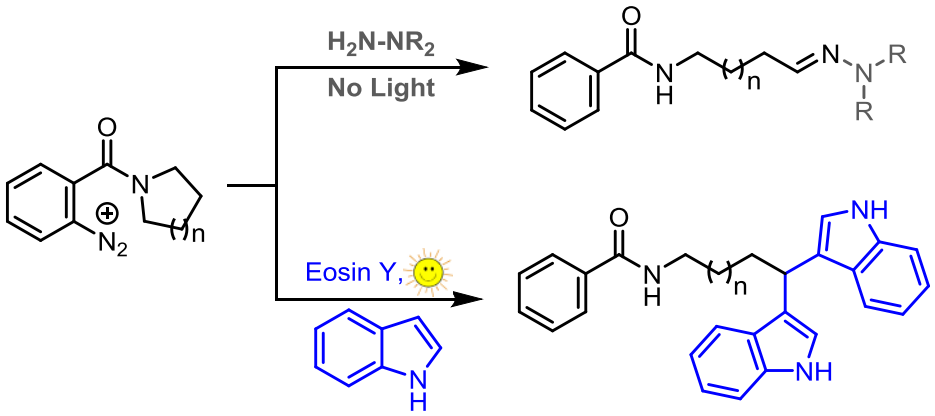
We have developed a family of low molecular-weight, organic catalysts that promote a range of C-C bond forming reactions of diazonium salts. These processes were achieved without the need for any metal adjuvant or irradiation with light. The newly discovered catalysts efficiently promoted a range of transformations with competitive yields (Scheme 2.44). Scale up reactions to show the practicality of these catalysts was also carried out and mechanistic studies supported their role in the reduction of diazonium salts and generation of the corresponding aryl radicals.



Scheme 2.45. Hydrazines as catalytic reducing agents for diazonium salts.

In addition, we have achieved a metal-free, mild process for redox-neutral α-amino functionalisation with concomitant C-N as well as C-C bond formation (Scheme 2.46). In this case, hydrazines played a dual role; as both the catalyst and the nucleophile.

The same azacarbenium intermediate could be captured by indole derivatives, delivering Bis(indolyl)alkanes.



Scheme 2.46. α-Amino functionalisation with C-N and C-C bond formation.

Chapter III: Experimental section

3.1. General conditions

All glassware was oven dried at 110 °C before use and all reactions were performed under an atmosphere of argon unless otherwise stated. All reagents were used as received from commercial suppliers unless otherwise stated. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with Kieselgel F_{254} with 0.2 mm thickness. Visualisation was achieved by a combination of ultraviolet light (254 nm) and potassium permanganate or phosphomolybdic acid solutions. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.).

^{1}H- and ^{13}C-NMR spectra were recorded on either Bruker DPX-300, AV-400 (^{1}H: 400 MHz, ^{13}C: 100.8 MHz), or AV 600 spectrometers. ^{19}F-NMR spectra were recorder on Bruker DPX-300, AV-700 spectrometer. Chemical shifts (δ) values are presented in parts per million (ppm), referenced to the solvent peak ($CDCl_3$, defined at δ 7.26 for ^{1}H, δ 77.0 for ^{13}C; $(CD_3)_2SO$: δ 2.50 for ^{1}H, δ 39.5 for ^{13}C and $(CD_3)_2CO$: δ 2.05 for ^{1}H, δ 206.5 for ^{13}C.

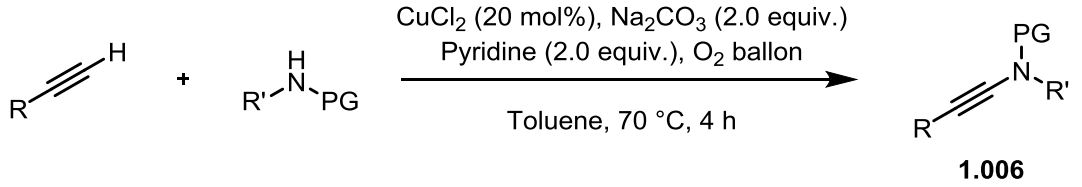
Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = doublet of doublet, dt = doublet of triplets, tt = triplet of triplet), coupling constants (*J*, Hz) and integration.

Mass spectra were measured on a Finnigan MAT 8200 (70 eV) or MAT 8400 (70 eV) by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques. High resolution mass spectra were obtained on a Bruker APEX III FT-MS (7 T magnet). All masses are given in atomic units/elementary charge (*m*/*z*) and reported in percentage relative to the basic peak.

Infrared spectra were recorded with a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Triflic anhydride Tf_2O was distilled from appropriate drying agents prior to use.

3.2 Ynamides

3.2.1 General procedure for the synthesis of ynamides:

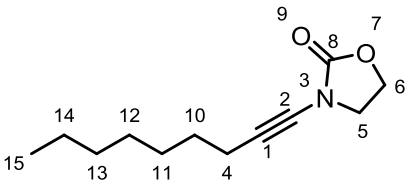


1.006

To a flask were added $CuCl_2$ (20 mol%), 2-oxazolidone or sulphonamide (5.0 equiv.) and Na_2CO_3 (2.0 equiv.). The reaction flask was purged with oxygen for 15 min. A solution of pyridine (2.0 equiv.) in dry toluene (0.2 M) was then added. A balloon filled with oxygen was connected to the flask and the flask was heated at 70 °C. After 15 min, a solution of alkyne (1.0 equiv.) in dry toluene (0.2 M) was added over 4 h using syringe pump. After this addition was completed, the mixture was cooled down to room temperature. Reaction mixture was then filtered over celite, washed with ethyl acetate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using (heptane/ethyl acetate = 3/1) as eluent to give the title ynamides.

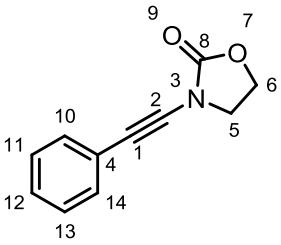
Spectroscopic data for the ynamides match those reported in the literature. [17,24,53]

3-(Non-1-yn-1-yl)oxazolidin-2-one (1.006a)



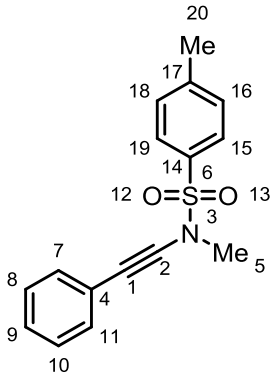
(Colourless oil, 62%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 4.42-4.38 (m, 2H, H_6), 3.88-3.84 (m, 2H, H_5), 2.29 (t, *J* = 7.2 Hz, 2H, H_4), 1.55-1.49 (m, 2H, H_{10}), 1.41-1.35 (m, 2H, H_{11}), 1.32-1.26 (m, 6H, $H_{12,13,14}$), 0.88 (t, *J* = 7.0 Hz, 3H, H_{15}).

3-(Phenylethynyl)oxazolidin-2-one (1.006b)



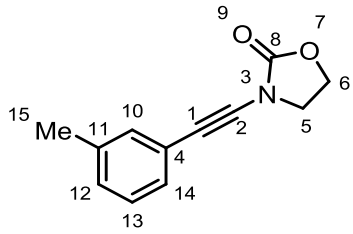
(White solid, 74%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.46-7.42 (m, 2H, $H_{10,14}$), 7.32-7.28 (m, 3H, $H_{11,12,13}$), 4.48 (t, *J* = 7.2 Hz, 2H, H_6), 4.01 (t, *J* = 7.3 Hz, 2H, H_5).

***N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide** (**1.006c**)



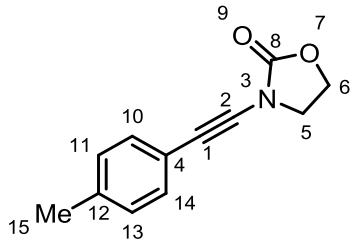
(White solid, 62%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.84 (d, *J* = 8.3 Hz, 2H, $H_{15,19}$), 7.38-7.35 (m, 4H, $H_{7,11,16,18}$), 7.30-7.28 (m, 3H, $H_{8,9,10}$), 3.16 (s, 3H, H_5), 2.46 (s, 3H, H_{20}).

3-(*m*-tolylethynyl)oxazolidian-2-one (1.006d)



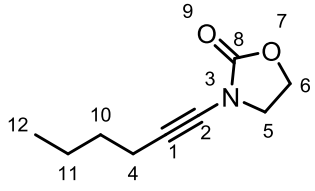
(White solid, 53%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.29-7.08 (m, 4H, $H_{10,12,13,14}$), 4.49 (t, *J* = 8.0 Hz, 2H, H_6), 4.01 (t, *J* = 8.0 Hz, 2H, H_5), 2.32 (s, 3H, H_{15}).

3-(*p*-tolylethynyl)oxazolidin-2-one (1.006e)



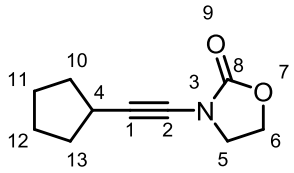
(White solid, 71%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.33 (d, *J* = 8.0 Hz, 2H, $H_{10,14}$), 7.11 (d, *J* = 8.0 Hz, 2H, $H_{11,13}$), 4.46 (t, *J* = 7.2 Hz, 2H, H_6), 4.01-3.97 (m, 2H, H_5), 2.34 (s, 3H, H_{15}).

3-(Hex-1-yn-1-yl)oxazolidin-2-one (1.006f)



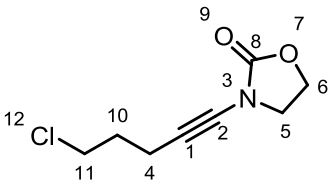
(Colourless oil, 43%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 4.43 (t, *J* = 8.2 Hz, 2H, H_6), 3.89 (t, *J* = 8.2 Hz, 2H, H_5), 2.32 (t, *J* = 7.1 Hz, 2H, H_4), 1.56-1.50 (m, 2H, H_{10}), 1.46-1.39 (m, 2H, H_{11}), 0.93 (t, *J* = 7.3 Hz, 3H, H_{12}).

3-(Cyclopentylethynyl)oxazolidin-2-one (1.006g)



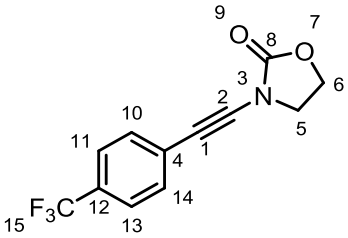
(Colourless oil, 35%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 4.32 (t, *J* = 8.2 Hz, 2H, H_6), 3.79 (t, *J* = 8.2 Hz, 2H, H_5), 2.70-2.61 (m, 1H, H_4), 1.90-1.82 (m, 2H, H_{10}), 1.69-1.60 (m, 2H, H_{13}), 1.58-1.44 (m, 4H, $H_{11,12}$).

3-(5-Chloropent-1-yn-1-yl)oxazolidin-2-one (1.006h)



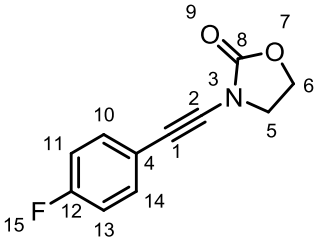
(Colourless oil, 66%),**^{1}H-NMR (400 MHz, $CDCl_3$):** δ 4.44 (t, *J* = 7.9 Hz, 2H, H_6), 3.91 (t, *J* = 8.0 Hz, 2H, H_5), 3.67 (t, *J* = 6.4 Hz, 2H, H_{11}), 2.54 (t, *J* = 6.8 Hz, 2H, H_4), 2.05-1.97 (m, 2H, H_{10}).

3-((4-(Trifluoromethyl)phenyl)ethynyl)oxazolidin-2-one (1.006i)



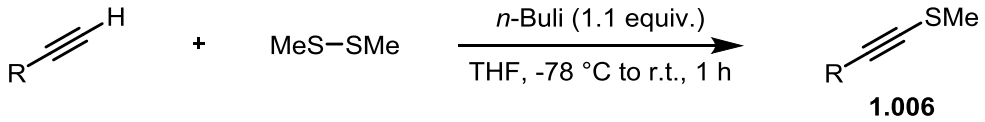
(Yellow solid, 68%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.53-7.45 (m, 4H, $H_{10,11,13,14}$), 4.42 (t, *J* = 7.9 Hz, 2H, H_6), 3.90 (t, *J* = 8.0 Hz, 2H, H_5).

3-((4-Fluorophenyl)ethynyl)oxazolidin-2-one (1.006j)



(White solid, 61%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.44-7.41 (m, 2H, $H_{10,14}$), 7.03-6.98 (m, 2H, $H_{11,13}$), 4.48 (t, *J* = 8.0 Hz, 2H, H_6), 3.99 (t, *J* = 8.0 Hz, 2H, H_5).

3.2.2 General procedure for the synthesis of thioalkynes:

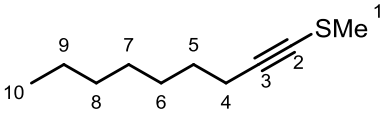


1.006

In a dry argon-flushed Schlenk flask, alkyne (1.0 equiv., 5 mmol) was dissolved in THF (5 ml). The solution was cooled to -78 °C and *n*-BuLi (1.1 equiv., 1.6 M in hexane, 5.5 mmol) was added dropwise. After 10 min of stirring at -78 °C, dimethyl disulphide (1.2 equiv., 6 mmol) was added and the solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuum. The crude product was purified by column chromatography (Al_2O_3 neutral, heptane).

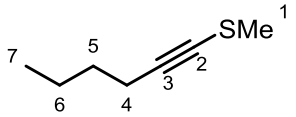
Spectroscopic data for the thioalkynes match those reported in the literature. [53]

Methyl(non-1-yn-1-yl)sulfane (1.006k)



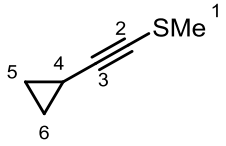
(Colourless oil, 40%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 2.35 (s, 3H, H_1), 2.28 (t, *J* = 7.1 Hz, 2H, H_4), 1.54-1.47 (m, 2H, H_5), 1.39-1.27 (m, 8H, $H_{6,7,8,9}$), 0.89 (t, *J* = 7.0 Hz, 3H, H_{10}).

Hex-1-yn-1-yl(methyl)sulfane (1.006l)



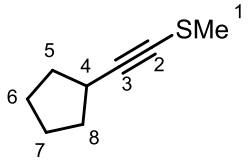
(Colourless oil, 41%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 2.37 (s, 3H, H_1), 2.31 (t, *J* = 6.9 Hz, 2H, H_4), 1.56-1.37 (m, 4H, $H_{5,6}$), 0.92 (t, *J* = 7.3 Hz, 3H, H_7).

(Cyclopropylethynyl)(methyl)sulfane (1.006m)



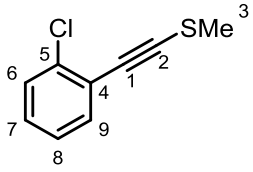
(Colourless oil, 52%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 2.33 (s, 3H, H_1), 1.36-1.30 (m, 1H, H_4), 0.81-0.76 (m, 2H, H_5), 0.75-0.69 (m, 2H, H_6).

(Cyclopentylethynyl)(methyl)sulfane (1.006n)



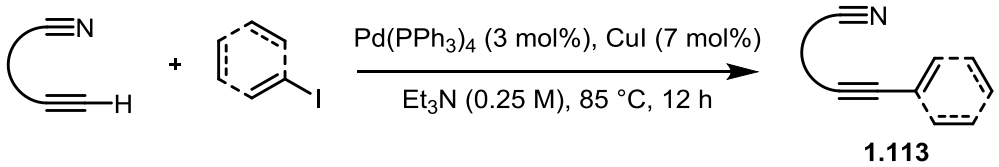
(Colourless oil, 55%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 2.69 (m, 1H, H_4), 2.34 (s, 3H, H_1), 1.94-1.85 (m, 2H, H_5), 1.74-1.67 (m, 2H, H_8), 1.63-1.51 (m, 4H, $H_{6,7}$).

((2-Chlorophenyl)ethynyl)(methyl)sulfane (1.006o)



(Colourless oil, 60%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.43-7.41 (m, 1H, H_6), 7.39-7.36 (m, 1H, H_9), 7.21-7.18 (m, 2H, $H_{7,8}$), 2.52 (s, 3H, H_3).

3.2.3 General procedure for the synthesis of cyanoalkynes:

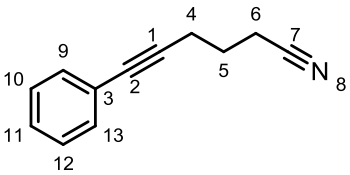


1.113

A dry Schlenk was charged with the mixture of cyanoalkyne (1.0 equiv., 3 mmol), $Pd(PPh_3)_4$ (3 mol%) and CuI (7 mol%) and evacuated and recharged with Argon for 3 times. After trimethylamine Et_3N (12 ml) and iodoarene/alkene (1.2 equiv., 3.6 mmol) were added by syringes, the mixture was stirred at 85 °C for 12 h. The mixture was then cooled down to room temperature, then $NaHCO_3$ aq. (10 ml) was added and the mixture was extracted with DCM (3 x 15 ml), dried on anhydrous $MgSO_4$. Evaporation of the solvent followed by purification on silica gel (heptane/ethyl acetate: 5/1) provided the title compound.

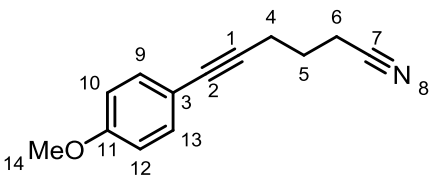
Spectroscopic data for the cyanoalkynes match those reported in the literature. [185]

6-Phenylhex-5-ynenitrile (1.113a)



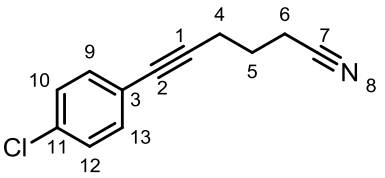
(Yellow oil, 85% yield), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.41-7.39 (m, 2H, $H_{9,13}$), 7.31-7.28 (m, 3H, $H_{10,11,12}$), 2.61 (t, *J* = 6.7 Hz, 2H, H_6), 2.56 (t, *J* = 7.2Hz, 2H, H_4), 2.00-1.93 (m, 2H, H_5).

6-(4-Methoxyphenyl)hex-5-ynenitrile (1.113b)



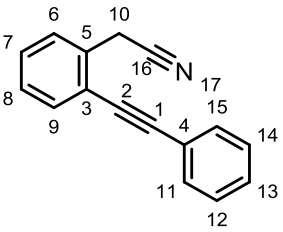
(Yellow oil, 59% yield), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.33 (d, *J* = 8.9 Hz, 2H, $H_{9,13}$), 6.82 (t, *J* = 8.9 Hz, 2H, $H_{10,12}$), 3.81 (s, 3H, H_{14}), 2.58 (t, *J* = 6.7 Hz, 2H, H_6), 2.56 (t, *J* = 7.1 Hz, 2H, H_4), 1.95 (m, 2H, H_5).

6-(4-Chlorophenyl)hex-5-ynenitrile (1.113c)



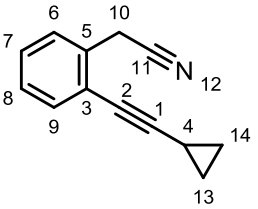
(Yellow oil, 72%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.32 (d, *J* = 8.6 Hz, 2H, $H_{10,12}$), 7.27 (td, *J* = 8.6 Hz, 2H, $H_{9,13}$), 2.60 (t, *J* = 6.8 Hz, 2H, H_6), 2.55 (t, *J* = 7.1 Hz, 2H, H_4), 2.00-1.93 (m, 2H, H_5).

2-(2-(Phenylethynyl)phenyl)acetonitrile (1.113d)



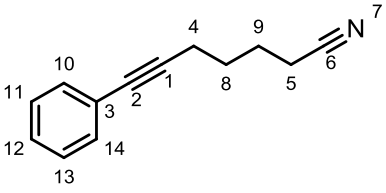
(Yellow solid, 60%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.59-7.51 (m, 4H, H_{Ar}), 7.41-7.33 (m, 5H, H_{Ar}), 3.98 (s, 2H, H_{10}).

2-(2-(Cyclopropylethynyl)phenyl)acetonitrile (1.113e)



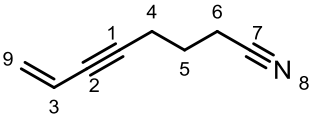
(Yellow oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.43-7.40 (m, 2H, $H_{6,9}$), 7.31-7.23 (m, 2H, $H_{7,8}$), 3.85 (s, 2H, H_{10}), 1.53-1.46 (m, 1H, H_4), 0.95-0.90 (m, 2H, H_{13}), 0.87-0.82 (m, 2H, H_{14}).

7-Phenylhept-6-ynenitrile (1.113f)



(Yellow oil, 85%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.40-7.38 (m, 2H, $H_{10,14}$), 7.30-7.28 (m, 3H, $H_{11,12,13}$), 2.49 (t, *J* = 6.6 Hz, 2H, H_5), 2.43 (t, *J* = 7.1 Hz, 2H, H_4), 1.91-1.84 (m, 2H, H_9), 1.81-1.74 (m, 2H, H_8).

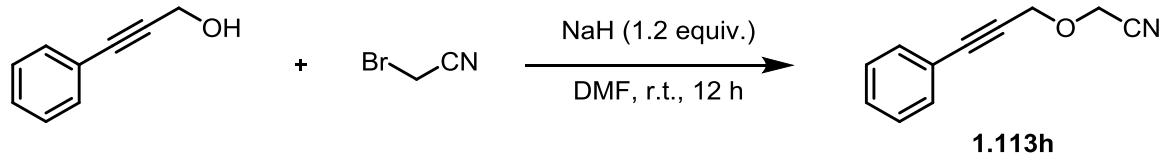
Oct-7-en-5-ynenitrile (1.113g)



(Colourless oil, 70%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 5.77 (ddt, *J* = 13.0, 8.1, 1.6 Hz, 1H, H_9), 5.58 (dd, *J* = 13.0, 1.6 Hz, 1H, H_3),

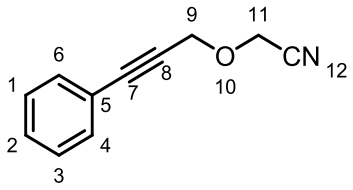
5.44 (dd, J = 8.1, 1.6 Hz, 1H, H_9), 2.51 (t, J = 7.1 Hz, 2H, H_6), 2.50 (t, J = 6.7 Hz, 2H, H_4), 1.89-1.82 (m, 2H, H_5).

2-((3-Phenylprop-2-yn-1-yl)oxy)acetonitrile (1.113h)



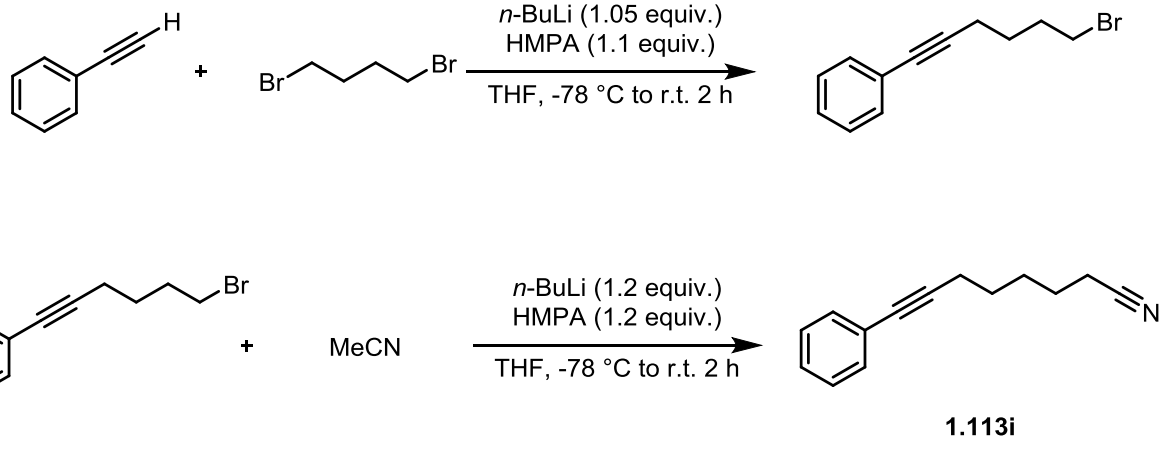
1.113h

To a stirring suspension of NaH (1.2 equiv., 6 mmol, 60% in mineral oil) in 10 ml DMF was added 3-phenylprop-2-yn-1-ol (1.0 equiv., 5 mmol) under Argon. The resulting solution was stirred at room temperature for 1 hour. Then bromoacetonitrile (1.2 equiv., 6 mmol) was added. The mixture was stirred at room temperature for another 12 hours. The solution was cooled down with ice and quenched with 50 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with diethyl ether Et_2O (2 x 50 mL). The combined organic layers were washed with brine (40 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuum. The resulting crude was purified by flash column chromatography (heptane/ethyl acetate: 5/1) to yield title compound **1.113h** (0.61 g, 71%) as pale yellow oil.



^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.48-7.46 (m, 2H, $H_{4,6}$), 7.37-7.31 (m, 3H, $H_{1,2,3}$), 4.55 (s, 2H, H_9), 4.44 (s, 2H, H_{11}).

8-Phenyloct-7-ynenitrile (1.113i)

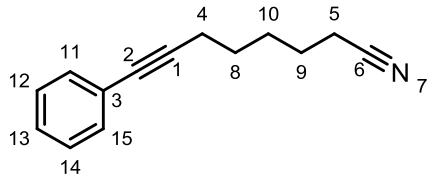


1.113i

To a solution of phenyl acetylene (1 equiv., 9 mmol) in THF (10 ml) at -78 ˚C was added *n*-BuLi (1.05 equiv., 1.6 M in hexane, 9.5 mmol), and the mixture was allowed to warm to room temperature over 30 min. The mixture was then cooled to -78 ˚C, and HMPA (1.1 equiv., 10 mmol) and 1,4-dibromobutane (1.0 equiv., 9 mmol) were added. The mixture was allowed to warm to room temperature in about 2 h and then was quenched with water and extracted with

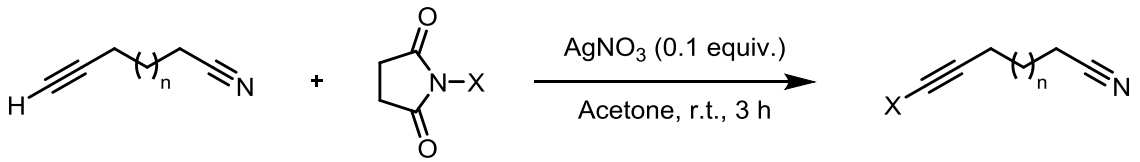
ether (3 x 10 ml). The organic layer was washed brine (20 ml), dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by silica gel column chromatography with petroleum ether as eluent to give 6-bromo-1-phenylhexyne as colourless oil (1.63g, 76%).

To a solution of CH_3CN (1.2 equiv., 3 mmol) in THF (10 ml) at -78 ˚C was added *n*-BuLi (1.2 equiv., 1.6 M in hexane, 3 mmol), and the mixture was allowed to warm to room temperature over 30 min. The mixture was then cooled to -78 ˚C, and HMPA (1.2 equiv., 3 mmol) and 6-bromo-1-phenylhexyne (1.0 equiv., 2.5 mmol) were added. The mixture was allowed to warm to room temperature about 2 h and then was quenched with water and extracted with ether (2 x 15 ml). The organic layer was washed brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was purified by silica gel column chromatography (heptane/diethyl ether/triethylamine: 12/5/1) to give 8-phenyloct-7-ynenitrile **1.113i** as yellow oil (350 mg, 70%)



^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45-7.33 (m, 2H, $H_{11,15}$), 7.33-7.18 (m, 3H, $H_{12,13,14}$), 2.50-2.29 (m, 4H, $H_{4,5}$), 1.86-1.53 (m, 6H, $H_{8,9,10}$).

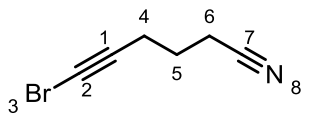
3.2.4 General procedure for the synthesis of halo-cyanoalkynes:



1.113

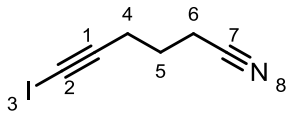
To a solution of the cyanoalkyne (1.0 equiv., 2.5 mmol) in acetone (12.5 ml) was added NXS (1.2 equiv., 2.75 mmol) and $AgNO_3$ (0.1 equiv., 0.25 mmol). The reaction was stirred at room temperature for 3 hours. Then the reaction mixture was diluted with heptane (25 ml) and the formed crystals were filtered off. The filtrate was concentrated under reduced pressure and passed through a pad of silica gel using heptane as an eluent. The filtrate was collected and evaporated under reduced pressure to afford the halo-cycnoalkynes.

6-Bromohex-5-ynenitrile (1.113j)



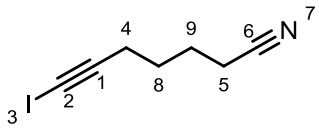
(Yellow oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 2.47 (t, *J* = 7.2 Hz, 2H, H_4), 2.38 (t, *J* = 6.8 Hz, 2H, H_6), 1.91 - 1.79 (m, 2H, H_5).

6-Iodohex-5-ynenitrile (1.113k)



(Yellow oil, 57%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 2.56 (t, *J* = 6.9 Hz, 2H, H_4), 2.50 (t, *J* = 7.2 Hz, 2H, H_6), 1.91-1.85 (m, 2H, H_5).

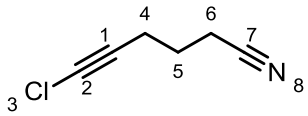
7-Iodohept-6-ynenitrile (1.113l)



(White solid, 61%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 2.42 (t, *J* = 6.8 Hz, 2H, H_4), 2.37 (t, *J* = 7.0 Hz, 2H, H_5), 1.81-1.71 (m, 2H, H_8), 1.70-1.61 (m, 2H, H_9).

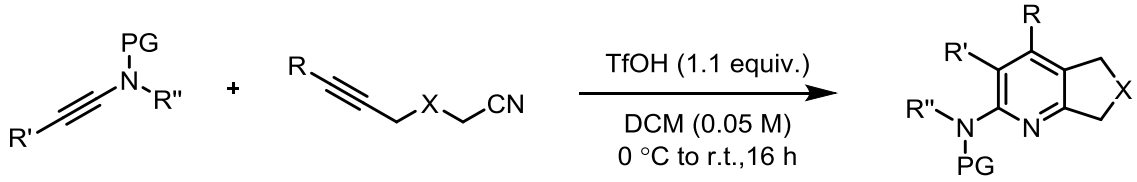
6-Chlorohex-5-ynenitrile (1.113m)

To a solution of hex-5-ynenitrile (1.0 equiv., 3 mmol) in acetone (16 ml) was added *N*-chlorosuccinimide NCS (1.2 equiv., 3.6 mmol) and AgOAc (0.1 equiv., 0.3 mmol) and the solution was heated to reflux for 12 h. The mixture was poured onto ice, and the resulting aqueous layer was extracted with heptane (3 x 15 ml). The combined yellow layers were washed with brine (10 ml), dried over $MgSO_4$, filtered, and the solvent was removed in vacuum. Purification by column chromatography (SiO_2, heptane) afforded 6-chlorohex-5-ynenitrile as a yellow oil (262 mg, 68%).



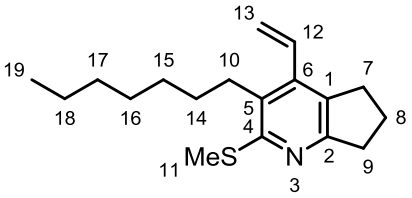
^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.51 (t, *J* = 7.3 Hz, 2H, H_4), 2.40 (t, *J* = 6.9 Hz, 2H, H_6), 1.89-1,81 (m, 2H, H_5).

3.2.5 General procedure for the synthesis of pyridines from ynamides and cycnoalkynes:



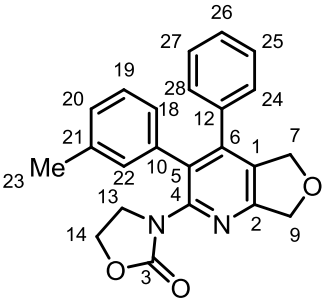
Under Argon, TfOH (1.1 equiv., 0.22 mmol) was slowly added to a cooled solution (0 ˚C) of ynamide (or thioalkyne) (1.1 equiv., 0.22 mmol) and cynoalkynes (1.0 equiv., 0.2 mmol) in DCM (4 ml). The mixture was warmed up to room temperature and stirred for another 16 h at room temperature. The reaction was then quenched with saturated solution of $NaHCO_3$ (10 ml), extracted with DCM (3 x 10 ml) and dried over $MgSO_4$. The solvent was then removed in vacuum. The crude product was purified by column chromatography on silica gel with (heptane/ethyl acetate: 1/1) to give the desired compounds.

3-Heptyl-2-(methylthio)-4-vinyl-6,7-dihydro-5H-cyclopenta[b]pyridine (1.119)



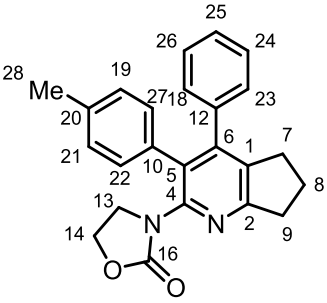
(Yellow oil, 51%), **IR (neat) ν_{max}:** 2954, 2853, 2170, 1692, 1550, 1464, 1299, 1264, 1170, 1021, 963; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 6.70 (dd, *J* = 11.8, 11.9 Hz, 1H, H_{12}),5.51 (ddd, *J* = 11.5, 1.8, 17.8 Hz, 2H, H_{13}), 3.01 (t, *J* = 7.7 Hz, 2H, H_7), 2.91 (t, *J* = 7.7 Hz, 2H, H_9), 2.66 (t, *J* = 7.7 Hz, 2H, H_{10}), 2.56 (s, 3H, H_{11}), 2.06-1.98 (m, 2H, H_8), 1.42-1.36 (m, 2H, H_{14}), 1.23-1.13 (m, 8H, $H_{15,16,17,18}$), 0.83 (t, *J* = 7.3 Hz, 3H, H_{19}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 162.7(C_4), 156.0(C_2), 140.7(C_6), 132.9(C_{12}), 130.8(2C, $C_{1,5}$), 121.1(C_{13}), 34.7(C_9), 31.8(C_7), 30.2(C_{10}), 29.9(C_{14}), 29.4(3C, $C_{15,16,17}$), 23.1(C_8), 22.7 (C_{18}), 14.2(C_{11}), 13.8(C_{19}); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}SN$) requires *m*/*z* 290.1942, found *m*/*z* 290.1937.

3-(4-Phenyl-3-(*m*-tolyl)-5,7-dihydrofuro[3,4-b]pyridin-2-yl)oxazolidin-2-one (1.127)



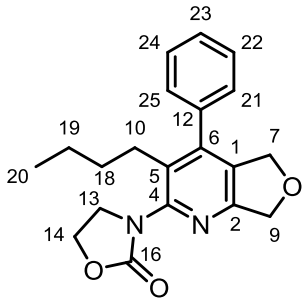
(Yellow solid, 71%), **IR (neat) ν_{max}:** 3053, 2957, 2918, 1902, 1753, 1576, 1516, 1497, 1269, 1067, 1046, 924; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.18-7.14 (m, 3H, H_{Ar}), 7.05 (t, *J* = 7.7 Hz, 1H, H_{26}), 6.97-6.90 (m, 3H, H_{Ar}), 6.87-6.84 (m, 2H, H_{Ar}), 5.11 (s, 2H, H_9), 5.00 (s, 2H, H_7), 4.18 (t, *J* = 8.3 Hz, 2H, H_{14}), 3.66 (t, *J* = 7.9 Hz, 2H, H_{13}), 2.16 (s, 3H, H_{23}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 159.5(C_4), 156.5(C_2), 149.4(C_3), 146.1(C_6), 137.5(C_{Ar}), 136.0(C_{Ar}), 134.9(C_{Ar}), 132.8(C_{Ar}), 131.7(C_{Ar}), 130.6(C_{Ar}), 128.4(2C, C_{Ar}), 128.3(C_{Ar}), 128.1(2C, C_{Ar}), 128.0(C_{Ar}), 127.8(C_{Ar}), 127.0(C_{Ar}), 73.1(C_9), 72.3(C_7), 62.6(C_{14}), 46.3(C_{13}), 21.2(C_{23}); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{23}H_{20}N_2O_3$) requires *m*/*z* 373.1552, found *m*/*z* 373.1544.

3-(4-Phenyl-3-(p-tolyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.128)



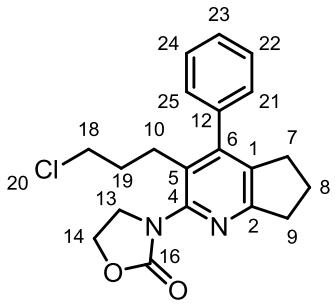
(Yellow solid, 62%), **IR (neat) ν_{max}:** 3050, 2922, 1899, 1749, 1576, 1513, 1477, 1246, 1067, 1042, 927; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.14-7.09 (m, 3H, H_{Ar}), 6.93-6.87 (m, 6H, H_{Ar}), 4.13 (t, *J* = 8.2 Hz, 2H, H_{13}), 3.58 (t, *J* = 8.0 Hz, 2H, H_{14}), 3.05 (t, *J* = 8.1 Hz, 2H, H_9), 2.72 (t, *J* = 7.4 Hz, 2H, H_7), 2.19 (s, 3H, H_{28}), 2.06 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 164.7(C_4), 157.0(C_2), 147.9(C_{16}), 147.5(C_6), 137.2(C_{Ar}), 136.7(C_{Ar}), 136.5(C_{Ar}), 132.8(C_{Ar}), 131.9(C_{Ar}), 129.8(2C, C_{Ar}), 128.8(2C, C_{Ar}), 128.6(2C, C_{Ar}), 127.8(2C, C_{Ar}), 127.3(C_{Ar}), 62.4(C_{14r}), 46.4(C_{13}), 34.4(C_9), 30.7(C_7), 23.2(C_8), 21.2(C_{28}); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{24}H_{22}N_2O_2$) requires *m*/*z* 371.1760, found *m*/*z* 371.1759.

3-(3-Butyl-4-phenyl-5,7-dihydrofuro[3,4-b]pyridin-2-yl)oxazolidin-2-one (1.129)



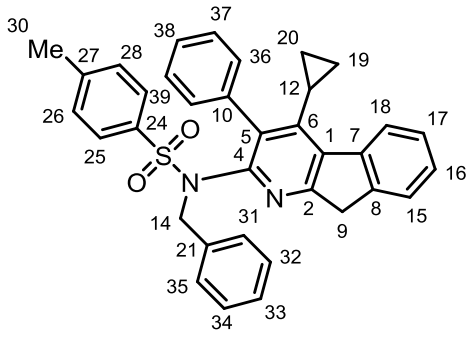
(Orange oil, 57%), **IR (neat) ν_{max}:** 3058, 2958, 2926, 1791, 1752, 1593, 1480, 1394, 1357, 1267, 1135, 1079, 1029, 920; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.41-7.32 (m, 3H, $H_{22,23,24}$), 7.17-7.13 (m, 2H, $H_{21,25}$), 4.98 (s, 2H, H_9), 4.81 (s, 2H, H_7), 4.48 (t, *J* = 7.9 Hz, 2H, H_{14}), 4.12 (t, *J* = 7.9 Hz, 2H, H_{13}), 2.54 (t, *J* = 8.0 Hz, 2H, H_{10}), 1.25-1.18 (m, 2H, H_{18}), 1.10-1.03 (m, 2H, H_{19}), 0.64 (t, *J* = 7.3 Hz, 2H, H_{20}); **^{13}C-NMR (100 MHz, $CDCl_3$)**: δ 157.3(C_4), 156.3(C_2), 150.1(C_{16}), 146.8(C_6), 136.8(C_{Ar}), 132.1(C_{Ar}), 131.7(C_{Ar}), 128.7(2C, C_{Ar}), 128.3(C_{Ar}), 127.8(2C, C_{Ar}), 72.9(C_9), 72.2(C_7), 62.8(C_{14}), 47.0(C_{13}), 32.3(C_{10}), 27.4(C_{18}), 22.6(C_{19}), 13.6(C_{20}); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}N_2O_3$) requires *m*/*z* 339.1709, found *m*/*z* 339.1702.

3-(3-(3-Chloropropyl)-4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.130)



(Yellow oil, 68%), **IR (neat) ν_{max}:** 3055, 2958, 2913, 1799, 1750, 1581, 1497, 1393, 1266, 1081, 1036, 983; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.41-7.21 (m, 3H, $H_{22,23,24}$), 7.16-7.09 (m, 2H, $H_{21,25}$), 4.47 (t, *J* = 7.9 Hz, 2H, H_{14}), 4.12 (t, *J* = 7.9 Hz, 2H, H_{13}), 3.24 (t, *J* = 6.3 Hz, 2H, H_9), 2.94 (t, *J* = 7.8 Hz, 2H, H_7), 2.64 (t, *J* = 7.8 Hz, 2H, H_{18}), 2.56 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.04-1.95 (m, 2H, H_{19}), 1.71-1.62 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 163.0(C_4), 157.2(C_2), 148.8(C_{16}), 148.4(C_6), 137.5(C_{Ar}), 136.5(C_{Ar}), 129.0(C_{Ar}), 128.7(2C, C_{Ar}), 127.9(2C, C_{Ar}), 127.8(C_{Ar}), 62.8(C_{14}), 46.9(C_{13}), 44.7(C_{18}), 34.2(C_9), 32.8(C_{10}), 30.3(C_7), 25.4(C_{19}), 23.1(C_8); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{20}H_{21}N_2O_2Cl$) requires *m*/*z* 357.1370, found *m*/*z* 357.1370.

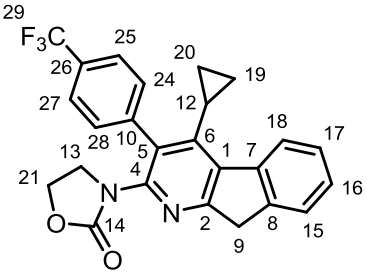
***N*-Benzyl-*N*-(4-cyclopropyl-3-phenyl-9H-indeno[2,1-b]pyridin-2-yl)-4-methylbenzenesulfonamide (1.131)**



(Orange solid, 87%), **IR (neat) ν_{max}:** 3056, 2977, 2034, 1598, 1535, 1443, 1410, 1397, 1210, 1089, 1061, 923; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.19 (d, *J* = 7.6 Hz, 2H, $H_{25,39}$), 7.57 (d, *J* = 8.2 Hz, 2H, $H_{26,28}$), 7.40-7.34 (m, 2H, H_{Ar}), 7.26-7.22 (m, 2H, H_{Ar}), 7.19 (d, *J* = 8.3 Hz, 3H, H_{Ar}), 7.06 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 6.96 (t, *J* = 7.5 Hz, 2H, H_{Ar}), 6.65 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 4.39 (s, 2H, H_{14}), 3.95 (s, 2H, H_9), 2.39 (s, 3H, H_{30}), 1.90-1.81 (m, 1H, H_{12}), 0.72-0.66 (m, 2H, H_{19}),

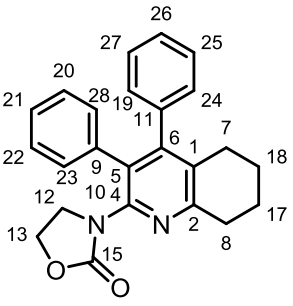
0.22-0.16 (m, 2H, H_{20}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 162.6(C_4), 148.7(C_2), 146.2(C_{24}), 143.3(C_6), 142.3(C_{Ar}), 139.5(C_{Ar}), 138.5(C_{Ar}), 137.0(C_{Ar}), 136.5(C_{Ar}), 135.7(C_{Ar}), 135.0(C_{Ar}), 130.1(C_{Ar}), 129.7(2C, C_{Ar}), 129.2(2C, C_{Ar}), 129.0(2C, C_{Ar}), 128.0(2C, C_{Ar}), 127.4(C_{Ar}), 127.3(2C, C_{Ar}), 126.8(C_{Ar}), 126.6(C_{Ar}), 125.4(C_{Ar}), 124.9(C_{Ar}), 54.1(C_{14}), 38.5(C_9), 21.6(C_{30}), 13.6(C_{12}), 10.3(2C, $C_{20,19}$); **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{35}H_{30}N_2O_2S$) requires *m*/*z* 543.2106, found *m*/*z* 543.2094.

3-(4-Cyclopropyl-3-(4-(trifluoromethyl)phenyl)-9H-indeno[2,1-b]pyridin-2-yl)oxazolidin-2-one (1.132)



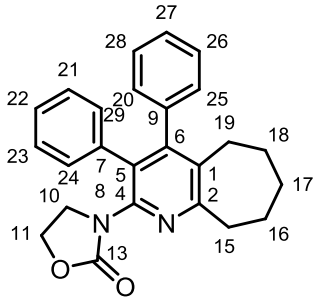
(Orange solid, 64%), **IR (neat) ν_{max}:** 3058, 2958, 2926, 1811, 1752, 1593, 1267, 1135, 1079, 1029, 922; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.17 (d, *J* = 7.6 Hz, 1H, H_{18}), 7.64 (d, *J* = 8.0 Hz, 2H, $H_{25,27}$), 7.55 (d, *J* = 7.1 Hz, 1H, H_{15}), 7.45 (d, *J* = 8.0 Hz, 2H, $H_{24,28}$), 7.40-7.31 (m, 2H, $H_{16,17}$), 4.20 (t, *J* = 7.9 Hz, 2H, H_{21}), 3.97 (s, 2H, H_9), 3.37 (t, *J* = 7.9 Hz, 2H, H_{13}), 2. 05-1.96 (m, 1H, H_{12}), 0.84-0.76 (m, 2H, H_{19}), 0.21-0.15 (m, 2H, H_{20}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 164.2(C_4), 156.8(C_2), 146.4(C_{14}), 145.9(C_6), 142.0(C_{26}), 141.3(C_{Ar}), 138.9(C_{Ar}), 136.4(C_{Ar}), 134.1(C_{Ar}), 130.2(2C, C_{Ar}), 127.7(2C, C_{Ar}), 126.9(2C, C_{Ar}), 125.3, (C_{Ar}) 125.0(2C, C_{Ar}), 124.7(C_{29}), 62.7(C_{21}), 46.6(C_9), 38.8(C_{13}), 13.1(C_{12}), 10.4(2C, $C_{19,20}$); **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{25}H_{19}N_2O_2F_3$) requires *m*/*z* 437.1477, found *m*/*z* 437.1467.

3-(3,4-Diphenyl-5,6,7,8-tetrahydroquinolin-2-yl)oxazolidin-2-one (1.133)



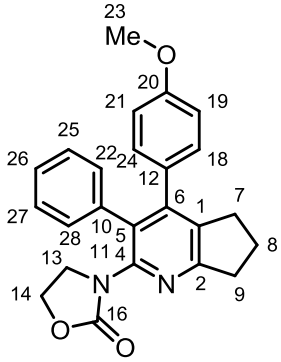
(Yellow oil, 67%), **IR (neat) ν_{max}:** 3055, 2932, 1789, 1751, 1602, 1564, 1267, 1117, 1075, 969, 890; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.14-7.08 (m, 3H, H_{Ar}), 7.07-7.02 (m, 3H, H_{Ar}), 6.99-6.95 (m, 2H, H_{Ar}), 6.87-6.82 (m, 2H, H_{Ar}), 4.11 (t, *J* = 8.0 Hz, 2H, H_{13}), 3.62 (t, *J* = 7.9 Hz, 2H, H_{12}), 2.95 (t, *J* = 6.5 Hz, 2H, H_8), 2.35 (t, *J* = 6.4 Hz, 2H, H_7), 1.86-1.78 (m, 2H, H_{17}), 1.69-1.62 (m, 2H, H_{18}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 156.9(C_4), 156.7(C_2), 151.9(C_{15}), 145.6(C_6), 137.3(C_{Ar}), 135.9(C_{Ar}), 132.3(C_{Ar}), 131.1(C_{Ar}), 129.8(2C, C_{Ar}), 128.7(2C, C_{Ar}), 127.9(2C, C_{Ar}), 127.6(2C, C_{Ar}), 127.1(C_{Ar}), 126.9(C_{Ar}), 62.5(C_{13}), 46.4(C_{12}), 32.7(C_8), 27.9(C_7), 22.9(C_{17}), 22.7(C_{18}); **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{24}H_{22}N_2O_2$) requires *m*/*z* 371.1760, found *m*/*z* 371.1751.

3-(3,4-Diphenyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-2-yl)oxazolidin-2-one (1.134)



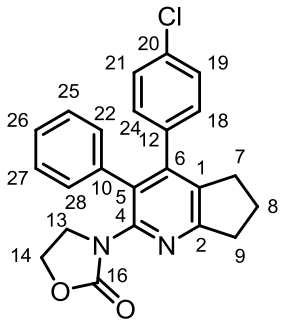
(Yellow solid, 42%), **IR (neat) ν_{max}:** 3058, 2932, 1799, 1752, 1577, 1559, 1267, 1115, 1069, 932; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.13-7.06 (m, 3H, H_{Ar}), 7.05-7.02 (m, 3H, H_{Ar}), 6.98-6.93 (m, 2H, H_{Ar}), 6.84-6.80 (m, 2H, H_{Ar}), 4.12 (t, *J* = 8.2 Hz, 2H, H_{11}), 3.65 (t, *J* = 7.9 Hz, 2H, H_{10}), 3.08-3.04 (m, 2H, H_{15}), 2.53-2.48 (m, 2H, H_{19}), 1.84-1.77 (m, 2H, H_{16}), 1.76-1.70 (m, 2H, H_{18}), 1.54-1.48 (m, 2H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 163.1(C_4), 156.7(C_2), 150.9(C_{13}), 144.7(C_6), 137.9(C_{Ar}), 136.6(C_{Ar}), 136.2(C_{Ar}), 132.4(C_{Ar}), 131.5(C_{Ar}), 129.8(2C, C_{Ar}), 129.3(C_{Ar}), 128.2(C_{Ar}), 127.7(2C, C_{Ar}), 127.5(C_{Ar}), 126.8(C_{Ar}), 126.7(C_{Ar}), 62.5(C_{11}), 46.3(C_{10}), 39.1(C_{15}), 32.6(C_{19}), 30.4(C_{16}), 27.4(C_{18}), 26.3(C_{17}); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{25}H_{24}N_2O_2$) requires *m*/*z* 385.1916, found *m*/*z* 385.1915.

3-(4-(4-Methoxyphenyl)-3-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.135)



(Orange solid, 82%), **IR (neat) ν_{max}:** 3054, 2958, 2838, 2178, 1792, 1753, 1608, 1578, 1461, 1289, 1176, 1027, 923, 836; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.15-7.09 (m, 3H, $H_{25,26,27}$), 7.04-7.02 (m, 2H, $H_{22,28}$), 6.82 (d, *J* = 8.8 Hz, 2H, $H_{21,19}$), 6.64 (d, *J* = 8.7 Hz, 2H, $H_{18,24}$), 4.11 (t, *J* = 8.0 Hz, 2H, H_{14}), 3.66 (s, 3H, H_{23}), 3.58 (t, *J* = 8.1 Hz, 2H, H_{13}), 3.05 (t, *J* = 7.7 Hz, 2H, H_9), 2.75 (t, *J* = 7.5 Hz, 2H, H_7), 2.10-2.02 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 164.8(C_4), 158.7(C_2), 157.0(C_{16}), 147.6(C_{12}), 147.4(C_{20}), 136.6(C_{Ar}), 136.1(C_{Ar}), 132.1(C_{Ar}), 130.3(2C, C_{Ar}), 130.1(2C, C_{Ar}), 129.3(C_{Ar}), 127.9(2C, C_{Ar}), 127.1(C_{Ar}), 113.3(2C, C_{Ar}), 62.5(C_{14}), 55.1(C_{23}), 46.7(C_{13}), 34.8(C_9), 30.9(C_7), 23.4(C_8); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{24}H_{22}N_2O_3$) requires *m*/*z* 387.1709, found *m*/*z* 387.1692.

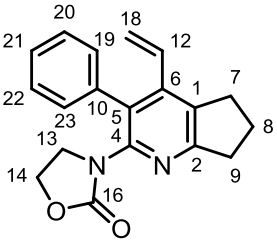
3-(4-(4-Chlorophenyl)-3-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.136)



(Yellowish solid, 75%), **IR (neat) ν_{max}:** 3054, 2963, 2904, 2248, 1980, 1752, 1599, 1492, 1407, 1222, 1089, 1036, 972, 910; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.15-7.07 (m, 5H, H_{Ar}), 7.02-6.98 (m, 2H, $H_{19,21}$), 6.84 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 4.12 (t, *J* = 8.0 Hz, 2H, H_{14}), 3.62 (t, *J* = 8.0 Hz, 2H, H_{13}), 3.07 (t, *J* = 7.7 Hz, 2H, H_9), 2.72 (t, *J* = 7.4 Hz, 2H, H_7), 2.11-2.03 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.2(C_4), 156.9(C_2), 147.6(C_{16}), 146.5(C_{20}), 136.3(C_6), 135.6(C_{Ar}), 135.5(C_{Ar}), 133.4(C_{Ar}), 131.8(C_{Ar}), 130.3(2C, C_{Ar}), 129.9(2C, C_{Ar}), 128.3(2C, C_{Ar}), 128.0(2C, C_{Ar}),

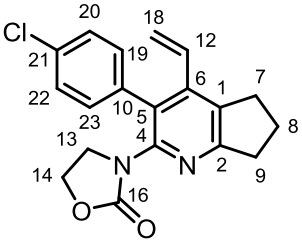
127.4(C_{Ar}), 62.5(C_{14}), 46.4(C_{13}), 34.4(C_9), 30.5(C_7), 23.2(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{23}H_{19}N_2O_2Cl$) requires *m*/*z* 391.1213, found *m*/*z* 391.1206.

3-(3-Phenyl-4-vinyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.137)



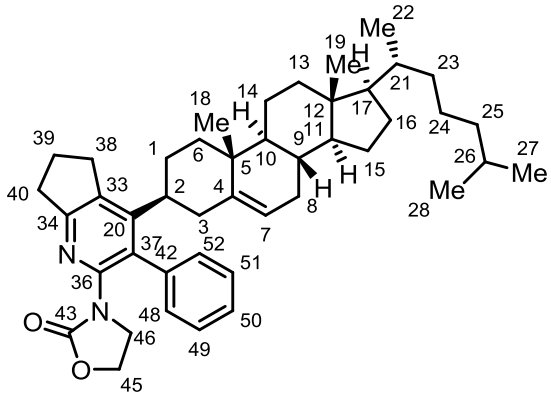
(Yellow oil, 71%), **IR (neat) ν_{max}:** 3054, 2987, 2305, 1758, 1575, 1480, 1420, 1264, 1118, 1050, 791; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.46-7.36 (m, 3H, $H_{20,21,22}$), 7.31-7.28 (m, 2H, $H_{19,23}$), 6.93 (dd, *J* = 11.7, 11.5 Hz, 1H, H_{12}), 5.15 (dd, *J* = 18.0, 11.7 Hz, 2H, H_{18}), 4.20 (t, *J* = 8.0 Hz, 2H, H_{14}), 3. 17 (t, *J* = 8.0 Hz, 2H, H_{13}), 3.11 (t, *J* = 7.6 Hz, 4H, $H_{7,9}$), 2.27-2.18 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.5(C_4), 156.8(C_2), 147.2(C_{16}), 142.8(C_6), 135.8(C_{Ar}), 134.8(C_{12}), 133.4(C_{Ar}), 131.7(C_{Ar}), 129.8(2C, C_{Ar}), 128.3(2C, (C_{Ar}), 127.8(C_{Ar}), 121.9(C_{18}), 62.5(C_{14}), 46.5(C_{13}), 34.2(C_9), 31.6(C_7), 22.4(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}N_2O_2$) requires *m*/*z* 307.1447, found *m*/*z* 307.1440.

3-(3-(4-Chlorophenyl)-4-vinyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.138)



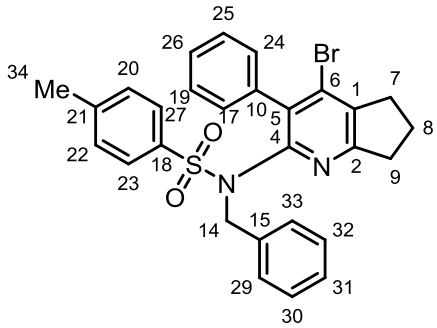
(Yellowish oil, 70%), **IR (neat) ν_{max}:** 3052, 2987, 1758, 1570, 1467, 1415, 1264, 1115, 1068, 791; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.40 (d, *J* = 8.6 Hz, 2H, $H_{20,22}$), 7.23 (d, *J* = 8.4 Hz, 2H, $H_{19,23}$), 6.33 (dd, *J* = 11.5, 11.7 Hz, 1H, H_{12}), 5.50 (t, *J* = 14.7 Hz, 2H, H_{18}), 4.26 (t, *J* = 7.9 Hz, 2H, H_{14}), 3. 80 (t, *J* = 7.9 Hz, 2H, H_{13}), 3.08 (t, *J* = 7.6 Hz, 4H, $H_{7,9}$), 2.25-2.16 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.8(C_4), 156.7(C_2), 147.2(C_{16}), 142.8(C_{21}), 134.7(C_6), 134.3(C_{Ar}), 133.8(C_{Ar}), 133.0(C_{Ar}), 131.3(2C, C_{Ar}), 130.3(C_{Ar}), 128.5(2C, C_{Ar}), 122.3(C_{Ar}), 62.4(C_{14}), 46.4(C_{13}), 34.1(C_9), 31.6(C_7), 23.4(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{19}H_{17}N_2O_2Cl$) requires *m*/*z* 341.1057, found *m*/*z* 341.1055.

3-(4-((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-3-Phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.139)



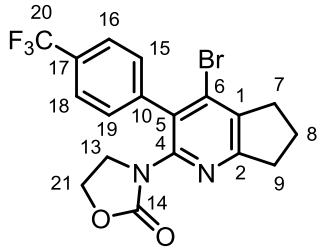
(White solid, 56%), **IR (neat) ν_{max}:** 3053, 2928, 1447, 1765, 1633, 1601, 1594, 1464, 1410, 1377, 1306, 1264, 1241, 1219, 1189, 1109, 1042, 1024, 985, 970, 931, 909, 879, 843, 812, 798; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.35-7.26 (m, 3H, $H_{49,50,51}$), 7.18-7.12 (m, 2H, $H_{48,52}$), 5.01 (s, 1H, H_7), 4.05, 3.99 (m, 2H, H_{45}), 3.61-3.52 (m, 2H, H_3), 3.09 (t, *J* = 7.5 Hz, 1H, H_2), 2.96-2.88 (m, 2H, H_{Alk}), 2.61-2.44 (m, 1H, H_{Alk}), 2.17-2.01 (m, 3H, H_{Alk}), 1.93-1.67 (m, 6H, H_{Alk}), 1.64-1.55 (m, 1H, H_{Alk}), 1.52-1.39 (m, 4H, H_{Alk}), 1.38-1.19 (m, 8H, H_{Alk}), 1.09-0.90 (m, 10H, H_{Alk}), 0.83-0.80 (m, 6H, H_{Alk}), 0.79-0.76 (m, 9H, H_{Alk}), 0.60-0.56 (m, 3H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.6(C_{36}), 156.9(C_{34}), 151.7(C_{43}), 147.4(C_{20}), 141.5(C_{37}), 136.7(C_{Ar}), 136.3(C_{Ar}), 135.5(C_{Ar}), 129.4(C_4), 128.0(C_7), 127.7(C_{Ar}), 120.4(C_{Ar}), 62.5(C_{45}), 56.8(C_{46}), 56.2(C_2), 54.4(C_5), 50.0(C_3), 46.8(C_{40}), 43.2(C_{38}), 42.5(C_8), 39.8(C_{Alk}), 39.6(C_{Alk}), 39.3(C_{Alk}), 37.6(C_{Alk}), 36.8(C_{Alk}), 36.2(C_{Alk}), 35.7(C_{Alk}), 33.7(C_{Alk}), 32.4(C_{Alk}), 31.8(C_{Alk}), 30.5(C_{Alk}), 28.3(C_{Alk}), 27.9(C_{Alk}), 25.8(C_{Alk}), 24.3(C_{Alk}), 23.5(C_{Alk}), 22.9(C_{Alk}), 22.1(C_{Alk}), 21.1(C_{Alk}), 20.8(C_{Alk}), 19.6(C_{Alk}), 18.7(C_{Alk}), 12.1(C_{Alk}), 11.7(C_{Alk}); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{44}H_{60}N_2O_2$) requires *m*/*z* 671.4522, found *m*/*z* 671.4519.

_N_-Benzyl-_N_-(4-bromo-3-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-4-methylbenzenesulfonamide (1.145)



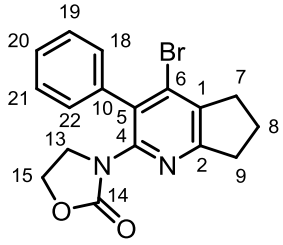
(White solid, 66%), **IR (neat) ν_{max}:** 3056, 2977, 1598, 1535, 1443, 1397, 1264, 1185, 1113, 1089, 1026, 791; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.40 (d, *J* = 8.3 Hz, 2H, $H_{23,27}$), 7.26-7.24(m, 1H, H_{Ar}), 7.20-7.10 (m, 6H, H_{Ar}), 7.02-7.00 (m, 2H, H_{Ar}), 6.69-6.62 (m, 3H, H_{Ar}), 4.34 (s, 2H, H_{14}), 3.06 (t, *J* = 7.9 Hz, 2H, H_9), 2.92 (t, *J* = 7.6 Hz, 2H, H_7), 2.35 (s, 3H, H_{34}), 2.19-2.13 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 163.8(C_4), 149.4(C_2), 143.6(C_6), 139.1(C_{18}), 137.1(C_{Ar}), 136.6(C_{Ar}), 136.0(C_{Ar}), 134.8(C_{Ar}), 134.0(2C, C_{Ar}), 130.4(2C, C_{Ar}), 129.8(2C, C_{Ar}), 129.1(2C, C_{Ar}), 129.0(2C, C_{Ar}), 128.1(2C, C_{Ar}), 127.7(C_{Ar}), 127.3(2C, C_{Ar}), 53.8(C_{14}), 35.1(C_9), 32.8(C_7), 22.1(C_{34}), 21.5(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{28}H_{25}N_2O_2SBr$) requires *m*/*z* 555.0718, found *m*/*z* 555.0694.

3-(4-Bromo-3-(4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.146)



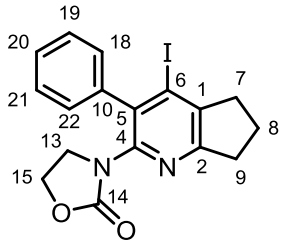
(Orange solid, , 31%), **IR (neat) ν_{max}:** 3056, 2958, 1751, 1572, 1406, 1222, 1115, 1075, 701; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.62 (d, *J* = 8.3 Hz, 2H, $H_{16,18}$), 7.36 (d, *J* = 8.1 Hz, 2H, $H_{15,19}$), 4.19 (t, *J* = 7.9 Hz, 2H, H_{21}), 3.80 (t, *J* = 8.0 Hz, 2H, H_{13}), 3.09 (t, *J* = 7.8 Hz, 2H, H_9), 2.92 (t, *J* = 7.5 Hz, 2H, H_7), 2.21-2.14 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.2(C_4), 156.2(C_2), 147.6(C_{14}), 140.1(C_6), 139.2(C_{Ar}), 133.7(C_{Ar}), 132.5(C_{Ar}), 130.2(3C, C_{Ar}), 125.1(2C, C_{Ar}), 122.7(C_{20}), 62.6(C_{21}), 46.4(C_{13}), 35.2(C_9), 32.8(C_7), 22.1(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{14}N_2O_2F_3Br$) requires *m*/*z* 449.0088, found *m*/*z* 449.0073.

3-(4-Bromo-3-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.147)



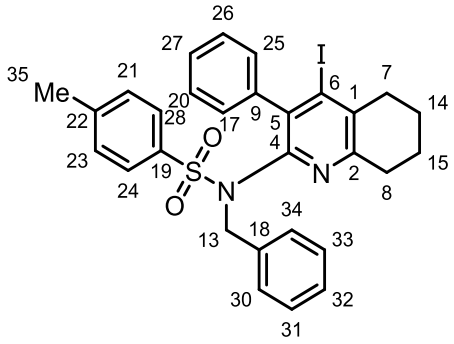
(Orange oil, 43%), **IR (neat) ν_{max}:** 3054, 2987, 1761, 1581, 1530, 1480, 1412, 1264, 1156, 1109, 1051, 932; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.39-7.30 (m, 3H, $H_{19,20,21}$), 7.24-7.20 (m, 2H, $H_{18,22}$), 4.12 (t, *J* = 7.8 Hz, 2H, H_{15}), 3.64 (t, *J* = 8.0 Hz, 2H, H_{13}), 3.09 (t, *J* = 7.8 Hz, 2H, H_9), 2.96 (t, *J* = 7.6 Hz, 2H, H_7), 2.20-2.12 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 164.7(C_4), 156.4(C_2), 147.7(C_{14}), 139.3(C_6), 136.2(C_{Ar}), 134.1(C_{Ar}), 133.8(C_{Ar}), 129.4(2C, C_{Ar}), 128.3(C_{Ar}), 128.1(2C, C_{Ar}), 62.5(C_{15}), 46.4(C_{13}), 35.1(C_9), 32.8(C_7), 22.1(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{15}N_2O_2Br$) requires *m*/*z* 381.0215, found *m*/*z* 381.0214.

3-(4-Iodo-3-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.144)



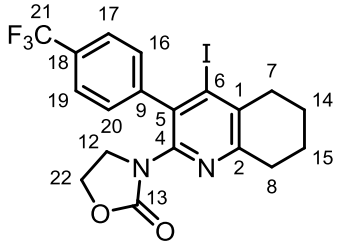
(Violet solid, 49%), **IR (neat) ν_{max}:** 3056, 2987, 1755, 1571, 1530, 1476, 1396, 1264, 1115, 1058, 932; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.47-7.40 (m, 3H, $H_{19,20,21}$), 7.28-7.23 (m, 2H, $H_{18,22}$), 4.17 (t, *J* = 7.9 Hz, 2H, H_{15}), 3.72 (t, *J* = 7.8 Hz, 2H, H_{13}), 3.23 (t, *J* = 7.7 Hz, 2H, H_9), 2.99 (t, *J* = 7.6 Hz, 2H, H_7), 2.27-2.18 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 163.1(C_4), 156.4(C_2), 146.1($C1_4$), 144.2(C_6), 139.6(C_{Ar}), 138.2(C_{Ar}), 129.6(2C, C_{Ar}), 128.4(C_{Ar}), 128.2(2C, C_{Ar}), 113.5(C_{Ar}), 62.6(C_{15}), 46.4(C_{13}), 37.1(C_9), 35.7(C_7), 21.8(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{15}N_2O_2I$) requires *m*/*z* 429.0076, found *m*/*z* 429.0069.

***N*-benzyl-*N*-(4-iodo-3-phenyl-5,6,7,8-tetrahydroquinolin-2-yl)-4-methylbenzenesulfonamide (1.142)**



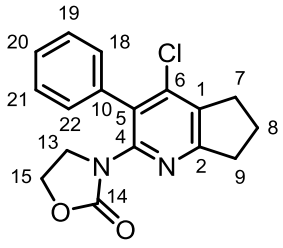
(Yellow solid, 50%), **IR (neat) ν_{max}:** 3058, 3028, 2931, 1495, 1427, 1379, 1306, 1228, 1205, 1160, 929, 859, 837; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.54 (d, *J* = 8.4 Hz, 2H, $H_{21,23}$), 7.39 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 7.31-7.20 (m, 5H, H_{Ar}), 7.13 (t, *J* = 7.5 Hz, 2H, H_{Ar}), 6.78 (d, *J* = 8.2 Hz, 2H, $H_{24,28}$), 6.72-6.67 (m, 2H, H_{Ar}), 4.42 (s, 2H, H_{13}), 2.93-2.88 (m, 2H, H_8), 2.75-2.70 (m, 2H, H_7), 2.47 (s, 3H, H_{35}), 1.94-1.87 (m, 4H, $H_{14,15}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 156.4(C_4), 146.5(C_2), 143.4(C_6), 141.7(C_{19}), 140.9(C_{Ar}), 136.1(C_{Ar}), 136.0(C_{Ar}), 134.9(C_{Ar}), 130.4(2C, C_{Ar}), 129.8(2C, C_{Ar}), 129.1(2C, C_{Ar}), 128.9(2C, C_{Ar}), 128.1(2C, C_{Ar}), 127.6(C_{Ar}), 127.5(C_{Ar}), 127.3(2C, C_{Ar}), 123.6(C_{Ar}), 54.1(C_{13}), 36.4(C_8), 32.8(C_7), 23.7(C_{35}), 22.5(C_{14}), 21.6(C_{15}); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{29}H_{27}N_2O_2SI$) requires *m*/*z* 617.0736, found *m*/*z* 617.0730.

3-(4-Iodo-3-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroquinolin-2-yl)oxazolidin-2-one (1.141)



(Yellow solid, 45%) **IR (neat) ν_{max}:** 3056, 2958, 1751, 1572, 1406, 1222, 1115, 1075, 701; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.62 (d, *J* = 8.2 Hz, 2H, $H_{17,19}$), 7.31 (d, *J* = 8.1 Hz, 2H, $H_{16,20}$), 4.17 (t, *J* = 8.0 Hz, 2H, H_{22}), 3.77 (t, *J* = 7.9 Hz, 2H, H_{12}), 2.90-2.85 (m, 2H, H_8), 2.69-2.62 (m, 2H, H_7), 1.86-1.74 (m, 4H, $H_{14,15}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 157.8(C_4), 156.3(C_2), 144.9(C_6), 144.1(C_{13}), 137.5(C_{Ar}), 136.3(C_{Ar}), 130.6(C_{Ar}), 130.1(3C, C_{Ar}), 125.1(2C, C_{Ar}), 122.4(C_{21}), 62.5(C_{22}), 46.4(C_{12}), 36.3(C_8), 32.9(C_7), 23.6(C_{14}), 22.5(C_{15}); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{19}H_{16}N_2O_2F_3I$) requires *m*/*z* 511.0106, found *m*/*z* 511.0103.

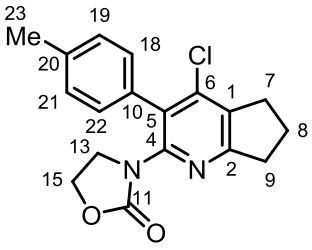
3-(4-Chloro-3-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.148)



(Orange solid, 81%), **IR (neat) ν_{max}:** 3054, 2963, 2904, 2248, 1752, 1599, 1492, 1407, 1222, 1116, 1036, 972, 910; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.39-7.30 (m, 3H, $H_{19,20,21}$), 7.27-7.22 (m, 2H, $H_{18,22}$), 4.14 (t, *J* = 8.1 Hz, 2H, H_{15}), 3.66 (t, *J* = 7.8 Hz, 2H, H_{13}), 3.06 (t, *J* = 7.8 Hz, 2H, H_9), 2.98 (t, *J* = 7.5 Hz, 2H, H_7), 2.21-2.12 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.3(C_4), 156.4(C_2), 148.3(C_6), 141.9(C_{14}), 136.5(C_{Ar}), 134.3(C_{Ar}), 132.0(C_{Ar}), 129.5(2C, C_{Ar}), 128.4(C_{Ar}), 128.3(2C, C_{Ar}), 62.6(C_{15}), 46.4(C_{13}),

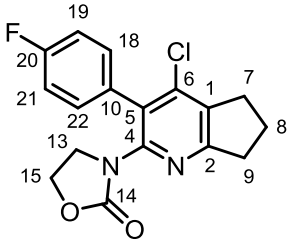
34.9(C_9), 30.5(C_7), 23.4(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{15}N_2O_2Cl$) requires *m*/*z* 337.0720, found *m*/*z* 337.0712.

3-(4-Chloro-3-(p-tolyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.149)



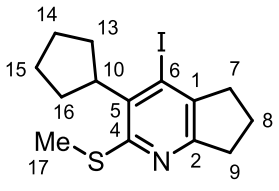
(Orange oil, 43%), **IR (neat) ν_{max}:** 3053, 2984, 2916, 2306, 1759, 1590, 1480, 1407, 1265, 1110, 1050, 973; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.18-7.11 (m, 4H, H_{Ar}), 4.15 (t, *J* = 7.9 Hz, 2H, H_{15}), 3.65 (t, *J* = 7.9 Hz, 2H, H_{13}), 3.06 (t, *J* = 8.0 Hz, 2H, H_9), 2.98 (t, *J* = 7.4 Hz, 2H, H_7), 2.33 (s, 3H, H_{23}), 2.19-2.12 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.1(C_4), 156.4(C_2), 148.3(C_{11}), 142.1(C_6), 138.1(C_{Ar}), 136.5(C_{Ar}), 131.9(C_{Ar}), 131.3(C_{Ar}), 129.3(2C, C_{Ar}), 128.9(2C, C_{Ar}), 62.6(C_{15}), 46.3(C_{13}), 34.8(C_9), 30.6(C_7), 22.4(C_{23}), 21.4(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{17}N_2O_2Cl$) requires *m*/*z* 351.0876, found *m*/*z* 351.0856.

3-(4-Chloro-3-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.150)



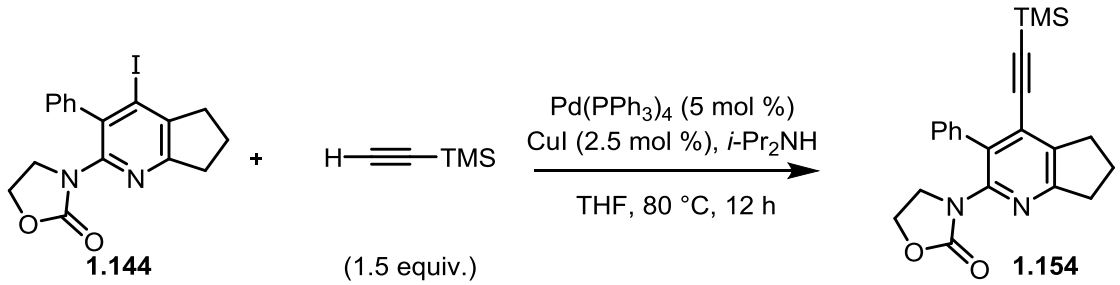
(Orange oil, 47%), **IR (neat) ν_{max}:** 3053, 2963, 2843, 1987, 1752, 1590, 1512, 1480, 1402, 1273, 1110, 1016, 973, 930; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.24-7.19 (m, 2H, $H_{19,21}$), 7.06 (t, *J* = 8.8 Hz, 2H, $H_{18,22}$), 4.19 (t, *J* = 7.9 Hz, 2H, H_{15}), 3.75 (t, *J* = 7.8 Hz, 2H, H_{13}), 3.05 (t, *J* = 7.8 Hz, 2H, H_9), 2.96 (t, *J* = 7.6 Hz, 2H, H_7), 2.20-2.12 (m, 2H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.4(C_4), 163.7(C_2), 161.7(C_{20}), 156.2(C_6), 148.3(C_{14}), 142.1(C_{Ar}), 136.5(C_{Ar}), 131.4(C_{Ar}), 131.2(C_{Ar}), 130.3(C_{Ar}), 115.3(C_{Ar}), 115.1(C_{Ar}), 62.6(C_{15}), 46.3(C_{13}), 34.9(C_9), 30.5(C_7), 22.4(C_8); **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{14}N_2O_2ClF$) requires *m*/*z* 355.0626, found *m*/*z* 355.0609.

3-Cyclopentyl-4-iodo-2-(methylthio)-6,7-dihydro-5H-cyclopenta[b]pyridine (1.143)



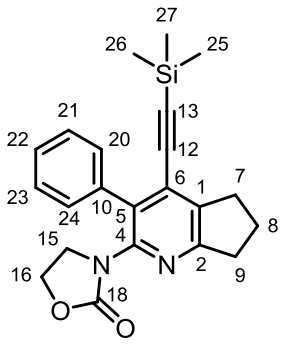
(Orange oil, 31%), **IR (neat) ν_{max}:** 2945, 2867, 1549, 1382, 1246, 1139, 702; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.68-3.55 (m, 1H, H_{10}), 3.02 (t, *J* = 8.8 Hz, 2H, H_9), 2.80 (t, *J* = 7.9 Hz, 2H, H_7), 2.46 (s, 3H, H_{17}), 2.25-2.15 (m, 2H, H_8), 2.06-1.96 (m, 2H, H_{13}), 1.96-1.83 (m, 2H, H_{16}), 1.79-1.69 (m, 2H, H_{14}), 1.68-1.60 (m, 2H, H_{15}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 160.1(2C, $C_{4,2}$), 139.1(C_6), 135.6(2C, $C_{1,5}$), 37.9(2C, $C_{7,9}$), 35.7(C_{10}), 32.3(C_{13}), 28.8(C_{16}), 27.1(C_8), 24.9(C_{14}), 21.6(C_{15}), 14.6(C_{17}); **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{14}H_{18}NSI$) requires *m*/*z* 360.0283, found *m*/*z* 360.0278.

3.2.6 Procedure for the cross-coupling of pyridine **1.144** with trimethylsilyl alkyne



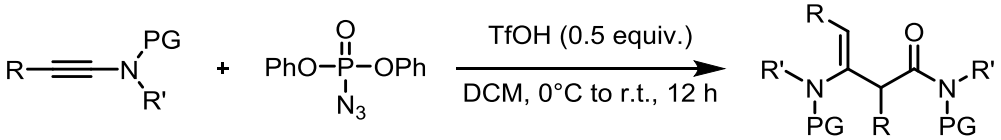
Iodopyridine **1.144** (1.0 equiv., 53 mg, 0.13 mmol), [$Pd(PPh_3)_4$] (5 mol%, 7.5 mg, 0.007 mmol) and CuI (2 mol%, 0.5 mg, 0.001 mmol) were placed in a flame-dried flask under Argon, and dissolved in (0.7 ml) THF and (0.1 ml) $(i\text{-Pr})_2NH$. To this solution, trimethylsilylacetylene (1.2 equiv., 0.16 mmol, 22 µl) was added. The mixture was stirred under argon at room temperature for 12 h. Solvents were removed under vacuum and the crude product was purified by column chromatography using (heptane/ Ethyl acetate: 1/1) to afford compound **1.154** as orange oil (41 mg, 83%).

3-(3-Phenyl-4-((trimethylsilyl)ethynyl)-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)oxazolidin-2-one (1.154)



IR (neat) ν_{max}: 3056, 2958, 2899, 1779, 1754, 1572, 1480, 1310, 1248, 1111, 1009, 973; **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.34-7.28 (m, 5H, H_{Ar}), 4.15 (t, *J* = 7.9 Hz, 2H, H_{16}), 3.65 (t, *J* = 8.0 Hz, 2H, H_{15}), 3.04-2.95 (m, 4H, $H_{7,9}$), 2.18-2.09 (m, 2H, H_8), 0.02 (s, 9H, $H_{25,26,27}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 165.1(C_4), 157.1(C_2), 147.6(C_{18}), 139.9(C_6), 136.2(C_{Ar}), 131.5(C_{Ar}), 134.5(C_{Ar}), 130.3(C_{Ar}), 129.8(2C, C_{Ar}), 128.4(2C, C_{Ar}), 107.4(C_{12}), 100.3(C_{13}), 63.4(C_{16}), 46.7(C_{15}), 34.9(C_9), 31.3(C_7), 23.3(C_8), 0.07(3C, $C_{25,26,27}$); **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{22}H_{24}SiN_2O_2$) requires *m*/*z* 377.1685, found *m*/*z* 377.1677.

3.2.7 General procedure for synthesis of ynamide dimerisation products

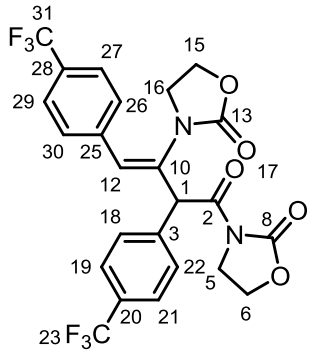


A flame-dried Schlenk was charged with ynamide (1.0 equiv., 0.6 mmol). The flask was evacuated and backfilled with Argon. Then 0.5 ml of DCM was added and the solution was cooled to 0 °C. Diphenyl phosphoryl azide (dppa) (0.5 equiv., 0.3 mmol) was added as a solution in 1 ml of DCM, followed by the addition of TfOH (0.5 equiv.,0.3 mmol) and the

mixture was slowly warmed to room temperature. After stirring for 12 h, the mixture was washed with 10 ml of a solution of NaOH (1M) and brine (1:1 mixture), extracted with DCM (3 x 10 ml) and dried over $MgSO_4$. Purification through column chromatography using DCM to DCM/DMA (9/1) led to desired dimers.

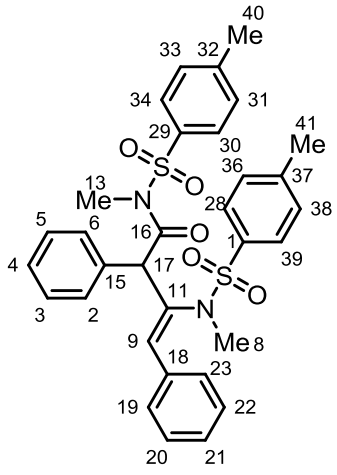
DMA stands for (DCM: Methanol: Ammonia)/ (9:1:0.15)

(*Z*)-3,3'-(1-Oxo-2,4-bis(4-(trifluoromethyl)phenyl)but-3-ene-1,3-diyl)bis(oxazolidin-2-one) (1.187)



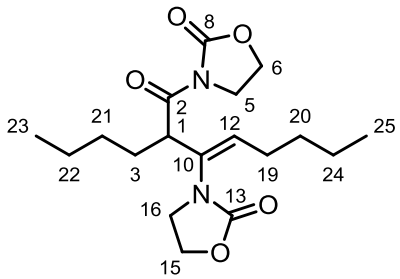
(Brownish solid, 34%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.62-7.46 (m, 6H, H_{Ar}), 7.27 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 6.61 (s, 1H, H_{12}), 5.88 (s, 1H, H_1), 4.40-4.12 (m, 4H, $H_{6,15}$), 3.98-3.82 (m, 2H, H_5), 3.60-3.42 (m, 2H, H_{16}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 170.4(C_2), 156.4(C_8), 152.5(C_{13}), 138.6(C_{Ar}), 138.0(2C, C_{Ar}), 134.7(2C, C_{Ar}), 130.4(C_{Ar}), 130.1(2C, C_{Ar}), 129.2(C_{Ar}), 128.3(C_{Ar}), 126.1(C_{10}), 125.9(C_{Ar}), 125.6(C_{Ar}), 122.5(C_{12}), 64.8(C_6), 61.8(C_{15}), 53.0(C_5), 45.8(C_{16}), 42.7(C_1); **HRMS (ESI$^+$)** $[M+Na]^+$ calculated for $C_{24}H_{18}O_5N_2F_6$ *m*/*z* = 551.1018, found *m*/*z* = 551.1021; **IR (neat) ν_{max}:** 2924, 1751, 1698, 1480, 1388, 1365, 1265, 1221, 1165, 1040, 963, 847, 733, 635.

(*Z*)-3-((N,4-Dimethylphenyl)sulfonamido)-*N*-methyl-2,4-diphenyl-*N*-tosylbut-3-enamide (1.188)



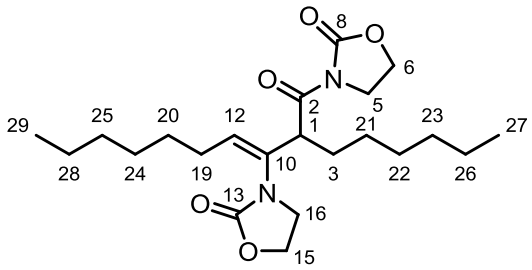
(Yellowish solid, 58%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.82-7.77 (m, 1H, H_{Ar}), 7.55-7.51 (m, 1H, H_{Ar}), 7.44-7.40 (m, 1H, H_{Ar}), 7.38-7.32 (m, 1H, H_{Ar}), 7.27-7.20 (m, 3H) , H_{Ar}, 7.19-7.15 (m, 1H, H_{Ar}), 7.10-7.04 (m, 2H, H_{Ar}), 7.03-6.95 (m, 3H, H_{Ar}), 3.49 (s, 1H, H_9), 2.71 (s, 3H, H_{13}), 2.66 (d, *J* = 5.5 Hz, 1H, H_{17}), 2.47 (s, 6H, $H_{40,41}$), 2.40 (s, 3H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 144.8(C_{16}), 143.5(2C, C_{Ar}), 136.8(C_{Ar}), 135.6(2C, C_{Ar}), 135.2(C_{Ar}), 134.4(C_{Ar}), 129.8(2C, C_{Ar}), 129.2(2C, C_{Ar}), 128.8(2C, C_{Ar}), 128.1(2C, C_{Ar}), 127.6(2C, C_{Ar}), 127.2(2C, C_{Ar}), 98.5(C_9), 38.7(C_8), 37.1(C_{13}), 22.7(C_{17}), 21.5 (C_{40}), 21.4 (C_{41}); **HRMS (ESI$^+$)** $[M+Na]^+$ calculated for $C_{33}H_{33}N_2O_5S_2$ *m*/*z*=611.1650, found *m*/*z*= 611.1648; **IR (neat) ν_{max}:** 3308, 3055, 2942, 1752, 1597, 1493, 1410, 1340, 1265, 1155, 1088, 1010, 948, 881, 786, 754, 696, 602.

3,3'-(2-Butyl-1-oxooct-3-ene-1,3-diyl)bis(oxazolidin-2-one) (1.190)



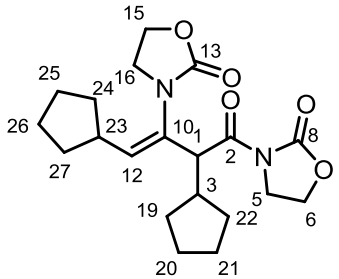
(Yellow oil, 83%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 5.68 (t, *J* = 7.3Hz, 1H, H_{12}), 4.57 (t, *J* = 7.4 Hz, 1H, H_1), 4.41-4.33 (m, 4H, $H_{6,15}$), 4.01 (t, *J* = 8.2 Hz, 2H, H_5), 3.82-3.65 (m, 2H, H_{16}), 2.05-1.96 (m, 2H, H_{Alk}), 1.71-1.60 (m, 2H, H_{Alk}), 1.43-1.29 (m, 8H, H_{Alk}), 0.94-0.83 (m, 6H, $H_{23,25}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 172.8(C_2), 157.6(C_8), 153.6(C_{13}), 133.6(C_{10}), 131.5(C_{12}), 62.4(C_6), 62.1(C_{15}), 46.9(C_5), 46.1(C_{16}), 43.2(C_1), 30.7(C_{Alk}), 30.5(C_{Alk}), 29.7(C_{Alk}), 27.3(C_{Alk}), 22.5(C_{Alk}), 22.2(C_{Alk}), 13.9(C_{23}), 13.7(C_{25}); **HRMS (ESI$^+$)** $[M+Na]^+$ calculated for $C_{18}H_{28}O_5N_2$ m/z = 375.1896, found m/z = 375.1878; **IR (neat) ν_{max}:** 3535, 2956, 2927, 2860, 1747, 1694, 1479, 1409, 1384, 1362, 1196, 1096, 1037, 970, 929, 830, 758, 731, 700, 619.

3,3'-(2-Hexyl-1-oxodec-3-ene-1,3-diyl)bis(oxazolidin-2-one) (1.191)



(Yellow oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 5.68 (t, *J* = 7.2 Hz, 1H, H_{12}), 4.57 (t, *J* = 7.5 Hz, 1H, H_1), 4.41-4.34 (m, 4H, $H_{6,15}$), 4.00 (t, *J* = 8.0, 7.8 Hz, 2H, H_5), 3.82-3.67 (m, 2H, H_{16}), 2.34-2.17 (m, 2H, H_{Alk}), 2.05-1.97 (m, 2H, H_{Alk}), 1.93-1.21 (m, 14H, H_{Alk}), 0.93-0.83 (m, 8H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 172.8(C_2), 156.6(C_8), 153.6(C_{13}), 133.7(C_{10}), 131.4(C_{12}), 62.3(C_6), 62.1(C_{15}), 46.9(C_5), 46.1(C_{16}), 43.3(C_1), 31.7(C_{Alk}), 31.5(C_{Alk}), 30.8(C_{Alk}), 29.1(C_{Alk}), 28.9(C_{Alk}), 28.6(C_{Alk}), 27.5(C_{Alk}), 27.4(C_{Alk}), 22.5(2C, C_{Alk}), 14.0(2C, C_{Alk}); **HRMS (ESI$^+$)** $[M+Na]^+$ calculated for $C_{22}H_{36}O_5N_2$ m/z = 431.2522, found m/z = 431.2521; **IR (neat) ν_{max}:** 2954, 2923, 2855, 1749, 1695, 1479, 1408, 1384, 1362, 1216, 1100, 1038, 966, 895, 758, 725, 700.

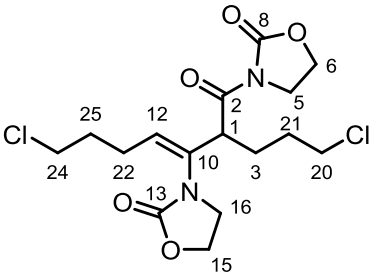
3,3'-(2,4-Dicyclopentyl-1-oxobut-3-ene-1,3-diyl)bis(oxazolidin-2-one) (1.192)



(Yellowish oil, 80%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 5.68 (t, *J* = 7.2 Hz, 1H, H_{12}), 4.57 (t, *J* = 7.5 Hz, 1H, H_1), 4.41-4.34 (m, 4H, $H_{6,15}$), 4.00 (t, *J* = 8.0, 7.8 Hz, 2H, H_5), 3.82-3.67 (m, 2H, H_{16}), 2.05-1.97 (m, 2H, H_{Alk}), 1.72-1.62 (m, 2H, H_{Alk}), 1.93-1.21 (m, 14H, H_{Alk}), 0.93-0.83 (m, 8H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 172.8(C_2), 156.6(C_8), 153.6(C_{13}), 133.7(C_{10}), 131.4(C_{12}), 62.3(C_6), 62.1(C_{15}), 46.9(C_5), 46.1(C_{16}), 43.3(C_1), 31.7(C_3), 31.5(C_{23}), 29.1(C_{Alk}), 28.9(C_{Alk}), 28.6(C_{Alk}), 27.5(2C, C_{Alk}), 22.5(2C, C_{Alk}), 14.0(2CC_{Alk}); **HRMS (ESI$^+$)** $[M+Na]^+$

calculated for $C_{22}H_{36}O_5N_2$ m/z = 431.2522, found m/z = 431.2521; **IR (neat) ν_{max}:** 2950, 2866, 1770, 1746, 1693, 1410, 1383, 1216, 1103, 1037, 731, 703, 645.

3,3'-(7-Chloro-2-(3-chloropropyl)-1-oxohept-3-ene-1,3-diyl)bis(oxazolidin-2-one) (1.189)

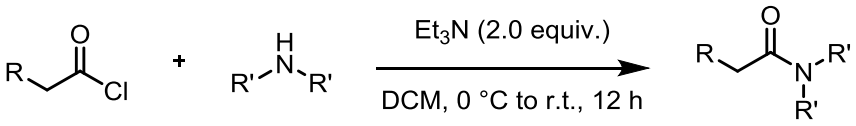


(Yellowish oil, 64%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 5.69 (t, *J* = 7.3Hz, 1H, H_{12}), 4.61 (t, *J* = 7.2 Hz, 1H, H_1), 4.44-4.38 (m, 4H, $H_{6,15}$), 4.05-3.98 (m, 2H, H_5), 3.87-3.74 (m, 2H, H_{16}), 3.61-3.50 (m, 4H, $H_{20,24}$), 2.25-2.18 (m, 2H, H_{22}), 1.93-1.77 (m, 6H, $H_{3,21,25}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 172.1(C_2), 156.6(C_8), 153.6(C_{13}), 132.5(C_{12}), 132.0(C_{10}), 62.6(C_6), 62.1(C_{15}), 46.6(C_5), 46.2(C_{16}), 44.5(2C, $C_{2,024}$), 43.3(C_1), 31.5(C_{22}), 30.8(C_3), 28.2(C_{21}), 24.8(C_{25}); **HRMS (ESI$^+$)** $[M+Na]^+$ calculated for $C_{16}H_{22}O_5N_2Cl_2$ m/z = 415.0803, found m/z = 415.0803; **IR (neat) ν_{max}:** 3363, 2958, 2919, 1771, 1747, 1693, 1479, 1409, 1385, 1363, 1219, 1110, 1037, 958, 821, 757, 732, 700, 646.

3.3 Amides Activation

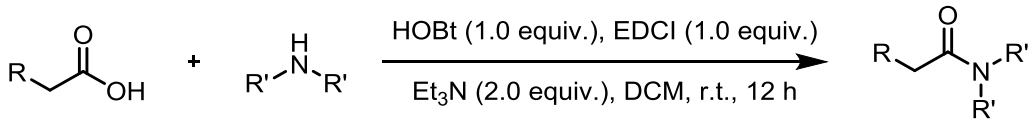
3.3.1 General procedures for the synthesis of amides:

General procedure A:



To a solution of the amine (1.0 equiv.) and triethylamine (2.0 equiv.) in dichloromethane DCM (0.1 M) at 0 °C, the corresponding acyl chloride (1.2 equiv.) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature and stirred for another 12 h. A saturated aqueous solution of sodium bicarbonate $NaHCO_3$ (20 ml) was then added and the biphasic system was separated. The aqueous phase was extracted with dichloromethane (2 x 15 ml). The organic phases were washed with brine (10 ml) and then dried over anhydrous $MgSO_4$. The dried solution was filtered and concentrated under vacuum. The resulting crude was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired amide.

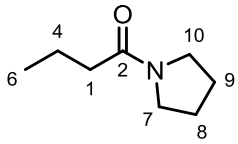
General procedure B:



To a solution of the amine (1.0 equiv.), triethylamine (2.0 equiv.), hydroxybenzotriazole (HOBt) (1.0 equiv.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (1.0 equiv.) in dichloromethane DCM (0.1 M), the corresponding carboxylic acid (1.0 equiv.) was added and the resulting solution was stirred at room temperature for 12 h. Then the organic solution was extracted sequentially with (0.5 M) aqueous hydrochloric acid, saturated aqueous $NaHCO_3$ and brine. The washed solution was dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting crude was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired amide.

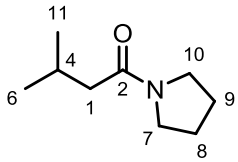
Spectroscopic data for the amide products match those reported in the literature. [62,92]

1-(Pyrrolidin-1-yl)butan-1-one (1.199a)



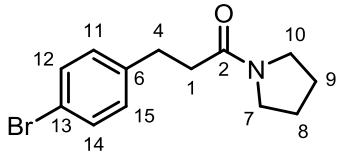
(Colourless oil, 99%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.39 (t, *J* = 7.1 Hz, 2H, H_7), 3.34 (t, *J* = 6.8 Hz, 2H, H_{10}), 2.17 (t, *J* = 7.3 Hz, 2H, H_1), 1.91-1.83 (m, 2H, H_8), 1.80-1.73 (m, 2H, H_9), 1.65-1.56 (m, 2H, H_4), 0.89 (t, *J* = 7.0 Hz, 3H, H_6).

3-Methyl-1-(pyrrolidin-1-yl)butan-1-one (1.199b)



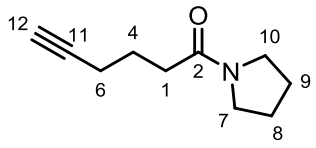
(Yellowish oil, 95%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.50-3.40 (m, 4H, $H_{7,10}$), 2.24-2.14 (m, 3H, $H_{1,4}$), 1.97-1.83 (m, 4H, $H_{8,9}$), 0.99-0.96 (m, 6H, $H_{6,11}$).

3-Methyl-1-(pyrrolidin-1-yl)butan-1-one (1.199c)



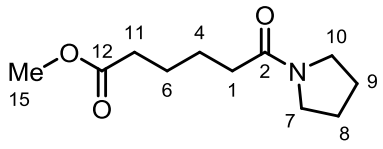
(Brownish oil, 43%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.32 (d, *J* = 8.4 Hz, 2H, $H_{12,14}$), 7.03 (d, *J* = 8.5 Hz, 2H, $H_{11,15}$), 3.38 (t, *J* = 6.7 Hz, 2H, H_4), 3.23(t, *J* = 6.8 Hz, 2H, H_7), 2,85 (t, *J* = 7.7 Hz, 2H, H_{10}), 2.46 (t, *J* = 7.8 Hz, 2H, H_1) 1.81-1.70 (m, 4H, $H_{8,9}$).

1-(Pyrrolidin-1-yl)hex-5-yn-1-one (1.199d)



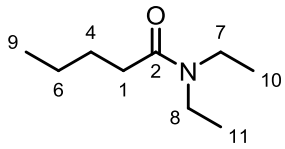
(Yellowish oil, 91%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.48-3.42 (m, 4H, $H_{7,10}$), 2.40 (t, *J* = 7.3 Hz, 2H, H_1), 2.29 (t, *J* = 6.8 Hz, 2H, H_6), 1.99-1.81 (m, 7H, $H_{4,8,9,12}$).

Methyl 6-oxo-6-(pyrrolidin-1-yl)hexanoate (1.199e)



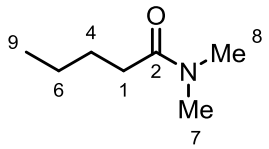
(Yellow oil, 78%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.67 (s. 3H, H_{15}), 3.47 (t, *J* = 6.8 Hz, 2H, H_7), 3.41 (t, *J* = 6.7 Hz, 2H, H_{10}), 2.38-2.26 (m, 4H, $H_{1,11}$), 2.00-1.91 (m, 2H, H_8), 1.89-1.82 (m, 2H, H_9), 1.73-1.67 (m, 4H, $H_{4,6}$).

***N*,*N*-diethylpentanamide (1.199f)**



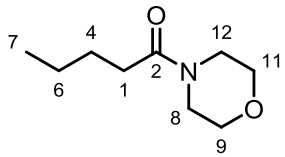
(Colourless oil, 99%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.30 (q, *J* = 7.1 Hz, 2H, H_7), 3.23 (q, *J* = 7.1 Hz, 2H, H_7), 2.21 (t, *J* = 8.3 Hz, 2H, H_1), 1.65-1.57 (m, 2H, H_4), 1.34-1.24 (m, 2H, H_6), 1.10 (t, *J* = 7.2 Hz, 3H, H_{10}), 1.03 (t, *J* = 7.1 Hz, 3H, H_{11}), 0.85 (t, *J* = 7.4 Hz, 3H, H_9).

***N*,*N*-dimethylpentanamide (1.199g)**



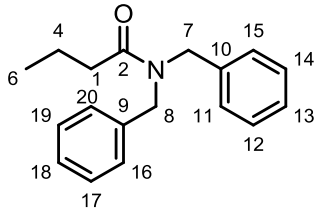
(Colourless oil, 99%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.01 (s, 3H, H_7), 2.95 (s, 3H, H_8), 2.32 (t, *J* = 7.6 Hz, 2H, H_1), 1.67-1.58 (m, 2H, H_4), 1.42-1.33 (m, 2H, H_6), 0.94 (t, *J* = 7.3 Hz, 3H, H_9).

1-Morpholinopentan-1-one (1.199h)



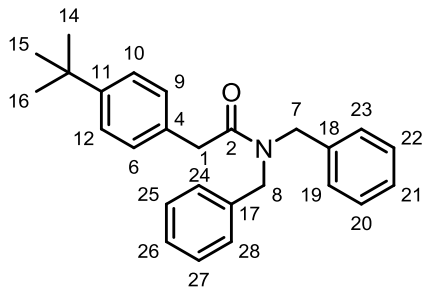
(Colourless oil, 94%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 3.67 (t, *J* = 5.4 Hz, 4H, $H_{9,11}$), 3.64-3.60 (m, 2H, H_8), 3.50-3.45 (m, 2H, H_{12}), 2.32 (t, *J* = 7.5 Hz, 2H, H_1), 1.67-1.58 (m, 2H, H_4), 1.43-1.32 (m, 2H, H_6), 0.94 (t, J = 7.3 Hz, 3H, H_7).

***N*,*N*-dibenzylbutyramide (1.199i)**



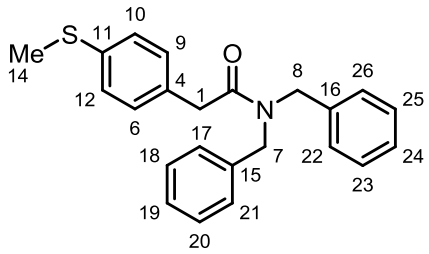
(Yellowish oil, 97%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.39 (t, *J* = 7.5 Hz, 2H, $H_{13,17}$), 7.35-7.28 (m, 4H, H_{Ar}), 7.24 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.18 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 4.62 (s, 2H, H_7), 4.46 (s, 2H, H_8), 2.42 (t, *J* = 7.5Hz, 2H, H_1), 1.79-1.74 (m, 2H, H_4), 0.98 (t, *J* = 7.4Hz, 3H, H_6).

***N*,*N*-dibenzyl-2-(4-(tert-butyl)phenyl)acetamide (1.199k)**



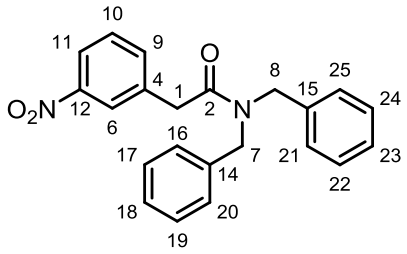
(White solid, 90%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.32-6.91 (m, 14H, H_{Ar}), 4.52 (s, 2H, H_7), 4.38 (s, 2H, H_8), 3.70 (s, 2H, H_1), 1,25 (s, 9H, $H_{14,15,16}$).

***N*,*N*-dibenzyl-2-(4-(methylthio)phenyl)acetamide (1.199l)**



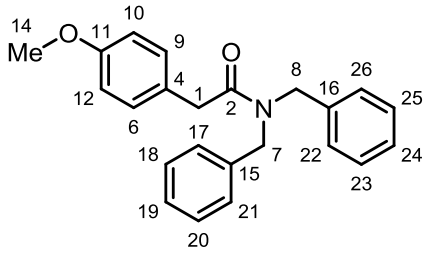
(Yellowish oil, 82%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 732-7.19 (m, 6H, H_{Ar}), 7.15- 7.08 (m, 6H, H_{Ar}), 7.04 (d, *J* = 7.6 Hz, 2H, H_{Ar}), 4.54 (s, 2H, H_7), 4.36 (s, 2H, H_8), 3.67 (s, 2H, H_1), 2.39 (s, 3H, H_{14}).

_N_,_N_-dibenzyl-2-(3-nitrophenyl)acetamide (1.199m)



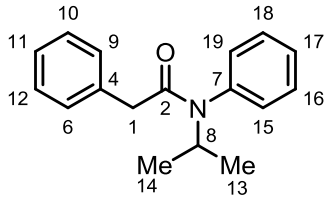
(Yellow solid, 79%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 8.6 Hz, 1H, H_{11}), 7.95 (s, 1H, H_6), 7.48 (d, *J* = 7.9 Hz, 1H, H_9), 7.37 (t, *J* = 7.9 Hz, 1H, H_{10}), 7.31-7.13 (m, 8H, H_{Ar}), 7.06 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 4.57 (s, 2H, H_7), 4.42 (s, 2H, H_8), 3.76 (s, 2H, H_1).

_N_,_N_-dibenzyl-2-(4-methoxyphenyl)acetamide (1.199n)



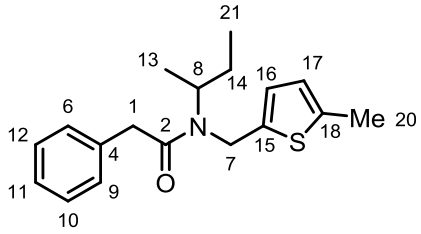
(White solid, 69%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 732-7.19 (m, 6H, H_{Ar}), 7.15- 7.08 (m, 6H, H_{Ar}), 6.91 (d, *J* = 7.6 Hz, 2H, H_{Ar}), 4.66 (s, 2H, H_7), 4.49 (s, 2H, H_8), 3.82 (s, 3H, H_{14}), 3.77 (s, 3H, H_1).

_N_-isopropyl-_N_,2-diphenylacetamide (1.199o)



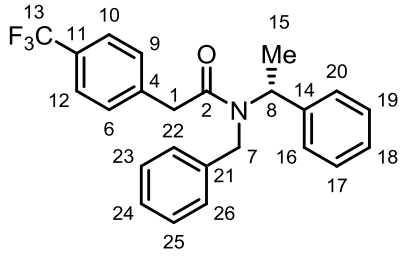
(Orange solid, 37%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.29-7.25 (m, 3H, H_{Ar}), 7.14-7.04 (m, 3H, H_{Ar}), 6.95-6.88 (m, 4H, H_{Ar}), 4.98-4.89 (m, 1H, H_8), 3.22 (s, 2H, H_1), 0.94 (d, *J* = 6.8, 6H, $H_{13,14}$).

_N_-(sec-butyl)-_N_-((5-methylthiophen-2-yl)methyl)-2-phenylacetamide (1.199p)



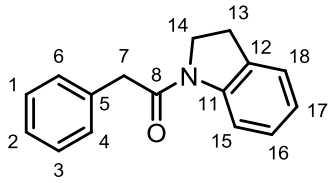
(Red solid, 73%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.35-7.29 (m, 3H, $H_{10,11,12}$), 7.27-7.22 (m, 2H, $H_{6,9}$), 6.71 (d, *J* = 3.6 Hz, 1H, H_{17}), 6.57 (d, 3.6 Hz, 1H, H_{16}), 4.63-4.37 (m, 2H, H_7), 3.89-3.73 (m, 3H, $H_{1,8}$), 2.49 (s, 3H, H_{20}), 1.66-1.41 (m, 2H, H_{14}), 1.09 (d, *J* = 6.7 Hz, 3H, H_{13}), 0.84 (t, *J* = 7.5 Hz, 3H, H_{21}).

***(R)*-_N_-benzyl-_N_-(1-phenylethyl)-2-(4-(trifluoromethyl)phenyl)acetamide (1.199q)**



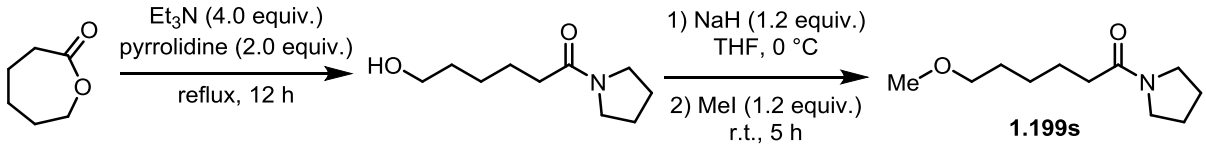
(colourless oil, 78%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.640-7.55 (m, 3H, H_{Ar}), 7.38-7.27 (m, 9H, H_{Ar}), 7.16 (d, *J* = 7.3 Hz, 4H, H_{Ar}), 6.24 (q, *J* = 7.5 Hz, 1H, H_8), 4.47 (d, *J* = 17.9 Hz, 2H, H_7), 3.69 (m, 2H, H_1), 1.53 (d, *J* = 7.2 Hz, 3H, H_{15}).

1-(Indolin-1-yl)-2-phenylethan-1-one (1.199r)



(Violet solid, 82%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.32 (d, *J* = 8.2 Hz, 1H, H_{15}), 7.40-7.27 (m, 5H, H_{Ar}), 7.25-7.16 (m, 2H, H_{Ar}), 7.04 (t, *J* = 7.3 Hz, 1H, H_{17}), 4.06 (t, *J* = 8.5 Hz, 2H, H_{14}), 3.82 (s, 2H, H_7), 3.16 (t, *J* = 8.7 Hz, 2H, H_{13}).

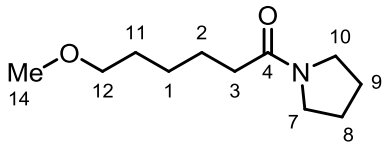
3.3.2 Procedure for the preparation of amide **1.199s**



A mixture of ε-butyrolactone (1.0 equiv., 10 mmol, 1.1 g), pyrrolidine (2.0 equiv., 20 mmol, 1.6 ml) and triethylamine (4.0 equiv., 40 mmol, 5.6 ml) was refluxed for 12 hours. After cooling down to room temperature the mixture was concentrated in vacuum to yield 6-hydroxy-1-(pyrrolidin-1-yl)hexan-1-one (quantitative yield, orange oil) which was directly used in the next step with no further purification.

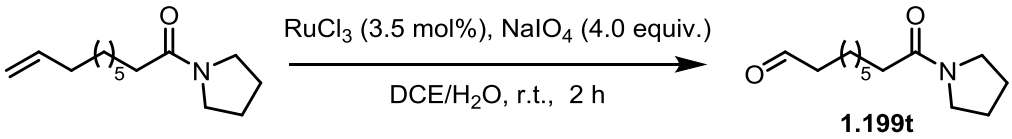
The hydroxylamide (1.0 equiv., 2.5 mmol, 463 mg) was dissolved in THF (5 ml). To this solution was added sodium hydride (1.2 equiv., 60% suspension in mineral oil, 150 mg) portion wise at 0 °C. After stirring for 1 hour, Methyl iodide (1.2 eq., 5 mmol, 0.13 ml) was added dropwise and the reaction mixture was warmed up to room temperature and stirred for another 5 hours. The mixture was then quenched at 0 °C by slow addition of saturated NH_4Cl. The aqueous phase was separated and extracted with ethyl acetate (3 x 15 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuum. The resulting crude product was purified by column chromatography (heptane/ethyl acetate: 2/1) to give amide **1.199s** in 71% yield as a colourless oil.

6-Methoxy-1-(pyrrolidin-1-yl)hexan-1-one (1.199s)



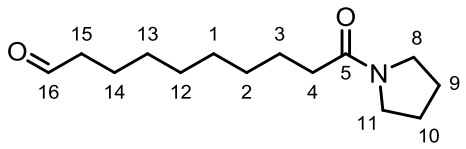
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.47 (t, *J* = 6.8 Hz, 2H, H_{12}), 3.43-3.36 (m, 4H, $H_{7,10}$), 3.33 (s. 3H, H_{14}), 2.28 (t, *J* = 7.8 Hz, 2H, H_3), 2.00-1.91 (m, 2H, H_{11}), 1.90-1.81 (m, 2H, H_2), 1.73-1.57 (m, 4H, $H_{8,9}$), 1.46-1.37 (m, 2H, H_1); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 171.6(C_4), 72.6(C_{14}), 58.5(C_{12}), 46.6(C_7), 45.6(C_{10}), 34.7(C_3), 29.4(C_{11}), 26.1(C_8), 26.0(C_9), 24.7(C_2), 24.4(C_1); **IR (neat) ν_{max}:** 2935, 2888, 1732, 1641, 1434, 1194, 1119; **HRMS (ESI^+):** exact mass calculated for ($C_{11}H_{21}O_2N$) requires *m*/*z* 199.1578, found *m*/*z* 199.1570.

3.3.3 Procedure for the preparation of amide **1.199t**



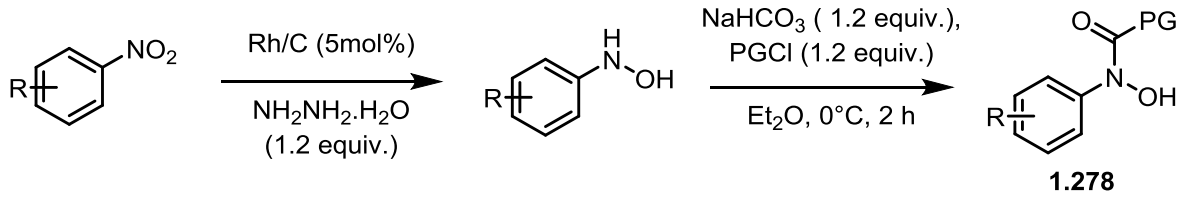
To a stirred mixture of the alkene-amide (1.0 equiv., 2 mmol, 475 mg) and $RuCl_3$ (3.5 mol%, 0.035 mmol, 16 mg) in 1,2-dichloroethane DCE (10 ml) and distilled water (8 ml) was added in portions sodium periodate $NaIO_4$ (4.0 equiv., 4 mmol, 856 mg) over a period of 5 min at room temperature. A colour changed from black to yellow was directly observed. After 2 h, the reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$, and the two layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 ml). The combined organic layers were washed brine (10 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography (heptane/ethyl acetate: 3/1) to give amide **1.199t** in 52% yield as a light yellow oil.

10-Oxo-10-(pyrrolidin-1-yl)decanal (1.199t)



^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H, H_{16}), 3.47 (t, *J* = 6.9 Hz, 2H, H_8), 3.42 (t, *J* = 6.7 Hz, 2H, H_{11}), 2.43 (t, *J* = 7.4 Hz, 2H, H_{15}), 2.26 (t, *J* = 7.3 Hz, 2H, H_4), 2.00-1.92 (m, 2H, H_3), 1.90-1.82 (m, 2H, H_{14}), 1.70-1.59 (m, 4H, $H_{9,10}$), 1.39-1.29 (m, 8H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 202.8(C_{16}), 171.7(C_5), 46.6(C_8), 45.6(C_{11}), 43.9(C_{15}), 34.8(C_4), 29.4(C_{Alk}), 29.2(C_{Alk}), 29.1(C_{Alk}), 29.0(C_{Alk}), 26.1(C_{Alk}), 24.8(C_{Alk}), 24.4(C_{Alk}), 22.0(C_{Alk}); **IR (neat) ν_{max}:** 2925, 2854, 1722, 1635, 1432, 1256, 1170, 1037, 915, 649; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{14}H_{25}O_2N$) requires *m*/*z* 262.1783, found *m*/*z* 262.1769.

3.3.4 General procedure for the preparation of hydroxamic acid **1.278**:



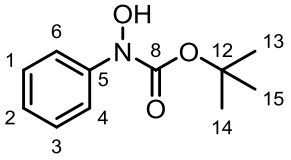
1.278

Under Argon atmosphere, a suspension of the nitrobenzene derivatives (1.0 equiv.) and 5% Rh/C (0.3 mol% Rh) in THF (0.25 M) was cooled to 0 °C. Hydrazine monohydrate (1.2 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was then filtered through a short pad of celite and concentrated in vacuum. The corresponding hydroxylamine was used directly for the next step.

To a stirred suspension of the hydroxamic acid (1.0 equiv.) and $NaHCO_3$ (1.2 equiv.) in Et_2O (0.3 M) at 0 °C under Argon was dropwise added a solution of the corresponding acyl chloride (1.2 equiv.) in Et_2O (0.2 M). The reaction was stirred for another 2 hours at the room temperature. Then the reaction mixture was filtered through a short pad of celite and washed with ethyl acetate. The organic layers were combined and concentrated in vacuum. The crude was purified by chromatography on silica gel (heptane/ethyl acetate: 4/1) to afford the hydroxamic acids **1.278**.

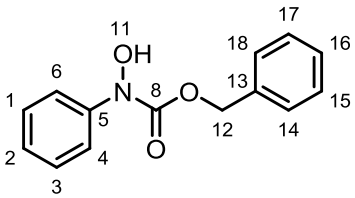
Spectroscopic data for the hydroxamic acids match those reported in the literature. [186]

***tert*-butyl hydroxy(phenyl)carbamatel (1.278a)**



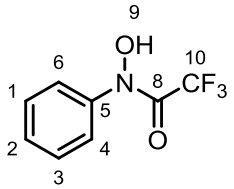
(Yellowish solid, 75%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.48 (d, *J* = 8.3 Hz, 2H, $H_{4,6}$), 7.36 (t, *J* = 7.7 Hz, 2H, $H_{1,3}$), 7.17 (t, *J* = 7.4 Hz, 1H, H_2), 1.55 (s, 9H, $H_{13,14,15}$).

Benzyl hydroxy(phenyl)carbamate (1.278b)



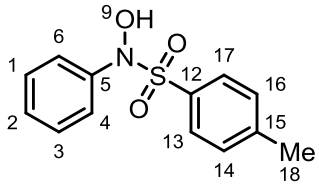
(Yellowish solid, 73%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.40 (d, *J* = 8.3 Hz, 2H, $H_{4,6}$), 7.30-7.23 (m, 7H, H_{Ar}), 7.11 (t, *J* = 7.4 Hz, 1H, H_2), 6.96 (s br, 1H, H_{11}), 5.19 (s, 2H, H_{12}).

2,2,2-Trifluoro-*N*-hydroxy-*N*-phenylacetamide (1.278c)



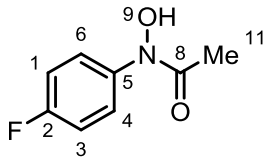
(Yellow solid, 52%), **^{1}H-NMR (400 MHz, d$_6$-DMSO):** δ 8.37 (s, 1H, H_9), 7.60-7.37 (m, 5H, H_{Ar}).

_N_-hydroxy-4-methyl-_N_-phenylbenzenesulfonamide (1.278d)



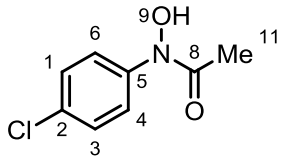
(Yellow solid, 63%), **^{1}H-NMR (400 MHz, d$_6$-DMSO):** δ 11.02 (s, 1H, H_9), 7.40-7.27 (m, 7H, H_{Ar}), 7.11 (d, J = 8.3 Hz, 2H, $H_{13,17}$), 2.37 (s, 3H, H_{18}).

_N_-(4-fluorophenyl)-_N_-hydroxyacetamide (1.278e)



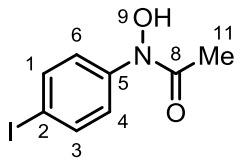
(Yellowish solid, 68%), **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 9.13 (s, 1H, H_9), 7.54-7.39 (m, 2H, $H_{1,3}$), 7.22-7.05 (m, 2H, $H_{4,6}$), 2.08 (s, 3H, H_{11}).

_N_-(4-chlorophenyl)-_N_-hydroxyacetamide (1.278f)



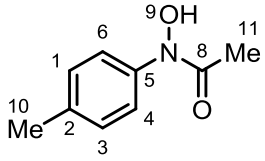
(Orange solid, 77%), **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 8.95 (s, 1H, H_9), 7.47-7.22 (m, 4H, H_{Ar}), 2.07 (s, 3H, H_{11}).

_N_-(4-iodophenyl)-_N_-hydroxyacetamide (1.278g)



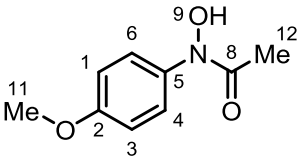
(Violet solid, 71%), **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 8.89 (s, 1H, H_9), 7.71-7.58 (m, 2H, $H_{1,3}$), 7.17-7.02 (m, 2H, $H_{4,6}$), 2.06 (s, 3H, H_{11}).

_N_-hydroxy-_N_-(_p_-tolyl)acetamide (1.278h)



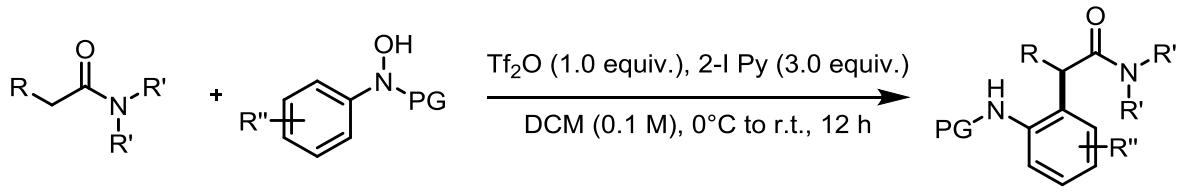
(Red oil, 79%), **^{1}H-NMR (400 MHz, d$_6$-DMSO):** δ 10.52 (s, 1H, H_9), 7.48 (d, J = 8.4 Hz, 2H, $H_{1,3}$), 7.16 (d, J = 8.5 Hz, 2H, $H_{4,6}$), 2.28 (s, 3H, H_{10}), 2.06 (s, 3H, H_{11}).

_N_-hydroxy-_N_-(4-methoxyphenyl)acetamide (1.278i)



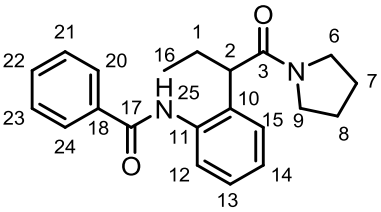
(Dark pink oil, 53%), **^{1}H-NMR (400 MHz, d_6-DMSO):** δ 10.58 (s, 1H, H_9), 7.45 (d, *J* = 8.8 Hz, 2H, $H_{1,3}$), 6.92 (d, *J* = 9.0 Hz, 2H, $H_{4,6}$), 3.75 (s, 3H, H_{11}), 2.14 (s, 3H, H_{12}).

3.3.4 General procedure for the α-arylation of amide with hydroxamic acids:



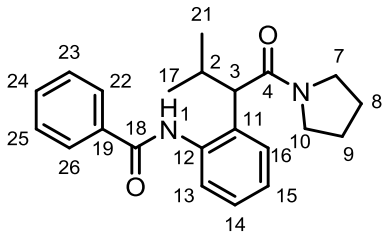
To a stirred solution of the amide (1.0 equiv., 0.2 mmol) and 2-iodopyridine (3.0 equiv., 0.6 mmol, 64 µl) in DCM (2 ml, 0.1 M) was added triflic anhydride Tf_2O (1 equiv., 0.2 mmol, 34 µl) at 0 °C under an argon atmosphere. After 15 min the hydroxamic acid (2 equiv., 0.4 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for another 12 hours. The reaction mixture was then quenched with 10 ml NaOH (0.1 M), extracted with DCM (2 x 15 ml), dried over $MgSO_4$ and concentrated in vacuum. The crude residue was purified by flash chromatography on silica gel using (heptane/ethyl acetate: 5/1 to 2/1) to afford the desired products.

***N*-(2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)benzamide (1.254)**



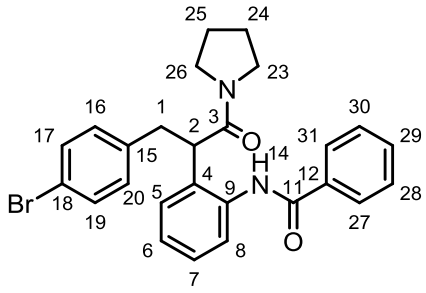
(White solid, 87%) mp 127-129 °C, **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.46 (s, 1H, H_{25}), 8.29 (d, *J* = 7.3 Hz, 1H, H_{Ar}), 8.24-8.20 (m, 2H, H_{Ar}), 7.50-7.46 (m, 1H, H_{Ar}), 7.34- 7.24 (m, 4H, H_{Ar}), 7.16 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 7.07 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 3.69-3.40 (m, 5H, $H_{2,6,9}$), 2.24-2.12 (m, 2H, H_1), 2.05-1.79 (m, 4H, $H_{7,8}$), 0.85 (t, *J* = 7.5 Hz, 3H, H_{16}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 173.4(C_3), 165.6(C_{17}), 137.9(C_{Ar}), 134.9(C_{Ar}), 131.8(C_{Ar}), 131.4(C_{Ar}), 130.8(C_{Ar}), 128.9(C_{Ar}), 128.7(C_{Ar}), 128.0(C_{Ar}), 127.9(C_{Ar}), 127.6(C_{Ar}), 125.0(C_{Ar}), 124.3(C_{Ar}), 53.9(C_2), 47.2(C_6), 46.7(C_9), 26.0(C_1), 24.3(C_7), 23.9(C_8), 12.6(C_{16}); **IR (neat) ν_{max}:** 3057, 2981, 1734, 1670, 1537, 1440, 1373, 1241, 1045, 735, 636; **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{21}H_{24}N_2O_2$) requires *m*/*z* 337.1916, found *m*/*z* 337.1909.

***N*-(2-(3-methyl-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)benzamide (1.260)**



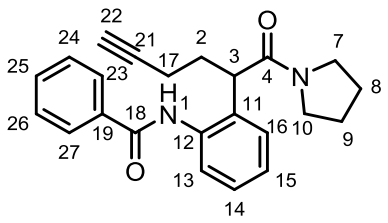
(Yellowish solid, 74%) mp 143-146 °C, **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.61 (s, 1H, H_1), 8.21 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 8.17-8.13 (m, 2H, H_{Ar}), 7.47-7.41 (m, 3H, H_{Ar}), 7.25 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.04-6.95 (m, 2H, H_{Ar}), 3.65-3.46 (m, 2H, H_7), 3.45-3.36 (m, 2H, H_{10}), 3.26 (d, *J* = 11.1 Hz, 1H, H_3), 2.75-2.60 (m, 1H, H_2); 2.00-1.74 (m, 4H, $H_{8,9}$), 0.92 (d, *J* = 6.4 Hz, 3H, H_{17}), 0.59 (d, *J* = 6.7 Hz, 3H, H_{21}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 173.3(C_4), 165.3(C_{18}), 138.2(C_{Ar}), 135.0(C_{Ar}), 132.3(C_{Ar}), 128.5(2C, C_{Ar}), 128.2(C_{Ar}), 128.0(C_{Ar}), 127.8(2C, C_{Ar}), 125.1(C_{Ar}), 124.0(C_{Ar}), 60.8(C_3), 47.3(C_7), 46.4(C_{10}), 28.6(C_2), 26.1(C_8), 24.3(C_9), 21.8(C_{17}), 20.8(C_{21}); **IR (neat) ν_{max}:** 3056, 2984, 1733, 1669, 1588, 1537, 1440, 1375, 1309, 1244, 1046, 897, 734, 705; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_2$) requires *m*/*z* 373.1892, found *m*/*z* 373.1894.

***N*-(2-(3-(4-bromophenyl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)phenyl)benzamide (1.261)**



(Reddish solid, 61%) mp 181-183 °C, **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.08 (s, 1H, H_{14}), 8.17-8.11 (m, 3H, H_{Ar}), 7.49-7.44 (m, 3H, H_{Ar}), 7.27-7.22 (m, 3H, H_{Ar}), 6.97-6.93 (m, 2H, H_{Ar}), 6.84 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 3.82 (t, *J* = 7.6 Hz, 1H, H_2), 3.42-3.31 (m, 4H, $H_{23,26}$), 3.25-3.17 (m, 1H, H_1), 3.01 (dd, *J* = 7.1, 7.4 Hz, 1H, H_1), 1.82-1.66 (m, 4H, $H_{24,25}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.2(C_3), 165.8(C_{11}), 138.3(C_{Ar}), 137.8(C_{Ar}), 134.7(C_{Ar}), 131.6(C_{Ar}), 131.4(C_{Ar}), 131.1(C_{Ar}), 130.6(C_{Ar}), 129.1(C_{Ar}), 128.8(C_{Ar}), 128.6(C_{Ar}), 128.3(C_{Ar}), 128.1(C_{Ar}), 127.7(C_{Ar}), 125.9(C_{Ar}), 125.6(C_{Ar}), 124.7(C_{Ar}), 120.4(C_{Ar}), 54.1(C_2), 46.9(C_{23}), 46.5(C_{26}), 36.6(C_1), 25.9(C_{24}), 24.1(C_{25}); **IR (neat) ν_{max}:** 3056, 2984, 1733, 1627, 1536, 1306, 1244, 1046, 1012, 897, 733, 704, 640; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{26}H_{25}N_2O_2Br$) requires *m*/*z* 499.0997, found *m*/*z* 499.1001.

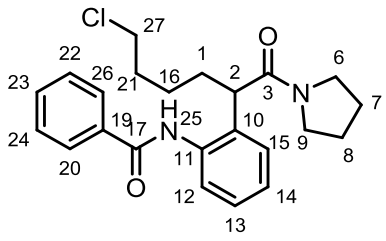
***N*-(2-(1-oxo-1-(pyrrolidin-1-yl)hex-5-yn-2-yl)phenyl)benzamide (1.263)**



(Yellowish oil, 77%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.22 (s, 1H, H_1), 8.30 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 8.24-8.19 (m, 2H, H_{Ar}), 7.56-7.51 (m, 3H, H_{Ar}), 7.36 (t, *J* = 7.7 H, 1H, H_{Ar}), 7.24 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 7.11 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 4.14 (t,

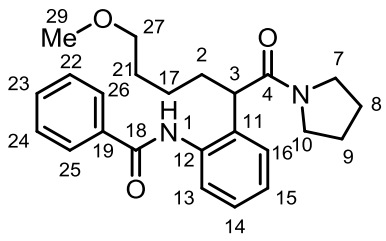
J = 7.4 Hz, 1H, H_3), 3.81-3.73 (m, 1H, H_7), 3.62-3.46 (m, 3H, $H_{7,10}$), 2.39-2.29 (m, 1H, H_{Alk}), 2.28-2.26 (m, 3H, H_{Alk}), 2.01 (t, *J* = 2.5 Hz, 1H, H_{22}), 2.00-1.85 (m, 4H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.4(C_4), 165.6(C_{18}), 138.0(C_{Ar}), 134.8(C_{Ar}), 131.8(C_{Ar}), 131.4(C_{Ar}), 128.6(2C, C_{Ar}), 128.2(C_{Ar}), 127.8(2C, C_{Ar}), 127.6(C_{Ar}), 125.1(C_{Ar}), 124.4(C_{Ar}), 83.5(C_{21}), 69.6(C_{22}), 49.6(C_3), 47.0(C_7), 46.6(C_{10}), 29.0(C_{17}), 26.1(C_8), 24.2(C_9), 16.5(C_2); **IR (neat) ν_{max}:** 3056, 2983, 1733, 1670, 1601, 1537, 1243, 1096, 1045, 897, 733, 703, 643; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{23}H_{24}N_2O_2$) requires *m*/*z* 383.1735, found *m*/*z* 383.1732.

***N*-(2-(6-chloro-1-oxo-1-(pyrrolidin-1-yl)hexan-2-yl)phenyl)benzamide (1.265)**



(Yellowish oil, 67%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.24 (s, 1H, H_{25}), 8.21 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 8.16-8.11 (m, 2H, H_{Ar}), 7.47-7.42 (m, 3H, H_{Ar}), 7.26 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.06 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 6.99 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 3.67 (t, *J* = 7.6 Hz, 1H, H_2), 3.62-3.38 (m, 4H, $H_{6,9}$), 3.34 (t, *J* = 6.6 Hz, 2H, H_{27}), 2.14-2.03 (m, 1H, H_1), 1.98-1.73 (m, 5H, $H_{1,7,8}$), 1.64-1.55 (m, 2H, H_{21}), 1.39-1.19 (m, 2H, H_{16}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.9(C_3), 165.5(C_{17}), 138.0(C_{Ar}), 134.8(C_{Ar}), 131.7(C_{Ar}), 131.5(C_{Ar}), 128.6(2C, C_{Ar}), 128.1(C_{Ar}), 127.7(2C, C_{Ar}), 125.2(C_{Ar}), 124.3(C_{Ar}), 52.1(C_2), 47.2(C_6), 46.6(C_9), 44.7(C_{27}), 32.3(C_1), 29.8(C_7), 29.1(C_8), 26.9(C_{21}), 25.3(C_{19}); **IR (neat) ν_{max}:** 3056, 2981, 1733, 1669, 1625, 1586, 1497, 1307, 1265, 1189, 1096, 1045, 939, 900, 848, 733, 704, 647; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{23}H_{27}N_2O_2Cl$) requires *m*/*z* 421.1659, found *m*/*z* 421.1663.

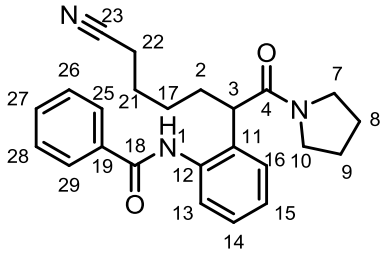
***N*-(2-(6-methoxy-1-oxo-1-(pyrrolidin-1-yl)hexan-2-yl)phenyl)benzamide (1.266)**



(Yellowish oil, 73%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.39 (s, 1H, H_1), 8.31 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 8.25-8.21 (m, 2H, H_{Ar}), 7.57-7.51 (m, 1H, H_{Ar}), 7.34 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.15 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.07 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 3.78 (t, *J* = 7.6 Hz, 1H, H_3), 3.70-3.45 (m, 4H, $H_{7,10}$), 3.28-3.24 (m, 2H, H_{27}), 3.23 (s, 3H, H_{29}), 2.23-2.12 (m, 1H, H_2), 2.07-1.82 (m, 5H, $H_{1,8,9}$), 1.57-1.44 (m, 2H, H_{21}), 1.39-1.19 (m, 2H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 173.1(C_4), 165.5(C_{18}), 138.1(C_{Ar}), 134.9(C_{Ar}), 131.8(C_{Ar}), 131.4(C_{Ar}), 128.6(2C, C_{Ar}), 128.4(C_{Ar}), 128.0(C_{Ar}), 127.7(2C, C_{Ar}), 125.1(C_{Ar}), 124.2(C_{Ar}), 72.3(C_{29}), 58.4(C_{27}), 52.1(C_3), 47.1(C_7), 46.5(C_{10}), 30.4(C_{21}), 29.3(C_2), 26.0(C_8), 24.6(C_9), 24.1(C_{17}); **IR (neat) ν_{max}:** 3057, 2985,

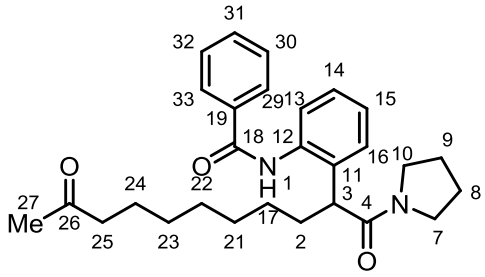
1733, 1669, 1601, 1540, 1374, 1115, 1046, 940, 848, 732, 704, 642; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{24}H_{30}N_2O_3$) requires *m*/*z* 417.2154, found *m*/*z* 417.2134.

***N*-(2-(6-cyano-1-oxo-1-(pyrrolidin-1-yl)hexan-2-yl)phenyl)benzamide (1.264)**



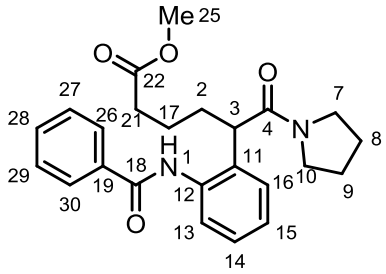
(Colourless oil, 82%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.20 (s, 1H, H_1), 8.18 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 8.15-8.11 (m, 2H, H_{Ar}), 7.48-7.43 (m, 3H, H_{Ar}), 7.26 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.06 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.00 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 3.67 (t, *J* = 7.6 Hz, 1H, H_3), 3.62-3.37 (m, 4H, $H_{7,10}$), 2.16-2.11 (m, 2H, H_{22}), 2.09-2.01 (m, 1H, H_2), 1.96-1.75 (m, 5H, $H_{2,8,9}$), 1.51-1.41 (m, 2H, H_{21}), 1.38-1.21 (m, 2H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.7(C_4), 165.5(C_{18}), 138.0(C_{Ar}), 134.7(C_{Ar}), 131.7(C_{Ar}), 131.7(C_{Ar}), 131.6(C_{Ar}), 128.6(2C, C_{Ar}), 128.2(C_{Ar}), 127.9(C_{Ar}), 127.7(C_{Ar}), 125.3(C_{Ar}), 124.4(C_{Ar}), 119.5(C_{23}), 52.0(C_3), 47.2(C_7), 46.5(C_{10}), 29.7(C_2), 27.0(C_8), 26.0(C_9), 25.1(C_{22}), 24.2(C_{21}), 16.8(C_{17}); **IR (neat) ν_{max}:** 3056, 2985, 1733, 1669, 1601, 1540, 1443, 1374, 1306, 1244, 1046, 898, 732, 703, 643; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{24}H_{27}N_3O_2$) requires *m*/*z* 412.2001, found *m*/*z* 412.1992.

***N*-(2-(1,10-dioxo-1-(pyrrolidin-1-yl)undecan-2-yl)phenyl)benzamide (1.268)**



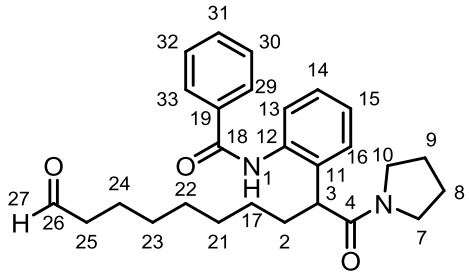
(Yellowish oil, 66%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.42 (s, 1H, H_1), 8.31 (d, *J*= 8.4 Hz, 1H, H_{Ar}), 8.25-8.21 (m, 2H, H_{Ar}), 7.56-7.51 (m, 3H, H_{Ar}), 7.34 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.14 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.07 (t, *J* = 7.6, Hz, 1H, H_{Ar}), 3.75 (t, *J* = 7.7, Hz, 1H, H_3), 3.70-3.45 (m, 4H, $H_{7,10}$), 2.34 (t, *J* = 7.6, 2H, H_{25}), 2.10 (s, 3H, H_{27}), 2.05-1.82 (m, 5H, $H_{8,9}$), 1.50-1.42 (m, 2H, H_{17}), 1.22-1.15 (m, 6H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 209.3(C_{26}), 173.3(C_4), 165.5(C_{18}), 138.1(C_{Ar}), 134.9(C_{Ar}), 131.7(C_{Ar}), 131.4(C_{Ar}), 128.6(2C, C_{Ar}), 128.5(C_{Ar}), 128.0(C_{Ar}), 127.7(2C, C_{Ar}), 125.1(C_{Ar}), 124.2(C_{Ar}), 52.2(C_3), 47.2(C_7), 46.5(C_{10}), 43.6(C_{27}), 30.4(C_{Alk}), 29.8(2C, C_{Alk}), 29.0(C_{Alk}), 28.9(C_{Alk}), 27.8(C_{Alk}), 26.1(C_{Alk}), 24.3(C_{Alk}), 23.6(C_{Alk}); **IR (neat) ν_{max}:** 3056, 2978, 2929, 2856, 1713, 1625, 1586, 1438, 1266, 1241, 1045, 900, 733, 672, 641; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{28}H_{36}N_2O_3$) requires *m*/*z* 471.2624, found *m*/*z* 471.2601.

Methyl 5-(2-benzamidophenyl)-6-oxo-6-(pyrrolidin-1-yl)hexanoate (1.269)



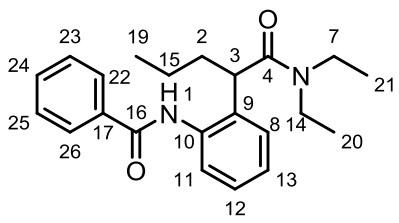
(Colourless oil, 55%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.22 (s, 1H, H_1), 8.22 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 8.15-8.11 (m, 2H, H_{Ar}), 7.47-7.41 (m, 3H, H_{Ar}), 7.25 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.07 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 6.98 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 3.69 (t, *J* = 7.6 Hz, 1H, H_3), 3.62-3.55 (m, 1H, H_7), 3.53-3.45 (m, 3H, $H_{7,10}$), 3.48 (s, 3H, H_{25}), 2.14 (t, *J* = 7.3 Hz, 2H, H_{21}), 2.11-2.03 (m, 1H, H_2), 1.95-1.73 (m, 5H, $H_{2,8,9}$), 1.57-1.38 (m, 2H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 173.4(C_{22}), 172.7(C_4), 165.6(C_{18}), 137.9(C_{Ar}), 134.8(C_{Ar}), 131.8(C_{Ar}), 131.4(C_{Ar}), 128.6(2C, C_{Ar}), 128.1(C_{Ar}), 128.0(C_{Ar}), 127.8(2C, C_{Ar}), 125.2(C_{Ar}), 124.3(C_{Ar}), 51.9(C_{25}), 51.4(C_3), 47.2(C_7), 46.7(C_{10}), 33.6(C_{21}), 29.9(C_2), 26.0(C_8), 24.3(C_9), 23.9(C_{17}); **IR (neat) ν_{max}:** 3056, 2983, 1732, 1669, 1587, 1538, 1439, 1373, 1243, 1096, 1046, 899, 733, 704; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{24}H_{28}N_2O_2$) requires *m*/*z* 431.1947, found *m*/*z* 431.1949.

***N*-(2-(1,10-dioxo-1-(pyrrolidin-1-yl)decan-2-yl)phenyl)benzamide (1.267)**



(Yellowish oil, 69%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.41 (s, 1H, H_1), 9.72 (s, 1H, H_{27}), 8.31 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 8.25-8.22 (m, 2H, H_{Ar}), 7.55-7.52 (m, 3H, H_{Ar}), 7.34 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.14 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.07 (t, *J* = 7.6, Hz, 1H, H_{Ar}), 3.75 (t, *J* = 7.7, Hz, 1H, H_3), 3.71-3.45 (m, 4H, $H_{7,10}$), 2.34 (t, *J* = 7.6, 2H, H_{25}), 2.17-1.83 (m, 6H, H_{Alk}), 1.56-1.47 (m, 2H, H_{Alk}), 1.25-1.16 (m, 8H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 202.8(C_{26}), 173.3(C_4), 165.5(C_{18}), 138.1(C_{Ar}), 134.9(C_{Ar}), 131.7(C_{Ar}), 131.4(C_{Ar}), 128.6(2C, C_{Ar}), 128.4(C_{Ar}), 128.0(C_{Ar}), 127.7(2C, C_{Ar}), 125.1(C_{Ar}), 124.2(C_{Ar}), 52.3(C_3), 47.2(C_7), 46.5(C_{10}), 43.8(C_{25}), 30.4(C_{Alk}), 29.0(C_{Alk}), 28.9(C_{Alk}), 28.8(C_{Alk}), 27.7(C_{Alk}), 26.0(C_{Alk}), 24.2(C_{Alk}), 21.9(C_{Alk}); **IR (neat) ν_{max}:** 3055, 2928, 2856, 1732, 1667, 1585, 1438, 1265, 1242, 1188, 1074, 899, 733, 704, 673; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{27}H_{34}N_2O_3$) requires *m*/*z* 457.2467, found *m*/*z* 457.2459.

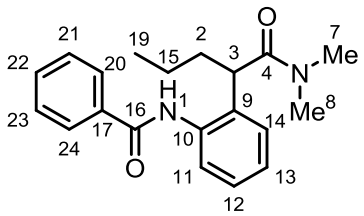
***N*-(2-(1-(diethylamino)-1-oxopentan-2-yl)phenyl)benzamide (1.270)**



(White solid, 88%) mp 117-119 °C, **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.42 (s, 1H, H_1), 8.34 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 8.25-8.20 (m, 2H, H_{Ar}), 7.57-7.51 (m, 3H, H_{Ar}), 7.33 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.15 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 7.08 (t, *J* =

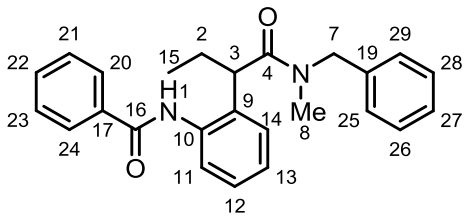
7.4 Hz, 1H, H_{Ar}), 3.86 (t, *J* = 7.6 Hz, 1H, H_3), 3.36-3.52 (m, 1H, H_7), 3.47-3.36 (m, 3H, $H_{7,14}$), 2.14-1.92 (m, 2H, H_2), 1.30-1.25 (m, 2H, H_{15}), 1.22 (t, *J* = 7.2 Hz, 3H, H_{20}), 1.13 (t, *J* = 7.2 Hz, 3H, H_{21}), 0.85 (t, *J* = 7.4 Hz, 3H, H_{19}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 174.2(C_4), 165.6(C_{16}), 138.1(C_{Ar}), 135.0(C_{Ar}), 131.6(C_{Ar}), 131.3(C_{Ar}), 128.9(C_{Ar}), 128.5(2C, C_{Ar}), 127.9(C_{Ar}), 127.7(2C, C_{Ar}), 124.9(C_{Ar}), 124.2(C_{Ar}), 49.7(C_3), 42.6, 41.3(C_7), 33.4(C_{14}), 21.2(C_2), 14.7(C_{20}), 13.8(C_{21}), 12.9(C_{19}); **IR (neat) ν_{max}:** 3055, 2963, 2873, 1735, 1667, 1622, 1585, 1500, 1264, 1244, 1143, 1046, 889, 734, 704, 672, 640; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{22}H_{28}N_2O_2$) requires *m*/*z* 375.2048, found *m*/*z* 375.2051.

***N*-(2-(1-(dimethylamino)-1-oxopentan-2-yl)phenyl)benzamide (1.271)**



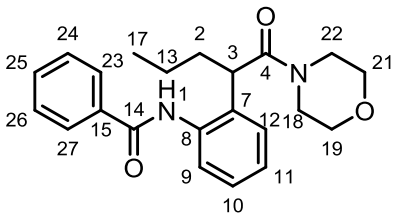
(Colourless oil, 81%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.05 (s, 1H, H_1), 8.24 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 8.15-8.10 (m, 2H, H_{Ar}), 7.48-7.42 (m, 3H, H_{Ar}), 7.42 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.06 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 6.98 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 3.86 (t, *J* = 7.6 Hz, 1H, H_3), 3.10 (s, 3H, H_7), 2.93 (s, 3H, H_8), 2.08-1.95 (m, 1H, H_2), 1.92-1.80 (m, 1H, H_2), 1.24-1.09 (m, 2H, H_{15}), 0.76 (t, *J* = 7.2 Hz, 3H, H_{19}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 174.9(C_4), 165.5(C_{16}), 138.1(C_{Ar}), 135.0(C_{Ar}), 131.6(C_{Ar}), 131.4(C_{Ar}), 128.5(2C, C_{Ar}), 128.4(C_{Ar}), 127.9(C_{Ar}), 127.7(2C, C_{Ar}), 124.9(C_{Ar}), 124.2(C_{Ar}), 49.4(C_3), 38.0(C_7), 36.5(C_8), 33.0(C_2), 21.2(C_{15}), 13.8(C_{19}); **IR (neat) ν_{max}:** 3057, 2984, 1733, 1669, 1604, 1444, 1307, 1265, 1045, 939, 733, 703; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{20}H_{24}N_2O_2$) requires *m*/*z* 347.1735, found *m*/*z* 347.1726.

***N*-(2-(1-(benzyl(methyl)amino)-1-oxobutan-2-yl)phenyl)benzamide (1.272)**



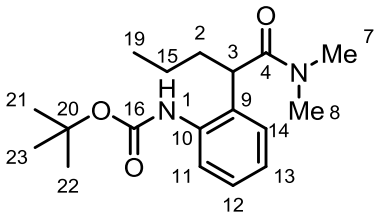
(Yellowish oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.99 (s, 1H, H_1), 8.25 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 8.15-8.08 (m, 2H, H_{Ar}), 7.47-7.39 (m, 3H, H_{Ar}), 7.31-7.17 (m, 6H, H_{Ar}), 7.10-7.00 (m, 4H, H_{Ar}), 6.95-6.85 (m, 1H, H_{Ar}), 4.81-4.47 (m, 2H, H_7), 3.73 (t, *J* = 7.6 Hz, 1H, H_3), 2.97 (s, 3H, H_8), 2.18-2.02 (m, 1H, H_2), 1.97-1.86 (m, 1H, H_2), 0.75 (t, *J* = 7.3 Hz, 3H, H_{15}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 175.4(C_4), 165.5(C_{16}), 138.0(C_{Ar}), 136.7(C_{Ar}), 134.9(C_{Ar}), 131.8(C_{Ar}), 131.5(C_{Ar}), 129.0(C_{Ar}), 128.7(2C, C_{Ar}), 128.1(C_{Ar}), 127.9(C_{Ar}), 127.7(2C, C_{Ar}), 127.6(C_{Ar}), 127.3(C_{Ar}), 126.2(C_{Ar}), 124.9(C_{Ar}), 124.3(C_{Ar}), 53.7(C_3), 51.6(C_7), 35.5(C_8), 24.4(C_2), 18.5(C_{15}); **IR (neat) ν_{max}:** 3056, 2984, 1733, 1670, 1586, 1373, 1243, 1097, 1045, 919, 848, 733, 704; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{25}H_{26}N_2O_2$) requires *m*/*z* 409.1892, found *m*/*z* 409.1887.

***N*-(2-(1-morpholino-1-oxopentan-2-yl)phenyl)benzamide (1.275)**



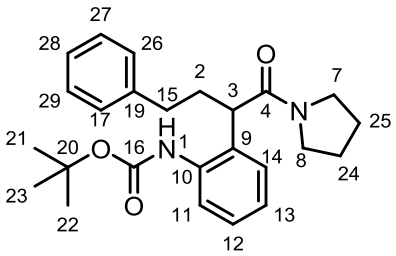
(Yellowish solid, 43%) mp 126-129 °C, **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 10.57 (s, 1H, H_1), 8.20 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 8.11-8.07 (m, 2H, H_{Ar}), 7.48-7.43 (m, 3H, H_{Ar}), 7.28-7.22 (m, 1H, H_{Ar}), 7.04-6.98 (m, 2H, H_{Ar}), 3.81 (t, *J* = 7.5 Hz, 1H, H_3), 3.69-3.46 (m, 8H, $H_{18,19,21,22}$), 2.10-1.98 (m, 1H, H_2), 1.91-1.81 (m, 1H, H_2), 1.24-1.13 (m, 2H, H_{13}), 0.77 (t, *J* = 7.4 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, CDCl$_3$):** δ 173.3(C_4), 165.5(C_{14}), 137.7(C_{Ar}), 134.8(C_{Ar}), 131.6(C_{Ar}), 131.0(C_{Ar}), 128.7(C_{Ar}), 128.5(2C, C_{Ar}), 128.1(C_{Ar}), 127.6(2C, C_{Ar}), 125.1(C_{Ar}), 124.6(C_{Ar}), 66.7(2C, $C_{19,21}$), 48.7(C_{18}), 46.7(C_{22}), 42.9(C_3), 33.0(C_2), 21.3(C_{13}), 13.8(C_{17}); **IR (neat) ν$_{max}$:** 3057, 2984, 1733, 1670, 1537, 1441, 1304, 1242, 1116, 1045, 939, 847, 733, 705; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}N_2O_3$) requires *m*/*z* 389.1841, found *m*/*z* 389.1839.

***tert*-butyl (2-(1-(dimethylamino)-1-oxopentan-2-yl)phenyl)carbamate (1.279)**



(White solid, 80%) mp 86-88 °C, **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 8.86 (s, 1H, H_1), 7.86 (d, *J* = 8.3 Hz, 1H, H_{11}), 7.24 (t, *J* = 7.8 Hz, 1H, H_{13}), 7.11 (d, *J* = 7.8 Hz, 1H, H_{14}), 7.00 (t, *J* = 7.4 Hz, 1H, H_{12}), 3.86 (t, *J* = 7.4 Hz, 1H, H_3), 3.07 (s, 3H, H_7), 2.98 (s, 3H, H_8), 2.16-2.06 (m, 1H, H_2), 1.91-1.80 (m, 1H, H_2), 1.54 (s, 9H, $H_{21,22,23}$), 1.34-1.15 (m, 2H, H_{15}), 0.91 (t, *J* = 7.3 Hz, 3H, H_{19}); **^{13}C-NMR (100 MHz, CDCl$_3$):** δ 174.2(C_4), 153.8(C_{16}), 137.8(C_{Ar}), 130.7(C_{Ar}), 127.7(2C, C_{Ar}), 123.7(C_{Ar}), 123.5(C_{Ar}), 79.7(C_{20}), 48.1(C_3), 37.6(C_7), 36.3(C_8), 33.5(C_2), 28.4(3C, $C_{21,22,23}$), 21.2(C_{15}), 13.9(C_{19}); **IR (neat) ν$_{max}$:** 3252, 2962, 2873, 1722, 1632, 1590, 1520, 1446, 1395, 1366, 1301, 1244, 1161, 1121, 1047, 1024; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{28}N_2O_3$) requires *m*/*z* 343.1998, found *m*/*z* 343.1993.

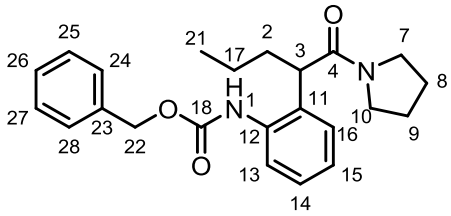
***tert*-butyl (2-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)carbamate (1.280)**



(Yellowish oil, 69%), **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 9.09 (s, 1H, H_1), 7.81 (d, *J* = 8.1 Hz, 1H, H_{11}), 7.22-7.12 (m, 4H, H_{Ar}), 7.09-7.04 (m, 2H, H_{Ar}), 6.94 (d, *J* = 7.7 Hz, 1H, H_{14}), 6.88 (t, *J* = 7.4 Hz, 1H, H_3), 3.53 (t, *J* = 7.6 Hz, 1H, H_3), 3.46-3.31 (m, 2H, H_7), 3.24-3.16 (m, 2H, H_8), 2.55-2.39 (m, 3H, $H_{15,2}$), 2.19-2.09 (m, 1H, H_2), 1.83-1.68 (m, 4H, $H_{24,25}$), 1.44 (s, 9H, $H_{21,22,23}$); **^{13}C-NMR (100 MHz, CDCl$_3$):** δ 172.0(C_4), 153.8(C_{16}), 141.3(C_{10}), 138.1(C_{Ar}), 131.1(C_{Ar}), 128.5(2C, C_{Ar}),

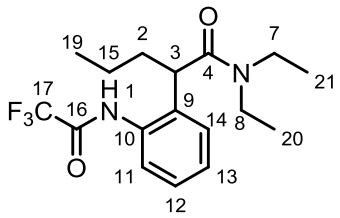
128.4(2C, C_{Ar}), 127.9(C_{Ar}), 126.0(2C, C_{Ar}), 123.6(C_{Ar}), 123.3(C_{Ar}), 79.7(C_{20}), 49.4(C_3), 46.5(C_7), 46.2(C_8), 33.6(C_3), 31.9(C_{15}), 28.4(3C, $C_{21,22,23}$), 25.9(C_2); **IR (neat) ν_{max}:** 3056, 2981, 1730, 1626, 1533, 1441, 1301, 1265, 1159, 1115, 1024, 915, 732, 701, 642; **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{25}H_{32}N_2O_3$) requires *m*/*z* 431.2311, found *m*/*z* 431.2306.

Benzyl (2-(1-oxo-1-(pyrrolidin-1-yl)pentan-2-yl)phenyl)carbamate (1.282)



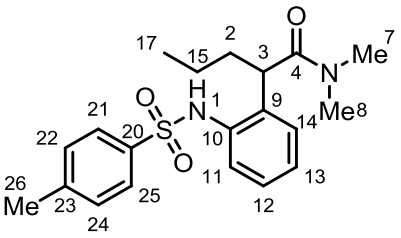
(Colourless oil, 77%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.01 (s, 1H, H_1), 7.91 (d, *J* = 7.9 Hz, 1H, H_{13}), 7.36 (d, *J* = 7.5, 2H, H_{Ar}), 7.26 (t, *J* = 7.4 Hz, 2H, H_{Ar}), 7.22-7.14 (m, 2H, H_{Ar}), 6.99 (d, *J* = 7.7, 1H, H_{16}), 6.89 (t, *J* = 7.4 Hz, 1H, H_{15}), 5.15 (q, *J* = 13.3 Hz, 2H, H_{22}), 3.60 (t, *J* = 7.6 Hz, 1H, H_3), 3.55-3.30 (m, 4H, $H_{7,10}$), 2.08-1.98 (m, 1H, H_2), 1.93-1.70 (m, 5H, $H_{2,8,9}$), 1.23-1.04 (m, 2H, H_{17}), 0.78 (t, *J* = 7.2 Hz, 3H, H_{21}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.8(C_4), 154.2(C_{18}), 138.0(C_{Ar}), 136.9(C_{Ar}), 131.4(C_{Ar}), 128.3(2C, C_{Ar}), 128.0(C_{Ar}), 127.9(2C, C_{Ar}), 127.8(C_{Ar}), 123.3(2C, C_{Ar}), 66.3(C_{22}), 51.4(C_3), 46.9(C_7), 46.3(C_{10}), 32.9(C_2), 26.1(C_8), 24.2(C_9), 21.1(C_{17}), 13.8(C_{21}); **IR (neat) ν_{max}:** 2960, 2875, 1731, 1626, 1592, 1443, 1373, 1341, 1220, 1098, 1042, 848, 733, 699, 640; **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{23}H_{28}N_2O_3$) requires *m*/*z* 403.1998, found *m*/*z* 403.1996.

***N*,*N*-diethyl-2-(2-(2,2,2-trifluoroacetamido)phenyl)pentanamide (1.283)**



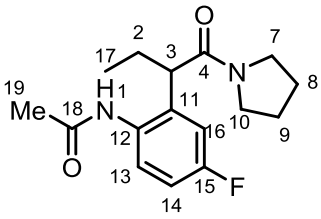
(Yellowish oil, 67%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 12.46 (s, 1H, H_1), 8.06 (d, *J* = 8.2 Hz, 1H, H_{11}), 7.27-7.21 (m, 1H, H_{12}), 7.04 (d, *J* = 4.4 Hz, 2H, $H_{13,14}$), 3.77 (t, *J* = 7.7 Hz, 1H, H_3), 3.49-3.25 (m, 4H, $H_{7,8}$), 2.02-1.79 (m, 2H, H_2), 1.18 (t, *J* = 7.2 Hz, 3H, H_{20}), 1.15-1.08 (m, 2H, H_{15}), 1.04 (t, *J* = 7.2 Hz, 3H, H_{21}), 0.80 (t, *J* = 7.4 Hz, 3H, H_{19}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 174.5(C_4), 155.4(C_{16}), 135.7(C_{Ar}), 131.7(C_{Ar}), 129.5(C_{Ar}), 128.2(C_{Ar}), 125.7(C_{Ar}), 124.3(C_{Ar}), 114.9(C_{17}), 49.4(C_3), 42.9(C_7), 41.4(C_8), 33.6(C_2), 21.1(C_{15}), 14.9(C_{20}), 13.7(C_{21}), 12.8(C_{19}); **^{19}F-NMR (700 MHz, $CDCl_3$):** δ -75.51; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{23}N_2O_2F_3$) requires *m*/*z* 367.1609, found *m*/*z* 367.1606.

***N*,*N*-dimethyl-2-(2-((4-methylphenyl)sulfonamido)phenyl)pentanamide (1.284)**



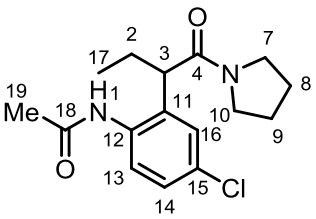
(Yellowish solid, 18%) mp 158-160 °C, **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.27 (s, 1H, H_1), 7.80 (d, *J* = 8.4 Hz, 2H, $H_{21,25}$), 7.55 (d, *J* = 8.1 Hz, 1H, H_{11}), 7.24 (d, *J* = 8.1 Hz, 2H, $H_{22,24}$), 7.17 (t, *J* = 7.8 Hz, 1H, H_{12}), 7.05 (d, *J* = 7.6 Hz, 1H, H_{14}), 6.98 (t, *J* = 7.4 Hz, 1H, H_{13}), 3.83 (t, *J* = 7.6 Hz, 1H, H_3), 3.09 (s, 3H, H_7), 3.00 (s, 3H, H_8), 2.39 (s, 3H, H_{26}), 2.00-1.89 (m, 1H, H_2), 1.66-1.59 (m, 1H, H_2), 1.21-0.99 (m, 2H, H_{15}), 0.80 (t, *J* = 7.3 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 174.4(C_4), 143.1(C_{10}), 137.9(C_{Ar}), 137.3(C_{Ar}), 131.7(C_{Ar}), 129.5(2C, C_{Ar}), 128.1(2C, C_{Ar}), 127.3(2C, C_{Ar}), 123.8(C_{Ar}), 121.1(C_{Ar}), 48.7(C_3), 37.8(C_7), 36.4(C_8), 33.5(C_2), 21.5(C_{26}), 21.0(C_{15}), 13.7(C_{17}); **IR (neat) ν_{max}:** 2959, 2871, 1735, 1621, 1494, 1443, 1332, 1241, 1157, 1091, 1045, 934, 815, 754, 734, 701; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{20}H_{26}N_2O_3S$) requires *m*/*z* 397.1562, found *m*/*z* 397.1558.

***N*-(4-fluoro-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide (1.285)**



(Red oil, 54%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.43 (s, 1H, H_1), 8.06 (dd, *J* = 5.8, 5.6 Hz, 1H, H_{16}), 6.89 (t, *J* = 8.4 Hz, 1H, H_{14}), 6.73 (d, *J* = 9.0 Hz, 1H, H_{13}), 3.58-3.51 (m, 1H, H_3), 3.49-3.36 (m, 4H, $H_{7,10}$), 2.13 (s, 3H, H_{19}), 2.11-2.02 (m, 1H, H_2), 1.98-1.76 (m, 5H, $H_{2,8,9}$), 0.80 (t, *J* = 7.4 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.3(C_4), 168.7(C_{18}), 159.8(C_{15}), 134.0(C_{12}), 129.2(C_{14}), 125.3(C_{16}), 117.8(C_{11}), 114.3(C_{13}), 53.5(C_3), 47.1(C_7), 46.4(C_{10}), 26.0(C_{19}), 24.5(C_8), 24.2(C_9), 23.8(C_2), 12.5(C_{17}); **^{19}F-NMR (700 MHz, $CDCl_3$):** δ -119.19; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}N_2O_2F$) requires *m*/*z* 315.1485, found *m*/*z* 315.1482.

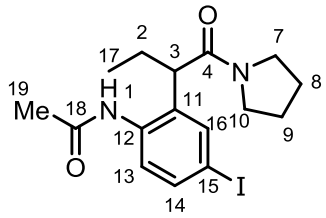
***N*-(4-chloro-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide (1.286)**



(Orange solid, 62%) mp 133-135 °C, **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.63 (s, 1H, H_1), 8.13 (d, *J* = 8.8 Hz, 1H, H_{13}), 7.15 (dd, *J* = 2.4, 2.5 Hz, 1H, H_{16}), 6.98 (d, *J* = 2.4 Hz, 1H, H_{14}), 3.59-3.51 (m, 1H, H_3), 3.49-3.37 (m, 4H, $H_{7,10}$), 2.13 (s, 3H, H_{19}), 2.11-2.02 (m, 1H, H_2), 1.97-1.77 (m, 5H, $H_{2,8,9}$), 0.79 (t, *J* = 7.4 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.3(C_4), 168.7(C_{18}), 136.7(C_{15}), 131.2(C_{12}), 128.7(C_{Ar}), 128.3(C_{Ar}), 127.9(C_{Ar}), 124.7(C_{Ar}), 53.6(C_3), 47.1(C_7), 46.5(C_{10}), 26.0(C_{19}), 24.7(C_8), 24.2(C_9), 23.7(C_2), 12.6(C_{17}); **IR (neat) ν_{max}:** 3056, 2983, 1733, 1693, 1535, 1398, 1301, 1243, 1079, 1046, 732, 703, 642;

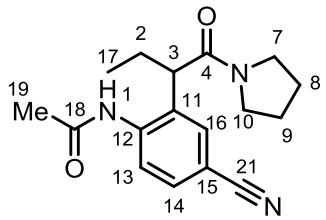
HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}N_2O_2Cl$) requires *m*/*z* 331.1189, found *m*/*z* 331.1182.

***N*-(4-iodo-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide (1.287)**



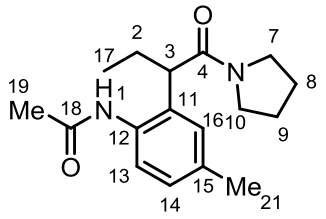
(Violet solid, 46%) mp 145-147 °C, **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.77 (s, 1H, H_1), 8.05 (d, *J* = 8.6 Hz, 1H, H_{13}), 7.56 (dd, J_1 = 2.2, J_2 = 2.3 Hz, 1H, H_{16}), 7.42 (d, *J* = 2.1 Hz, 1H, H_{14}), 3.68-3.60 (m, 1H, H_3), 3.58-3.44 (m, 4H, $H_{7,10}$), 2.22 (s, 3H, H_{19}), 2.20-2.12 (m, 1H, H_2), 2.08-1.86 (m, 5H, $H_{2,8,9}$), 0.88 (t, *J* = 7.2 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.3(C_4), 168.7(C_{18}), 139.8(C_{Ar}), 138.0(C_{Ar}), 137.0(C_{Ar}), 129.3(C_{Ar}), 125.2(C_{Ar}), 86.7(C_{15}), 53.5(C_3), 47.2(C_7), 46.5(C_{10}), 26.1(C_{19}), 24.7(C_8), 24.2(C_9), 23.8(C_2), 12.6(C_{17}); **IR (neat) ν_{max}:** 3055, 2878, 1733, 1693, 1596, 1526, 1442, 1392, 1372, 1342, 1300, 1265, 1241, 1097, 1045, 961, 733, 667; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}N_2O_2I$) requires *m*/*z* 423.0545, found *m*/*z* 423.0547.

***N*-(4-cyano-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide (1.288)**



(Yellowish oil, 53%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 11.10 (s, 1H, H_1), 8.42 (d, *J* = 8.6, 1H, H_{13}), 7.47 (dd, *J* = 2.0, 2.1 Hz, 1H, H_{16}), 7.29 (d, *J* = 2.1 Hz, 1H, H_{14}), 3.62-3.31 (m, 5H, $H_{3,7,10}$), 2.17 (s, 3H, H_{19}), 2.15-1.78 (m, 6H, $H_{2,8,9}$), 0.79 (t, *J* = 7.4 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 171.9(C_4), 169.3(C_{18}), 142.6(C_{12}), 135.3(C_{Ar}), 133.3(C_{Ar}), 132.3(C_{Ar}), 127.3(C_{Ar}), 123.0(C_{Ar}), 118.8(C_{21}), 106.4(C_{15}), 53.8(C_3), 47.4(C_7), 46.5(C_{10}), 26.0(C_{19}), 24.2(C_8), 23.7(C_9), 12.4(C_{17}); **IR (neat) ν_{max}:** 2974, 2878, 2226, 1701, 1592, 1531, 1446, 1408, 1370, 1304, 1230, 1175, 841; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{21}N_3O_2$) requires *m*/*z* 322.1531, found *m*/*z* 322.1530.

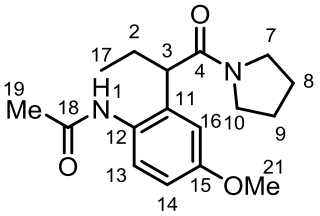
***N*-(4-methyl-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide (1.291)**



(Yellowish oil, 78%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.40 (s, 1H, H_1), 7.97 (d, *J* = 8.4, 1H, H_{13}), 6.99 (d, *J* = 8.3 Hz, 1H, H_{14}), 6.79 (s, 1H, H_{16}), 3.58-3.51 (m, 1H, H_3), 3.49-3.33 (m, 4H, $H_{7,10}$), 2.21 (s, 3H, H_{19}), 2.12 (s, 3H, H_{21}), 1.96-1.74 (m, 6H, $H_{2,8,9}$), 0.78 (t, *J* = 7.4 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 173.0(C_4), 168.6(C_{18}), 135.4(C_{Ar}), 133.3(C_{Ar}), 132.2(C_{Ar}), 128.6(C_{Ar}), 127.3(C_{Ar}), 123.8(C_{Ar}), 53.7(C_3), 47.1(C_7), 46.3(C_{10}),

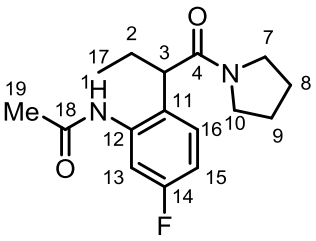
26.0(C_{19}), 24.6(C_{21}), 24.2(C_8), 24.1(C_9), 20.7(C_2), 12.4(C_{17}); **IR (neat) ν_{max}:** 2974, 2877, 1685, 1597, 1535, 1443, 1370, 1341, 1305, 1228, 816, 632; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}N_2O_2$) requires *m*/*z* 311.1735, found *m*/*z* 311.1729.

***N*-(4-methoxy-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide (1.292)**



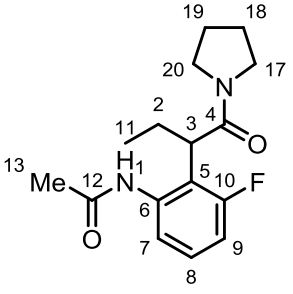
(Reddish oil, 43%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.20 (s, 1H, H_1), 7.96 (d, *J* = 8.9, 1H, H_{13}), 6.74 (dd, J_1 = 2.8, J_2 = 2.9 Hz, 1H, H_{16}), 6.57 (d, *J* = 2.9 Hz, 1H, H_{14}), 3.71, (s, 3H, H_{21}), 3.55-3.34 (m, 5H, $H_{3,7,10}$), 2.12 (s, 3H, H_{19}), 1.96-1.74 (m, 6H, $H_{2,8,9}$), 0.79 (t, *J* = 7.5 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.7(C_4), 168.6(C_{18}), 155.7(C_{15}), 131.2(C_{12}), 129.2(C_{Ar}), 125.3(C_{Ar}), 118.2(C_{Ar}), 111.8(C_{Ar}), 55.6(C_{21}), 53.8(C_3), 47.1(C_7), 46.3(C_{10}), 26.0(C_{19}), 24.5(C_8), 24.4(C_9), 24.1(C_2), 12.6(C_{17}); **IR (neat) ν_{max}:** 2974, 1679, 1606, 1510, 1443, 1371, 1275, 1250, 1164, 1039, 940, 631; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}N_2O_3$) requires *m*/*z* 327.1685, found *m*/*z* 327.1681.

***N*-(5-fluoro-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide (1.294)**



(Reddish oil, 67% yield for both regioisomers), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 10.84 (s, 1H, H_1), 7.97 (d, *J* = 8.3, 1H, H_{13}), 6.15-7.11 (m, 1H, H_{16}), 6.72 (t, *J* = 9.1 Hz, 1H, H_{15}), 4.15 (t, *J* = 7.7 Hz, 1H, H_3), 3.61-3.54 (m, 1H, H_7), 3.50-3.35 (m, 3H, $H_{7,10}$), 2.15 (s, 3H, H_{19}), 2.11-2.04 (m, 1H, H_2), 1.96-1.78 (m, 5H, $H_{2,8,9}$), 0.79 (t, *J* = 7.5 Hz, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.7(C_4), 168.6(C_{18}), 161.8(C_{14}), 159.4(C_{13}), 139.3(C_{12}), 128.7(C_{Ar}), 118.9(C_{Ar}), 110.3(C_{Ar}), 46.9(C_7), 46.4(C_{10}), 42.1(C_3), 25.9(C_{19}), 24.7(C_8), 24.4(C_9), 23.4(C_2), 12.3(C_{17}); **^{19}F-NMR (700 MHz, $CDCl_3$):** δ -116.39; **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}N_2O_2F$) requires *m*/*z* 293.1665, found *m*/*z* 293.1658.

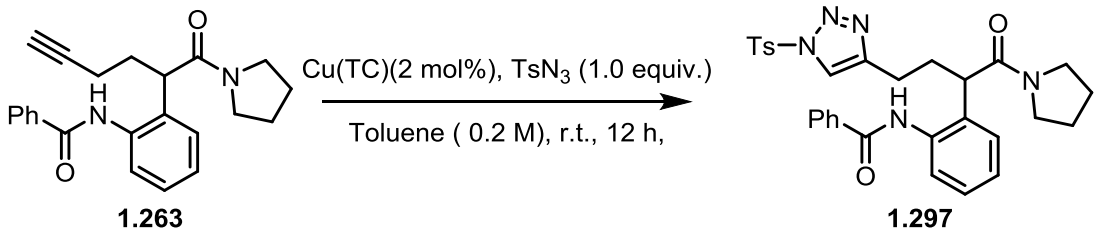
***N*-(3-fluoro-2-(1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)phenyl)acetamide**



^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.76 (s, 1H, H_1), 8.05 (dd, *J* = 2.7, 9.3 Hz, 1H, H_9), 6.93 (t, *J* = 7.5 Hz, 1H, H_7), 6.61 (tt, *J* = 8.1, 8.4 Hz, 1H, H_8), 3.57-3.35 (m, 5H, $H_{3,17,20}$), 2.15 (s, 3H, H_{13}), 2.10-2.02 (m, 1H, H_2), 1.96-1.75 (m, 5H, $H_{2,18,19}$), 0.77 (t, *J* = 7.4 Hz, 3H, H_{11}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.8(C_4), 169.0(C_{12}), 163.5(C_{10}), 161.0(C_5), 139.6(C_6), 132.5(C_{Ar}), 122.3(C_{Ar}), 110.3(C_9), 53.3(C_3),

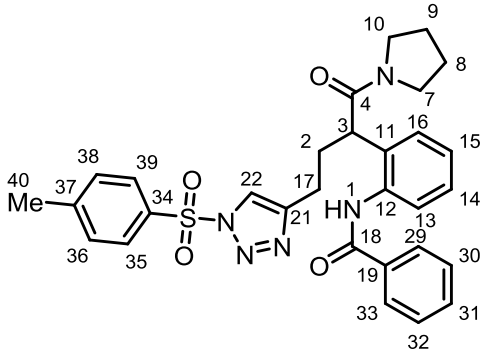
47.0(C_{17}), 46.4(C_{20}), 26.0(C_{13}), 24.6(C_{18}), 24.1(C_{19}), 23.9(C_2), 12.5(C_{11}); **^{19}F-NMR (700 MHz, $CDCl_3$):** δ -112.97; **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}N_2O_2F$) requires *m*/*z* 293.1665, found *m*/*z* 293.1658.

3.3.5 Procedure for the preparation of triazole **1.297**:



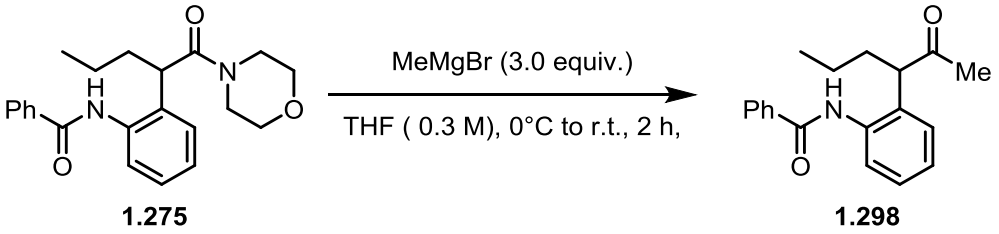
The alkyne-amide **1263** (1.0 equiv., 0.2 mmol, 72 mg) and copper thiophene-2-carboxylate (2 mol%, 0.02 mmol, 3.8 mg) were dissolved in toluene (1 ml). The reaction mixture was cooled to 0 °C. Subsequently, tosyl azide TsN_3(1.0 equiv., 0.2 mmol, 39.4 mg) was added slowly, and the reaction mixture was allowed to warm to room temperature and stirred for another 12 h. The mixture was diluted with saturated NH_4Cl (10 ml), extracted with ethyl acetate (2 x 10 ml), dried over $MgSO_4$ and concentrated in vacuum. Purification by flash chromatography on silica gel using (heptane/ethyl acetate: 5/1) afforded **1.297** in 91% as viscous yellowish oil.

***N*-(2-(1-oxo-1-(pyrrolidin-1-yl)-4-(1-tosyl-1H-1,2,3-triazol-4-yl)butan-2-yl)phenyl)benzamide (1.297)**



^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.29 (s, 1H, H_1), 8.25-8.18 (m, 3H, H_{Ar}), 7.94 (d, *J* = 8.5 Hz, 2H, $H_{35,39}$), 7.73 (s, 1H, H_{22}), 7.59-7.52 (m, 3H, H_{Ar}), 7.39-7.31 (m, 3H, H_{Ar}), 7.11-7.05 (m, 2H, H_{Ar}), 3.95 (t, *J* = 7.7 Hz, 1H, H_3), 3.62-3.54 (m, 1H, H_7), 3.49-3.40 (m, 3H, H_{10}), 2.69-2.56 (m, 2H, H_{17}), 2.53-2.47 (m, 1H, H_2), 2.45 (s, 3H, H_{40}), 2.38-2.29 (m, 1H, H_2), 2.00-1.78 (m, 4H, $H_{8,9}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.3(C_4), 165.7(C_{18}), 147.2(C_{Ar}), 146.9(C_{Ar}), 137.8(C_{Ar}), 133.2(C_{Ar}), 131.6(C_{Ar}), 131.5(C_{Ar}), 130.4(2C, C_{Ar}), 128.6(2C, C_{Ar}), 128.5(2C, C_{Ar}), 128.2(C_{Ar}), 127.8(2C, C_{Ar}), 125.6(C_{Ar}), 124.6(C_{Ar}), 120.9(C_{Ar}), 49.6(C_3), 46.9(C_7), 46.5(C_{10}), 29.7(C_{17}), 26.0(C_{40}), 24.2(C_8), 22.9(C_9), 21.8(C_2); **IR (neat) ν_{max}:** 3056, 2984, 1733, 1668, 1600, 1442, 1305, 1265, 1195, 1093, 1046, 910, 732, 703, 672; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{30}H_{31}N_5O_4S$) requires *m*/*z* 580.1994, found *m*/*z* 580.1996.

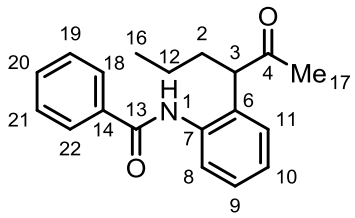
3.3.6 Procedure for the preparation of ketone **1.298**:



1.275 **1.298**

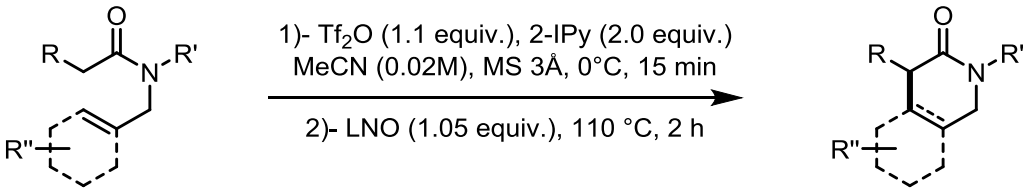
To a stirred solution of amide **1.275** (1.0 equiv., 37mg, 0.1 mmol) in 0.33 ml THF (0.3 M), was added dropwise a solution of methyl magnesium bromide in THF (3.0 equiv., 3.0 M, 0.3 mmol) at 0 °C. The mixture was stirred for 1 hour at 0 °C and 1 hour at room temperature. Then an aqueous solution of HCl (1 M, 2 ml) was carefully added at 0 °C. The aqueous layer was extracted with ethyl acetate (2 x 5 ml). The organic phases were combined, washed with water (10 ml), brine (10 ml), dried over $MgSO_4$, filtered and concentrated in vacuum. Purification by flash chromatography on silica gel using (heptane/ethyl acetate: 4/1) afforded **1.298** in 73% as colourless oil.

***N*-(2-(2-oxohexan-3-yl)phenyl)benzamide (1.298)**



^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.14 (s, 1H, H_{1}), 8.06-7.99 (m, 3H, H_{Ar}), 7.52-7.42 (m, 3H, H_{Ar}), 7.27 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.21 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.11 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 3.75 (t, *J* = 7.6 Hz, 1H, H_3), 2.13 (s, 3H, H_{17}), 2.07-1.96 (m, 1H, H_2), 1.86-1.76 (m, 1H, H_2), 1.28-1.16 (m, 2H, H_{12}), 0.83 (t, *J* = 7.3 Hz, 3H, H_{16}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 212.2(C_4), 165.4(C_{13}), 137.0(C_{Ar}), 134.5(C_{Ar}), 131.8(C_{Ar}), 128.9(C_{Ar}), 128.8(2C, C_{Ar}), 128.3(C_{Ar}), 128.2(C_{Ar}), 127.4(2C, C_{Ar}), 125.4(C_{Ar}), 125.0(C_{Ar}), 57.3(C_3), 31.8(C_{17}), 27.6(C_2), 21.0(C_{12}), 14.0(C_{16}); **IR (neat) ν_{max}:** 3312, 2958, 2932, 1708, 1651, 1604, 1582, 1517, 1450, 1356, 1302, 1166, 754, 709; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{19}H_{21}NO_2$) requires *m*/*z* 318.1470, found *m*/*z* 318.1463.

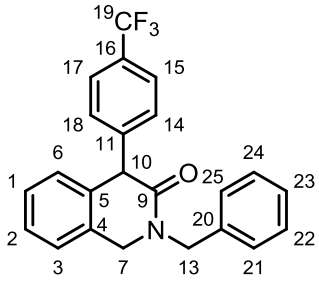
3.3.7 General procedure for the synthesis of dihydroisoquinolines



A solution of the amide (1.0 equiv.) and 2-iodopyridine (2.0 equiv.) in acetonitrile (0.02M) was introduced to a Schlenk flask that contains activated molecular sieves. After cooling to

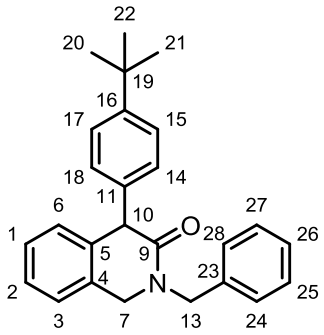
0°C, triflic anhydride (1.1 equiv.) was added dropwise and the resulting solution was stirred at the same temperature for another 15 min. Then, lutidine *N*-oxide (1.05 equiv.) was added and the reaction mixture was subsequently heated at 110 °C for 2 h. The reaction mixture was then allowed to cool to room temperature before filtration through a pad of celite and washed the celite with ethyl acetate (10 ml). The resulting filtrate was concentrated in vacuum. The crude material was subsequently purified by flash column chromatography (heptane/ethyl acetate) to afford the title products.

2-Benzyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydroisoquinolin-3(2H)-one (1.331)



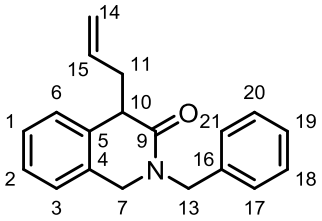
(Bright yellow oil, 81%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.35-7.27 (m, 7H, H_{Ar}), 7.21-7.16 (m, 2H, H_{Ar}), 7.15-7.12 (m, 1H, H_{Ar}), 5.03 (s, 1H, H_{10}), 4.76 (s, 2H, H_7), 4.47 (d, *J* = 16.0 Hz, 1H, H_{13}), 4.31 (d, *J* = 15.9 Hz, 1H, H_{13}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 169.2(C_9), 142.7(C_{Ar}), 136.4(C_{Ar}), 134.5(C_{Ar}), 131.6(C_{Ar}), 129.4(C_{Ar}), 129.1(C_{Ar}), 128.7(C_{Ar}), 128.5(C_{Ar}), 128.3(2C, C_{Ar}), 128.1(C_{Ar}), 127.9(2C, C_{Ar}), 127.6(C_{Ar}), 127.5(C_{Ar}), 126.2(C_{Ar}), 125.6(C_{Ar}), 125.3(C_{Ar}), 52.7(C_{10}), 50.4(C_7), 49.8(C_{13}); **IR (neat) ν_{max}:** 3106, 2990, 1716, 1586, 1117, 1029, 843, 730; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{23}H_{18}ONF_3$) requires *m*/*z* 382.1419, found *m*/*z* 382.1424.

2-Benzyl-4-(4-(tert-butyl)phenyl)-1,4-dihydroisoquinolin-3(2H)-one (1.333)



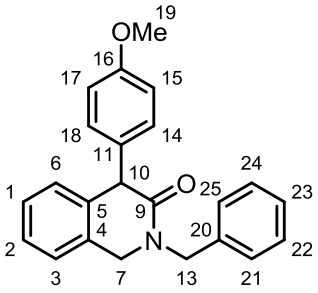
(White solid, 82%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.22-7.18 (m, 3H, H_{Ar}), 7.17-7.12 (m, 4H, H_{Ar}), 7.09 (d, *J* = 7.4 Hz, 1H, H_{Ar}), 7.06-7.01 (m, 3H, H_{Ar}), 6.99 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 4.87 (s, 1H, H_{10}), 4.64 (d, *J* = 5.8 Hz, 2H, H_7), 4.38 (d, *J* = 15.4 Hz, 1H, H_{13}), 4.12 (d, *J* = 15.7 Hz, 1H, H_{13}), 1.20 (s, 9H, $H_{20,21,22}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 170.4(C_9), 150.1(C_{16}), 136.7(C_{Ar}), 135.8(C_{Ar}), 135.4(C_{Ar}), 131.8(C_{Ar}), 128.8(2C, C_{Ar}), 128.4(C_{Ar}), 128.0(C_{Ar}), 127.5(2C, C_{Ar}), 127.3(C_{Ar}), 127.1 (2C, C_{Ar}), 125.6(2C, C_{Ar}), 124.9(C_{Ar}), 52.7(C_{10}), 50.3(C_7), 49.8(C_{13}), 34.4(C_{19}), 31.3(3C, $C_{20,21,22}$); **IR (neat) ν_{max}:** 3008, 2818, 1712, 1549, 1119, 1094, 1010, 965, 926, 838; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{26}H_{27}ON$) requires *m*/*z* 370.2171, found *m*/*z* 370.2178.

4-Allyl-2-benzyl-1,4-dihydroisoquinolin-3(2H)-one (1.323)



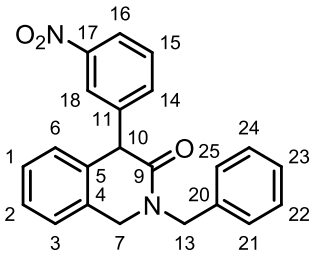
(Orange oil, 60%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.26-7.17 (m, 6H, H_{Ar}), 7.14-7.05 (m, 2H, H_{Ar}), 6.98 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 5.69-5.57 (m, 1H, H_{15}), 4.94-4.87 (m, 2H, H_{14}), 4.80 (d, *J* = 14.7 Hz, 1H, H_7), 4.55 (d, *J* = 14.8 Hz, 1H, H_7), 4.42 (d, *J* = 15.7 Hz, 1H, H_{13}), 4.12 (d, *J* = 15.8 Hz, 1H, H_{13}), 3.63 (t, *J* = 6.6 Hz, 1H, H_{10}), 2.58 (t, *J* = 7.1 Hz, 2H, H_{11}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 171.1(C_9), 136.8(C_{Ar}), 135.7(C_{Ar}), 134.3(C_{Ar}), 131.1(C_{Ar}), 128.9(C_{Ar}), 128.6(C_{Ar}), 128.1(2C, C_{Ar}), 127.7(C_{Ar}), 127.6(C_{Ar}), 127.3(C_{Ar}), 126.6(C_{Ar}), 125.2(C_{Ar}), 117.9(C_{14}), 50.3(C_7), 49.9(C_{13}), 47.4(C_{10}), 38.6(C_{11}); **IR (neat) ν_{max}:** 3108, 3008, 2770, 1841, 1630, 1298, 1126, 985, 743; **HRMS (ESI$^+$):** exact mass calculated for $[M+Na]^+$ ($C_{19}H_{19}ON$) requires *m*/*z* 300.1364, found *m*/*z* 300.1352.

2-Benzyl-4-(4-methoxyphenyl)-1,4-dihydroisoquinolin-3(2H)-one (1.334)



(Bright yellow oil, 79%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.21-7.14 (m, 5H, H_{Ar}), 7.09-7.03 (m, 4H, H_{Ar}), 6.98 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 6.73 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 4.83 (s, 1H, H_{10}), 4.64 (s, 2H, H_7), 4.35 (d, *J* = 15.8 Hz, 1H, H_{13}), 4.13 (d, *J* = 16.0 Hz, 1H, H_{13}), 3.68(s, 3H, H_{19}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 170.3(C_9), 158.8(C_{16}), 136.7(C_{Ar}), 135.8(C_{Ar}), 131.8(C_{Ar}), 130.8(C_{Ar}), 128.9(2C, C_{Ar}), 128.6(2C, C_{Ar}), 128.4(C_{Ar}), 127.9(C_{Ar}), 127.8(2C, C_{Ar}), 127.5(C_{Ar}), 126.9(C_{Ar}), 125.3(C_{Ar}), 114.1(2C, C_{Ar}), 55.3(C_{10}), 52.3(C_{19}), 50.3(C_7), 49.8(C_{13}); **IR (neat) ν_{max}:** 3105, 2867, 1912, 1776, 1654, 1276, 1143, 1034, 822, 765; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{23}H_{21}O_2N$) requires *m*/*z* 344.1651, found *m*/*z* 344.1648.

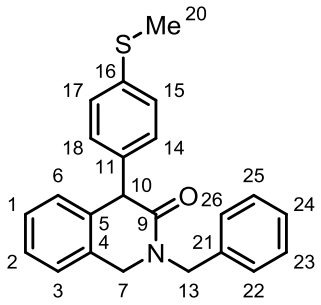
2-Benzyl-4-(3-nitrophenyl)-1,4-dihydroisoquinolin-3(2H)-one (1.335)



(Brown oil, 79%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.03 (d, *J* = 8.3 Hz, 1H, H_{16}), 7.87 (s, 1H, H_{18}), 7.52 (d, *J* = 7.7 Hz, 1H, H_{14}), 7.40 (t, *J* = 8.0 Hz, 1H, H_{15}), 7.24-7.18 (m, 5H, H_{Ar}), 7.14-7.09 (m, 3H, H_{Ar}), 7.02-6.98 (m, 1H, H_{Ar}), 4.95 (s, 1H, H_{10}), 4.66 (s, 2H, H_7), 4.40 (d, *J* = 16.0 Hz, 1H, H_{13}), 4.25 (d, *J* = 16.1 Hz, 1H, H_{13}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 168.7(C_9), 148.5(C_{17}), 141.1(C_{14}), 136.3(C_{Ar}), 134.6(C_{Ar}), 133.9(C_{Ar}), 131.4(C_{Ar}), 129.6(C_{Ar}), 128.8(2C, C_{Ar}), 128.3(C_{Ar}), 128.2(C_{Ar}), 127.9(C_{Ar}), 127.7(C_{Ar}), 127.6(C_{Ar}), 127.5(C_{Ar}), 125.7(C_{Ar}), 123.1(C_{Ar}), 122.4(C_{Ar}), 52.4(C_{10}), 50.5(C_7),

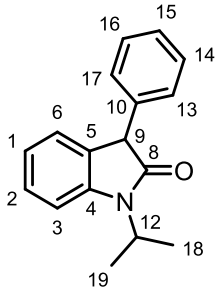
49.8(C_{13}); **IR (neat) ν_{max}:** 3145, 2958, 1891, 1780, 1568, 1394, 1086, 869; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{22}H_{18}O_3N_2$) requires *m*/*z* 381.1215, found *m*/*z* 381.1221.

2-Benzyl-4-(4-(methylthio)phenyl)-1,4-dihydroisoquinolin-3(2H)-one (1.332)



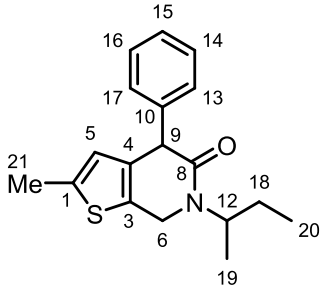
(Yellow oil, 81%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.22-7.15 (m, 5H, H_{Ar}), 7.10-7.04 (m, 6H, H_{Ar}), 6.99 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 4.84 (s, 1H, H_{10}), 4.64 (s, 2H, H_7), 4.35 (d, *J* = 15.9 Hz, 1H, H_{13}), 4.14 (d, *J* = 15.9 Hz, 1H, H_{13}), 2.36 (s, 3H, H_{20}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 170.0(C_9), 137.4(C_{Ar}), 136.6(C_{Ar}), 135.6(C_{Ar}), 135.3(C_{Ar}), 131.8(C_{Ar}), 128.7(2C, C_{Ar}), 128.4(2C, C_{Ar}), 128.0(C_{Ar}), 127.9(2C, C_{Ar}), 127.6(C_{Ar}), 127.2(C_{Ar}), 126.9(2C, C_{Ar}), 125.4(C_{Ar}), 52.6(C_{10}), 50.4(C_7), 49.8(C_{13}), 15.9(C_{20}); **IR (neat) ν_{max}:** 3103, 3959, 1903, 1635, 1447, 1403, 1298, 1205, 1021, 743; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{23}H_{21}ONS$) requires *m*/*z* 382.1242, found *m*/*z* 382.1242.

1-Isopropyl-3-phenylindolin-2-one (1.342)



(Yellowish solid, 42%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.28-7.19 (m, 4H, H_{Ar}), 7.12-7.05 (m, 3H, H_{Ar}), 6.99 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 6.95 (t, *J* = 7.4 Hz, 1H, H_{Ar}) 4.65-4.55 (m, 1H, H_{12}), 4.47 (s, 1H, H_9), 1.45 (d, *J* = 2.1 Hz, 3H, H_{18}), 1.43 (d, *J* = 2.2 Hz, 3H, H_{19}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 175.7(C_8), 143.2(C_4), 137.2(C_5), 129.5(C_{Ar}), 128.8(2C, C_{Ar}), 128.3(2C, C_{Ar}), 128.0(C_{Ar}), 127.5(C_{Ar}), 125.3(C_{Ar}), 122.0(C_{Ar}), 109.9(C_3), 52.1(C_{12}), 43.9(C_9), 19.4(C_{18}), 19.3(C_{19}); **IR (neat) ν_{max}:** 3034, 2786, 1798, 1515, 1241, 1159, 1109, 1004, 985, 863, 605 **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{17}ON$) requires *m*/*z* 274.1208, found *m*/*z* 274.1204.

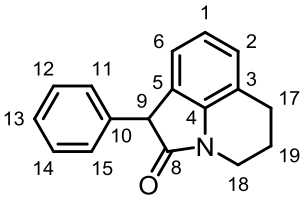
6-(*sec*-butyl)-2-methyl-4-phenyl-6,7-dihydrothieno[2,3-c]pyridin-5(4H)-one (1.344)



(Red oil, 33%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.27-7.18 (m, 3H, H, $H_{14,15,16}$), 7.14-7.04 (m, 2H, $H_{13,17}$), 6.49 (d, *J* = 11.6 Hz, 1H, H_5), 5.67-5.39 (m, 1H, H_{12}), 4.94 (m, 1H, H_9), 4.31-4.19 (m, 1H, H_6), 4.00-3.95 (m, 1H, H_6), 3.62-3.45 (m, 2H, H_{18}), 1.52-1.44 (m, 3H, H_{21}), 1.19-1.09 (m, 3H, H_{19}), 0.95-0.86 (m, 3H, H_{20}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 172.2(C_8), 148.8(C_3), 140.0(C_{Ar}), 136.9(C_{Ar}), 133.1(C_{Ar}), 129.3(2C, C_{Ar}), 128.4(C_{Ar}), 127.3(2C, C_{Ar}), 103.1(C_5), 68.4(C_{12}),

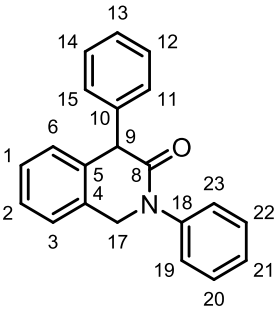
61.2(C_9), 53.4(C_6), 27.2(C_{18}), 17.8(C_{19}), 15.3(C_{21}), 11.2(C_{20}); **IR (neat) ν_{max}:** 3034, 2784, 1806, 16003, 1224, 940, 736; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{18}H_{21}ONS$) requires *m*/*z* 322.1242, found *m*/*z* 322.1240.

1-Phenyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one (1.343)



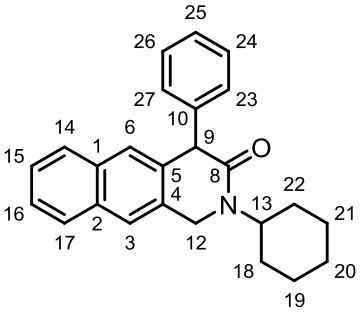
(Yellowish solid, 38%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.28-7.19 (m, 3H, $H_{12,13,14}$), 7.18-7.14 (m, 2H, $H_{11,15}$), 7.00 (d, *J* = 7.6 Hz, 1H, H_6), 6.94 (d, *J* = 7.4 Hz, 1H, H_2), 6.88 (t, *J* = 7.5, 7.4 Hz, 1H, H_1) 4.53 (s, 1H, H_9), 3.73-3.61 (m, 2H, H_{18}), 2.75 (t, *J* = 6.0, 6.2 Hz, 2H, H_{17}), 2.02-1.93 (m, 2H, H_{19}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 174.8(C_8), 140.3(C_4), 136.6(C_{Ar}), 128.7(2C, C_{Ar}), 128.4(2C, C_{Ar}), 127.4(2C, C_{Ar}), 127.1(C_{Ar}), 122.8(C_{Ar}), 122.1(C_{Ar}), 120.3(C_{Ar}), 53.0(C_9), 39.1(C_{18}), 24.6(C_{17}), 21.3(C_{19}); **IR (neat) ν_{max}:** 3084, 2889, 1758, 1515, 1456, 1312, 1196, 897, 754; **HRMS (ESI+):** exact mass calculated for $[M+Na]^+$ ($C_{17}H_{15}ON$) requires *m*/*z* 272.1051, found *m*/*z* 272.1050.

2,4-Diphenyl-1,4-dihydroisoquinolin-3(2H)-one (1.345)



Red oil (68%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.33-7.25 (m, 4H, H_{Ar}), 7.22-7.17 (m, 7H, H_{Ar}), 7.15-7.10 (m, 3H, H_{Ar}), 4.98 (s, 1H, H_9), 4.81 (d, *J* = 15.4 Hz, 1H, H_{17}), 4.50 (d, *J* = 15.3 Hz, 1H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 170.0(C_8), 142.5(C_{18}), 137.3(C_{Ar}), 135.7(C_{Ar}), 132.7(C_{Ar}), 129.0(2C, C_{Ar}), 128.7(2C, C_{Ar}), 128.5(C_{Ar}), 128.2(C_{Ar}), 127.7(2C, C_{Ar}), 127.3(C_{Ar}), 127.2(C_{Ar}), 126.7(C_{Ar}), 125.6(2C, C_{Ar}), 125.4(C_{Ar}), 54.1(C_9), 53.5(C_{17}); **IR (neat) ν_{max}:** 3059, 2978, 1630, 1598, 1456, 1377, 1205, 1067, 869, 733; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{21}H_{17}ON$) requires *m*/*z* 322.1208, found *m*/*z* 322.1197.

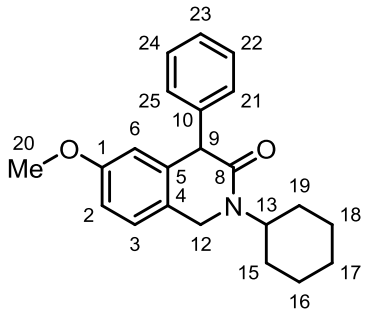
2-Cyclohexyl-4-phenyl-1,4-dihydrobenzo[*g*]isoquinolin-3(2H)-one (1.347)



(Yellow solid, 81%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.79-7.72 (m, 3H, H_{Ar}), 7.41-7.34 (m, 2H, H_{Ar}), 7.30-7.25 (m, 1H, H_{Ar}), 7.23-7.17 (m, 1H, H_{Ar}), 7.12-7.06 (m, 4H, H_{Ar}), 5.52 (s, 1H, H_9), 4.53-4.33 (m, 3H, $H_{12,13}$), 1.76-1.68 (m, 2H, H_{Alk}), 1.63-1.54 (m, 3H, H_{Alk}), 1.48-1.17 (m, 5H, H_{Alk}), 1.12-1.00 (m, 1H, H_{Alk}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 169.2(C_8), 150.7(C_3), 138.1(C_{Ar}), 133.0(C_{Ar}), 130.7(C_{Ar}), 130.5(C_{Ar}), 129.9(C_{Ar}), 128.6(2C, C_{Ar}), 127.8(C_{Ar}),

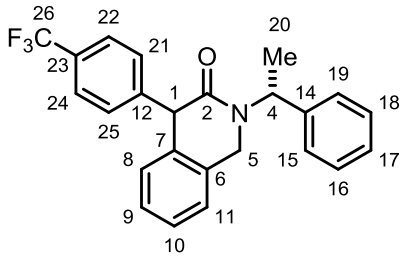
127.6(2C, C_{Ar}), 127.2(C_{Ar}), 126.9(C_{Ar}), 125.9(C_{Ar}), 123.4(C_{Ar}), 123.2(C_{Ar}), 52.8(C_9), 49.8(C_{12}), 45.2(C_{13}), 30.1(C_{18}), 29.3(C_{22}), 25.7(C_{19}), 25.6(C_{21}), 25.4(C_{20}); **IR (neat) ν_{max}:** 3005, 2801, 1984, 1583, 1429, 1093, 822, 796; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{25}H_{25}ON$) requires *m*/*z* 356.2014, found *m*/*z* 356.2004.

2-Cyclohexyl-6-methoxy-4-phenyl-1,4-dihydroisoquinolin-3(2H)-one (1.349)



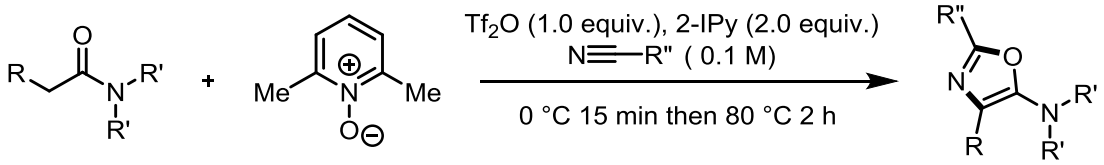
(Bright yellow oil, 52%) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.18-7.11 (m, 2H, H_{Ar}), 7.10-7.05 (m, 3H, H_{Ar}), 6.83-6.69 (m, 2H, H_{Ar}), 6.63 (d, *J* = 32.8 Hz, 1H, H_{Ar}), 4.76 (s, 1H, H_9), 4.42-4.37 (m, 1H, H_{13}), 4.12 (d, *J* = 3.3 Hz, 2H, H_{12}), 3.70 (s, 3H, H_{20}), 1.75-1.59 (m, 3H), 1.44-1.16 (m, 6H), 1.09-0.99 (m, 1H); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 169.5(C_8), 159.3(C_1), 138.0(C_{Ar}), 137.4(C_{Ar}), 128.6(2C, C_{Ar}), 127.7(2C, C_{Ar}), 127.0(C_{Ar}), 126.4(C_{Ar}), 125.1(C_{Ar}), 114.1(C_6), 113.0(C_2), 55.4(C_{20}), 54.1(C_9), 52.8(C_{12}), 43.9(C_{13}), 30.1(C_{15}), 29.4(C_{19}), 25.8(C_{16}), 25.4(2C, $C_{17,18}$); **IR (neat) ν_{max}:** 3083, 2733, 1827, 1630, 1456, 1186, 1003, 844, 725; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{22}H_{25}O_2N$) requires *m*/*z* 358.1783, found *m*/*z* 358.1778.

(*R*)-2-(1-phenylethyl)-4-(4-(trifluoromethyl)phenyl)-1,4-dihydroisoquinolin-3(2H)-one (1.353)



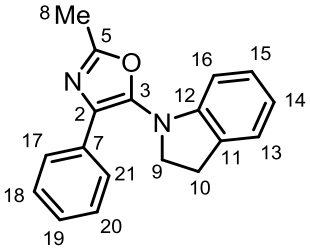
(Yellowish oil, 63%, 7.1/1 diastereomeric ratio, for simplicity only the major isomer is reported here) **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.45 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.21-7.15 (m, 7H, H_{Ar}), 7.07-7.02 (m, 4H, H_{Ar}), 6.03 (q, *J* = 7.3 Hz, 1H, H_4), 4.93 (s, 1H, H_1), 4.02 (d, *J* = 16.2 Hz, 1H, H_5), 3.75 (d, *J* = 16.3 Hz, 1H, H_5), 1.49 (d, *J* = 7.1 Hz, 3H, H_{20}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 169.1(C_2), 142.3(C_{Ar}), 139.6(C_{Ar}), 134.7(C_{Ar}), 132.4(C_{Ar}), 129.4(2C, C_{Ar}), 128.4(2C, C_{Ar}), 128.1(C_{Ar}), 128.0(C_{Ar}), 127.6(2C, C_{Ar}), 127.3(2C, C_{Ar}), 127.1(C_{Ar}), 125.5(2C, C_{Ar}), 125.4(C_{Ar}), 53.5(C_4), 50.7(C_1), 44.7(C_5), 15.3(C_{20}); **IR (neat) ν_{max}:** 1644, 1323, 1164, 1110, 1066, 1018, 753, 741, 698; **HRMS (ESI^+):** exact mass calculated for $[M+Na]^+$ ($C_{24}H_{20}F_3NO$) requires *m*/*z* 418.1395, found *m*/*z* 418.1394.

3.3.8 General procedure for the synthesis of 5-amino-oxazoles



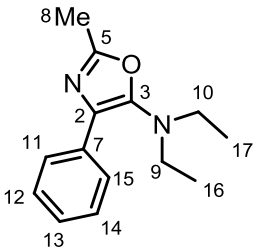
To a stirred solution of the amide (1.0 equiv., 0.2 mmol) and 2-iodopyridine (2.0 equiv., 0.4 mmol, 42.5 µl) in the proper nitrile (2 ml, 0.1M) was added triflic anhydride Tf_2O (1.0 equiv., 0.2 mmol, 34 µl) at 0 °C under an argon atmosphere. After 15 min LNO (1.05 equiv., 0.21 mmol, 23.5 µl) was added and the reaction mixture was heated at 80 °C for another 2 h. After cooling down to room temperature, the reaction mixture was quenched with Saturated $NaHCO_3$ (10 ml), extracted with DCM (2 x 10 ml), dried over $MgSO_4$ and concentrated in vacuum. The crude residue was purified by flash chromatography on silica gel using (heptane/ethyl acetate: 10/1) to afford the desired oxazoles.

5-(Indolin-1-yl)-2-methyl-4-phenyloxazole (1.369)



(Orange solid, 59%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.74-7.71 (m, 2H, H_{Ar}), 7.26 (t, *J* = 7.7 Hz, 2H, H_{Ar}), 7.18-7.10 (m, 2H, H_{Ar}), 6.93 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 6.73 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 6.27 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 3.84 (t, *J* = 8.6 Hz, 2H, H_9), 3.15 (t, *J* = 8.7 Hz, 2H, H_{10}), 2.07 (s, 3H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 157.7(C_5), 147.8(C_{12}), 143.3(C_3), 131.2(C_{Ar}), 129.4(C_{Ar}), 128.4(2C, C_{Ar}), 127.5(C_{Ar}), 127.2(C_{Ar}), 126.1(2C, C_{Ar}), 125.0(C_{Ar}), 120.1(2C, C_{Ar}), 109.2(C_{Ar}), 52.2(C_9), 28.7(C_{10}), 14.4(C_8); **IR (neat) ν_{max}:** 3055, 2984, 1733, 1648, 1484, 1374, 1265, 1046, 736, 705, 631; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}N_2O$) requires *m*/*z* 277.1341, found *m*/*z* 277.1329.

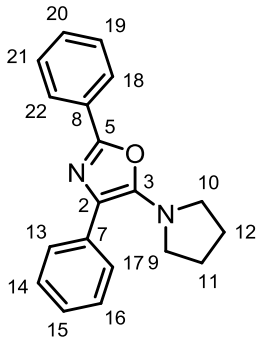
***N*,*N*-diethyl-2-methyl-4-phenyloxazol-5-amine (1.370)**



(Colourless oil, 44%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.95 (d, *J* = 8.6 Hz, 2H, $H_{11,15}$), 7.28 (t, *J* = 7.8 Hz, 2H, $H_{12,14}$), 7.14 (t, *J* = 7.2 Hz, 1H, H_{13}), 2.99 (q, *J* = 7.1 Hz, 4H, $H_{9,10}$), 2.34 (s, 3H, H_8), 0.98 (t, *J* = 7.2 Hz, 6H, $H_{16,17}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 156.8(C_5), 149.7(C_3), 143.3(C_2), 132.2(C_{Ar}), 128.2(2C, C_{Ar}), 126.6(C_{Ar}), 125.8(2C, C_{Ar}), 47.6(2C, $C_{9,10}$), 14.5(C_8), 13.0(2C, $C_{16,17}$); **IR (neat) ν_{max}:** 2972, 1705, 1634, 1589, 1447,

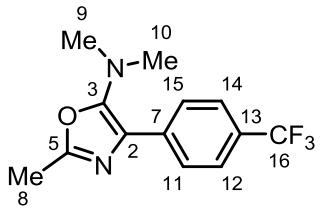
1344, 1257, 1219, 1147, 1043, 957, 715, 694; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{14}H_{18}N_2O$) requires *m*/*z* 231.1497, found *m*/*z* 231.1485.

2,4-Diphenyl-5-(pyrrolidin-1-yl)oxazole (1.373)



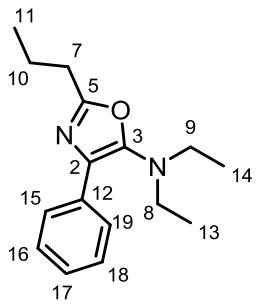
(Yellowish oil, 60%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.91 (d, *J* = 7.9 Hz, 2H, $H_{13,17}$), 7.66 (d, *J* = 8.2 Hz, 2H, $H_{18,22}$), 7.37-7.25 (m, 5H, H_{Ar}), 7.15 (t, *J* = 7.2 Hz, 1H, H_{15}), 3.31-3.25 (m, 4H, $H_{9,10}$), 1.94-1.88 (m, 4H, $H_{11,12}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 153.0(C_5), 150.6(C_3), 133.0(C_2), 129.0(C_{Ar}), 128.6(2C, C_{Ar}), 128.1(2C, C_{Ar}), 127.0(2C, C_{Ar}), 126.0(C_{Ar}), 125.3(2C, C_{Ar}), 119.7(C_{Ar}), 50.1(2C, $C_{9,10}$), 25.4(2C, $C_{11,12}$); **IR (neat) ν_{max}:** 2967, 2932, 2872, 1638, 1583, 1497, 1378, 1341, 1289, 1150, 1068, 1043, 1023, 981, 958, 716, 695; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{19}H_{18}N_2O$) requires *m*/*z* 291.1497, found *m*/*z* 291.1491.

***N*,*N*,2-trimethyl-4-(4-(trifluoromethyl)phenyl)oxazol-5-amine (1.376)**



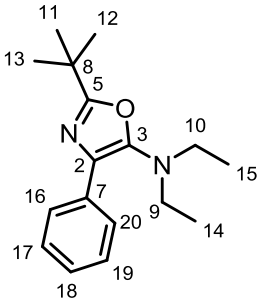
(Brownish oil, 39%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 8.4 Hz, 2H, $H_{12,14}$), 7.63 (d, *J* = 8.6 Hz, 2H, $H_{11,15}$), 2.82 (s, 6H, $H_{9,10}$), 2.44 (s, 3H, H_8); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 155.6(C_5), 153.5(C_3), 136.0(C_2), 125.7(4C, C_{Ar}), 125.2(2C, C_{Ar}), 121.3(C_{16}), 42.3(2C, $C_{9,10}$), 14.2(C_8); **^{19}F-NMR (700 MHz, $CDCl_3$):** δ - 62.32; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}N_2OF_3$) requires *m*/*z* 271.1058, found *m*/*z* 271.1045.

***N*,*N*-diethyl-4-phenyl-2-propyloxazol-5-amine (1.371)**



(Colourless oil, 33%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 8.2 Hz, 2H, $H_{15,19}$), 7.28 (t, *J* = 7.9 Hz, 2H, $H_{16,18}$), 7.14 (t, *J* = 7.2 Hz, 1H, H_{17}), 3.00 (q, *J* = 7.2 Hz, 4H, $H_{8,9}$), 2.62 (t, *J* = 7.5 Hz, 2H, H_7), 1.78-1.67 (m, 2H, H_{10}), 0.97 (t, *J* = 7.0 Hz, 6H, $H_{13,14}$), 0.93 (t, *J* = 7.3 Hz, 3H, H_{11}); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 160.3(C_5), 149.5(C_3), 132.4(C_{Ar}), 128.1(2C, C_{Ar}), 127.3(C_{Ar}), 126.6(C_{Ar}), 125.8(2C, C_{Ar}), 47.6(2C, $C_{8,9}$), 30.7(C_7), 20.7(C_{10}), 13.7(C_{11}), 13.0(2C, $C_{13,14}$); **IR (neat) ν_{max}:** 3057, 2969, 2873, 1737, 1603, 1497, 1342, 1290, 1218, 1181, 1090, 1046, 982, 738, 698; **HRMS (ESI$^+$):** exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}N_2O$) requires *m*/*z* 259.1810, found *m*/*z* 259.1800.

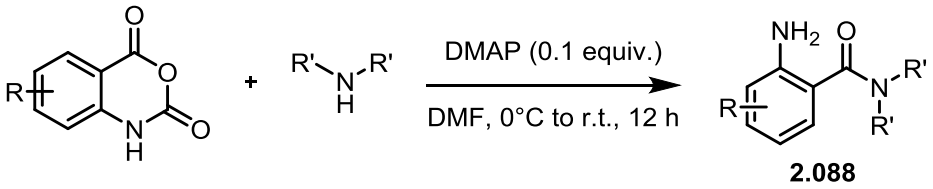
2-(*tert*-butyl)-*N*,*N*-diethyl-4-phenyloxazol-5-amine (1.372)



(Colourless oil, 57% yield), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 8.2 Hz, 2H, $H_{16,20}$), 7.27 (t, *J* = 7.9 Hz, 2H, $H_{17,19}$), 7.13 (t, *J* = 7.2 Hz, 1H, H_{18}), 3.00 (q, *J* = 7.2 Hz, 4H, $H_{9,10}$), 1.31 (s, 9H, $H_{11,12,13}$), 0.97 (t, *J* = 7.2 Hz, 6H, $H_{14,15}$); **^{13}C-NMR (100 MHz, $CDCl_3$):** δ 166.1(C_5), 149.3(C_3), 132.7(C_{Ar}), 131.3(C_{Ar}), 128.1 (2C, C_{Ar}), 126.4(C_{Ar}), 125.9 (2C, C_{Ar}), 47.5 (2C, $C_{9,10}$), 33.9(C_8), 28.3 (3C, $C_{11,12,13}$), 13.0 (2C, $C_{14,15}$); **IR (neat) ν_{max}:** 2972, 2932, 1640, 1604, 1449, 1378, 1087, 978; **HRMS (ESI^+):** exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}N_2O$) requires *m*/*z* 273.1967, found *m*/*z* 273.1963.

3.4 Redox reactions

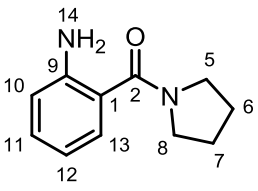
3.4.1 General procedure for the preparation of benzamides **2.088**



Isatoic anhydride (1.0 equiv.) and 4-Dimethylaminopyridine DMAP (0.1 equiv.) were dissolved in dry DMF (1 M) and the reaction mixture was cooled down to 0 ºC. Then amine (1.2 equiv.) was then added dropwise. The reaction mixture was warmed up to room temperature and stirred for another 12 hours. The reaction mixture was quenched with water, extracted with ethyl acetate (3 x 15 ml), washed with brine (15 ml), dried over $MgSO_4$ and the solvent was evaporated under vacuum. Column chromatography purification (heptane: ethyl acetate/ 2:1) afforded the desired benzamide **2.088**.

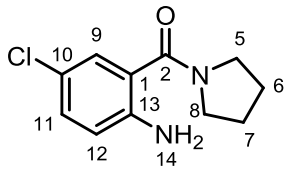
Spectroscopic data for the benzamide products match those reported in the literature. [170]

(2-Aminophenyl)(pyrrolidin-1-yl)methanone (2.088a)



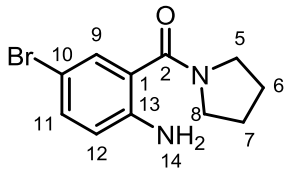
(Brownish solid, 89%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.32-7.19 (d, *J* = 8.2 Hz, 1H, H_{10}), 7.16 (t, *J* = 7.9 Hz, 1H, H_{12}), 6.70 (t, *J* = 8.1 Hz, 2H, H_{11}), 4.60 (bs, 2H, H_{14}), 3.71-3.41 (m, 4H, $H_{5,8}$) 2.02-1.81 (m, 4H, $H_{6,7}$).

(2-Amino-5-chlorophenyl)(pyrrolidin-1-yl)methanone (2.088b)



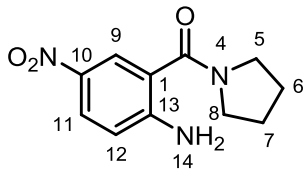
(Yellowish solid, 78%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7. 18 (d, *J* = 2.6 Hz, 1H, H_9), 7.12 (dd, *J* = 2.5, 2.4 Hz, 1H, H_{11}), 6.64 (d, *J* = 8.6 Hz, 1H, H_{12}), 4.60 (bs, 2H, H_{14}), 3.70-3.44 (m, 4H, $H_{5,8}$) 2.02-1.85 (m, 4H, $H_{6,7}$).

(2-Amino-5-bromophenyl)(pyrrolidin-1-yl)methanone (2.088c)



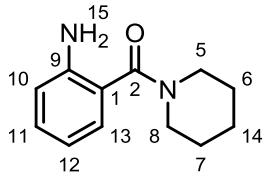
(White solid, 72%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.23 (d, *J* = 2.3 Hz, 1H), 7.17 (dd, *J* = 2.5 Hz, 2.4 Hz, 1H), 6.52 (d, *J* = 8.7 Hz, 1H), 4.53 (bs, 2H), 3.60-3.37 (m, 4H) 1.94-1.76 (m, 4H).

(2-Amino-5-nitrophenyl)(pyrrolidin-1-yl)methanone (2.088d)



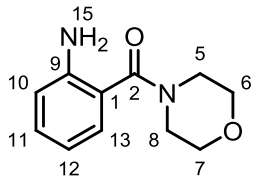
(Yellow solid, 70%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 2.6 Hz, 1H, H_{11}), 7.99 (dd, *J* = 2.5 Hz, 2.6 Hz, 1H, H_{12}), 6.64 (d, *J* = 9.0 Hz, 1H, H_9), 5.58 (bs, 2H, H_{14}), 3.62-3.54 (m, 4H, $H_{5,8}$) 1.96-1.81 (m, 4H, $H_{6,7}$).

(2-Aminophenyl)(piperidin-1-yl)methanone (2.088e)



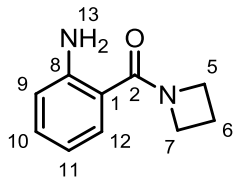
(Brownish solid, 92%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.16 (t, *J* = 8.3 Hz, 1H, H_{12}), 7.12 (d, *J* = 7.8 Hz, 1H, H_{10}), 6.75-6.70 (m, 2H, $H_{11,13}$), 4.30 (bs, 2H, H_{14}), 3.64-3.48 (m, 4H, $H_{5,8}$) 1.73-1.58 (m, 6H, $H_{6,7,14}$).

(2-Aminophenyl)(morpholino)methanone (2.088f)



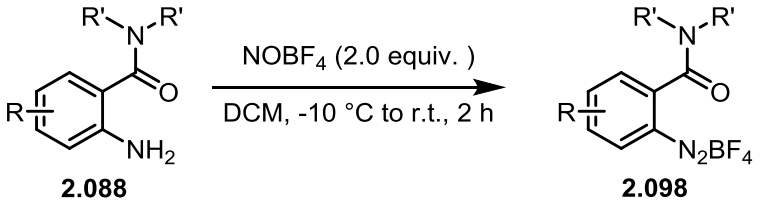
(White solid, 59%), **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.21-7.16 (t, *J* = 7.9 Hz, 1H, H_{12}), 7.08 (d, *J* = 8.0 Hz, 1H, H_{10}), 6.76-6.70 (m, 2H, $H_{11,13}$), 4.37 (bs, 2H, H_{15}), 3.74-3.69 (m, 4H, $H_{6,7}$), 3.67-3.62 (m, 4H, $H_{5,8}$).

(2-Aminophenyl)(azetidin-1-yl)methanone (2.088g)



(Brownish solid, 77%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.10-7.05 (m, 2H, $H_{10,12}$), 6.61 (d, *J* = 8.2, 1H, H_9), 6.55 (t, *J* = 7.4 Hz, 1H, H_{11}), 5.15 (bs, 2H, H_{13}), 4.17 (m, 4H, $H_{5,7}$), 2.28-2.19 (m, 2H, H_6).

3.4.2 General procedure for the preparation of diazonium salts **2.098**

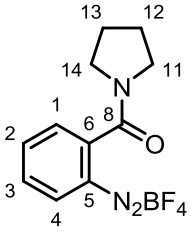


2.088 **2.098**

A solution of the benzamide **2.088** (1.0 equiv.) in dry DCM (2 M) was added to a stirred suspension of nitrosonium tetrafluoroborate (1.5 equiv.) in dry dichloromethane (0.5 M) under argon at -10 °C. After 1 hour, additional nitrosonium tetrafluoroborate (0.5 equiv.) was added to the reaction mixture. After 30 min, the solvent was removed under vacuum. The residue was dissolved in a small amount of acetone and precipitated from iced-cooled dry diethyl ether. The precipitate was filtered and dried under vacuum to give the corresponding diazonium salts **2.098**.

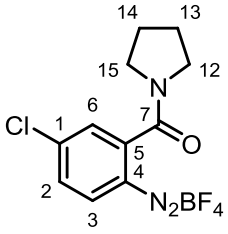
Spectroscopic data for the diazonium salt products match those reported in the literature. [170]

(2-(4-Diazynyl)phenyl)(pyrrolidin-1-yl)methanone tetrafluoroborate (2.098a)



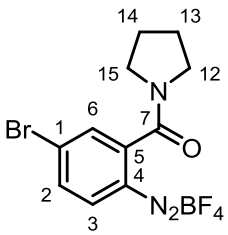
(Orange solid, 85%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)**: δ 9.00 (d, *J* = 8.4 Hz, 1H, H_4), 8.40-8.38 (m, 2H, $H_{1,3}$), 8.17 (t, *J* = 7.6 Hz, 1H, H_2), 3.78 (t, *J* = 6.4 Hz, 2H, H_{11}), 3.66 (t, *J* = 7.0 Hz, 2H, H_{14}), 2.04-1.93 (m, 4H, $H_{12,13}$).

(2-(4-Diazynyl)phenyl-5-chloro)(pyrrolidin-1-yl)methanone tetrafluoroborate (2.098b)



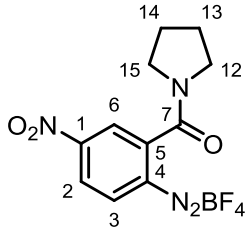
(Yellow solid, 88%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)**: δ 9.01 (d, *J* = 8.9 Hz, 1H, H_6), 8.41 (d, *J* = 2.1 Hz, 1H, H_3), 8.24 (dd, *J* = 2.1 Hz, 2.2 Hz, 1H, H_2), 3.81 (t, *J* = 6.5 Hz, 2H, H_{12}), 3.65 (t, *J* = 7.2 Hz, 2H, H_{15}), 2.04-1.95 (m, 4H, $H_{13,14}$).

(2-(4-Diazynyl)phenyl-5-bromo)(pyrrolidin-1-yl)methanone tetrafluoroborate (2.098c)



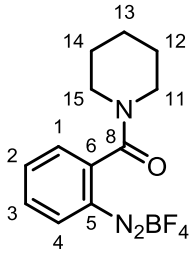
(White solid, 83%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)**: δ 8.93 (d, *J* = 9.1 Hz, 1H, H_3), 8.58 (s, 1H, H_6), 8.42 (d, *J* = 8.9 Hz, 1H, H_2), 3.82 (t, *J* = 6.7 Hz, 2H, H_{12}), 3.65 (t, *J* = 6.7 Hz, 2H, H_{15}), 2.02-1.96 (m, 4H, $H_{13,14}$).

(2-(4-Diazynyl)phenyl-5-nitro)(pyrrolidin-1-yl)methanone tetrafluoroborate (2.098d)



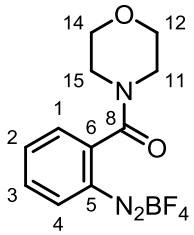
(Yellow solid, 80%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)**: δ 9.36 (d, *J* = 8.9 Hz, 1H, H_3), 9.06 (d, *J* = 2.3 Hz, 1H, H_6), 8.95 (dd, *J* = 2.3 Hz, 2.3 Hz, 1H, H_2), 3.85 (t, *J* = 6.4 Hz, 2H, H_{12}), 3.70 (t, *J* = 6.9 Hz, 2H, H_{15}), 2.04-1.97 (m, 4H, $H_{13,14}$).

(2-(4-Diazynyl)phenyl)(piperidin-1-yl)methanone tetrafluoroborate (2.098e)



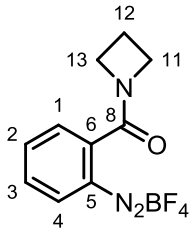
(Yellow solid, 80%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)**: δ 9.00 (d, *J* = 8.4 Hz, 1H, H_4), 8.42 (t, *J* = 7.9 Hz, 1H, H_2), 8.22-8.15 (m, 2H, $H_{1,3}$), 3.79-3.59 (m, 4H, $H_{11,15}$), 1.76-1.69 (m, 6H, $H_{12,13,14}$).

(2-(4-Diazynyl)phenyl)(morpholino)methanone tetrafluoroborate (2.098f)



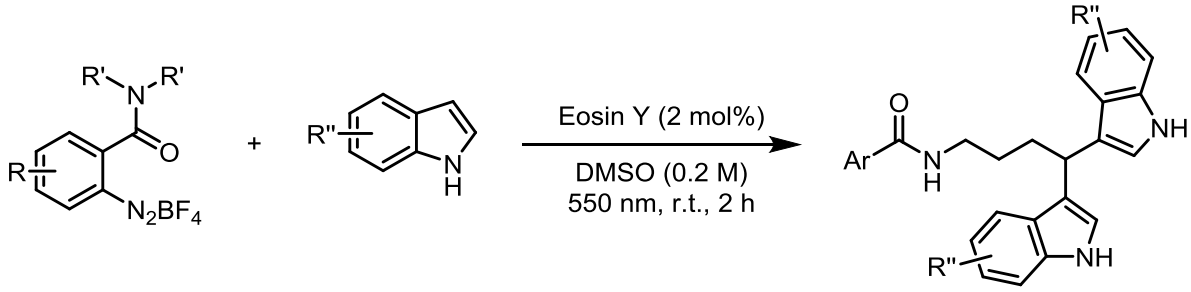
(Orange solid, 84%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)**: δ 9.05 (d, *J* = 8.8 Hz, 1H, H_4), 8.43 (t, *J* = 8.1 Hz, 1H, H_2), 8.29 (d, *J* = 7.8 Hz ,2H, H_1), 8.23-8.18 (t, *J* = 8.1 Hz, 1H, H_3), 3.83-3.77 (m, 4H, $H_{12,14}$), 3.76-3.71 (m, 4H, $H_{11,15}$).

Azetidin-1-yl(2-((tetrafluoro-l5-boranyl)diazenyl)phenyl)methanone (2.098g)



(White solid, 81%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)**: δ 9.02 (d, *J* = 8.3 Hz, 1H, H_4), 8.42 (t, *J* = 7.9 Hz, 1H, H_2), 8.28 (d, *J* = 7.9 Hz, 1H, H_1), 8.21 (t, *J* = 8.1 Hz, 1H, H_3), 4.64 (t, *J* = 7.6 Hz, 2H, H_{11}), 4.28 (t, *J* = 8.1 Hz, 2H, H_{13}), 2.50-2.41 (m, 2H, H_{12}).

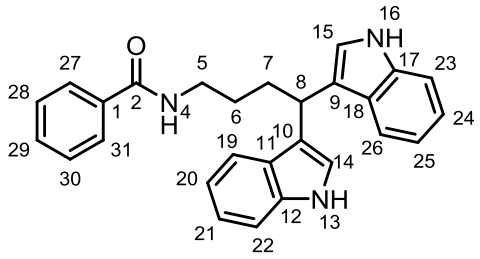
3.4.3 General procedure for the synthesis of bis(indolyl)alkanes



In a tube equipped with magnetic bar, Eosin Y (0.02 equiv.), aryl diazonium tetrafluoroborate (1 equiv.), and indole (2.5 equiv.) were dissolved in dry DMSO (0.2 M). The tube was irradiated through the tube's plane bottom side using green LEDs. After 2 hours of irradiation,

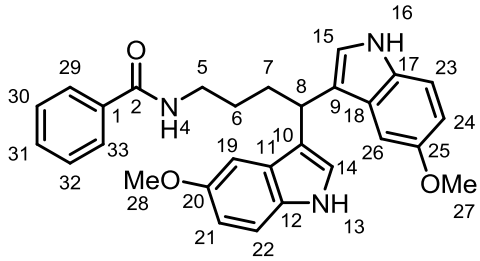
the reaction mixture was transferred to a separating funnel, diluted with ethyl acetate (10 ml), washed with water (10 ml), extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using (Heptane/ethyl acetate :5/1 to 1/1) to give the corresponding bis(indolyl)alkanes.

***N*-(4,4-di(1H-indol-3-yl)butyl)benzamide (2.102)**



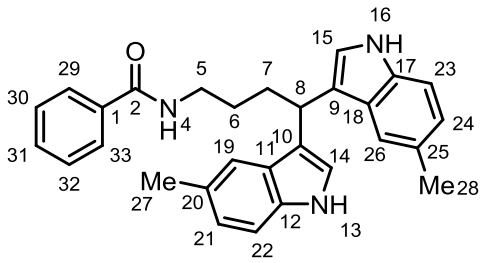
(Purple oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.88 (s, 2H, $H_{13,16}$), 7.56 (d, *J* = 7.8 Hz, 2H, $H_{27,31}$), 7.50 (d, *J* = 8.0 Hz, 2H, $H_{19,26}$), 7.37 (t, *J* = 7.2 Hz, 1H, H_{29}), 7.32 (t, *J* = 7.9 Hz, 2H, $H_{28,30}$), 7.22 (d, *J* = 8.5 Hz, 2H, $H_{22,23}$), 7.05 (t, *J* = 7.8 Hz, 2H, $H_{21,24}$), 6.94 (t, *J* = 7.5 Hz, 2H, $H_{20,25}$), 6.85 (d, *J* = 2.4 Hz, 2H, $H_{14,15}$), 5.91 (bs, 1H, H_4), 4.42 (t, *J* = 7.5 Hz, 1H, H_8), 3.40 (q, *J* = 6.8 Hz, 2H, H_6), 2.22 (q, *J* = 7.8 Hz, 2H, H_7), 1.66-1.57 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.6(C_2), 136.7(C_{Ar}), 134.2(C_{29}), 131.4(C_1), 128.5(C_{Ar}), 127.0(C_{Ar}), 128.5(2C, C_{Ar}), 126.9(C_{Ar}), 126.7(2C, C_{Ar}), 121.8(2C, C_{Ar}), 121.6(2C, C_{Ar}), 119.8(2C, C_{Ar}), 119.5(2C, C_{Ar}), 119.1(2C, C_{Ar}), 111.2(2C, $C_{22,23}$), 40.1(C_8), 33.9(C_5), 32.9(C_6), 28.3(C_7); **HRMS (ESI$^+$)** calculated for $C_{27}H_{25}N_3O$ $[M+Na]^+$ 430,1895, found 430,1886; **IR (neat) ν_{max}:** 3412, 3053, 3938, 1640, 1527, 1455, 1264, 1095, 1010, 791.

***N*-(4,4-bis(5-methoxy-1H-indol-3-yl)butyl)benzamide (2.103)**



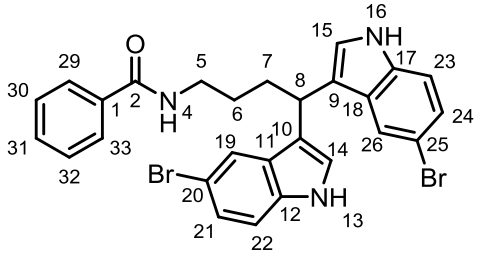
(Brown oil, 70%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.83 (s, 2H, $H_{13,16}$), 7.55 (d, *J* = 8.3 Hz, 2H, $H_{29,33}$), 7.36 (t, *J* = 7.5 Hz, 1H, H_{31}), 7.27 (t, *J* = 8.3 Hz, 2H, $H_{30,32}$), 7.11 (d, *J* = 8.8 Hz, 2H, $H_{19,26}$), 6.93 (d, *J* = 2.7 Hz, 2H, $H_{30,32}$), 6.86 (d, *J* = 2.6 Hz, 2H, $H_{21,24}$), 6.72 (dd, *J* = 2.5, 2.4 Hz, 2H, $H_{22,23}$), 5.93 (s, 1H, H_4), 4.31 (t, *J* = 7.6 Hz, 1H, H_8), 3.64 (s, 6H, $H_{27,28}$), 3.38 (q, *J* = 8.3 Hz, 2H, H_5), 2.20 (q, *J* = 8.3 Hz, 2H, H_7), 1.68-1.59 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.6(C_2), 153.6(2C, $C_{20,25}$), 134.6(C_{31}), 131.8(2C, C_{Ar}), 131.3(C_1), 128.4(2C, C_{Ar}), 127.3(2C, C_{Ar}), 126.8(2C, C_{Ar}), 122.5(2C, C_{Ar}), 119.4(2C, C_{Ar}), 111.8(2C, C_{Ar}), 111.6(2C, C_{Ar}), 101.8(2C, $C_{22,23}$), 55.9(2C, $C_{27,28}$), 40.1(C_5), 33.9(C_8), 32.7(C_7), 28.5(C_6); **HRMS (ESI$^+$)** calculated for $C_{29}H_{29}N_3O_3$ $[M+Na]^+$ 490,2107, found 490,2094; **IR (neat) ν_{max}:** 3286, 3052, 2933, 1635, 1577, 1485, 1454, 1266, 1171, 1027, 924, 732.

***N*-(4,4-bis(5-methyl-1H-indol-3-yl)butyl)benzamide (2.104)**



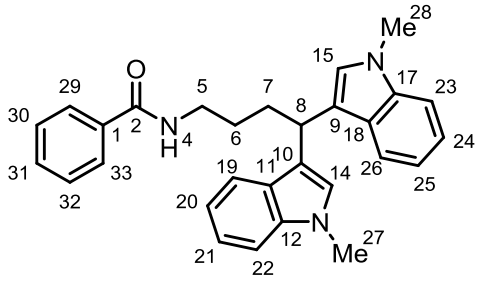
(Yellowish solid, 63%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.77 (s, 2H, $H_{13,16}$), 7.55 (d, *J* = 7.8 Hz, 2H, $H_{29,33}$), 7.26 (t, *J* = 7.2 Hz, 1H, H_{31}), 7.33-7.27 (m, 5H, H_{Ar}), 7.14 (d, *J* = 8.7 Hz, 2H, $H_{19,26}$), 6.90 (d, *J* = 8.5 Hz, 2H, $H_{21,24}$), 6.86 (d, *J* = 2.7 Hz, 2H, $H_{22,23}$), 5.90 (s, 1H, H_4), 4.39 (t, *J* = 7.6 Hz, 1H, H_8), 3.40 (q, *J* = 8.7 Hz, 2H, H_5), 2.30 (s, 6H, $H_{27,28}$), 2.21 (q, *J* = 8.7 Hz, 2H, H_7), 1.71-1.63 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.5(C_2), 135.5(2C, C_{Ar}), 134.8(C_{Ar}), 131.3(C_{Ar}), 128.5(3C, C_{Ar}), 128.3(C_{Ar}), 127.2(C_{Ar}), 126.8(3C, C_{Ar}), 123.5(2C, C_{Ar}), 121.8(2C, C_{Ar}), 119.4(2C, C_{Ar}), 119.2(2C, C_{Ar}), 110.8(2C, ($C_{22,23}$), 40.1(C_5), 33.9(C_8), 32.8(C_6), 28.4(C_7), 21.5(2C, $C_{27,28}$); **HRMS (ESI$^+$)** calculated for $C_{29}H_{29}N_3O$ $[M+Na]^+$ 458,2208, found 458,2215; **IR (neat) ν_{max}:** 3049, 3305, 2921, 1634, 1535, 1431, 1289, 1098, 795, 714, 625.

***N*-(4,4-bis(5-bromo-1H-indol-3-yl)butyl)benzamide (2.107)**



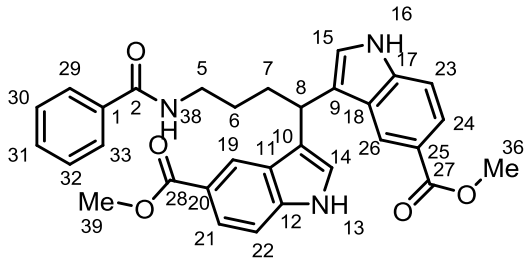
(Orange oil, 53%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.18 (s, 2H, $H_{13,16}$), 7.59 (d, *J* = 8.1 Hz, 2H, $H_{29,33}$), 7.53 (d, *J* = 2.0 Hz, 2H, $H_{19,26}$), 7.37 (t, *J* = 7.4 Hz, 1H, H_{31}), 7.31 (t, *J* = 8.1 Hz, 7.4 Hz, 2H, $H_{30,32}$), 7.12-7.03 (m, 4H, $H_{14,15,21,24}$), 6.82-6.79 (d, *J* = 3.0 Hz, 2H, $H_{22,23}$), 6.07 (s, 1H, H_4), 4.18 (t, *J* = 7.7 Hz, 1H, H_8), 3.33 (q, *J* = 6.7 Hz, 2H, H_5), 2.08 (q, *J* = 7.3 Hz, 2H, H_7), 1.57-1.48 (m, 2H, H_6); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.8(C_2), 135.2(2C, $C_{12,17}$), 134.6(C_{31}), 131.4(C_1), 128.6(2C, C_{Ar}), 128.5(C_{Ar}), 126.8(2C, C_{Ar}), 124.7(2C, C_{Ar}), 122.9(2C, C_{Ar}), 121.8(2C, C_{Ar}), 118.8(C_{Ar}), 112.8(C_{20}), 112.4(C25), 42.7(C_8), 40.1(C_5), 33.8(C_6), 28.3(C_7); **HRMS (ESI$^+$)** calculated for $C_{27}H_{23}Br_2N_3O$ $[M+Na]^+$ 586,0106, found 588,0094; **IR (neat) ν_{max}:** 3308, 3035, 2919, 1640, 1527, 1472, 1264, 1097, 1042, 732, 716.

***N*-(4,4-bis(1-methyl-1H-indol-3-yl)butyl)benzamide (2.105)**



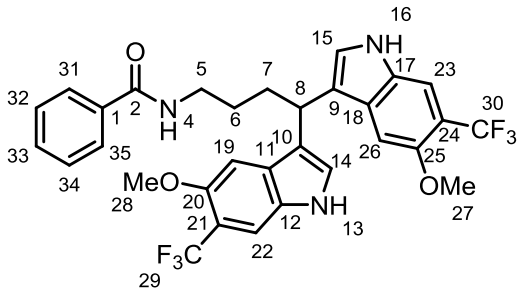
(Black oil, 69%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 7.8 Hz, 2H, $H_{29,33}$), 7.51 (d, *J* = 8.1 Hz, , 2H, $H_{19,26}$), 7.36 (t, *J* = 7.1 Hz, 1H, H_{31}), 7.27 (t, *J* = 7.4 Hz, 2H, $H_{30,32}$), 7.17 (d, *J* = 8.3 Hz, 2H, $H_{22,23}$), 7.01 (t, *J* = 2.7 Hz, 2H, $H_{20,25}$), 6.93 (t, *J* = 7.8 Hz, 2H, $H_{21,24}$), 6.77 (s, 2H, $H_{14,15}$), 5.91 (s, 1H, H_4), 4.41 (t, *J* = 8.7 Hz, 1H, H_8), 3.59 (s, 6H, $H_{27,28}$), 3.37 (q, *J* = 7.0 Hz, 2H, H_5), 2.20 (q, *J* = 7.6 Hz, 2H, H_7), 1.68-1.58 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.5(C_2), 137.4(2C, $C_{14,15r}$), 134.8(C_{31}), 131.2(2C, C_{Ar}), 128.5(2C, C_{Ar}), 127.4(2C, C_{Ar}), 126.9(2C, C_{Ar}), 126.4(2C, C_{Ar}), 121.3(2C, C_{Ar}), 119.6(2C, C_{Ar}), 118.6(2C, C_{Ar}), 109.3(2C, $C_{12,17}$), 40.1(C_8), 33.7(C_5), 33.4(C_6), 32.6(2C, $C_{27,28}$), 28.4(C_7); **HRMS (ESI$^+$)** calculated for $C_{29}H_{29}N_3O$ $[M+Na]^+$ 458,2208, found 458,2207; **IR (neat) ν_{max}:** 3317, 3051, 2927, 1638, 1531, 1468, 1371, 1265, 1155, 1076, 734, 698.

Dimethyl 3,3'-(4-benzamidobutane-1,1-diyl)bis(1H-indole-5-carboxylate) (2.106)



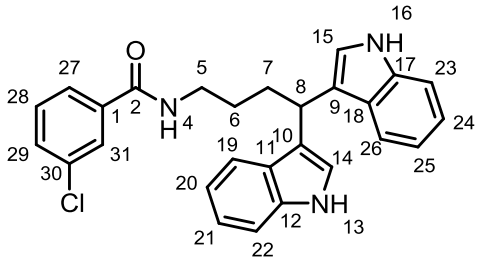
(Pink oil, 64%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.68 (s, 2H, $H_{13,16}$), 8.20 (s, 2H, $H_{19,26}$), 7.68 (d, *J* = 8.9 Hz, 2H, $H_{21,24}$), 7.56 (d, *J* = 8.0 Hz, 2H, $H_{29,33}$), 7.31 (t, *J* = 7.4 Hz, 1H, H_{31}), 7.21 (t, *J* = 8.0 Hz, 7.6 Hz, 2H, $H_{30,32}$), 7.11 (d, *J* = 8.6 Hz, 2H, $H_{22,23}$), 6.83 (s, 2H, $H_{14,15}$), 6.33 (s, 1H, H_{38}), 4.31 (t, *J* = 7.6 Hz, 1H, H_8), 3.72 (s, 6H, $H_{36,39}$), 3.32 (q, *J* = 6.8 Hz, 2H, H_5), 2.10 (q, *J* = 7.7 Hz, 2H, H_7), 1.54-1.45 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 168.4(2C, $C_{27,28}$), 167.9(C_2), 139.3(C_{Ar}), 134.4(C_{Ar}), 131.4(C_{Ar}), 128.7(4C, C_{Ar}), 126.7(4C, C_{Ar}), 126.3(C_{Ar}), 123.2(4C, C_{Ar}), 122.3(C_{Ar}), 120.9(2C, C_{Ar}), 120.6 C_{Ar}, 111.1(C_{Ar}), 51.8(2C, $C_{36,39}$), 40.1(C_8), 33.8(C_5), 32.7(C_6), 28.3(C_7); **HRMS (ESI$^+$)** calculated for $C_{31}H_{29}N_3O_5$ $[M+Na]^+$ 546,2005, found 546,1999; **IR (neat) ν_{max}:** 3057, 1503, 1262, 1164, 119, 1075, 1013, 794, 734, 696, 593.

***N*-(4,4-bis(5-methoxy-6-(trifluoromethyl)-1H-indol-3-yl)butyl)benzamide (2.112)**



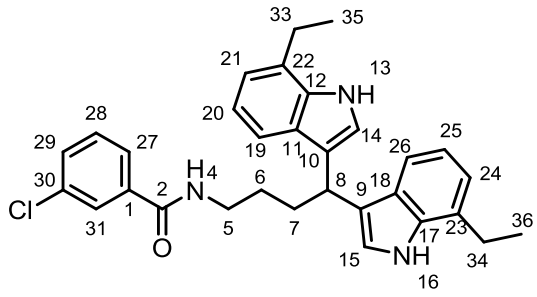
(Yellow solid, 53%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.25 (s, 2H, $H_{13,16}$), 7.58 (d, *J* = 8.5 Hz, 2H, $H_{31,35}$), 7.47 (s, 2H, $H_{19,26}$), 7.38 (t, *J* = 7.6 Hz, 1H, H_{33}), 7.30 (t, *J* = 8.0 Hz, 2H, $H_{32,34}$), 6.98 (d, *J* = 2.5 Hz, 2H, $H_{14,15}$), 6.89 (s, 2H, $H_{22,23}$), 6.02 (s, 1H, H_4), 4.32 (t, *J* = 7.8 Hz, 1H, H_8), 3.64 (s, 6H, $H_{27,28}$), 3.41 (q, *J* = 6.8 Hz, 2H, H_5), 2.18 (q, *J* = 7.4 Hz, 2H, H_7), 1.67-1.58 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.9(C_2), 151.4(2C, $C_{20,25}$), 134.4(C_{33}), 131.6(2C, C_{Ar}), 130.9(2C, C_{Ar}), 129.6(2C, C_{Ar}), 128.7(2C, C_{Ar}), 126.7(2C, C_{Ar}), 124.7(2C, C_{Ar}), 119.3(2C, C_{Ar}), 114.5(C_{Ar}), 114.2(C_{Ar}), 110.5(2C, $C_{29,30}$), 101.7(2C, $C_{19,26}$), 56.6(2C, $C_{27,28}$), 39.8(C_8), 33.5(C_5), 32.3(C_7), 28.3(C_6); **HRMS (ESI$^+$)** calculated for $C_{31}H_{27}F_6N_3O_3$ $[M+Na]^+$ 626,1854, found 626,1843; **IR (neat) ν_{max}:** 3312, 2931, 1630, 1473, 1267, 1143, 1110, 1043, 876, 737, 692.

3-Chloro-*N*-(4,4-di(1H-indol-3-yl)butyl)benzamide (2.108)



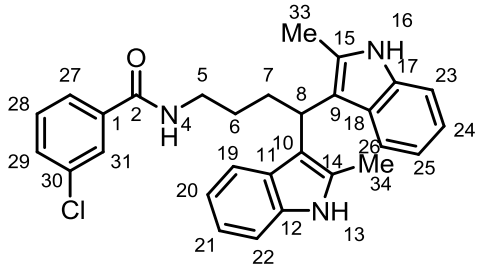
(Purple oil, 75%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.85 (s, 2H, $H_{13,16}$), 7.59 (t, *J* = 2.1 Hz, 1H, H_{28}), 7.49 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.40-7.31 (m, 2H, H_{Ar}), 7.26-7.21 (m, 3H, H_{Ar}), 7.06 (t, *J* = 7.6 Hz, 2H, H_{Ar}), 6.96 (t, *J* = 7.7 Hz, 2H, H_{Ar}), 6.90 (d, *J* = 2.7 Hz, 2H, $H_{14,15}$), 5.88 (s, 1H, H_4), 4.42 (t, *J* = 7.6 Hz, 1H, H_8), 3.36 (q, *J* = 6.7 Hz, 2H, H_5), 2.22 (q, *J* = 7.6 Hz, 2H, H_7), 1.67-1.58 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 166.2(C_2), 136.6(2C, C_{Ar}), 136.4(C_{30}), 134.7(C_1), 131.5(C_{31}), 129.8(2C, C_{Ar}), 127.2(2C, C_{Ar}), 126.9(2C, C_{Ar}), 124.9(C_{Ar}), 121.8(2C, C_{Ar}), 119.7(2C, C_{Ar}), 119.5(2C, C_{Ar}), 119.2(2C, C_{Ar}), 111.2(2C, $C_{22,23}$), 40.2(C_8), 33.9(C_5), 32.8(C_7), 28.2(C_6); **HRMS (ESI$^+$)** calculated for $C_{27}H_{24}ClN_3O$ $[M+Na]^+$ 464,1506, found 464,1504; **IR (neat) ν_{max}:** 3409, 3053, 2932, 1640, 1526, 1417, 1264, 1094, 895, 731, 701.

***N*-(4,4-bis(7-ethyl-1H-indol-3-yl)butyl)-3-chlorobenzamide (2.109)**



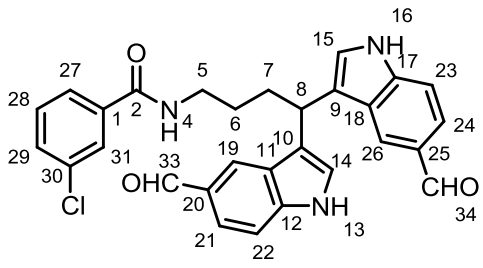
(Brown oil, 59%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.76 (s, 2H, $H_{13,16}$), 7.58 (t, *J* = 2.0 Hz, 1H, H_{28}), 7.36-7.30 (m, 4H, H_{Ar}), 7.16 (d, *J* = 3.7 Hz, 2H, H_{Ar}), 6.91-6.87 (m, 4H, H_{Ar}), 6.66 (d, *J* = 2.4 Hz, 2H, $H_{14,15}$), 5.95-5.90 (s, 1H, H_4), 4.33 (t, *J* = 7.7 Hz, 1H, H_8), 3.38 (q, 2H, H_5), 2.67 (q, 4H, $H_{33,34}$), 2.13 (q, 2H, H_7), 1.59-1.49 (m, 2H, H_6), 1.20 (t, *J* = 7.6 Hz, 6H, $H_{35,36}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 166.3(C_2), 136.4(C_{30}), 135.4(2C, C_{Ar}), 134.7(C_1), 131.4(C_{31}), 129.8(2C, C_{Ar}), 127.3(2C, C_{Ar}), 126.7(2C, C_{Ar}), 126.6(2C, C_{Ar}), 124.9(C_{Ar}), 121.4(2C, C_{Ar}), 120.1(2C, C_{Ar}), 119.3(2C, C_{Ar}), 117.3(2C, $C_{22,23}$), 40.3(C_5), 34.1(C_8), 33.0(C_6), 28.2(C_7), 23.9(2C, $C_{33,34}$), 13.8(2C, $C_{35,36}$); **HRMS (ESI$^+$)** calculated for $C_{31}H_{32}ClN_3O$ $[M+Na]^+$ 520,2132, found 520,2122; **IR (neat) ν_{max}:** 3415, 3051, 2966, 1645, 1525, 1435, 1349, 1264, 1098, 908, 730, 702.

***N*-(4,4-bis(2-methyl-1H-indol-3-yl)butyl)-3-chlorobenzamide (2.110)**



(Yellow solid, 77%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.60 (s, 2H, $H_{13,16}$), 7.55 (t, *J* = 2.0 Hz, 1H, H_{28}), 7.50 (d, *J* = 8.0 Hz, 2H, $H_{19,26}$), 7.28 (t, *J* = 7.0 Hz, 2H, H_{Ar}), 7.12 (t, *J* = 7.8 Hz, 1H, H_{28}), 7.01 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 6.92 (d, *J* = 7.2 Hz, 2H, H_{Ar}), 6.85 (t, *J* = 7.9 Hz, 2H, H_{Ar}), 5.96 (s, 1H, H_4), 4.25 (t, *J* = 7.9 Hz, 1H, H_8), 3.25 (q, *J* = 6.8 Hz, 2H, H_5), 2.38 (q, *J* = 7.8 Hz, 2H, H_7), 2.08 (s, 6H, $H_{33,34}$), 1.55-1.45 (m, 2H, H_6); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 166.2(C_2), 136.5(C_{30}), 135.2(2C, C_{Ar}), 134.6(C_{Ar}), 131.3(C_{Ar}), 131.0(2C, C_{Ar}), 128.3(C_{Ar}), 127.3(2C, C_{Ar}), 124.8(2C, C_{Ar}), 120.4(2C, C_{Ar}), 119.4(2C, C_{Ar}), 119.1(2C, C_{Ar}), 114.3(2C, C_{Ar}), 110.3(2C, C_{Ar}), 40.2(C_5), 34.6(C_8), 32.0(C_6), 28.7(C_7), 12.7(2C, $C_{33,34}$); **HRMS (ESI$^+$)** calculated for $C_{29}H_{28}ClN_3O$ $[M+Na]^+$ 492,1819, found 492,1826; **IR (neat) ν_{max}:** 3290, 3052, 2926, 1617, 1527, 1460, 1299, 1097, 895, 732, 702.

***N*-(4,4-bis(5-formyl-1H-indol-3-yl)butyl)-3-chlorobenzamide (2.111)**



(Pink oil, 58%), **^{1}H-NMR (400 MHz, d_6-Acetone)** δ 10.56 (s, 2H, $H_{13,16}$), 9.91 (s, 2H, $H_{33,34}$), 8.25-8.22 (s, 2H), 7.90 (s, 1H, H_4), 7.86 (t, *J* = 1.8 Hz, 1H, H_{31}), 7.80 (d, *J* = 7.8 Hz, 1H, H_{29}), 7.64 (dd, *J* = 1.6 Hz, 1.6 Hz, 2H, H_{Ar}), 7.51 (s, 2H, H_{Ar}), 7.51-7.48 (m, 3H,

H_{Ar}), 7.44 (t, *J* = 7.9 Hz, 1H, H_{28}), 4.76 (t, *J* = 7.7 Hz, 1H, H_8), 3.50 (q, *J* = 6.7 Hz, 2H, H_5), 2.45 (q, *J* = 7.8 Hz, 2H, H_7), 1.84-1.73 (m, 2H, H_6); **^{13}C NMR (100 MHz, d$_6$-Acetone)** δ 191.6(2C, $C_{33,34}$), 165.2(C_2), 140.5(2C, C_{Ar}), 137.3(C_{Ar}), 133.8(C_{Ar}), 130.7(C_{Ar}), 131.0(2C, C_{Ar}), 129.1(2C, C_{Ar}), 127.2(2C, C_{Ar}), 126.9(2C, C_{Ar}), 125.6(2C, C_{Ar}), 124.5(2C, C_{Ar}), 124.2(2C, C_{Ar}), 121.2(2C, C_{Ar}), 121.1(2C, C_{Ar}), 112.0(2C, C_{Ar}), 39.5(C_5), 33.6(C_8), 32.8(C_7), 28.1(C_6); **HRMS (ESI$^+$)** calculated for $C_{29}H_{24}ClN_3O_3$ $[M+Na]^+$ 520,1404, found 520,1397; **IR (neat) ν_{max}:** 3734, 3321, 2326, 2182, 2015, 1671, 1610, 1571, 1436, 1236, 1090, 809, 750

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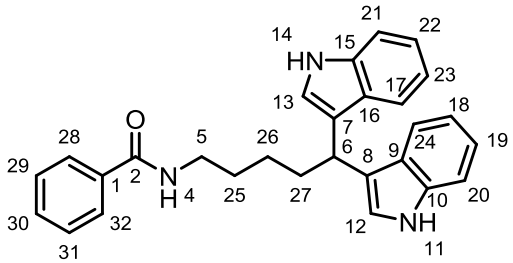
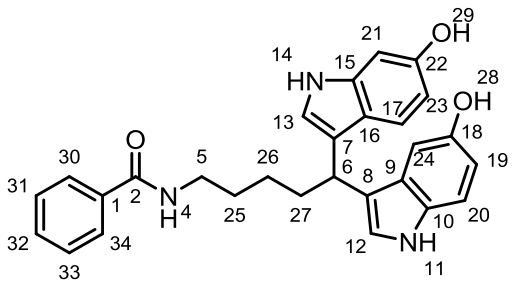
***N*-(5,5-di(1H-indol-3-yl)pentyl)benzamide (2.113)**



(Purple oil, 71%), **^{1}H-NMR (400 MHz, CDCl$_3$)** δ 7.85 (s, 2H, $H_{11,14}$), 7.51 (m, 4H, H_{Ar}), 7.38 (t, *J* = 7.6 Hz, 1H, H_{30}), 7.30 (t, *J* = 7.6 Hz, 2H, $H_{29,31}$), 7.21 (d, *J* = 8.2 Hz, 2H, $H_{17,24}$), 7.08 (t, *J* = 7.2 Hz, 2H, $H_{18,23}$), 6.94 (t, *J* = 7.5 Hz, 2H, $H_{19,22}$), 6.84 (d, *J* = 2.4 Hz, 2H, $H_{12,13}$), 5.89 (s, 1H, H_4), 4.38 (t, *J* = 7.6 Hz, 1H, H_6), 3.30 (q, *J* = 6.8 Hz, 2H, H_5), 2.18 (q, *J* = 7.6 Hz, 2H, H_{27}), 1.62-1.53 (m, 2H, H_{25}), 1.44-1.34 (m, 2H, H_{26}); **^{13}C-NMR (100 MHz, CDCl$_3$)** δ 167.7(C_2), 136.6(2C, $C_{28,32}$), 134.7(C_1), 131.3(C_{30}), 128.5(2C, C_{Ar}), 127.0(C_{Ar}), 126.8(2C, C_{Ar}), 121.7(2C, C_{Ar}), 121.6(2C, C_{Ar}), 120.0(C_{Ar}), 119.6(2C, C_{Ar}), 119.0(2C, C_{Ar}), 111.2(2C, C_{Ar}), 39.8(C_5), 35.2(C_6), 33.8(C_{25}), 29.5(C_{27}), 25.4(C_{26}); **HRMS (ESI$^+$)** calculated for $C_{28}H_{27}N_3O$ $[M+Na]^+$ 444,2052, found 444,2049; **IR (neat) ν_{max}:** 3292, 3055, 2930, 2858, 1630, 1533, 1455, 1388, 125, 1097, 1012, 909, 735.

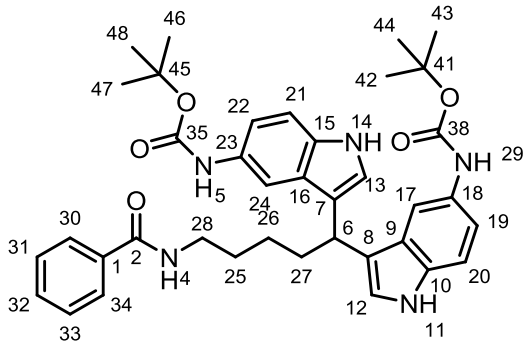
***N*-(5-(5-hydroxy-1H-indol-3-yl)-5-(6-hydroxy-1H-indol-3-yl)pentyl)benzamide (2.114)**



(Purple oil, 53%), **^{1}H-NMR (400 MHz, d$_6$-Acetone)** δ 9.62 (s, 2H, $H_{11,14}$), 7.88 (d, *J* = 7.8 Hz, 2H, $H_{30,34}$), 7.76 (s, 1H, H_4), 7.60 (s, 2H, $H_{21,20}$), 7.50 (t, *J* = 7.4 Hz, 1H, H_{32}), 7.43 (t, *J* = 7.4 Hz, 2H, $H_{31,33}$), 7.19 (d, *J* = 8.5 Hz, 2H, $H_{17,24}$), 7.05 (dd, *J* = 2.8 Hz, 2.5 Hz, 4H, H_{Ar}), 6.65 (dd, *J* = 2.5 Hz, 2.3 Hz , 2H, H_{Ar}), 4.33 (t, *J* = 7.7 Hz, 1H, H_6), 3.43 (q, *J* = 6.8 Hz, 2H, H_5), 2.96 (s, 2H, $H_{28,29}$), 2.23 (q, *J* = 7.5 Hz, 2H, H_{27}), 1.79-1.70 (m, 2H, H_{25}), 1.56-1.47 (m, 2H, H_{26}); **^{13}C NMR (100 MHz, d$_6$-Acetone)** δ 166.7(C_2), 150.3(2C, C_{Ar}), 135.3(C_{Ar}), 131.9(2C, C_{Ar}), 130.9(C_{Ar}), 128.2(2C, C_{Ar}), 128.1(2C, C_{Ar}), 127.0(2C, C_{Ar}), 122.5(2C, C_{Ar}), 118.8(2C, C_{Ar}),

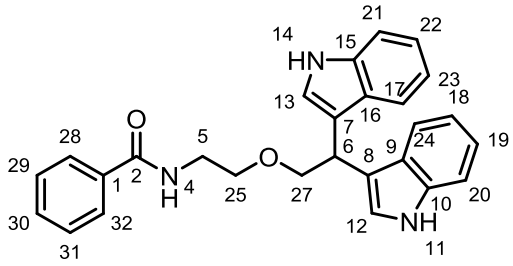
111.5(2C, C_{Ar}), 111.1(2C, C_{Ar}), 103.5(2C, C_{Ar}), 39.7(C_5), 35.1(C_6), 33.7(C_{25}), 29.5(C_{27}), 25.3(C_{26}); **HRMS (ESI$^+$)** calculated for $C_{28}H_{27}N_3O_3$ $[M+Na]^+$ 476,1950, found 476,1941; **IR (neat) ν_{max}:** 3316, 2929, 2858, 1691, 1625, 1456, 1255, 1193, 1024, 797, 734, 694.

Di-*tert*-butyl((5-benzamidopentane-1,1-diyl)bis(1H-indole-3,5-diyl))dicarbamate (2.115)



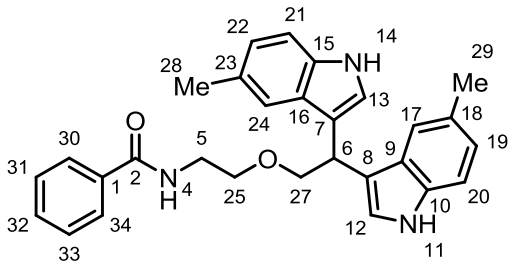
(Dark yellow oil, 63%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.17 (s, 2H, $H_{11,14}$), 7.55 (d, *J* = 8.2 Hz, 2H, $H_{24,17}$), 7.40 (s, 2H, $H_{5,29}$), 7.35 (t, *J* = 7.4 Hz, 1H, H_{32}), 7.28 (t, *J* = 7.6 Hz, 2H, $H_{31,33}$), 7.03 (s, 4H, H_{Ar}), 6.64 (s, 2H, H_{Ar}), 6.48 (s, 1H, H_4), 6.46 (d, *J* = 2.3 Hz, 2H, H_{Ar}), 4.12 (t, *J* = 7.5 Hz, 1H, H_6), 3.18 (q, *J* = 6.7 Hz, 2H, H_{28}), 1.92 (q, *J* = 7.3 Hz, 2H, H_{27}), 1.44-1.41 (m, 2H, H_{25}), 1.38 (s, 18H, $H_{42,43,44,46,47,48}$), 1.25-1.17 (m, 2H, H_{25}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.8(C_2), 154.2(2C, $C_{35,38}$), 134.8(C_{Ar}), 133.7(2C, C_{Ar}), 131.1(C_{Ar}), 129.8(2C, C_{Ar}), 128.4(4C, C_{Ar}), 127.2(C_{Ar}), 127.0(4C, C_{Ar}), 122.7(2C, C_{Ar}), 119.8(2C, C_{Ar}), 115.6(C_{Ar}), 111.3(C_{Ar}), 111.0(C_{Ar}), 79.8(2C, $C_{41,45}$), 39.8(C_{28}), 35.3(C_6), 33.2(C_{25}), 29.2(C_{27}), 28.4(6C, $C_{42,43,44,46,47,48}$), 25.1(C_{25}); **HRMS (ESI$^+$)** calculated for $C_{38}H_{45}N_5O_5$ $[M+Na]^+$ 647,3318, found 647,3311; **IR (neat) ν_{max}:** 3315, 2980, 1700, 1642, 1528, 1264, 1159, 1097, 1027, 909, 732, 702.

***N*-(2-(2,2-di(1H-indol-3-yl)ethoxy)ethyl)benzamide (2.116)**



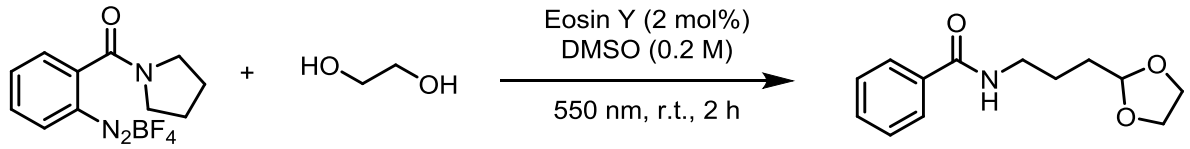
(Black oil, 52%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.91 (s, 2H, $H_{11,14}$), 7.51 (d, *J* = 8.2 Hz, 2H, $H_{28,32}$), 7.34 (t, *J* = 7.4 Hz, 1H, H_{30}), 7.22 (m, 6H, H_{Ar}), 7.09-7.03 (t, *J* = 7.2 Hz, 2H, $H_{29,31}$), 6.94 (t, *J* = 7.6 Hz, 2H, $H_{18,23}$), 6.81 (d, *J* = 2.3 Hz, 2H, $H_{12,13}$), 6.13(s, 1H, H_4), 4.78 (t, *J* = 6.9 Hz, 1H, H_6), 4.03 (d, *J* = 7.0 Hz, 2H, H_{27}), 3.55 (t, *J* = 5.1 Hz, 2H, H_{25}), 3.48 (t, *J* = 6.0 Hz, 2H, H_5); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.3(C_2), 136.5(2C, C_{Ar}), 134.2(C_{Ar}), 131.3(C_{Ar}), 128.4(2C, C_{Ar}), 127.1(C_{Ar}), 126.8(2C, C_{Ar}), 122.3(2C, C_{Ar}), 122.0(2C, C_{Ar}), 119.6(2C, C_{Ar}), 119.2(2C, C_{Ar}), 117.2(2C, C_{Ar}), 111.3(2C, C_{Ar}), 74.5(C_{27}), 69.3(C_{25}), 39.5(C_5), 34.5(C_6); **HRMS (ESI$^+$)** calculated for $C_{27}H_{25}N_3O_2$ $[M+Na]^+$ 446,1844, found 446,1855; **IR (neat) ν_{max}:** 3307, 3056, 2927, 1624, 1534, 1465, 1537, 1264, 1101, 937, 737, 713.

***N*-(2-(2,2-bis(5-methyl-1H-indol-3-yl)ethoxy)ethyl)benzamide (2.117)**



(Purple oil, 57%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.90 (s, 2H, $H_{11,14}$), 7.48-7.43 (m 3H, $H_{31,32,33}$), 7.34 (d, *J* = 8.2 Hz, 2H, $H_{30,34}$), 7.30 (d, *J* = 7.3 Hz, 2H, $H_{19,22}$), 7.23 (d, *J* = 8.3 Hz, 2H, $H_{20,21}$), 7.03-7.00 (dd, *J* = 1.8 Hz, 1.7 Hz, 2H, $H_{17,24}$), 6.90 (d, *J* = 2.6 Hz, 2H, $H_{12,13}$), 6.28 (s, 1H, H_4), 4.85 (t, *J* = 6.6 Hz, 1H, H_6), 4.14 (d, *J* = 6.8 Hz, 2H, H_{27}), 3.68 (t, *J* = 5.1 Hz, 2H, H_{25}), 3.62 (t, *J* = 5.7 Hz, 2H, H_5), 2.42 (s, 6H, $H_{28,29}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.2(C_2), 134.8(2C, C_{Ar}), 134.2(C_{Ar}), 131.2(2C, C_{Ar}), 128.5(2C, C_{Ar}), 128.3(2C, C_{Ar}), 127.3(C_{Ar}), 126.8(2C, C_{Ar}), 123.6(2C, C_{Ar}), 122.4(2C, C_{Ar}), 119.1(2C, C_{Ar}), 116.2(2C, C_{Ar}), 110.9(2C, C_{Ar}), 74.6(C_{27}), 69.3(C_{25}), 39.6(C_5), 34.8(C_6), 21.5(2C, $C_{28,29}$); **HRMS (ESI$^+$)** calculated for $C_{29}H_{29}N_3O_2$ $[M+Na]^+$ 474,2157, found 474,2147; **IR (neat) ν_{max}:** 3314, 2862, 1644, 1526, 1264, 1102, 895, 797, 732, 702.

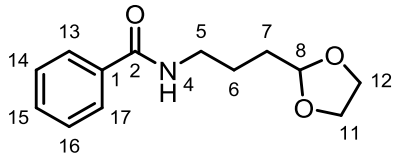
3.4.4 Procedure for the synthesis of acetal **2.118**



2.098a **2.118**

In a tube equipped with magnetic bar, Eosin Y (0.02 equiv.), aryl diazonium tetrafluoroborate (1 equiv.), and ethylene glycol (2.5 equiv.) were dissolved in dry DMSO (0.2 M). The tube was irradiated through the tube's plane bottom side using green LEDs. After 2 hours of irradiation, the reaction mixture was transferred to a separating funnel, diluted with ethyl acetate (10 ml), washed with water (10 ml), extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography using (Heptane/ethyl acetate :5/1 to 1/1) to give the corresponding acetal **2.118** as colourless oil in 85% yield.

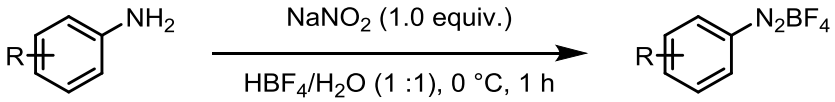
***N*-(3-(1,3-dioxolan-2-yl)propyl)benzamide (2.118)**



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 2H, $H_{13,17}$), 7.41 (t, *J* = 7.2 Hz, 1H, H_{15}), 7.35 (t, *J* = 7.5 Hz, 2H, $H_{14,16}$), 6.56 (s, 1H, H_4), 4.83 (t, *J* = 4.2 Hz, 1H, H_8), 3.93-3.87 (m, 2H, H_{11}), 3.81-3.76 (m, 2H, H_{12}), 3.42 (q, 2 *J* = 6.2 Hz, 2H, H_5), 1.78-1.66 (m, 4H, $H_{6,7}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.7(C_2), 134.8(C_{15}), 131.4(C_1), 128.6(2C, $C_{13,17}$),

126.9(2C, $C_{14,16}$), 104.2(C_8), 64.9(2C, $C_{11,12}$), 39.7(C_5), 31.1(C_7), 23.6(C_6); **HRMS (ESI$^+$)** calculated for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258,1106, found 258,1102; **IR (neat) ν_{max}:** 3320, 3056, 2881, 1635, 1538, 1267, 1141, 1026, 941, 732, 697.

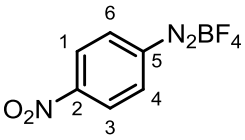
3.4.5 General procedure for the preparation of the diazonium salts **2.010**



The aniline (1.0 equiv., 10 mmol) was dissolved in a mixture of 3.4 ml of hydrofluoroboric acid (50%) and 4 ml of distilled water. The reaction mixture was cooled down to 0 °C. Then, a solution of sodium nitrite (1.0 equiv., 10 mmol) in 1.5 ml distilled water was added dropwise. The resulting reaction mixture was stirred for another 1 hour at 0 °C. The obtained precipitate was collected by filtration, re-dissolved in a minimum amount of acetone and precipitate again from ice-cooled diethyl ether. The precipitate filtered and washed several times with small portions of diethyl ether and was then dried under vacuum to give the title diazonium salt.

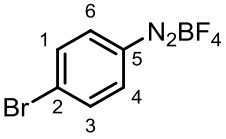
Spectroscopic data for the diazonium salt products match those reported in the literature. [128]

4-Nitrobenzenediazonium tetrafluoroborate (2.123)



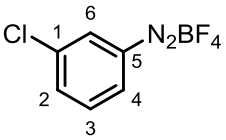
^{1}H-NMR (400 MHz, d_6-Acetone): δ 9.20 (d, *J* = 9.4 Hz, 2H, $H_{1,3}$), 8.87 (d, *J* = 9.4 Hz, 2H, $H_{4,6}$).

4-Bromobenzenediazonium tetrafluoroborate (2.010a)



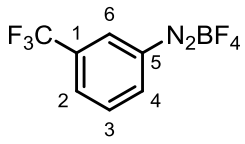
^{1}H-NMR (400 MHz, d_6-Acetone): δ 8.78 (d, *J* = 9.1 Hz, 2H, $H_{1,3}$), 8.32 (d, *J* = 9.2 Hz, 2H, $H_{4,6}$).

3-Chlorobenzenediazonium tetrafluoroborate (2.010b)



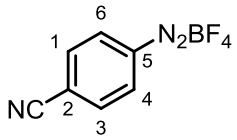
^{1}H-NMR (400 MHz, d_6-Acetone): δ 8.95 (t, *J* = 3.1 Hz, 1H, H_6), 8.86 (d, *J* = 8.5 Hz, 1H, H_2), 8.43 (d, *J* = 8.5 Hz, 1H, H_4), 8.14 (t, *J* = 8.4 Hz, 1H, H_3).

3-Trifluoromethylbenzenediazonium tetrafluoroborate (2.010c)



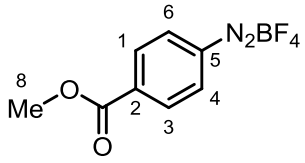
^{1}H-NMR (400 MHz, d$_6$-Acetone): δ 9.28 (s, 1H, H_6), 9.15 (d, *J* = 8.3 Hz, 1H, H_2), 8.73 (d, *J* = 8.3 Hz, 1H, H_4), 8.37 (t, *J* = 8.6 Hz, 1H, H_3).

4-Cyanobenzenediazonium tetrafluoroborate (2.010d)



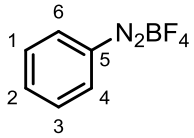
^{1}H-NMR (400 MHz, d$_6$-Acetone): δ 9.06 (d, *J* = 9.1 Hz, 2H, $H_{1,3}$), 8.51 (d, *J* = 9.1 Hz, 2H, $H_{4,6}$).

4-Carboxymethylbenzenediazonium tetrafluoroborate (2.010e)



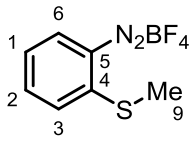
^{1}H NMR (400 MHz, d$_6$-Acetone): δ 8.98 (d, *J* = 9.0 Hz, 2H, $H_{1,3}$), 8.56 (d, *J* = 9.0 Hz, 2H, $H_{4,6}$), 4.03 (s, 3H, H_8).

Benzenediazonium tetrafluoroborate (2.156)



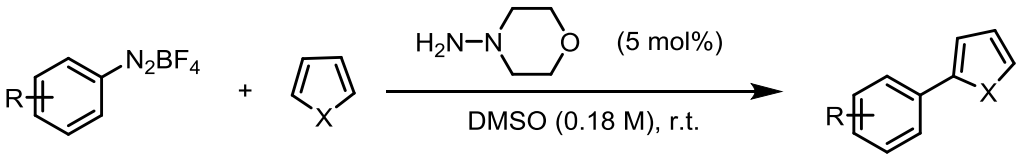
^{1}H-NMR (400 MHz, d$_6$-Acetone): δ 8.84 (d, *J* = 8.9 Hz, 2H, $H_{4,6}$), 8.38 (t, *J* = 7.8 Hz, 1H, H_2), 8.09 (t, *J* = 8.3 Hz, 2H, $H_{1,3}$).

2-Thiomethylbenzenediazonium tetrafluoroborate (2.150)



^{1}H-NMR (400 MHz, d$_6$-Acetone): δ 8.76 (d, *J* = 8.8 Hz, 1H, H_3), 8.27 (t, *J* = 7.5 Hz, 1H, H_2), 8.15 (d, *J* = 8.5 Hz, 1H, H_6), 7.81 (t, *J* = 8.0 Hz, 1H, H_1), 2.95 (s, 3H, H_9).

3.4.6 General procedure for arylation of heteroarenes with diazonium salts

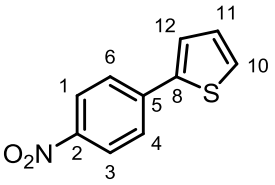


To a solution of diazonium salt (1.0 equiv., 0.3 mmol) and heteroarene (20 equiv., 6.0 mmol) in DMSO (2 ml) was added of 4-aminomorpholine (0.05 equiv.) at room temperature. The reaction mixture was stirred for the indicated time. The reaction mixture was then quenched with water (5 ml) and extracted with ethyl acetate (2 x 10 ml). The combined organic layers were dried on $MgSO_4$ and filtered. The solvent was then removed under vacuum and the crude

was purified by column chromatography (heptane to heptane/ethyl acetate :20/1) to afford the desired products.

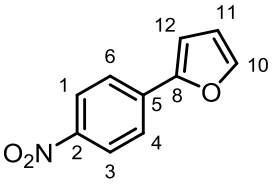
Spectroscopic data for the arylation products match those reported in the literature. [128]

2-(4-Nitrophenyl)thiophene (2.128)



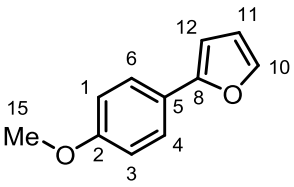
(Yellow solid, 63%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 9.0 Hz, 2H, $H_{1,3}$), 7.66 (d, *J* = 9.0 Hz, 2H, $H_{4,6}$), 7.40 (dd, *J* = 4.0 Hz, 1.0 Hz, 1H, H_{10}), 7.36 (dd, *J* = 4.0 Hz, 1.0 Hz, 1H, H_{12}), 7.07 (dd, *J* = 4.0 Hz, 1.0 Hz, 1H, H_{11}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 146.7(C_5), 141.6(C_2), 140.6(C_8), 128.7(C_{10}), 127.7(C_{12}), 126.0(2C, $C_{4,6}$), 125.7(C_{11}), 124.4(2C, $C_{1,3}$); **HRMS (ESI$^+$)** calculated for $C_{10}H_7NO_2S$ $[M+Na]^+$ 228.0095, found 228.0091.

2-(4-Nitrophenyl) furan (2.129)



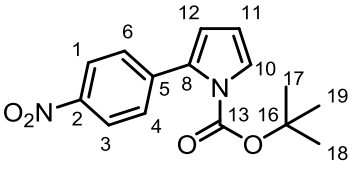
(Yellow solid, 95%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.23 (d, *J* = 9.0 Hz, 2H, $H_{1,3}$), 7.77 (d, *J* = 9.0 Hz, 2H, $H_{4,6}$), 7.56 (d, *J* = 1.2 Hz, 1H, H_{10}), 6.87 (d, *J* = 3.4 Hz, 1H, H_{12}), 6.54 (dd, *J* = 3.4 Hz, 1.8 Hz, 1H, H_{11}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 151.7(C_8), 146.4(C_2), 144.1(C_{10}), 136.4(C_5), 124.3(2C, $C_{1,3}$), 123.9(2C, $C_{4,6}$), 112.4(C_{11}), 108.9(C_{12}); **HRMS (ESI$^+$)** calculated for $C_{10}H_7NO_3$ $[M+Na]^+$ 212.0324, found 212.0322.

Methyl-4-(furan-2-yl)benzoate (2.136)



(Red solid, 55%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.52 (d, *J* = 8.9 Hz, 2H, $H_{1,3}$), 7.33 (dd, *J* = 0.8 Hz, 0.7 Hz, 1H, H_{10}), 6.83 (d, *J* = 8.9 Hz, 2H, $H_{4,6}$), 6.42 (d, *J* = 3.5 Hz, 1H, H_{12}), 6.35 (dd, *J* = 1.8 Hz, 1.9 Hz, 1H, H_{11}), 3.73 (s, 3H, H_{15}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 159.1(C_2), 154.1(C_{10}), 141.8(C_5), 125.3(2C, $C_{1,3}$), 124.7(C_8), 114.8 (2C, $C_{4,6}$), 111.5(C_{12}), 103.4(C_{11}), 55.3(C_{15}); **HRMS (EI)** calculated for $C_{10}H_{11}O_2$ 174.0675, found 174.0673.

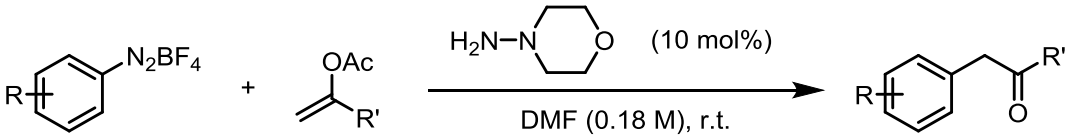
***tert*-butyl 2-(4-nitrophenyl)-1H-pyrrole-1-carboxylate (2.130)**



(Yellow solid, 81%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.22 (d, *J* = 8.9 Hz, 2H, $H_{1,3}$), 7.51 (d, *J* = 8.9 Hz, 2H, $H_{4,6}$), 7.41 (dd, *J* = 3.3 Hz, 1.8 Hz, 1H, H_{10}), 6.33 (dd, *J* = 3.4, 1.8 Hz, 1H, H_{12}), 6.27 (t, *J* = 3.3 Hz, 1H, H_{11}), 1.43 (s, 9H, $H_{17,18,19}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 148.8(C_{13}), 146.5(C_2), 140.6(C_8), 132.7(C_5), 129.5(2C, $C_{1,3}$),

124.3(C_{10}), 122.9(2C, $C_{4,6}$), 116.4(C_{11}), 111.1(C_{12}), 84.5(C_{16}), 27.7(3C, $C_{17,18,19}$); **HRMS (ESI$^+$)** calculated for $C_{15}H_{16}N_2O_4$ $[M+Na]^+$ 311.1008, found 311.1008.

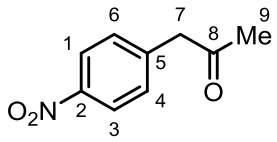
3.4.7 General Procedure for the synthesis of α-aryl ketones:



To a solution of diazonium salt (1.0 equiv., 0.3 mmol) and enol acetate (10.0 equiv., 3.0 mmol) in DMF (2 ml) was added 4-aminomorpholine (0.1 equiv.) at room temperature. The reaction mixture was stirred for the time indicated. The reaction mixture was quenched with water (10 ml), extracted with ethyl acetate (2 x 10 ml), dried over $MgSO_4$ and filtered. The solvent was then removed under vacuum and the crude was purified by column chromatography (heptane to heptane/ethyl acetate: 3/1) to afford the desired ketones.

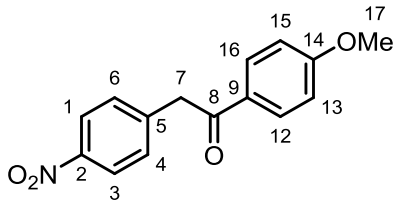
Spectroscopic data for the α-aryl-ketone products match those reported in the literature. [129]

1-(4-Nitrophenyl)propan-2-one (2.142)



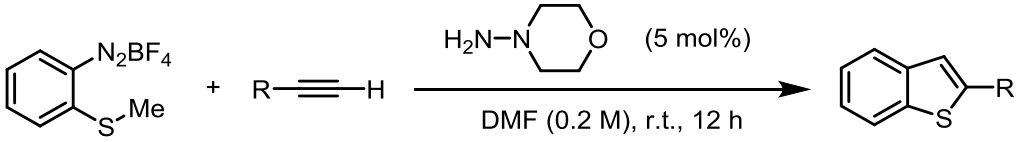
(Yellow oil, 58%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.12 (d, *J* = 8.8 Hz, 2H, $H_{1,3}$), 7.29 (d, *J* = 8.7 Hz, 2H, $H_{4,6}$), 3.78 (s, 2H, H_7), 2.17 (s, 3H, H_9); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 204.3(C_8), 147.2(C_2), 141.8(C_5), 130.5(2C, $C_{1,3}$), 123.8(2C, $C_{4,6}$), 50.1(C_7), 29.8(C_9); **HRMS (ESI$^+$)** calculated for $C_9H_9NO_3$ $[M+Na]^+$ 202.0480, found 202.0476.

1-(4-Methoxyphenyl)-2-(4-nitrophenyl)ethan-1-one (2.148)



(Yellow solid, 94%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.09 (d, *J* = 8.6 Hz, 2H, $H_{1,3}$), 7.91 (d, *J* = 8.8 Hz, 2H, $H_{13,15}$), 7.34 (d, *J* = 8.6 Hz ,2H, $H_{12,16}$), 6.87 (d, *J* = 8.9 Hz, 2H, $H_{4,6}$), 4.27 (s, 2H, H_7), 3.79 (s, 3H, H_{17}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 194.5(C_8), 164.1(C_{14}), 147.1(C_2), 142.7(C_9), 130.8(2C, $C_{13,15}$), 130.5(2C, $C_{1,3}$), 129.3(C_5), 123.7(2C, $C_{12,16}$), 114.1(2C, $C_{4,6}$), 55.5(C_7), 44.6(C_{17}); **HRMS (ESI$^+$)** calculated for $C_{15}H_{13}NO_4$ $[M+Na]^+$ 294.0742, found 294.0743.

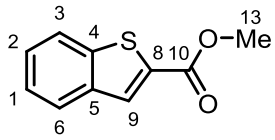
3.4.8 General procedure for the synthesis of 2-substituted benzothiophenes



Diazonium salt **2.150** (1.0 equiv., 0.2 mmol) was dissolved in DMSO (1 ml). The corresponding alkyne (5.0 equiv., 1.0 mmol) was added followed by addition of 4-aminomorpholine (0.05 equiv.). The reaction was stirred at room temperature. For another 12 h. the reaction mixture was then quenched with water (10 ml), extracted with ether (3 x 10 ml), dried over Na_2SO_4 and filtered. The solvent was then removed and the crude material was purified by column chromatography (heptane) to afford the desired benzothiophenes.

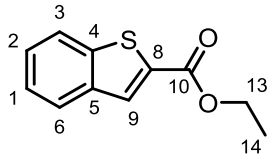
Spectroscopic data for the benzothiophens match those reported in the literature. [183]

Methyl benzo[b]thiophene-2-carboxylate (2.154)



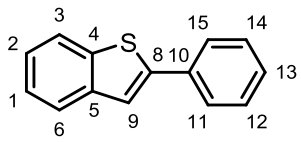
(Red oil, 68%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.99 (s, 1H, H_9), 7.82-7.77 (m, 2H, $H_{3,6}$), 7.41-7.31 (m, 2H, $H_{1,2}$), 3.88 (s, 3H, H_{13}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 163.3(C_{10}), 142.4(C_4), 138.6(C_8), 133.7(C_5), 130.6(C_3), 127.0(C_2), 125.6(C_1), 124.9(C_6), 122.7(C_9), 52.5(C_{13}); **HRMS (ESI$^+$)** calculated for $C_{10}H_8O_2S$ $[M+Na]^+$ 215.0143, found 215.0139.

Ethyl benzo[b]thiophene-2-carboxylate (2.155)



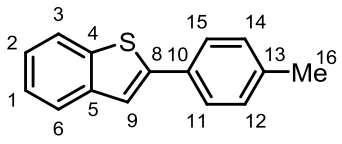
(Red solid, 54%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.98 (s, 1H, H_9), 7.81-7.77 (m, 2H, $H_{3,6}$), 7.40-7.31 (m, 2H, $H_{1,2}$), 4.34 (q, J = 7.2 Hz, 2H, H_{13}), 1.34 (t, J = 7.2 Hz, 3H, H_{14}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 162.8(C_{10}), 142.2(C_8), 138.7(C_4), 133.9(C_3), 130.4(C_5), 126.9(C_2), 125.4(C_1), 124.9(C_6), 122.8(C_9), 61.6(C_{13}), 14.3(C_{14}); **HRMS (ESI$^+$)** calculated for $C_{11}H_{10}O_2S$ $[M+Na]^+$ 229.0299, found 229.0296.

2-Phenylbenzo[b]thiophene (2.151)



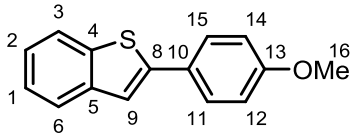
(White solid, 45%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.74 (d, J = 7.9 Hz, 1H, H_3), 7.68 (d, J = 8.1 Hz, 1H, H_6), 7.63 (d, J = 8.2 Hz, 2H, H_2, $H_{11,15}$) 7.45 (s, 1H, H_9), 7.35 (t, J = 7.4 Hz, 2H, $H_{1,2}$), 7.28-7.19 (m, 3H, $H_{12,13,14}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 144.3(C_8), 140.7(C_5), 139.5(C_{Ar}), 134.6(C_{Ar}), 128.9(C_{Ar}), 128.3(C_{Ar}), 126.6(2C, C_{Ar}), 124.5(2C, C_{Ar}), 124.3(2C, C_{Ar}), 123.6(C_{Ar}), 122.3(C_{Ar}); **HRMS (EI)** calculated for $C_{14}H_{10}S$: 210.0503, found 210.0506.

2-(*p*-tolyl)benzo[b]thiophene (2.152)



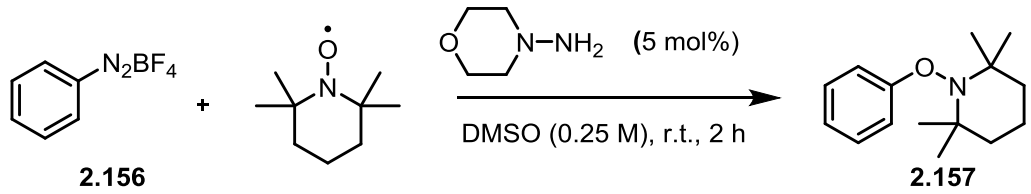
(White solid, 73%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 7.6 Hz, 1H, H_3), 7.67 (d, *J* = 8.1 Hz, 1H, H_6), 7.53 (d, *J* = 8.1 Hz, 2H, $H_{11,15}$) 7.42 (s, 1H, H_9), 7.28-7.21 (m, 2H, $H_{1,2}$), 7.14 (d, *J* = 8.3 Hz, 2H, $H_{12,14}$), 2.31 (s, 3H, H_{16}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 144.4(C_8), 140.8(C_4), 139.4(C_{Ar}), 138.3(C_{Ar}), 131.2(C_{Ar}), 129.6(2C, $C_{11,15}$), 126.4(2C, $C_{12,14}$), 124.4(C_{Ar}), 124.1(C_{Ar}), 123.4(C_{Ar}), 122.2(C_{Ar}), 118.8(C_9), 21.3(C_{16}); **HRMS (EI)** calculated for $C_{15}H_{12}S$: 224.0660, found 224.0660.

2-(4-Methoxyphenyl)benzo[b]thiophene (2.153)



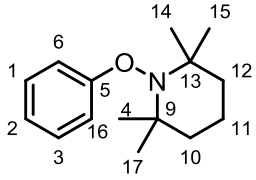
(Red solid, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 8.4 Hz, 1H, H_3), 7.66 (d, *J* = 8.6 Hz, 1H, H_6), 7.56 (d, *J* = 8.7 Hz, 2H, $H_{12,14}$) 7.34 (s, 1H, H_9), 7.28-7.18 (m, 2H, $H_{1,2}$), 6.88 (d, *J* = 8.6 Hz, 2H, $H_{11,15}$), 3.77 (s, 3H, H_{16}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 159.9(C_{13}), 144.1(C_8), 140.9(C_4), 139.2(C_5), 127.8 (2C, $C_{12,14}$), 127.1(C_{Ar}), 124.6(C_{Ar}), 123.9(C_{Ar}), 123.3(C_{Ar}), 122.2(C_{Ar}), 118.2(C_9), 114.8(2C, $C_{11,15}$), 55.4(C_{16}); **HRMS (EI)** calculated for $C_{15}H_{12}OS$: 240.0609, found 240.0609.

3.4.9 Procedure for trapping the phenyl radical with TEMPO



Diazonium salt **2.156** (1.0 equiv., 0.5 mmol) was dissolved in DMSO (2 ml). 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) (2.0 equiv., 1.0 mmol) was added under argon at room temperature. 4-aminomorpholine (0.05 equiv.) was added and the mixture was stirred for 2 h. Water (10 ml) was then added and the mixture was extracted with diethyl ether (3 x 10 ml). The organic layers were combined and washed with brine (10 ml) and dried over Na_2SO_4. The crude material was then purified by column chromatography (heptane to heptane/ethyl acetate: 10/1) to afford product **2.157** in 44% yield.

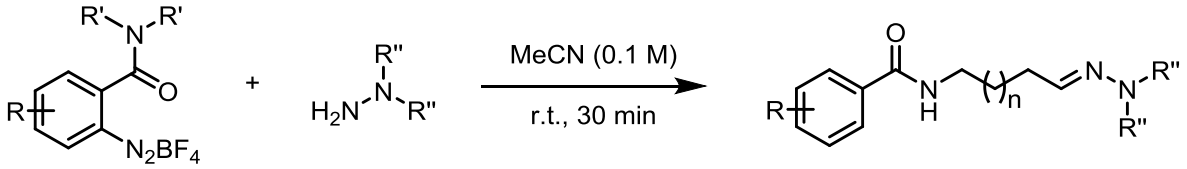
2,2,6,6-Tetramethyl-1-phenoxypiperidine (2.157)



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16-7.07 (m, 4H, H_{Ar}), 6.78-6.73 (m, 1H, H_{Ar}), 1.61-1.45 (m, 5H, $H_{10,11,12}$) 1.36-1.31 (m, 1H, H_{11}), 1.15 (s, 6H, $H_{4,17}$), 0.93 (s, 6H, $H_{14,15}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ

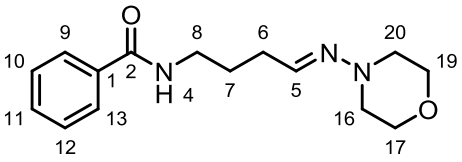
163.8(C_5), 128.8(2C, $C_{6,16}$), 119.8(C_2), 114.0(2C, $C_{1,3}$), 60.5(2C, $C_{9,13}$), 40.0(2C, $C_{4,17}$), 32.8(2C, $C_{14,15}$), 20.8(2C, $C_{10,12}$), 17.3(C_{11}); **HRMS (ESI$^+$)** calculated for $C_{15}H_{24}NO$ $[M+H]^+$ 234.1858, found 234.1858.

3.4.10 General procedure for the synthesis of hydrazones **2.162**



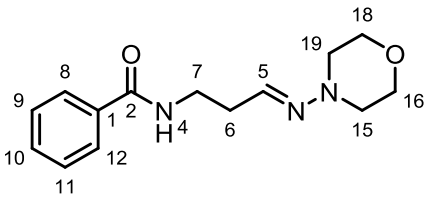
A solution of diazonium salt (1.0 equiv., 0.2 mmol) in dry MeCN (0.5 ml) was added dropwise to a solution of hydrazine (1.3 equiv., 0.26 mmol) in 1.5 ml MeCN (0.1M). The mixture was stirred at room temperature for another 30 minutes. The reaction mixture was transferred to a separating funnel, diluted with DCM (5 ml), washed with water (10 ml), and extracted (3 x 10 ml) with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification of the crude product was achieved by flash column chromatography (heptane/ethyl acetate/methanol: (1/1/0 to 1/1/0.1) to give the corresponding hydrazones.

(*E*)-*N*-(4-(morpholinoimino)butyl)benzamide (2.162)



(Colourless oil, 76%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ - 7.70 (d, *J* = 7.7 Hz, 2H, $H_{9,13}$), 7.42 (t, *J* = 7.3 Hz, 1H, H_{11}), 7.35 (t, *J* = 7.5 Hz, 2H, $H_{10.12}$), 6.94 (t, *J* = 5.0 Hz, 1H, H_5), 6.45 (s, 1H, H_4), 3.74 (t, *J* = 4.9 Hz, 4H, $H_{17,19}$), 3.45 (q, *J* = 6.8 Hz, 2H, H_8), 2.87 (t, *J* = 5.0 Hz, 4H, $H_{20,16}$), 2.31 (q, *J* = 6.7 Hz, 2H, H_6), 1.84-1.77 (m, 2H, H_7); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.5(C_2), 140.3(C_5), 134.8(C_1), 131.4(C_{11}), 128.5(2C, $C_{9,13}$), 127.0(2C, $C_{10,12}$), 66.4(2C, $C_{17,19}$), 52.3(2C, $C_{16,20}$), 39.6(C_8), 30.6(C_6), 26.6(C_7); **HRMS (ESI$^+$)** calculated for $C_{15}H_{21}N_3O_2$ $[M+Na]^+$ 298,1531, found 298,1526; **IR (neat) ν_{max}:** 3361, 2927, 1635, 1530, 1447, 1306, 1114, 992, 719, 645.

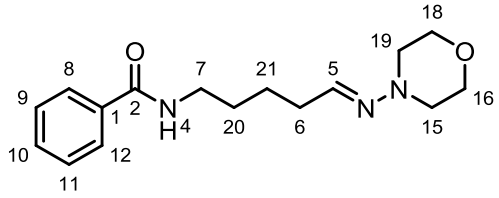
(*E*)-*N*-(3-(morpholinoimino)propyl)benzamide (2.163)



(Colourless oil, 42%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.67 (d, *J* = 8.3 Hz, 2H, $H_{8,12}$), 7.42 (t, *J* = 7.3 Hz, 1H, H_{10}), 7.36 (t, *J* = 7.7 Hz, 2H, $H_{9,11}$), 6.98 (t, *J* = 4.4 Hz, 1H, H_5), 6.72 (s, 1H, H_4), 3.77 (t, *J* = 4.9 Hz, 4H, $H_{16,18}$), 3.65 (q, 2H, *J* = 6.8 Hz, H_7), 2.90 (t, *J* = 5.0 Hz, 4H, $H_{15,19}$), 2.48 (q, *J* = 6.7 Hz, 2H, H_6); **^{13}C-**

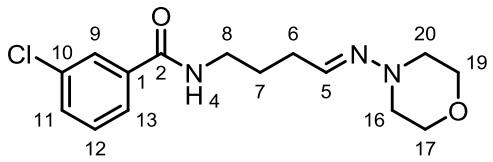
NMR (100 MHz, $CDCl_3$) δ 167.4(C_2), 138.2(C_5), 134.8(C_1), 131.4(2C, $C_{8,12}$), 128.5(2C, $C_{9,11}$), 126.7(C_{10}), 66.3(2C, $C_{16,18}$), 52.3(2C, $C_{15,19}$), 36.8(C_7), 32.5(C_6); **HRMS (ESI^+)** calculated for $C_{14}H_{19}N_3O_2$ $[M+Na]^+$ 284,1375, found 284,1370; **IR (neat) ν_{max}:** 3376, 2919, 1635, 1537, 1452, 1306, 1114, 714, 642.

(*E*)-*N*-(5-(morpholinoimino)pentyl)benzamide (2.164)



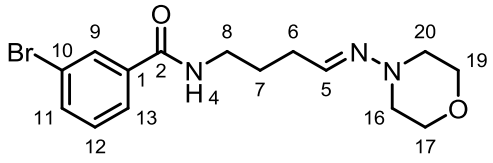
(Colourless oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 8.0 Hz, 2H, $H_{8,12}$), 7.42 (t, *J* = 7.3 Hz, 1H, H_{10}), 7.35 (t, *J* = 7.5 Hz, 2H, $H_{9,11}$), 6.90 (t, *J* = 5.3 Hz, 1H, H_5), 6.17 (s, 1H, H_4), 3.74 (t, *J* = 4.8 Hz, 4H, $H_{16,18}$), 3.41 (q, *J* = 6.9 Hz, 2H, H_7), 2.87 (t, *J* = 4.9 Hz, 4H, $H_{15,19}$), 2.25 (q, *J* = 6.7 Hz, 2H, H_6), 1.66-1.57 (m, 4H, $H_{20,21}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.6(C_2), 140.9(C_5), 134.8(C_1), 131.3(C_{10}), 128.5(2C, $C_{8,12}$), 126.8(2C, $C_{9,11}$), 66.4(2C, $C_{16,18}$), 52.4(2C, $C_{15,19}$), 39.8(C_7), 32.5(C_{20}), 29.1(C_6), 24.6(C_{21}); **HRMS (ESI^+)** calculated for $C_{16}H_{23}N_3O_2$ $[M+Na]^+$ 312,1686, found 312,1683; **IR (neat) ν_{max}:** 3678, 3312, 2959, 2245, 1777, 1530, 1307, 1091, 863, 731.

(*E*)-3-chloro-*N*-(4-(morpholinoimino)butyl)benzamide (2.165)



(Yellowish oil, 76%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.68 (s, 1H, H_9), 7.59 (d, *J* = 8.0 Hz, 1H, H_{11}), 7.38 (d, *J* = 7.7 Hz, 1H, H_{13}), 7.28 (t, *J* = 7.6 Hz, 1H, H_{12}), 6.94 (t, *J* = 5.0 Hz, 1H, H_5), 6.66 (s, 1H, H_4), 3.75 (t, *J* = 4.9 Hz, 4H, $H_{17,19}$), 3.43 (q, *J* = 6.8 Hz, 2H, H_8), 2.86 (t, *J* = 4.9 Hz, 4H, $H_{16,20}$), 2.32 (q, *J* = 6.7 Hz, 2H, H_6), 1.84-1.76 (m, 2H, H_7); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 166.1(C_2), 140.2(C_5), 136.6(C_{10}), 134.6(C_1), 131.3(C_{11}), 129.8(C_9), 127.2(C_{12}), 125.1(C_{13}), 66.4(2C, $C_{17,19}$), 52.3(2C, $C_{16,20}$), 39.9(C_8), 30.6(C_6), 26.0(C_7); **HRMS (ESI^+)** calculated for $C_{15}H_{20}ClN_3O_2$ $[M+Na]^+$ 332,1142, found 332,1135; **IR (neat) ν_{max}:** 3300, 2855, 1636, 1538, 1451, 1298, 1116, 989, 863, 753.

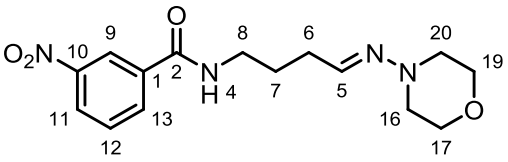
(*E*)-3-bromo-*N*-(4-(morpholinoimino)butyl)benzamide (2.166)



(Yellowish oil, 64%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.83 (s, 1H, H_9), 7.63 (d, *J* = 7.8 Hz, 1H, H_{11}), 7.53 (d, *J* = 8.0 Hz, 1H, H_{13}), 7.21 (t, *J* = 7.9 Hz, 1H, H_{12}), 6.93 (t, *J* = 5.0 Hz, 1H, H_5), 6.72 (s, 1H, H_4), 3.75 (t, *J* = 4.8 Hz, 4H, $H_{17,19}$), 3.42 (q, *J* = 6.7 Hz, 2H, H_8), 2.86 (t, *J* = 4.9 Hz, 4H, $H_{16,20}$), 2.31 (q, *J* = 6.7 Hz, 2H, H_6), 1.83-1.75 (m, 2H,

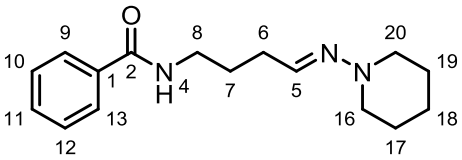
H_7); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 166.0(C_2), 140.2(C_5), 136.8(C_{10}), 134.8(C_1), 130.1(C_9), 129.8(C_{11}), 125.6(C_{13}), 122.6(C_{12}), 66.4(2C, $C_{17,19}$), 52.3(2C, $C_{16,20}$), 39.9(C_8), 30.6(C_6), 26.1(C_7); **HRMS (ESI$^+$)** calculated for $C_{15}H_{20}BrN_3O_2$ $[M+Na]^+$ 376,0637, found 376,0635; **IR (neat) ν_{max}:** 3326, 3049, 2920, 2858, 1652, 1469, 1374, 1275, 1093, 996, 806, 728, 649.

(*E*)-*N*-(4-(morpholinoimino)butyl)-3-nitrobenzamide (2.167)



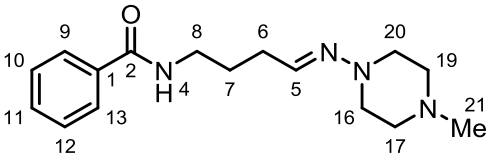
(Yellowish oil, 63%); **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.51 (s, 1H, H_9), 8.28 (d, *J* = 8.3 Hz, 1H, H_{11}) 8.08 (d, *J* = 7.7 Hz, 1H, H_{13}), 7.57 (t, *J* = 8.0 Hz, 1H, H_{12}), 6.96 (t, *J* = 4.8 Hz, 1H, H_5), 6.85 (s, 1H, H_4), 3.73 (t, *J* = 4.8 Hz, 4H, $H_{17,19}$), 3.48 (q, *J* = 6.7 Hz, 2H, H_8), 2.88 (t, *J* = 4.9 Hz, 4H, $H_{16,20}$), 2.35 (q, *J* = 6.9 Hz, 2H, H_6), 1.88-1.80 (m, 2H, H_7); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 165.0(C_2), 148.2(C_{10}), 139.9(C_5), 136.4(C_1), 133.2(C_9), 129.7(C_{11}), 126.0(C_{13}), 121.8(C_{12}), 66.4(2C, $C_{17,19}$), 52.3(2C, $C_{16,20}$), 40.0(C_8), 30.5(C_6), 25.9(C_7); **HRMS (ESI$^+$)** calculated for $C_{15}H_{20}N_4O_4$ $[M+Na]^+$ 343,1382, found 343,1382; **IR (neat) ν_{max}:** 3433, 2971, 2725, 1716, 1590, 1503, 1405, 1166, 1057, 949, 744.

(*E*)-*N*-(4-(piperidin-1-ylimino)butyl)benzamide (2.169)



(Yellowish oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 8.0 Hz, 2H, $H_{9,13}$), 7.40 (t, *J* = 7.4 Hz, 1H, H_{11}), 7.33 (t, *J* = 7.7 Hz, 2H, $H_{10,12}$), 6.89 (t, *J* = 5.2 Hz, 1H, H_5), 6.61 (s, 1H, H_4), 3.43 (q, *J* = 6.7 Hz, 2H, H_8), 2.83 (t, *J* = 5.5 Hz, 4H, $H_{16,20}$), 2.31 (q, *J* = 6.5 Hz, 2H, H_6), 1.83-1.74 (m, 2H, H_7), 1.65-1.57 (m, 4H, $H_{19,17}$), 1.43-1.39 (m, 2H, H_{18}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.4(C_2), 139.1(C_5), 134.9(C_1), 131.3(C_{11}), 128.4(2C, $C_{9,13}$), 126.9(2C, $C_{10,12}$), 52.8(2C, $C_{16,20}$), 39.7(C_8), 30.8(C_6), 26.4(C_7), 25.2(2C, $C_{17,19}$), 24.1(C_{18}); **HRMS (ESI$^+$)** calculated for $C_{16}H_{23}N_3O$ $[M+Na]^+$ 296,1739, found 296,1739; **IR (neat) ν_{max}:** 3306, 2925, 2852, 1639, 1577, 1530, 1451, 1350, 1116, 633.

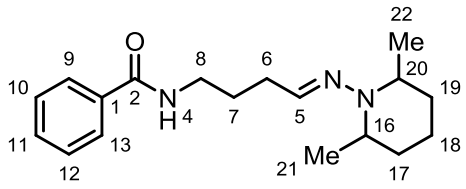
(*E*)-*N*-(4-((4-methylpiperazin-1-yl)imino)butyl)benzamide (2.170)



(Yellow oil, 68%); **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 7.8 Hz, 2H, $H_{9,13}$), 7.42 (t, *J* = 7.3 Hz, 1H, H_{11}), 7.35 (t, *J* = 7.5 Hz, 2H, $H_{10,12}$), 6.90 (t, *J* = 5.2 Hz, 1H, H_5), 6.52 (s, 1H, H_4), 3.44 (q, *J* = 6.3 Hz, 2H, H_8), 2.98-2.90 (m, 4H, $H_{17,19}$), 2.57-2.51 (m, 4H, $H_{16,20}$), 2.32 (q, *J* = 6.8 Hz, 2H, H_6), 2.28 (s, 3H, H_{21}), 1.83-1.75 (m, 2H, H_7);

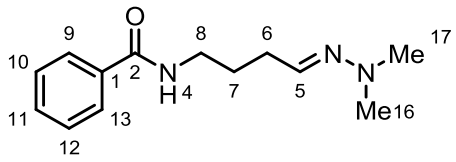
^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.4(C_2), 140.3(C_5), 134.8(C_1), 131.3(C_{11}), 128.4(2C, $C_{9,13}$), 126.8(2C, $C_{10,12}$), 54.3(2C, $C_{17,19}$), 51.9(2C, $C_{16,20}$), 45.7(C_{21}), 39.6(C_8), 30.6(C_6), 24.5(C_7); **HRMS (ESI$^+$)** calculated for $C_{16}H_{24}N_4O$ ([M+H]$^+$): 289,2028, found 289,2022; **IR (neat) ν_{max}:** 3046, 2917, 2803, 2362, 2193, 2013, 1639, 1157, 1076, 801, 733.

(*E*)-*N*-(4-((2,6-dimethylpiperidin-1-yl)imino)butyl)benzamide (2.171)



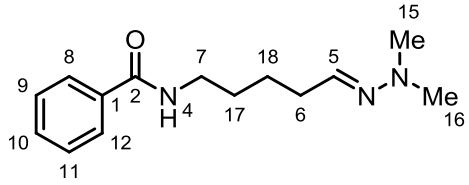
(Brownish oil, 81%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.07 (t, *J* = 5.0 Hz, 1H, H_5), 7.75 (d, *J* = 7.9 Hz, 2H, $H_{9,13}$), 7.40 (t, *J* = 7.5 Hz, 1H, H_{11}), 7.33 (t, *J* = 7.7 Hz, 2H, $H_{10,12}$), 6.98 (s, 1H, H_4), 3.45 (q, *J* = 6.5 Hz, 2H, H_8), 3.21-3.06(m, 2H, $H_{16,20}$), 2.46 (q, *J* = 6.6 Hz, 2H, H_6), 1.90-1.82 (m, 2H, H_7), 1.73-1.62 (m, 6H, $H_{17,18,19}$), 1.06 (s, 6H, $H_{21,22}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.8(C_2), 134.6(C_5), 131.4(2C, $C_{9,13}$), 128.5(2C, $C_{1,11}$), 127.1(2C, $C_{10,12}$), 62.6(2C, C_{1620}), 39.3(C_8), 30.2(3C, $C_{17,19,6}$), 25.4(C_7), 22.7(C_{18}), 18.7(2C, $C_{21,22}$); **HRMS (ESI$^+$)** calculated for $C_{18}H_{27}N_3O$ ([M+H]$^+$): 302,2232, found 302,2240; **IR (neat) ν_{max}:** 3320, 2922, 2859, 1643, 1530, 1470, 1275, 1116, 1092, 995, 863, 722, 649.

(*E*)-*N*-(4-(2,2-dimethylhydrazono)butyl)benzamide (2.172)



(Colourless oil, 86%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 7.5 Hz, 2H, $H_{9,13}$), 7.40 (t, *J* = 7.5 Hz, 1H, H_{11}), 7.34 (t, *J* = 7.5 Hz, 2H, $H_{10,12}$), 6.60 (t, *J* = 5.4 Hz, 1H, H_5), 6.57 (s, 1H, H_4), 3.42 (q, *J* = 6.5 Hz, 2H, H_8), 2.65 (s, 6H, $H_{16,17}$), 2.29 (q, *J* = 7.1 Hz, 2H, H_6), 1.81-1.73 (m, 2H, H_7); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.5(C_2), 137.5(C_5), 134.8(C_1), 131.1(C_{11}), 128.5(2C, $C_{9,13}$), 127.0(2C, $C_{10,12}$), 43.3(2C, $C_{16,17}$), 39.6(C_8), 30.5(C_6), 26.8(C_7); **HRMS (ESI$^+$)** calculated for $C_{13}H_{19}N_3O$ [M+Na]$^+$ 256,1426, found 256,1420; **IR (neat) ν_{max}:** 3321, 2941, 2856, 1642, 1578, 1444, 1309, 1251, 1187, 1037, 804, 748, 715, 695.

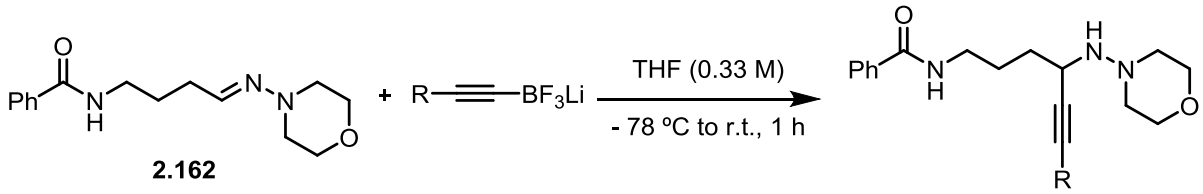
(*E*)-*N*-(5-(2,2-dimethylhydrazono)pentyl)benzamide (2.175)



(Colourless oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 8.1 Hz, 2H, $H_{8,12}$), 7.41 (t, *J* = 7.7 Hz, 1H, H_{10}), 7.34 (t, *J* = 7.3 Hz, 2H, $H_{9,11}$), 6.57 (t, *J* = 5.7 Hz, 1H, H_5), 6.25 (s, 1H, H_4), 3.40 (q, *J* = 6.8 Hz,2H, H_7), 2.64 (s, 6H, $H_{15,16}$), 2.22 (q, *J* = 7.0 Hz,2H, H_6), 1.65-1.48 (m, 4H, $H_{17,18}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.7(C_2), 138.5(C_5), 135.2(C_1), 131.1(C_{10}), 128.6(2C, $C_{8,12}$), 127.1(2C,

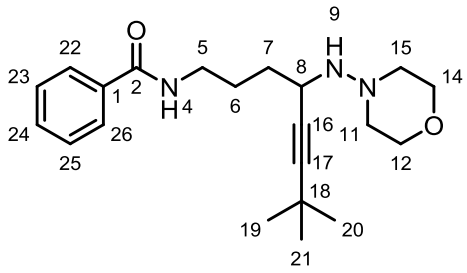
$C_{9,13}$), 43.3(2C, $C_{15,16}$), 39.9(C_7), 32.5(C_6), 29.1(C_{17}), 25.1(C_{18}); **HRMS (ESI$^+$)** calculated for $C_{14}H_{21}N_3O$ $[M+Na]^+$ 270,1582, found 270,1578; **IR (neat) ν_{max}:** 3319, 2936, 2856, 1639, 1578, 1488, 1444, 1307, 1251, 1182, 1030, 804, 748, 715, 695.

3.4.11 General procedure for the functionalisation of hydrazones:



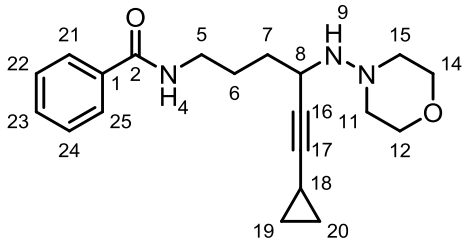
The corresponding terminal alkyne (5 equiv.) was dissolved in dry THF (0.33 M) and the mixture was cooled down to -78 ºC. *n*-BuLi (6 equiv., 2.5 M in hexane) was then added and the mixture was stirred for 20 min at the same temperature. Then, $BF_3.OEt_2$ (5 equiv.) was added dropwise and the mixture was allowed to stir at -78 ºC for additional 30 min. The hydrazone **2.162** (1 equiv.) was then added and the reaction mixture was stirred at -78 ºC for another 1 hour. The mixture was warmed up to room temperature, quenched with a saturated aqueous solution of NH_4Cl (10 ml), extracted with DCM (3 x 10 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (heptane/ethyl acetate/methanol: 1/1/0 to 1/1/0.1) affords the desired compounds 1,4 diamines.

***N*-(7,7-dimethyl-4-(morpholinoamino)oct-5-yn-1-yl)benzamide (2.178)**



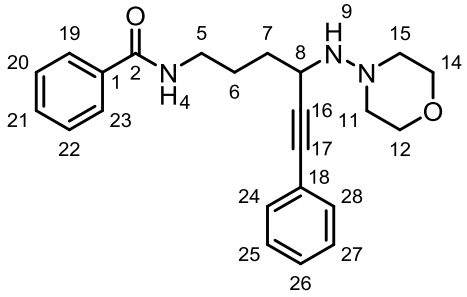
(Yellowish oil, 71%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 8.1 Hz, 2H, $H_{22,26}$), 7.41 (t, *J* = 7.3 Hz, 1H, H_{24}), 7.35 (t, *J* = 7.7 Hz, 2H, $H_{23,25}$), 6.44 (s, 1H, H_4), 3.64-3.59 (m, 4H, $H_{12,14}$), 3.59-3.56 (m, 1H, H_8), 3.53-3.43 (m, 1H, H_5), 3.42-3.31 (m, 1H, H_5), 2.78-2.70 (m, 2H, H_{11}), 2.60-2.51 (m, 2H, H_{15}) 1.77-1.58 (m, 4H, $H_{6,7}$), 1.11 (s, 9H, $H_{19,20,21}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.5(C_2), 135.1(C_1), 131.5(C_{24}), 128.6(2C, $C_{22,26}$), 126.8(2C, $C_{23,25}$), 93.4(C_{16}), 79.2(C_{17}), 67.1(2C, $C_{12,14}$), 57.2(2C, $C_{11,15}$), 49.9(C_{18}), 40.0(C_8), 32.1(C_5), 31.2(3C, $C_{19,20,21}$), 26.0(C_6); **HRMS (ESI$^+$)** calculated for $C_{21}H_{31}N_3O_2$ $[M+H]^+$ 358,2495, found 358,2489; **IR (neat) ν_{max}:** 3052, 2969, 2862, 2203, 1650, 1579, 1535, 1488, 1455, 1364, 1203, 1112, 893, 737, 631.

***N*-(6-cyclopropyl-4-(morpholinoamino)hex-5-yn-1-yl)benzamide (2.179)**



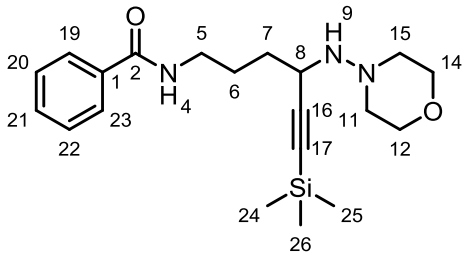
(Colourless oil, 66%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 7.8 Hz, 2H, $H_{21,25}$), 7.42 (t, *J* = 7.3 Hz, 1H, H_{23}), 7.35 (t, *J* = 7.7 Hz, 2H, $H_{22,24}$), 6.37 (s, 1H, H_4), 3.64-3.58 (m, 4H, $H_{12,14}$), 3.57-3.53 (m, 1H, H_8), 3.51-3.33 (m, 2H, H_5), 2.76-2.68 (m, 2H, H_{11}), 2.58-2.48 (m, 2H, H_{15}), 1.76-1.55 (m, 4H, $H_{6,7}$), 1.16-1.09 (m, 1H, H_{18}), 0.69-0.62 (m, 2H, H_{19}), 0.56-0.51 (m, 2H, H_{20}); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 168.1(C_2), 135.5(C_1), 131.8(C_{23}), 129.1(2C, $C_{21,25}$), 127.5(2C, $C_{22,24}$), 88.3(C_{16}), 76.3(C_{17}), 67.5(2C, $C_{12,14}$), 57.8(2C, $C_{11,15}$), 50.2(C_8), 40.3(C_5), 32.5(C_6), 26.4(C_{18}), 8.6(2C, $C_{19,20}$); **HRMS (ESI$^+$)** calculated for $C_{20}H_{27}N_3O_2$ ($[M+H]^+$): 342,2182, found 342,2176; **IR (neat) ν_{max}:** 3312, 2926, 2857, 2241, 1635, 1577, 1538, 1488, 1361, 1272, 1110, 1028, 876, 805, 696, 669.

***N*-(4-(morpholinoamino)-6-phenylhex-5-yn-1-yl)benzamide (2.180)**



(Yellow oil, 46%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.68 (d, *J* = 8.1 Hz, 2H, $H_{19,23}$), 7.40 (t, *J* = 7.7 Hz, 1H, H_{21}), 7.36-7.28 (m, 4H, H_{Ar}), 7.23-7.20 (m, 3H, H_{Ar}), 6.31 (s, 1H, H_4), 3.84 (s, 1H, H_9), 3.67-3.60 (m, 4H, $H_{12,14}$), 3.54-3.40 (m, 2H, H_{11}), 2.82-2.77 (m, 2H, H_{15}), 2.67-2.58 (m, 2H, H_5), 1.87-1.70 (m, 4H, $H_{6,7}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.5(C_2), 134.1(2C, C_{Ar}), 132.1(C_{Ar}), 131.6(3C, C_{Ar}), 128.1(C_{Ar}), 128.2(3C, C_{Ar}), 126.8(C_{Ar}), 122.9(C_{Ar}), 90.3(C_{17}), 84.3(C_{16}), 67.1(2C, $C_{12,14}$), 57.6(2C, $C_{11,15}$), 50.4(C_8), 39.7(C_5), 31.8(C_7), 26.1(C_6); **HRMS (ESI$^+$)** calculated for $C_{23}H_{27}N_3O_2$ ($[M+H]^+$): 378,2182, found 378,2176; **IR (neat) ν_{max}:** 3311, 3056, 2924, 2856, 1637, 1601, 1537, 1444, 1180, 1070, 1027, 916, 803, 733, 693.

***N*-(4-(morpholinoamino)-6-(trimethylsilyl)hex-5-yn-1-yl)benzamide (2.182)**



(Yellowish oil, 60%), **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.9 Hz, 2H, $H_{19,23}$), 7.35 (t, *J* = 7.7 Hz, 1H, H_{21}), 7.29 (t, *J* = 7.8 Hz, 2H, $H_{20,22}$), 6.26 (s, 1H, H_4), 3.59-3.51 (m, 4H, $H_{12,14}$), 3.44-3.29 (m, 2H, H_5), 2.72-2.63 (m, 2H, H_{11}), 2.55-2.46 (m, 2H, H_{15}), 1.71-1.52 (m, 4H, $H_{6,7}$), 0.01 (s, 9H, $H_{24,25,26}$); **^{13}C-NMR (100 MHz, $CDCl_3$)** δ 167.3(C_2), 135.1(C_1), 131.4(C_{21}), 128.7(2C, $C_{19,23}$), 127.2(2C, $C_{20,22}$), 93.5(C_{17}), 89.0(C_{16}), 67.2(2C, $C_{12,14}$), 57.4(2C, $C_{11,15}$), 50.4(C_8), 39.7(C_5), 31.8(C_7), 26.1(C_6), 0.17(3C, $C_{24,25,26}$); **HRMS (ESI$^+$)**

calculated for $C_{20}H_{31}N_3O_2Si$ ($[M+H]^+$): 374,2264, found 374,2250; **IR (neat) ν_{max}:** 3302, 3054, 2958, 2857, 2163, 1639, 1578, 1450, 1362, 1305, 1264, 111, 1027, 1009, 843, 733, 699, 637.

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5. Curriculum Vitae

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Publications

1. S. Shaaban, V. Tona*, B. Peng*, N. Maulide, *Angew. Chem. Int. Ed.* **2017**, *56*, 10938.
2. G. Di Mauro, B. Maryasin, D. Kaiser, S. Shaaban, L. González, N. Maulide, *Org. Lett*. **2017**, *19*, 3815.
3. D. Kaiser*, A. De la Torre*, S. Shaaban, N. Maulide, *Angew. Chem. Int. Ed.* **2017,** *56*, 5921.
4. S. Shaaban, N. Maulide, *Synlett* **2017,** *28,* A-G.
5. L. Xie*, S. Shaaban*****, N. Maulide, *Angew. Chem. Int. Ed.* **2016,** *55***,** 12864.
6. V. Tona, S. Ruider, M. Berger, S. Shaaban*****, M. Padmanaban*, L. Xie, L. Gonzalez, N. Maulide, *Chem. Sci*. **2016**, *7*, 6032.
7. S. Shaaban, J. Oh, N. Maulide, *Org. Lett*. **2016**, *18*, 345.
8. S. Shaaban, A. Roller, N. Maulide, *Eur. J. Org. Chem*. **2015**, 7643.
9. S. Shaaban, A. Jolit, D. Petkova, N. Maulide, *Chem. Commun*. **2015**, *51*, 13902.
10. S. Shaaban, B. Peng, N. Maulide, *Synlett* **2013**, *24*, 1722.

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Languages

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Conferences & Awards

- Poster presentation at "JCF 2015" in Münster, Germany
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