Methodology Development for the Electrophilic Aromatic Amination of Secondary Amides

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

The intramolecular electrophilic aromatic amination of secondary amides was developed. Secondary *N*-methoxy and *N*-*p*-methoxyphenyl amides were cyclized to oxindoles by triflic anhydride mediated electrophilic activation and subsequent oxidation with a pyridine *N*-oxide derivative. The electrophilic nitrogen species for the *N*-methoxy amide was isolated and characterized. Aryl tethered 2-amidopyridine- and 2-amidopyrimidine *N*-oxides were additionally discovered to be synthetically valuable sources of electrophilic nitrogen under mild conditions following a simple activation protocol of triflic anhydride and tertiary amine base.

Acknowledgements

The author wishes to thank the following people throughout their time at the University of Waterloo. First, I would like to greatly thank my supervisor Professor Eric Fillion who has provided me with inspiration and guidance over the past two years. You have always made yourself available when I needed help and I am very grateful for that. I would also like to thank my committee members Professor Michael Chong and Professor Graham Murphy for their time on my committee.

A special thanks to all the past members of the Fillion group including Steven, Meijing, Amir, Ryan, Alyssa, and Emma who have made my time in the lab much more enjoyable.

To the 3rd floor chemists, especially Ryan, Fabio, and Avery, thank you for answering all my chemistry questions and more importantly, thank you for the friendship during my time here at Waterloo. I hope we continue to golf next summer!

Thanks to the NMR manager Jan Venne who has helped me tremendously with many NMR experiments over the past two years.

Finally, to all the special people in my life who are non-work-related but have helped me tremendously well beyond the past two years. My parents Mom, Dad, and Liam who have always believed in me and supported me through every step of my life, I cannot thank you guys enough. To my sisters Ashleigh, Kayleigh, Amanda, and Nicole, thank you for all the good times and making the past two years fly by. To my girlfriend Cassandra, thank you for your companionship and encouraging me to pursue graduate school, I couldn't have done it without you by my side.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

2-ClPy	2-chloropyridine
2-FPy	2-fluoropyridine
AcOH	acetic acid
Ar	aryl/aromatic
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMSO	dimethyl sulfoxide
eq/equiv	equivalents
EtOAc	ethyl acetate
h	hour, hours
HFIP	hexafluoroisopropanol
LAH	lithium aluminum hydride
LNO	2,6-lutidine *N*-oxide
MeCN	acetonitrile
min	minutes
mp	melting point
NEt_3	triethylamine
NMO	*N*-methylmorpholine *N*-oxide
OAc	acetate
OTf	triflate
Ph	phenyl
PIDA	phenyliodine(III) diacetate
PIFA	(bis(trifluoroacetoxy)iodo)benzene
PNO	pyridine *N*-oxide
rt	room temperature
Tf	triflyl
Tf_2O	trifluoromethanesulfonic anhydride, triflic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

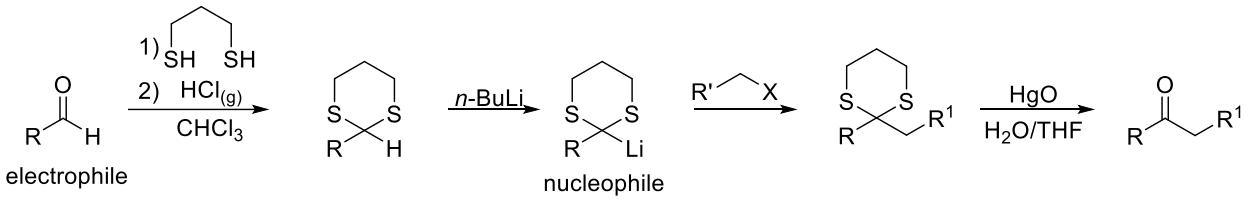
Abbreviations for multiplicities of NMR signals

bs	broad singlet
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dt	doublet of triplets
m	multiplet
q	quartet
s	singlet
t	triplet
td	triplet of doublets

List of Schemes

1. Introduction

Umpolung chemistry, originally described by Corey and Seebach,[1,2] is a synthetic methodology that requires modification of a functional group to reverse its inherent polarity. A classic textbook umpolung method is the Corey-Seebach reaction of lithiated 1,3-dithianes, synthetic equivalents of acyl anion synthons, with electrophiles such as alkyl halides (Scheme 1).



Scheme 1: Corey-Seebach Reaction of Lithiated 1,3-Dithianes.

The formation of carbon-nitrogen bonds using umpolung strategies has provided alternative methods and therefore new opportunities for the construction of pharmaceutically relevant heteroaromatic scaffolds.[3] In particular, carbon-nitrogen bond formation by electrophilic aromatic amination has been used for the preparation of biologically relevant such as benzodiazepine derivatives.[4]

The goal of this project was to develop new umpolung carbon-nitrogen bond formation methodologies for electrophilic aromatic aminations of secondary amides. It was proposed that this may be achieved by electrophilic activation of secondary amides with triflic anhydride followed by oxidation with a pyridine *N*-oxide derivative to form an electrophilic nitrogen center.

2. Literature Review

2.1 Electrophilic Amination of Amides via Nitrenium Ions

Trivalent nitrogen (sp^3) atoms in their natural form are nucleophiles, owing to their electronegativity and lone pair of electrons. Umpoled nitrogen species are electron deficient and consequently act as electrophiles. For example, nitrenium ions are divalent electrophilic nitrogen species that carry a positive charge and may exist in the singlet or triplet state (Figure 1).[5] The inherent instability of nitrenium ions may be overcome by the presence neighbouring groups that delocalize the positive charge on the nitrogen atom. Some examples of these functional groups are *N*-aryl and *N*-alkoxy groups. The presence of such stabilizing groups prolongs the lifetime of

highly reactive nitrenium ions allowing them to be versatile synthetic intermediates for electrophilic aminations. Despite the large body of literature regarding organometallic based electrophilic amination methods[6], the scope of this section will focus on metal free methodologies.

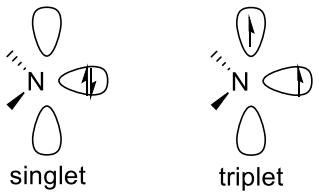


Figure 1: Nitrenium ions in the Singlet and Triplet State.

2.1.1 *N*-Acyl-*N*-Alkoxy Nitrenium Ions

Electron releasing alkoxy groups were anticipated to be suitable *N*-substituents to stabilize nitrenium ions by delocalizing the charge (Figure 2).

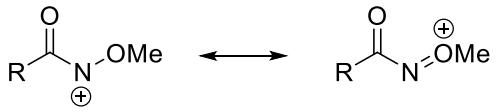
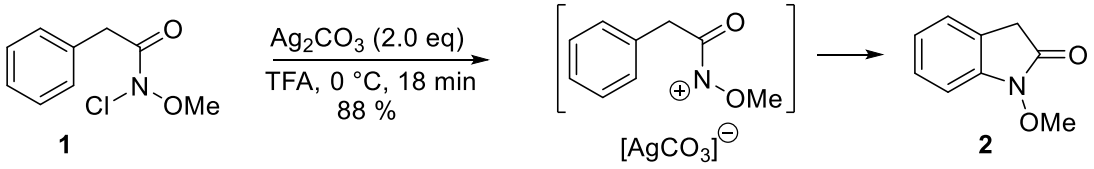
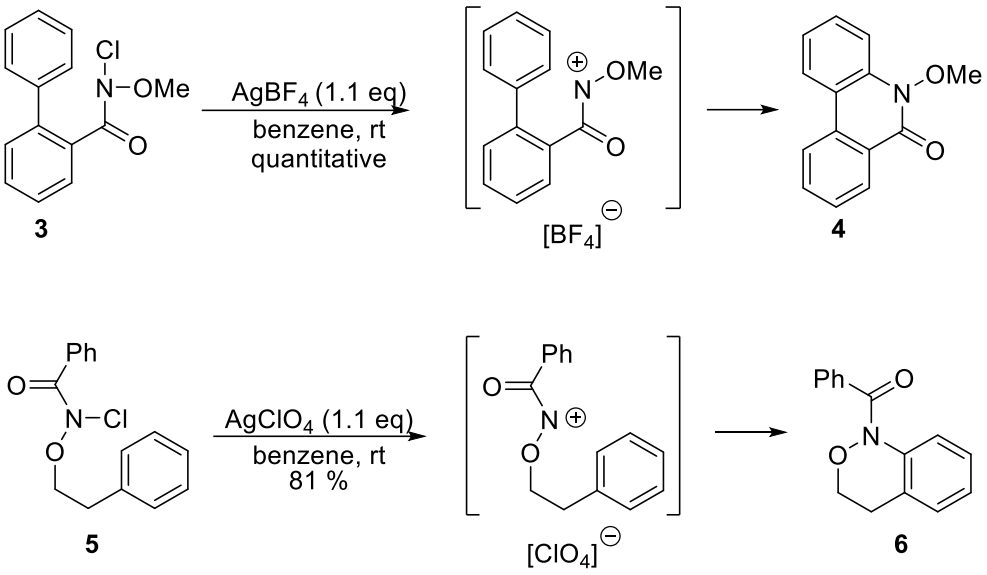


Figure 2: Stabilization of *N*-Acyl-*N*-Methoxy Nitrenium Ion.

Nitrenium ions of the *N*-acyl-*N*-methoxy type were first reported by Kikugawa[7] and Glover,[8] independently. Kikugawa and co-workers found that addition of silver carbonate to aryl-tethered *N*-chloro-*N*-methoxy amide **1** afforded cyclized *N*-methoxy oxindole **2** (Scheme 2). Glover and co-workers similarly found silver tetrafluoroborate and silver perchlorate to be ideal reagents for electrophilic amination of aryl tethered *N*-chloro-*N*-methoxy amides **3** and **5** to cyclized adducts **4** and **6**, respectively (Scheme 3). These researchers suggested a novel *N*-acyl-*N*-methoxy nitrenium ion to be the electrophilic nitrogen intermediate achieved through silver(I) ion provoked heterolysis of the nitrogen-chlorine bond.

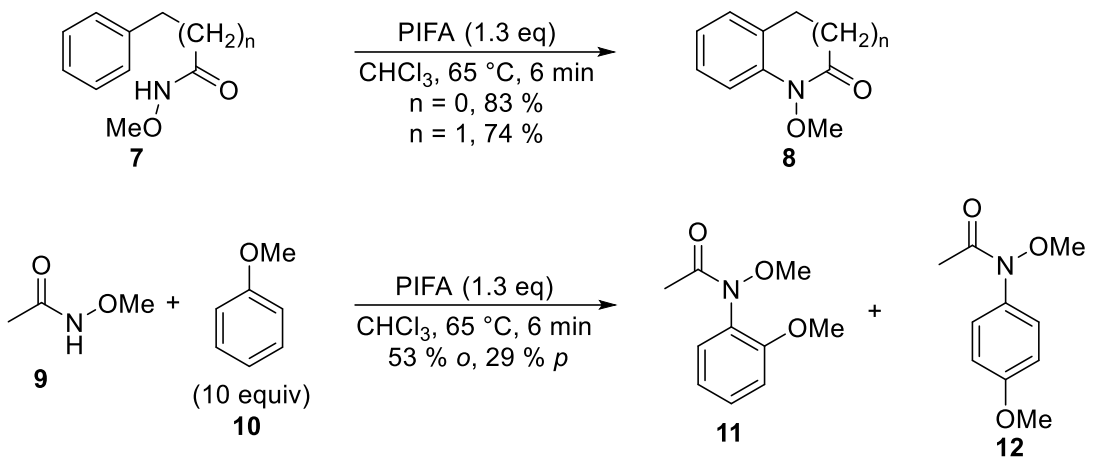


Scheme 2: Kikugawa's Electrophilic Amination of a *N*-Chloro-*N*-Methoxy Amide.



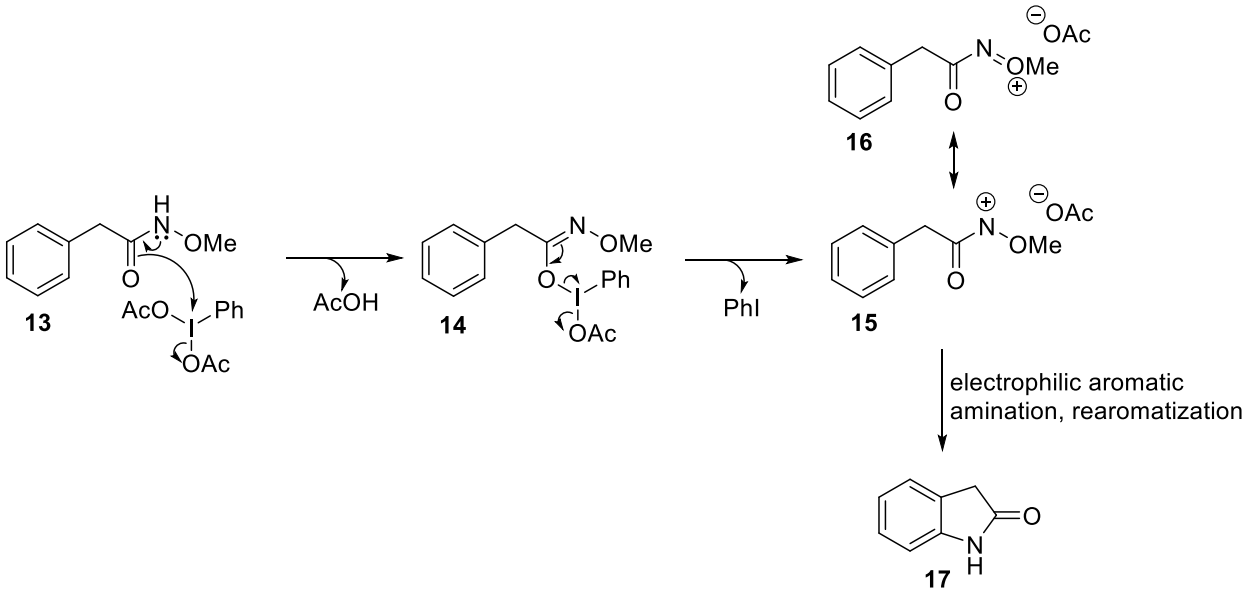
Scheme 3: Glover's Electrophilic Amination of *N*-Chloro-*N*-Alkoxy Amides.

A drawback of this method is the requirement of toxic chlorinating reagents such as *tert*-butyl hypochlorite to convert secondary *N*-alkoxy amides to *N*-chloro-*N*-alkoxy amides. Kikugawa and co-workers were able to avoid *N*-chloro-*N*-methoxy amides altogether when they discovered that secondary *N*-methoxy amides were directly converted to electrophilic nitrogen species with the hypervalent iodine (HVI) reagent (bis(trifluoroacetoxy)iodo)benzene (PIFA).[9] Addition of 1.3 equivalents of PIFA to secondary *N*-methoxy amides **7** with a 1- or 2-carbon phenyl tether gave the 5- or 6-membered *N*-heterocycles **8** in good yields (Scheme 4). Intermolecular electrophilic amination of *N*-methoxyacetamide **9** with excess anisole **10** was also achieved and gave a mixture of ortho product **11** and para product **12** in 53 % and 29 % yields, respectively (Scheme 4).



Scheme 4: Kikugawa's Electrophilic Amination of *N*-Methoxy Amides with HVI Reagent PIFA.

Although the mechanism is still debated in the literature, a plausible pathway is presented in Scheme 5.[10] The mechanism begins by ligand exchange at the iodine(III) center with *N*-methoxy amide **13** to give intermediate **14**. Reductive elimination of monovalent iodobenzene provides N-acyl-N-methoxy nitrenium ion **15**, in resonance with structure **16**, both of which are suitable for electrophilic aromatic amination to provide oxindole **17**.



Scheme 5: Speculative Mechanism for the Generation of a *N*-Acyl-*N*-Methoxy Nitrenium Ion with HVI.

Since Kikugawa's original publication, iodine (III) promoted electrophilic aminations of N-acyl-N-alkoxy secondary amides have received great attention in preparative organic chemistry.[10]

2.1.2 *N*-Acyl-*N*-Aryl Nitrenium Ions

Comparable to the alkoxy groups, aryl groups can stabilize nitrenium ions by delocalizing the positive charge throughout the aromatic ring and as a result, substitutions may occur on the nitrogen atom or aromatic ring (Figure 3). The focus for this section will be on substitutions at the nitrogen atom.

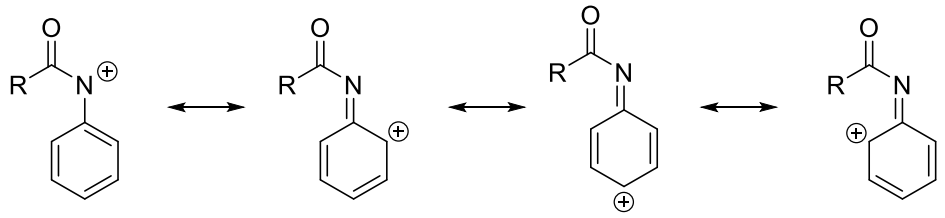
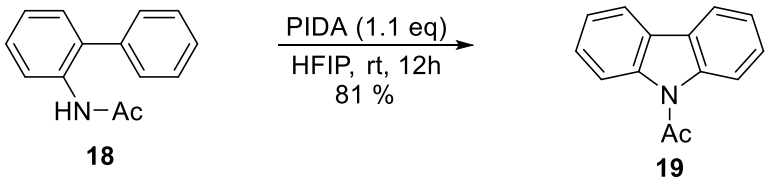
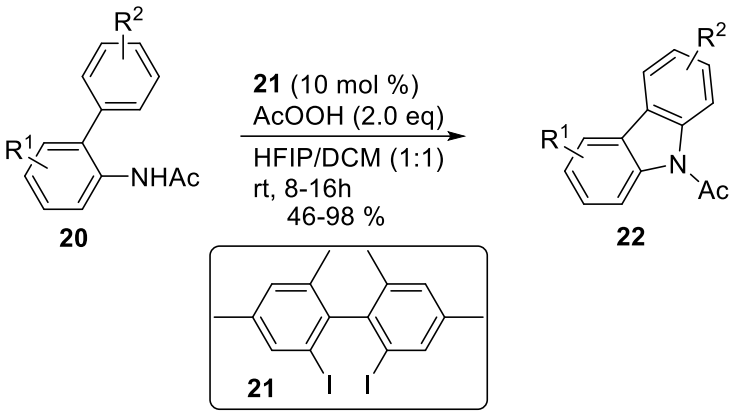


Figure 3: Stabilization of *N*-Acyl-*N*-Aryl Nitrenium Ion.

Antonchick and co-workers[11] prepared *N*-acetylcarbazole **19** from 2-acetaminobiphenyl **18** with stoichiometric quantities of phenyliodine(III) diacetate (PIDA) via a *N*-acyl-*N*-aryl nitrenium ion (Scheme 6). Interestingly, these researchers also developed an organocatalytic method using diiodo-biphenyl derivative **21** (10 mol %) and 2 equivalents of peracetic acid to transform various 2-acetaminobiphenyls **20** into the corresponding *N*-acetylcarbazoles **22** (Scheme 7). Highest yields of **22** were obtained when R^2 on **20** contained an electron donating group.

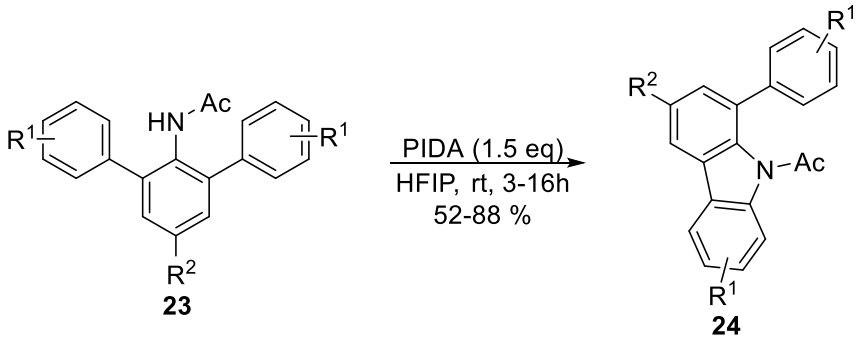


Scheme 6: Electrophilic Aromatic Amination of 2-Acetaminobiphenyl with PIDA.



Scheme 7: Organocatalytic Electrophilic Aromatic Aminations of 2-Acetaminobiphenyl Derivatives.

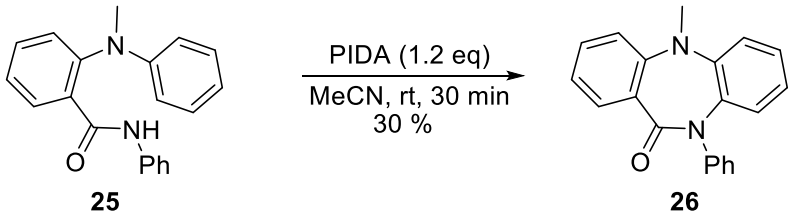
The same group of researchers also applied their methodology for the preparation of 1-aryl carbazoles **24**, a relevant motif in natural products hyellazole and 6-chlorohyellazole.[12] Symmetric diarylacetanilides **23** containing electron-donating or withdrawing groups were treated with a slight excess of PIDA, found to be more suitable than their previously developed organocatalytic method, and provided 1-aryl carbazoles **24** in up to 88 % yield when R^2 contained a chloro substituent (Scheme 8). Similarly, if R^1 was substituted with *p*-chloro or *p*-fluoro substituents on **23** the reaction proceeded smoothly affording **24** in 76 % and 73 % yields, respectively. A significant reduction in yield to 52 % was apparent when R^1 consisted of *p*-Me groups.



Scheme 8: Electrophilic Aromatic Amination of Diarylacetanilides with PIDA.

Construction of 1,4-benzodiazepine derivatives, a scaffold present in biologically active benzodiazepines and thienodiazepines, was likewise achievable though *N*-acyl-*N*-aryl nitrenium intermediacy and reported by the Zhao group. The researchers found that *N*-Ph amide **25** in the

presence of PIDA underwent intramolecular electrophilic aromatic amination in 30 % yield to give **26** (Scheme 9).[4]

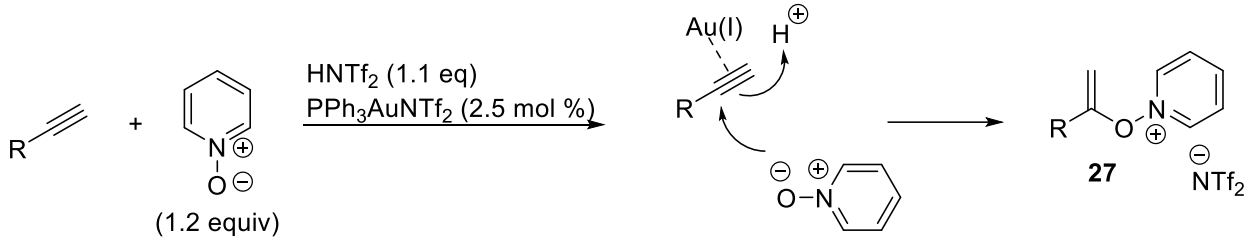


Scheme 9: Synthesis of 1,4-Benzodiazepine Scaffold by Electrophilic Aromatic Amination.

2.2 Umpoled Enolate Species

2.2.1 Umpolung Enolates by Oxidation of Terminal Alkynes

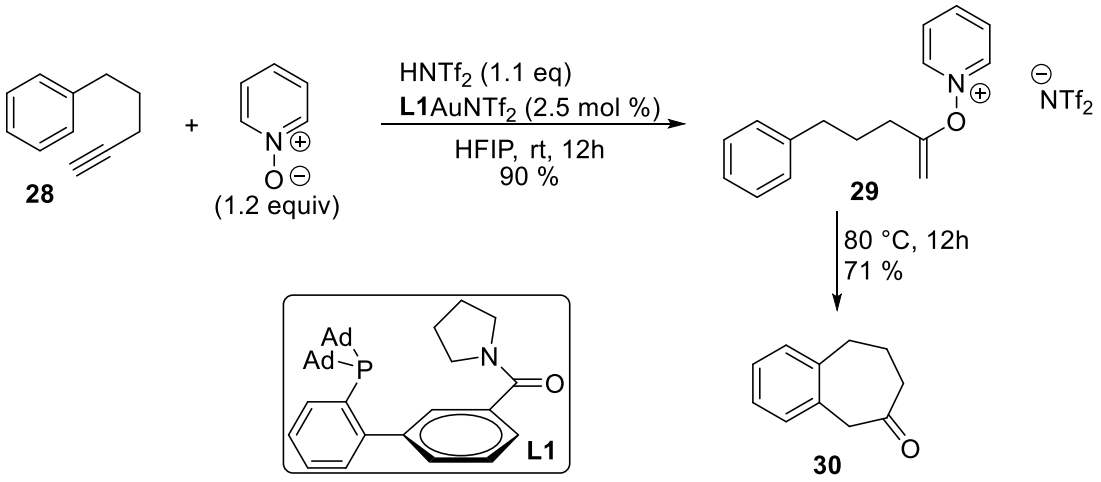
Enolates are one of the most versatile C-nucleophiles for organic chemists in carbon-carbon bond forming reactions. The aldol condensation and Claisen condensation are classic examples where enolates are employed as C-nucleophiles. Umpoled enolates, namely *N*-alkenoxypyridinium salts **27**, have recently been of great interest in the literature as they allow for the formation of α-aryl or α-heteroatom ketones that are indeed difficult to obtain through traditional methods.[13] Activation of terminal alkynes with a gold(I) catalyst, commonly PPh_3AuNTf_2, followed by oxidation with pyridine *N*-oxide (PNO) derivatives in the presence of stoichiometric strong acids permit the formation of *N*-alkenoxypyridinium salts **27** (Scheme 10). Conveniently, *N*-alkenoxypyridinium salts are usually isolable and thus can be prepared and used directly.



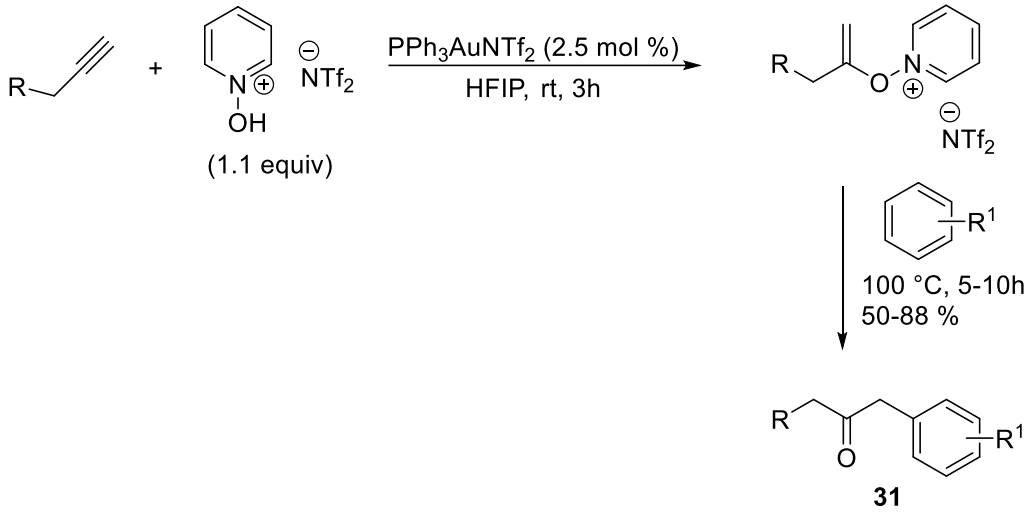
Scheme 10: Preparation of *N*-Alkenoxypyridinium Salts.

Intramolecular Friedel-Crafts type cyclization of *N*-alkenoxypyridinium salts was achieved by Zhang and co-workers with 5-phenylpent-1-yne **28**. Activation of **28** with gold catalysis in the presence of stoichiometric PNO and bistriflimide afforded **29** in 90 % NMR yield. Subsequent heating of **29** at 80 °C in hexafluoroisopropanol (HFIP) gave the benzene-fused cycloheptanone

30 in 71 % overall yield (Scheme 11).[14] Interestingly, benzene tethered propargyl ethers were also efficient as substrates and allowed the formation of more challenging eight-membered rings. Intermolecular arylation of umpoled enolates was also feasible with a wide variety of hetero(arenes) for the formation of α-(hetero)aryl ketones **31** as demonstrated by Xu and co-workers (Scheme 12).[15]

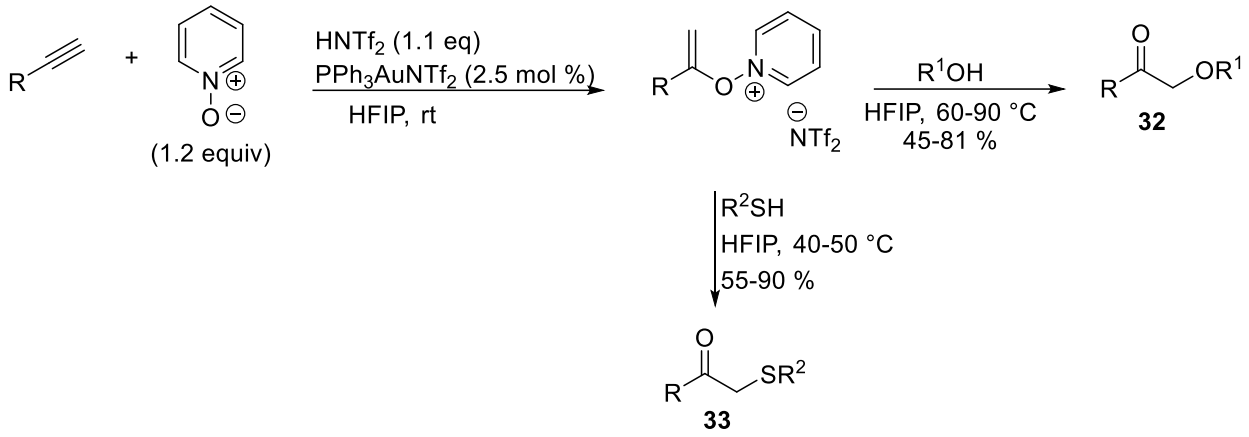


Scheme 11: Preparation of Benzene-fused Cycloheptanone via *N*-Alkenoxypyridinium Salts.

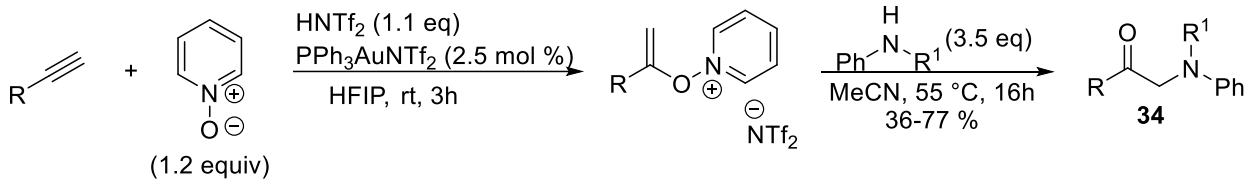


Scheme 12: Preparation of α-(Hetero)aryl Ketones via *N*-Alkenoxypyridinium Salts.

Heteroatom nucleophiles such as alcohols, thiols, and amines react efficiently with *N*-alkenoxypyridinium salts as well providing α-alkoxy (**32**), α-thio (**33**), and α-amino (**34**) ketones, respectively (Schemes 13, 14).[16, 17]

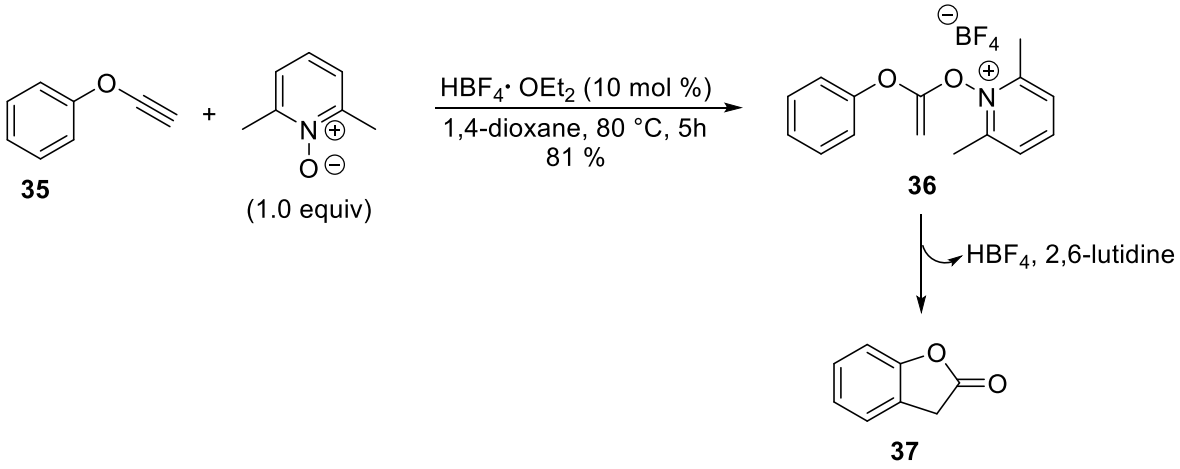


Scheme 13: Preparation of α-Alkoxy and α-Thio Ketones via *N*-Alkenoxypyridinium Salts.



Scheme 14: Preparation of α-Amino Ketones via *N*-Alkenoxypyridinium Salts.

Interestingly, transition metal-free methodologies have also been reported for the preparation of benzofuranone derivative **37** in 81 % yield from aryl alkynyl ether **35**.[18] The reaction proceeded under relatively mild conditions with catalytic amounts of $HBF_4 \cdot OEt_2$ and stoichiometric oxidant 2,6-dimethyl pyridine *N*-oxide (2,6-lutidine *N*-oxide, LNO). The researchers speculated that protonation of the activated alkyne **35** followed by oxidation with LNO formed the umpoled intermediate **36** that was able to cyclize with the loss of 2,6-lutidine and regeneration of the HBF_4-diethyl etherate catalyst (Scheme 15).



Scheme 15: Metal-free Formation of Benzofuranone via *N*-Alkenoxypyridinium Salt.

Therefore, *N*-alkenoxypyridinium salts are excellent umpoled enolate sources and can be generated in the absence of metal catalysts. Their ease of preparation, inherent stability, and versatile inter- and intramolecular nucleophilic coupling partners make them a powerful synthetic intermediate for the preparation of an array of α-substituted ketones.

2.2.2 Umpolung Enolonium Species

Amides are among the least reactive of the carboxylic acid derivatives owing to nitrogen lone pair donation onto the carbonyl carbon effectively reducing its electrophilicity. In effort to increase the electrophilicity of the amide carbonyl, trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O) as an activating reagent has been of great interest. Treatment of amides with triflic anhydride affords a highly electrophilic iminium triflate species **38** that has provided organic chemists with a broad scope of possible transformations (Figure 4).[19]

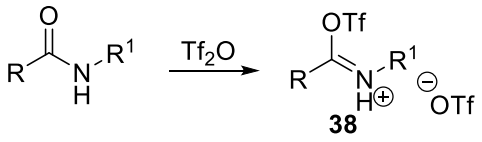
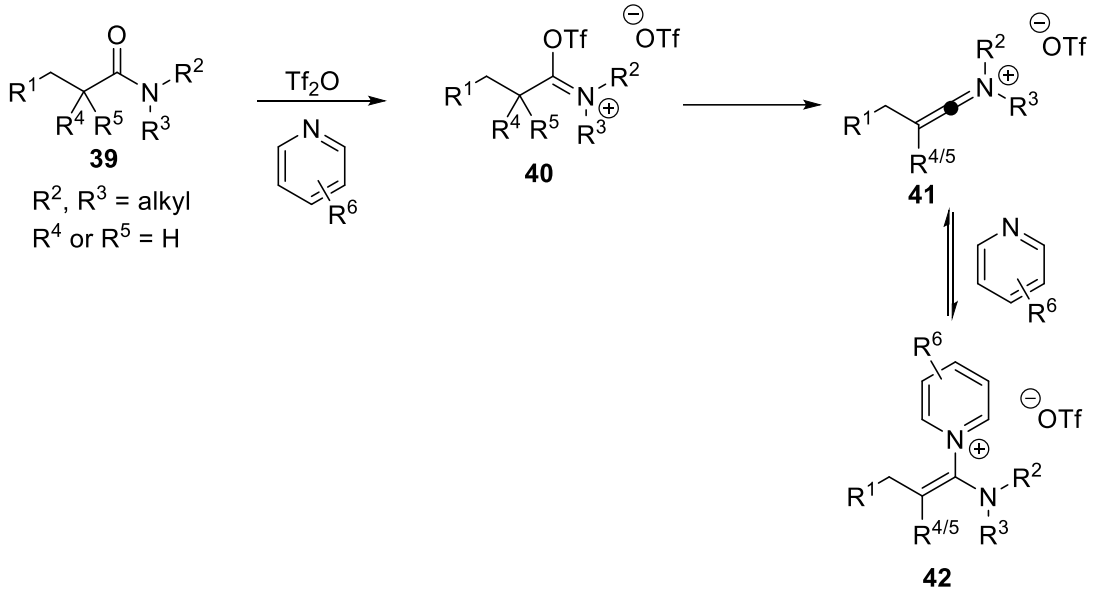


Figure 4: Amide Activation with Triflic Anhydride.

To understand the possibilities and limitations of triflic anhydride mediated amide activation, the mechanism must be well-understood as the structure of the amide greatly influences the mechanistic pathway. Pioneering spectroscopic studies (IR and NMR) by Charette[20], Maulide[21],

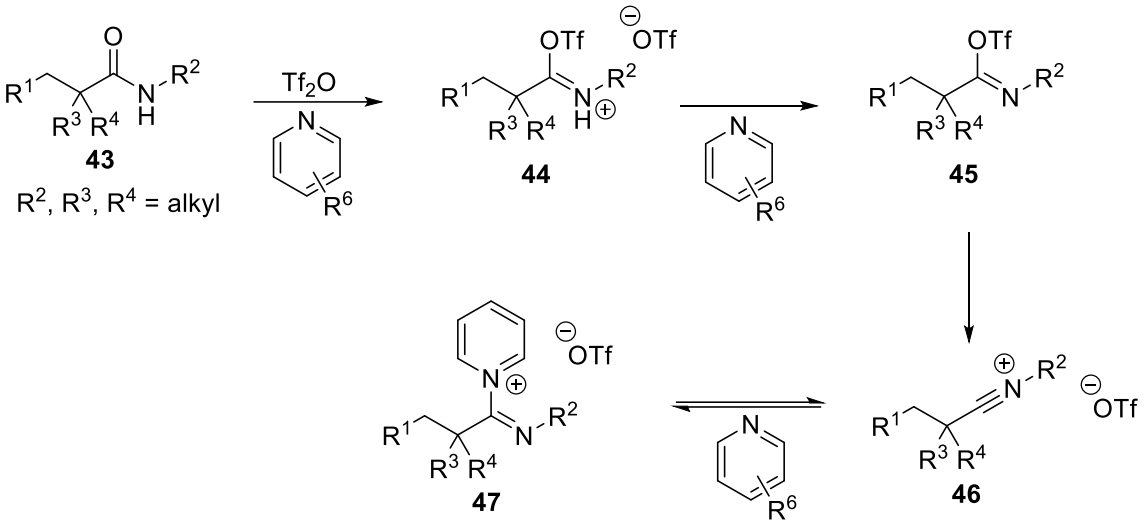
and Movassaghi[22] have elucidated the mechanistic pathway in great detail for the activation of amides with triflic anhydride in the presence of non-nucleophilic pyridine and amine bases.

The activation pathway for tertiary amide **39** with α-enolizable protons begins by triflation of the amide oxygen atom affording iminium triflate **40**, often through a pyridinium triflate intermediate (depending on the pyridine substituents, Scheme 16). Abstraction of an α-proton (R^4/R^5) on **40** yields keteniminium **41** that may combine with the pyridine base giving ketene-aminal **42** which lies in equilibrium with **41**.



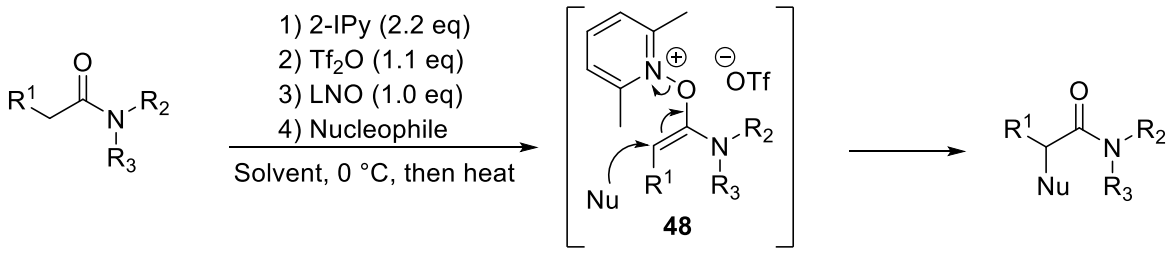
Scheme 16: Mechanistic Pathway for the Activation of a Tertiary Amide with α-Enolizable Protons.

With respect to a secondary amide lacking α-enolizable protons (**43**) the pathway begins similarly by triflation of the amide oxygen atom affording iminium triflate **44** (Scheme 17). The acidic nitrogen proton is then removed by the pyridine base furnishing imidoyl triflate **45** which may eliminate the triflate group to give nitrilium ion **46**. Nucleophilic attack of the pyridine base onto nitrilium ion **46** provides pyridinium **47** which may revert to **46** establishing an active equilibrium. For both mechanistic pathways the steric and electronic properties of the pyridine base are of utmost importance. In order to establish an active equilibrium bulky pyridines such as 2,4,6-collidine and 2,6-di-*tert*-butyl-4-methylpyridine or 2-halogenated pyridines must be used.



Scheme 17: Mechanistic Pathway for the Activation of a Secondary Amide Lacking α-Enolizable Protons.

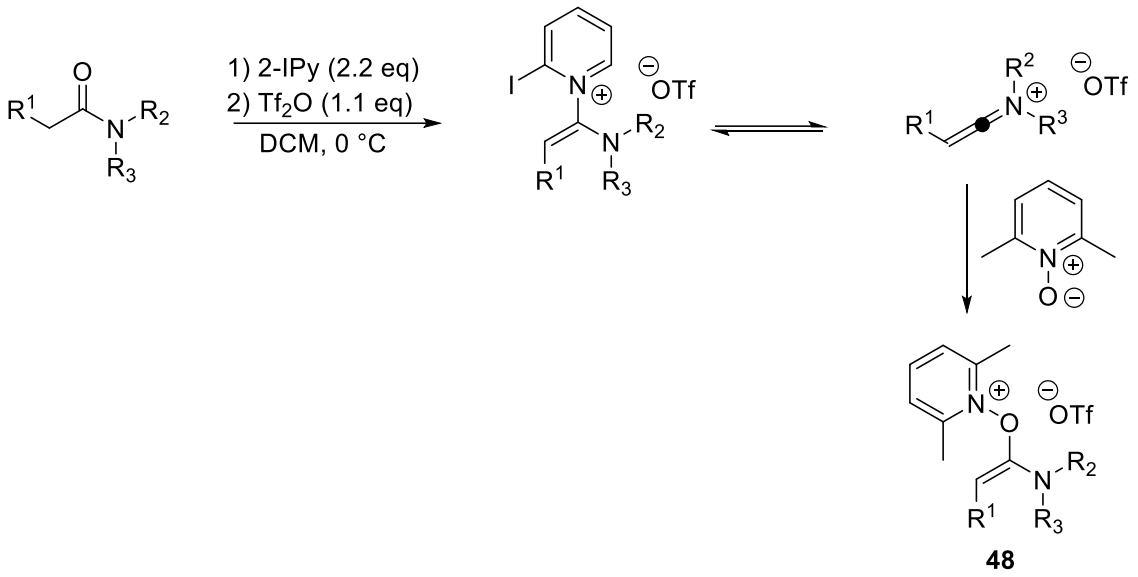
With the scope of the activation mechanism well understood, many breakthrough transformations of amides have been accomplished.[19] Of particular interest, Maulide has discovered a unique way to effectively umpole the α-amide carbon of tertiary amides with a combination of triflic anhydride and LNO in the presence of 2-iodopyridine. The novel umpoled enolonium electrophilic species **48** has been thoroughly investigated and coupled with a broad scope of inter- and intramolecular nucleophiles including enolates, halogens, amines, alkoxides, sulfoxides and arenes to name a few (Scheme 18).[23-25]



Scheme 18: Maulide's α-Functionalization of Tertiary Amides via Umpoled Enolonium Salts.

Formation of the novel enolonium species relies on an active equilibrium between a keteniminium intermediate and ketene-aminal intermediate and is induced by activating a tertiary amide with triflic anhydride in the presence of 2-iodopyridine (2-IPy). Oxidation of the keteniminium

intermediate would afford the umpoled enolonium species **48**, capable of nucleophilic substitution and subsequent removal of 2,6-lutidine would provide the α-substituted amides (Scheme 19).

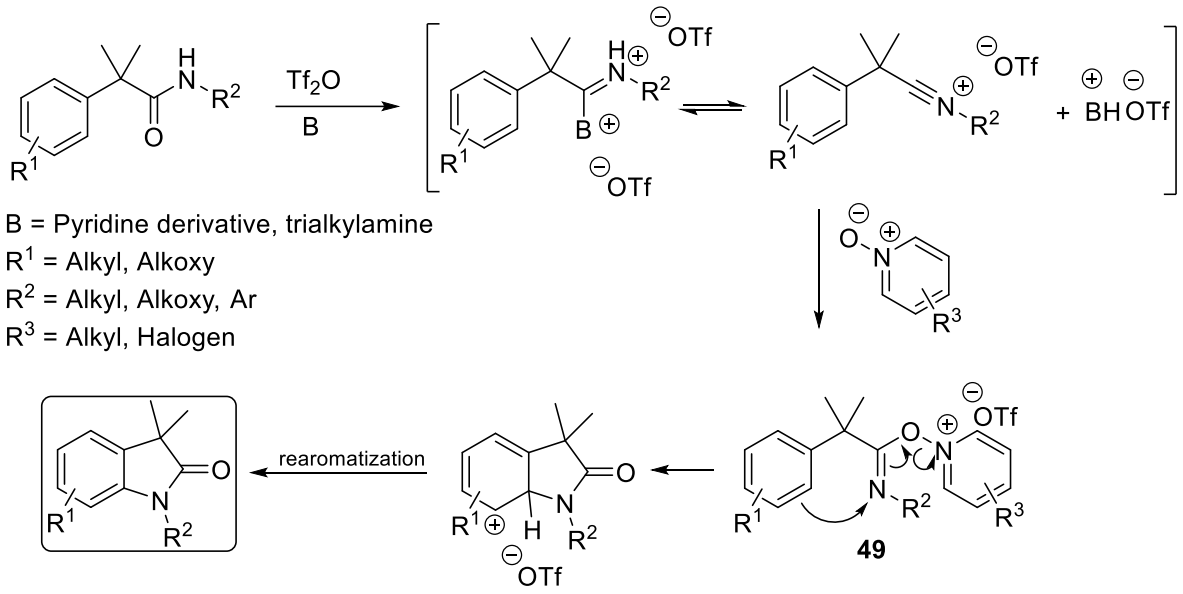


Scheme 19: Formation of Umpoled Enolonium Salts.

3.0 Research Project

Based on the reported umpolung reactivity of *N*-alkenoxypyridinium salts, enolonium salts, and secondary *N*-methoxy or *N*-aryl amides with HVI reagents, we hypothesized that carboximidate pyridinium salt intermediates **49** may be a source of electrophilic nitrogen suitable for intramolecular electrophilic aromatic amination.

It was postulated that these intermediates can be prepared *in situ* by electrophilic activation of non-enolizable secondary amides with triflic anhydride in the presence of a non-nucleophilic base followed by addition of a PNO derivative (Scheme 20). We anticipate that umpoled carboximidates **49** of this type would react intramolecularly with π-nucleophiles. The major limitation of the proposed method is ring size formation as competing *C*-substitution vs *N*-substitution may present a challenge for the formation of 6-membered rings and larger. The scope of the reaction will focus on the construction of 5-membered rings (oxindoles) with varying *N*-substituents.



Scheme 20: Proposed Formation and Substitution of Electrophilic Nitrogen Species.

Construction of the oxindole scaffold is relevant for the synthesis of biologically active molecules. Anticancer drugs Semaxanib and Sunitinib, along with natural product and analgesic Horsfiline, all contain the heterocyclic motif (Figure 5).

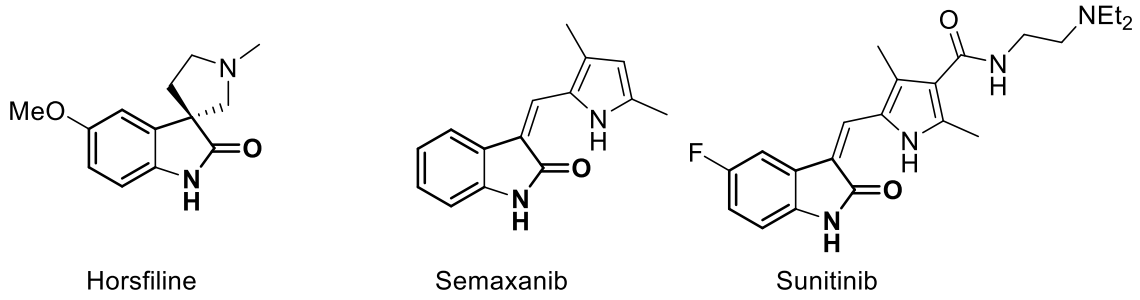


Figure 5: Relevance of the Oxindole Scaffold.

4. Results and Discussion

4.1 Substrate Design and Preparation

In order for the desired electrophilic aromatic amination to be successful, the model substrate had to be carefully designed (Figure 5). Firstly, to avoid the formation of a keteniminium species (vide supra) the secondary amide required dialkylation at the alpha position. Dialkylation would be advantageous to the intramolecular cyclization through the Thorpe-Ingold effect however, the

activation with triflic anhydride or addition of the PNO derivative to the activated species may be impeded due to stearic hindrance of the α-quaternary center. Secondly, symmetric methoxy substituents at the 3- and 5-position on the aromatic ring would provide a π-nucleophile with enhanced reactivity while preventing the formation of regioisomers. Finally, the benzeneacetamide skeleton was selected as the primary focus and was chosen to avoid the competing C-substitution of the electrophilically activated amide carbonyl carbon.

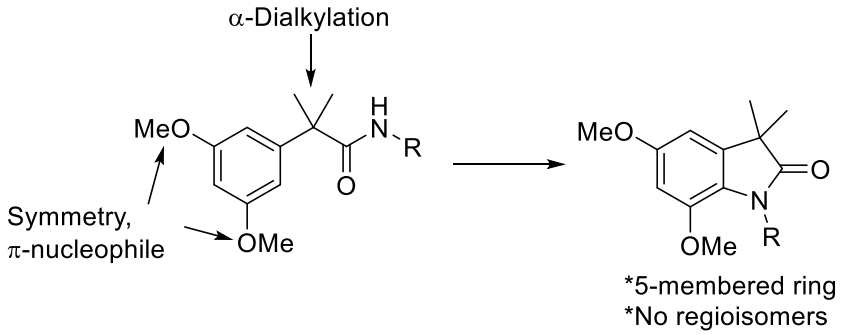
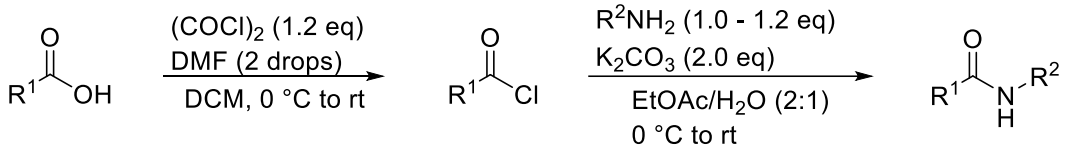


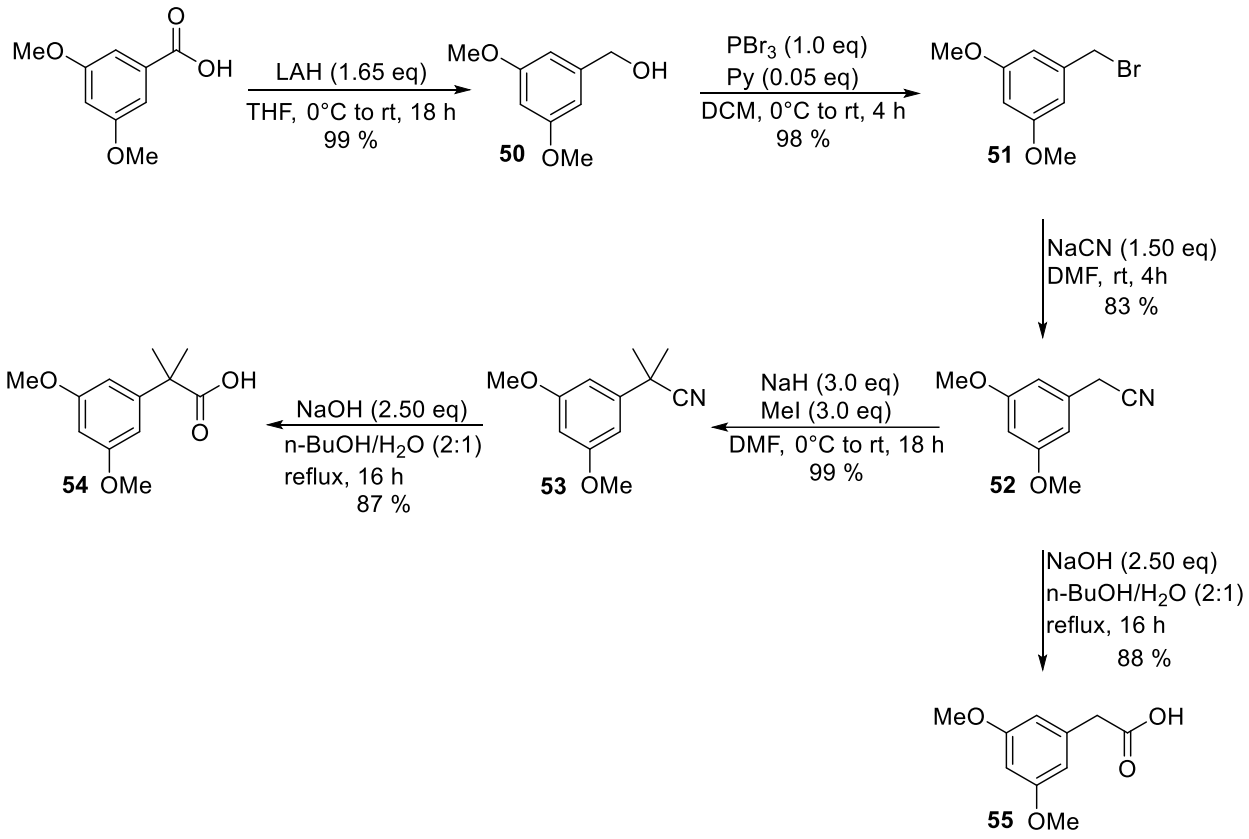
Figure 6: Substrate Design.

All secondary amides were prepared according to literature procedures from a Schotten-Baumann coupling between the appropriate crude acyl chlorides and primary amines (Scheme 21).

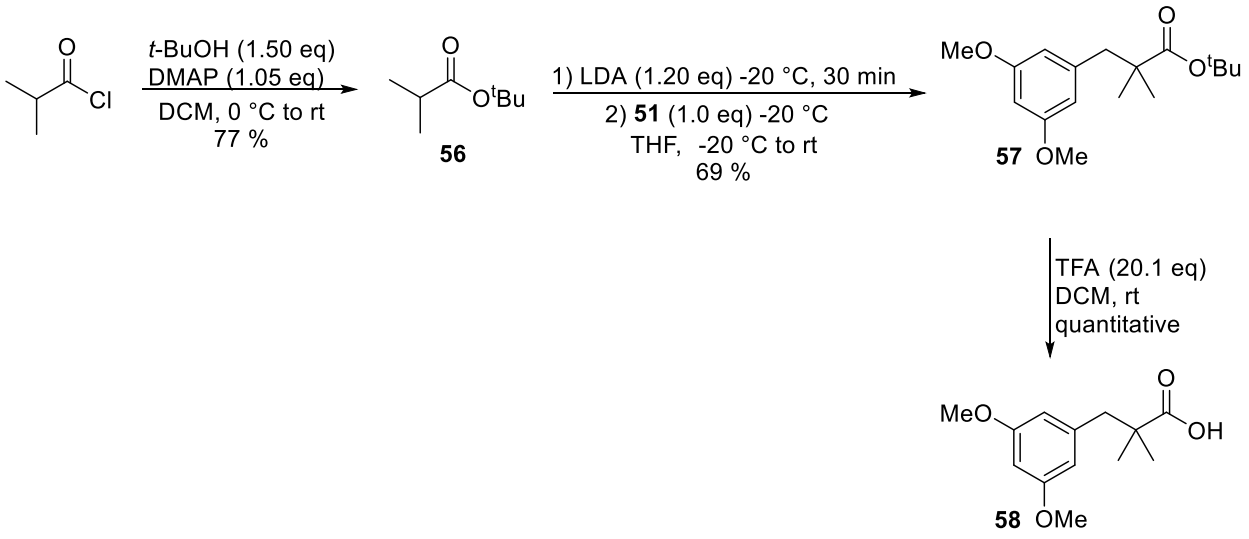


Scheme 21: Preparation of Secondary Amides.

The carboxylic acids **54**, **55,** and **58** were prepared according to literature procedures from 3,5-dimethoxybenzoic acid or 3,5-dimethoxybenzyl bromide **51** as outlined in Scheme 22 and Scheme 23, respectively. Synthetic routes to the carboxylic acids were expedient, high yielding, and reproducible.



Scheme 22: Preparation of Carboxylic Acids **54** and **55** from 3,5-Dimethoxybenzoic Acid.



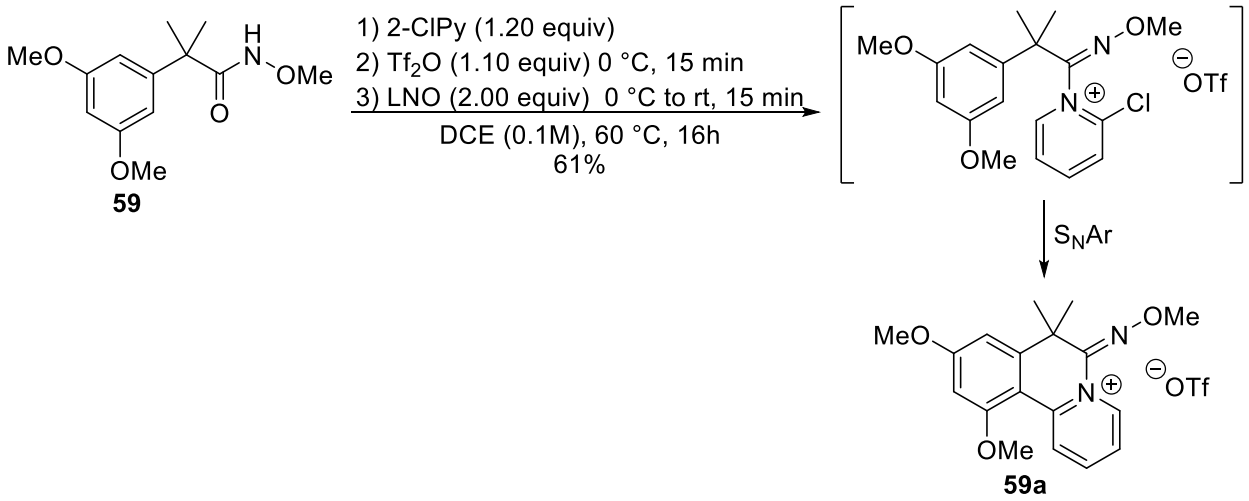
Scheme 23. Preparation of Carboxylic Acid **58** from 3,5-Dimethoxybenzyl Bromide **51**.

4.2 Electrophilic Aromatic Substitutions of Secondary Amides

4.2.1 Electrophilic Aromatic Substitutions of N-Methoxy Secondary Amides

The study was initiated using *N*-methoxy amide **59**. As electrophilic aminations of *N*-methoxy secondary amides with HVI have been established in the literature (vide supra), we decided that **59** would be an appropriate substrate to begin our studies with.

Initially, the activation of amide **59** using 2-chloropyridine (2-ClPy, 1.2 equivalents) and Tf_2O (1.1 equivalents) at 0 °C were inspired by the success of this combination in the literature for the electrophilic activation of secondary amides.[26] 1,2-Dichloroethane (DCE) was selected as the solvent for its inertness towards Tf_2O and its higher boiling point in comparison to dichloromethane (DCM), and LNO was employed as the *N*-oxide source to prevent the dehydrative *N*-pyridinylation described by Movassaghi.[27] These activation conditions unfortunately led to the formation of cyclized pyridinium **59a** likely proceeding through a S_NAr type reaction of the pyridinium intermediate (Scheme 24). Analogous results were obtained with 2-fluoropyridine (2-FPy) as the base.

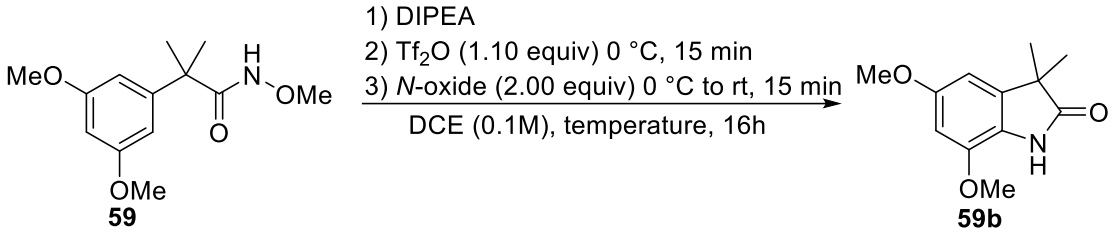


Scheme 24: Formation of **59a** via S_NAr of Pyridinium Intermediate.

When the base was changed to *N*,*N*-diisopropylethylamine (DIPEA) **59** underwent electrophilic amination along with an unexpected N-O bond cleavage affording **59b** in 30 % yield (entry 1, Table 1). The use of 2,6-dichloropyridine *N*-oxide (2,6-DiCl PNO) as the *N*-oxide source proved to be less effective then LNO, while *N*-methylmorpholine *N*-oxide (NMO) completely hampered

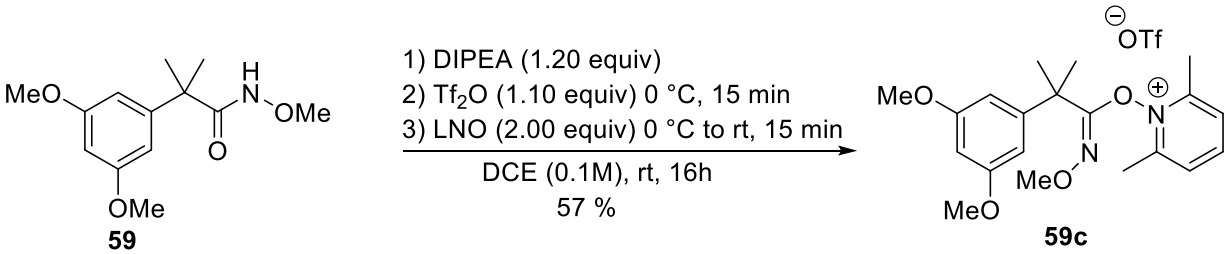
reactivity (entries 2 and 3, Table 1). Increasing the equivalents of base or temperature similarly suppressed the formation of **59b** (entries 4 and 5, Table 1).

Table 1. Optimization of Reaction Conditions for 59.

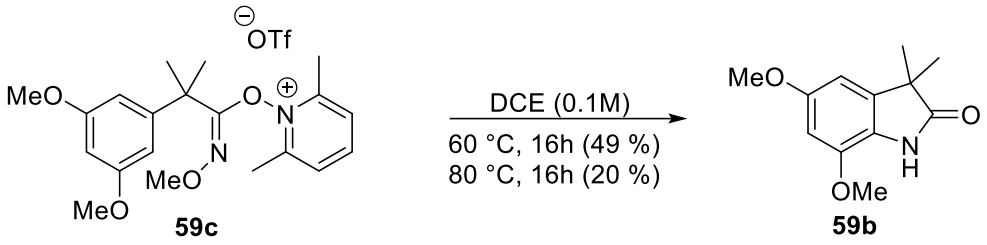


entry	base equiv	*N*-oxide	temperature (°C)	yield (%)
1	1.20	LNO	60	30
2	1.20	2,6-DiCl PNO	60	17
3	1.20	NMO	60	0
4	1.50	LNO	60	23
5	1.20	LNO	80	5
6	1.20	LNO	rt	0

Although no C-N bond formation was observed at rt (entry 6, Table 1), analysis of the crude ^{1}H NMR indicated the formation of the key carboximidate intermediate **59c.** Gratifyingly, intermediate **59c** was isolated in 57 % yield under said conditions and characterized by ^{1}H and ^{13}C NMR (Scheme 25). Subsequent heating of **59c** neat in DCE at 60 °C gave **59b** in 49 % yield and was accompanied by decomposition. When the temperature was increased to 80 °C further decomposition was observed and the yield of **59b** diminished to 20 % (Scheme 26). While trace amounts of the cyclized *N*-methoxy amide were observed in the crude ^{1}H NMR spectra for the 60 °C condition, the quantities were not sufficient to isolate. The isolation and cyclization of **59c** provided evidence that the carboximidate could act as an electrophilic nitrogen source.

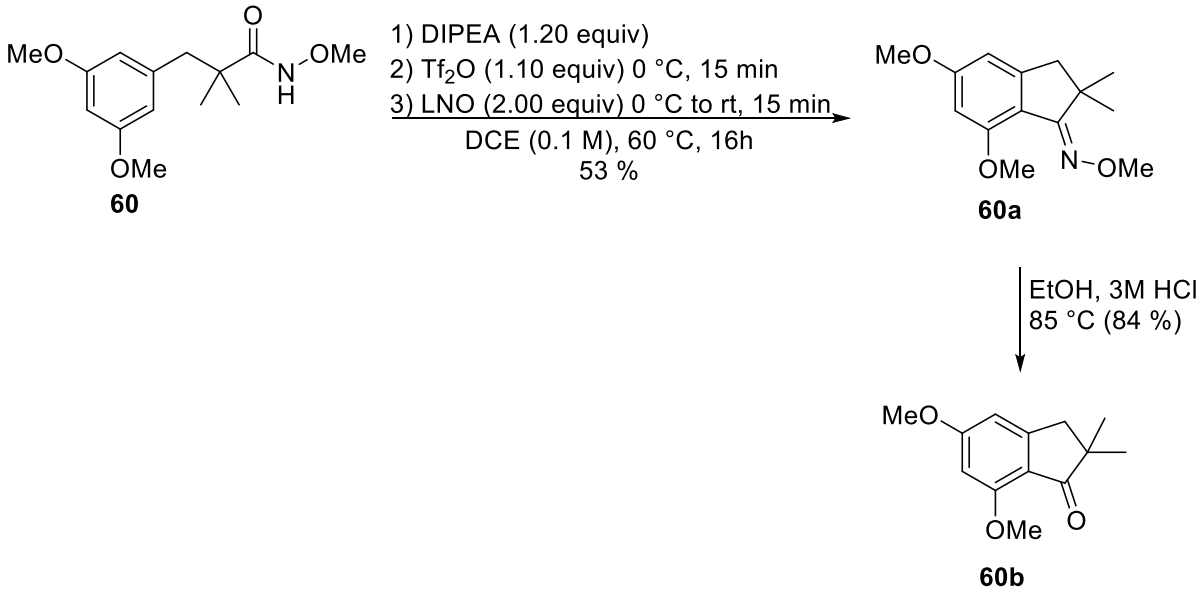


Scheme 25: Formation of Intermediate **59c**.



Scheme 26: Electrophilic Aromatic Amination of Intermediate **59c**.

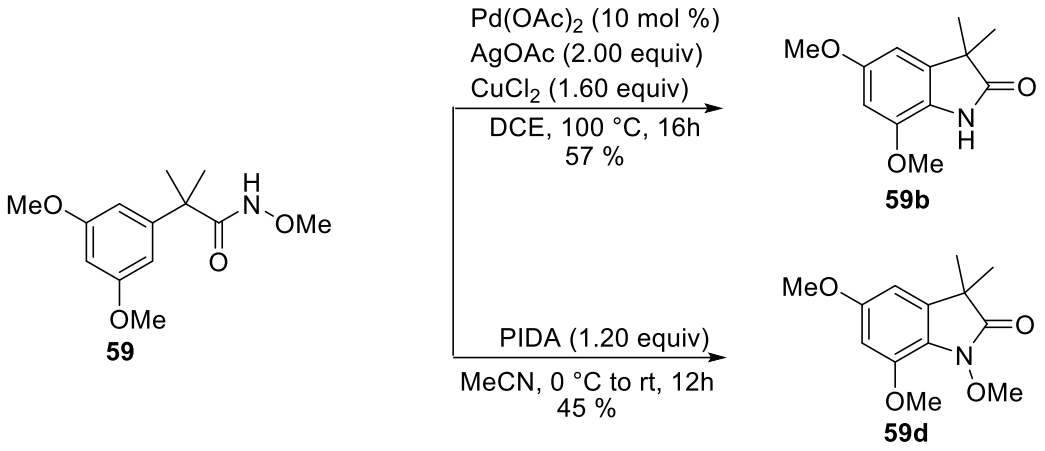
Electrophilic amination of *N*-OMe amide **60** containing an extra methylene group was briefly explored for the anticipated formation of 6-membered rings. However, treatment of **60** under the optimal conditions led to *O*-methyl oxime **60a** in 53 % yield (Scheme 27). Hydrolysis of **60a** with EtOH and 3M HCl at 85 °C gave the ketone **60b** in 84 % yield. Formation of **60a** can be attributed to nucleophilic attack of the aromatic ring onto the electrophilically activated carbonyl carbon. In attempt to hamper this undesired reactivity, **60** was activated at -78 °C in DCM, followed by addition of LNO at -78 °C with gradual warming to rt before heating at 60 °C; however, these conditions led to the same result.



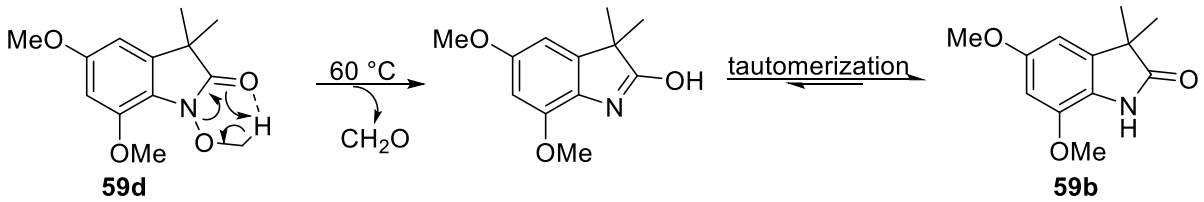
Scheme 27: Attempted Electrophilic Amination of **60** and Hydrolysis of **60a**.

4.2.2 Investigation of the N-O Bond Cleavage

Intrigued by the unexpected N-O bond cleavage, the synthesis of cyclized **59d** from **59** was attempted according to known literature procedures for C-N bond formation. Our first attempt with a palladium catalyzed C-H activation protocol described by Yu and co-workers[28] unfortunately led to **59b** with no detection of **59d** (Scheme 28). To our delight, **59d** could be isolated in 45 % yield by treatment of **59** with 1.2 equivalents of PIDA in MeCN under mild conditions (Scheme 28).[4] These results led us to believe that **59d** may be thermally unstable and decompose to **59b** under our reaction conditions. This hypothesis was tested by heating a solution of **59d** in d_6-DMSO at 60 °C in a sealed J-Young NMR tube overnight and recording the ^{1}H NMR thereafter. As anticipated, **59d** was converted to **59b** and a strong resonance was observed at 9.57 ppm, indicative of CH_2O formation. Extensive literature searches did not reveal any thermal decompositions of similar electron rich *N*-OMe oxindoles; however, a possible decomposition pathway may be envisioned via a 6-membered transition state (as displayed in Scheme 29) with loss of CH_2O followed by tautomerization.



Scheme 28: Preparation of **59d**.

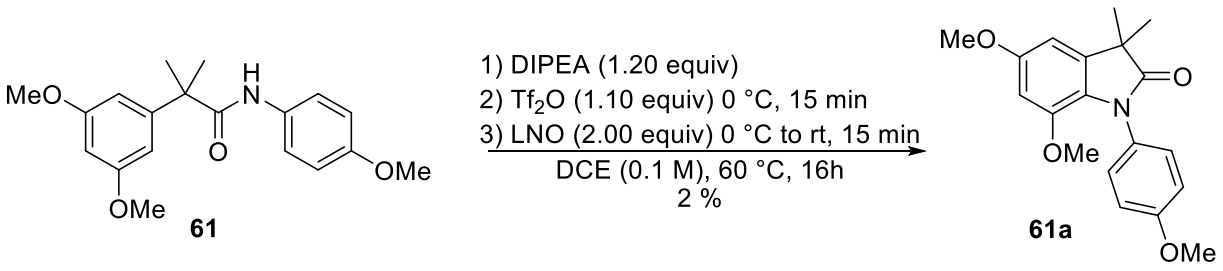


Scheme 29: Proposed Thermal Decomposition of **59d** to **59b**.

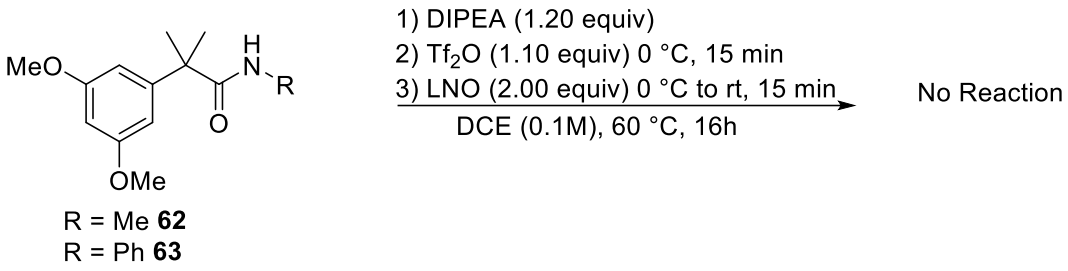
Based on these results, we propose that the electrophilic amination of **59** to **59d** is followed by thermal decomposition to **59b**. The difficulty in this transformation lies in the fact that while **59c** requires sufficient thermal energy to form the C-N bond, the desired product **59d** and intermediate **59c** are thermally unstable.

4.2.3 Electrophilic Aromatic Substitutions of *N*-Methyl and *N*-Aryl Secondary Amides

The next feasible substrate to examine was *N*-*p*-methoxyphenyl (PMP) amide **61**. Similar electronically to **59**, the paramethoxy substituent on **61** can donate electron density through the aromatic ring without the concern of any bond cleavage as previously discussed. Under the optimal conditions, **61** underwent electrophilic amination affording **61a** in a poor yield of 2 % with 76% of the starting material recovered (Scheme 30). Several unsuccessful attempts were made to increase the yield by varying the solvent, temperature, and base however, starting material was the major product in all cases. Secondary amides bearing *N*-Me **62** and *N*-Ph **63** substituents additionally proved to be poor substrates for this transformation, as no C-N bond formation was detected and similarly to **61**, the major product was starting material (Scheme 31). When monitoring reactions of **61**, **62** and **63** by thin layer chromatography (TLC), consumption of starting material was evident after Tf_2O addition. Therefore, it is likely that the iminium triflate or imidoyl triflate intermediate was the major species and the reluctance of LNO to exchange with the triflate was the issue. Hydrolysis of the iminium triflate or imidoyl triflate during the aqueous work-up would account for the isolation of starting material.



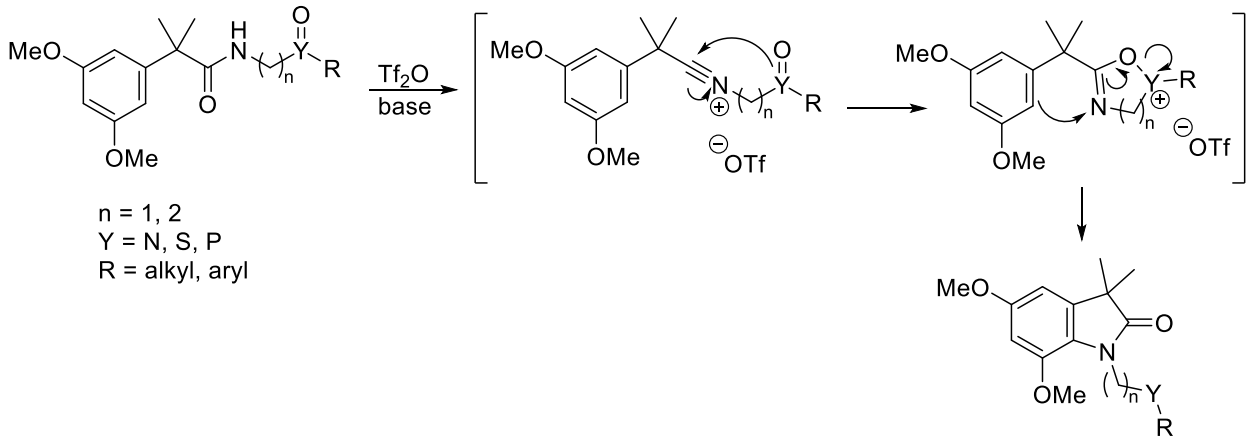
Scheme 30: Electrophilic Amination of *N*-PMP Secondary Amide **61**.



Scheme 31: Attempted Electrophilic Amination of *N*-Me and *N*-Ph Secondary Amides **62** and **63**.

4.3 Electrophilic Aromatic Aminations of Secondary Amides with Oxide Tether

Given the lackluster results obtained with the *N*-Me, -Ph and -PMP secondary amides, we opted to prepare and investigate electrophilic aminations of secondary amides bearing an *N*-, *S*-, or *P*-oxide tether group. While chemoselective triflation of the amide vs oxide was noted to be a potential limitation, if selectivity could be tuned to the amide functionality, intramolecular nucleophilic addition of the oxide onto the activated amido carbon would be favoured over the intermolecular counterpart previously explored. The result would be cyclic carboximidate, similar in nature to isolated intermediate **59c**, capable of intramolecular electrophilic aromatic amination (Scheme 32).



Scheme 32: Proposed Electrophilic Amination of Secondary Amides bearing Oxide Tether.

4.3.1 Substrate Scope

Substrates with tether lengths of 1 and 2 carbons between the amide nitrogen and hetero-oxide were chosen for the formation of 5- and 6-membered rings containing the electrophilic nitrogen

source. Pyridine *N*-oxides, pyrimidine *N*-oxides, tertiary amine *N*-oxides, sulfoxides, and phosphine oxides were selected as suitable hetero-oxides (Figure 7). The amido tethered oxides were prepared in two steps by coupling the heteroatom-containing primary amine with the acyl chloride followed by oxidation of the heteroatom (N, S, or P) with mCPBA.

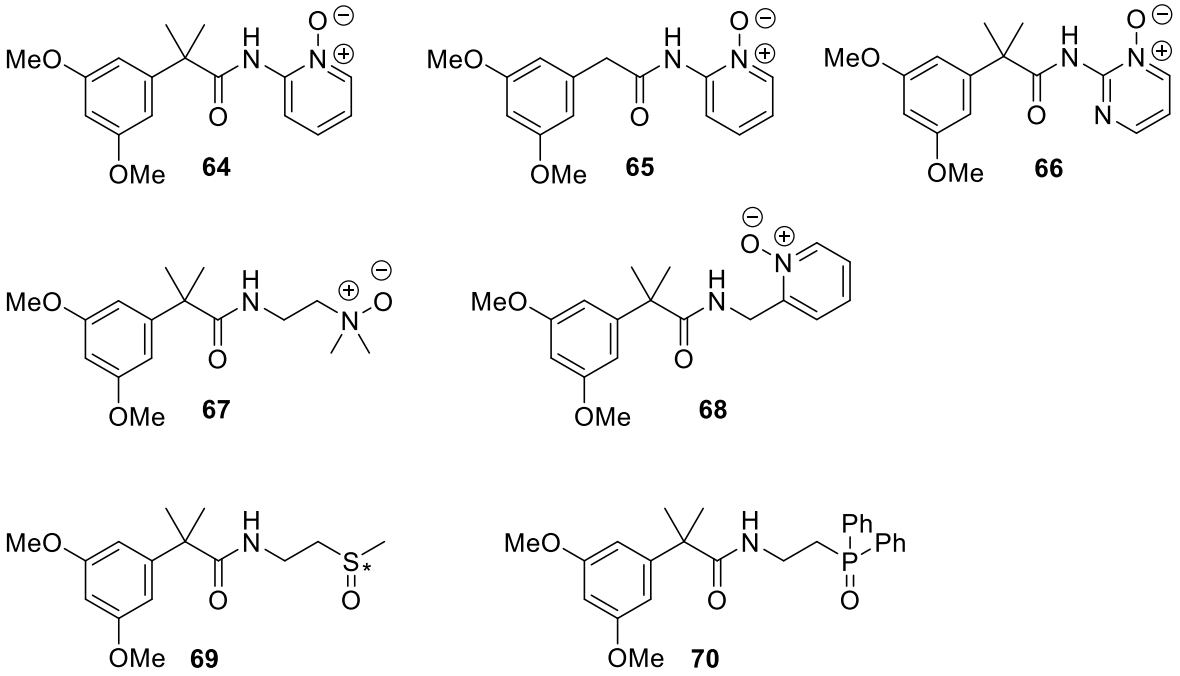


Figure 7: Substrate Scope.

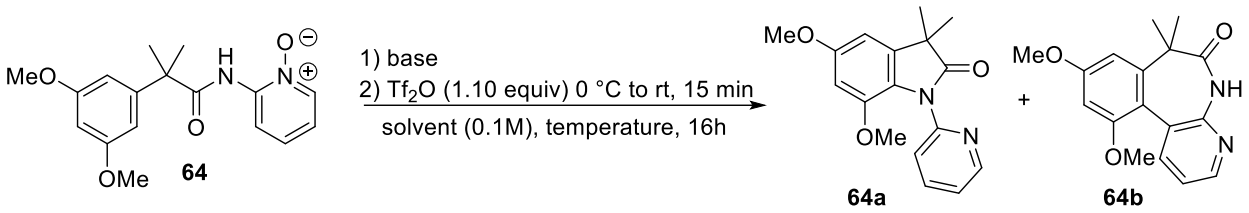
4.4 Electrophilic Aminations of Secondary Amides with *N*-oxide Tether

4.4.1 Electrophilic Aminations of 2-Amidopyridine- and 2-Amidopyrimidine *N*-oxides

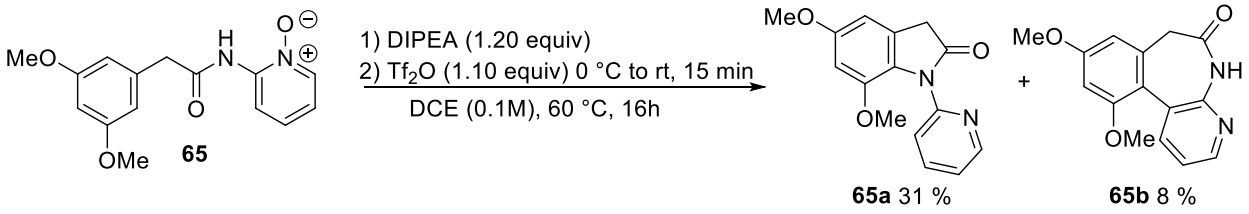
2-Amidopyridine *N*-oxide **64** served as the model substrate for the electrophilic amination of aryl tethered 2-amido *N*-oxides. To our delight, **64** underwent electrophilic amination forming **64a** in 44 % yield along with side product **64b** in 25 % yield under the optimal conditions (entry 1, Table 2). Interestingly, the nature of the base and reaction temperature did not have a profound effect on the reaction outcome (compare entries 1, 3, 4, 8, 9, and 10, Table 2). Lower yields were observed when the base additive was increased to 2 equivalents and when the less polar solvent toluene was used (entry 2 and 7, Table 2). The ratio of **64a** : **64b** was generally in the neighbourhood of ~1.9 : 1. Substrate **65** lacking α-dimethylation similarly underwent the desired transformation under the optimal conditions affording **65a** and **65b** in 31 % and 8 % yield, respectively (Scheme 33). The

inferior yield of **65a** in contrast to **64a** may be attributed to the absence of the kinetic Thorpe-Ingold effect.[29]

Table 2. Optimization of Reaction Conditions for 64.



entry	base (eq)	solvent	temperature (°C)	**64a** yield (%)	**64b** yield (%)
1	DIPEA (1.2)	DCE	60	44	25
2	DIPEA (2.0)	DCE	60	26	12
3	DIPEA (1.2)	DCE	100	43	22
4	DIPEA (1.2)	DCE	rt	39	23
5	DIPEA (1.2)	MeCN	60	35	19
6	DIPEA (1.2)	$MeNO_2$	60	43	22
7	DIPEA (1.2)	PhMe	60	31	24
8	2,4,6-collidine (1.2)	DCE	60	39	21
9	2-FPy (1.2)	DCE	60	41	20
10	DTBMP (1.2)	DCE	60	42	23

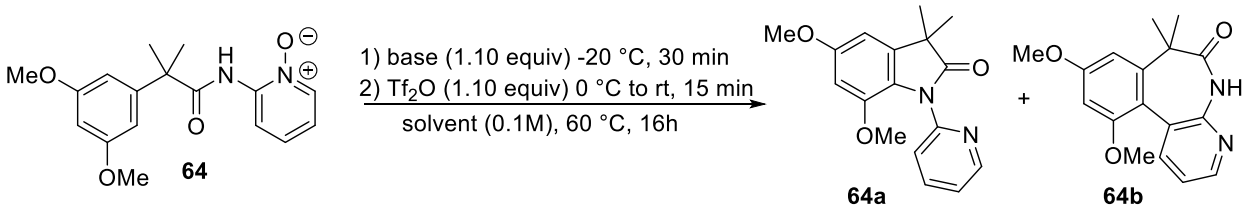


Scheme 33: Electrophilic Amination of **65**.

We suspected that the 3-substitution on the pyridine moiety forming side product **64b** was due to competitive *N*-oxide triflation (vide infra). In effort to attenuate this pathway, we modified the base strength along with the triflating reagent in separate experiments. With respect to the base, we opted to increase the nucleophilicity of the amide by deprotonating the amide nitrogen proton with a strong base prior to addition of Tf_2O. Unfortunately, the use of strong bases such as KHMDS and NaH led to lower yields of **64a** and the ratio of **64a** : **64b** appeared to be unaltered as conveyed in Table 3. In regards to the triflating reagent, *N*-phenyl-bis(triflimide) **Tf1** and *N*-(2-

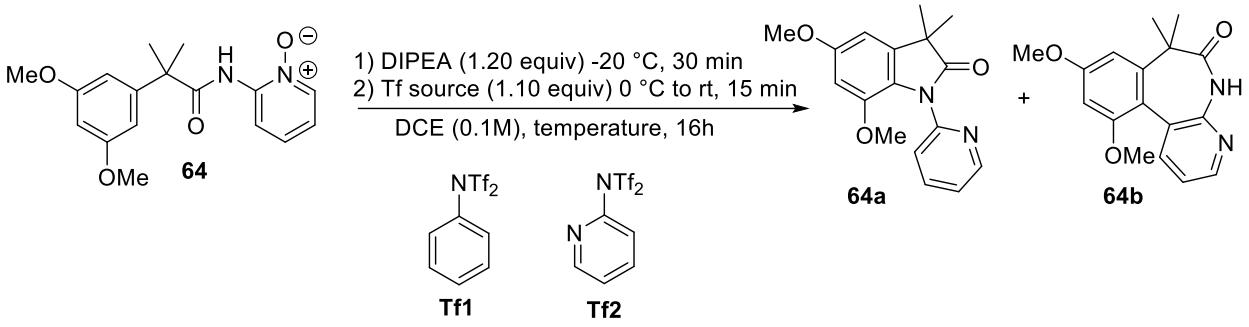
pyridyl)bis(triflimide) **Tf2** were explored to determine if these reagents offered greater chemoselectivity. **Tf1** afforded no reaction at 60 °C while **Tf2** only gave trace amounts of **64a** and **64b** under the same conditions (entries 1 and 2, Table 4). Increasing the temperature to 120 °C in tandem with **Tf2** gave **64a** : **64b** in a ratio of 2.8 : 1 and yields of 37 % and 13 %, respectively (entry 3, Table 4).

Table 3. Effect of Strong Base for the Electrophilic Amination of 64.



entry	base	Solvent	**64a** yield (%)	**64b** yield (%)
1	KHMDS	DCM	29	14
2	KHMDS	PhCl	24	12
3	KHMDS	PhMe	27	16
4	NaH	PhCl	31	16

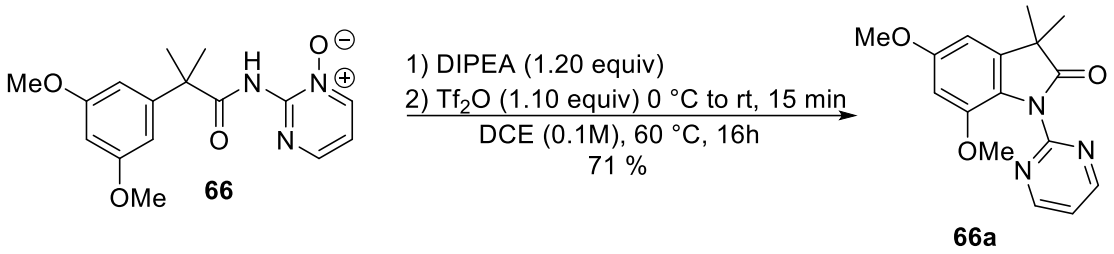
Table 4. Effect of Triflating Reagent for the Electrophilic Amination of 64.



entry	Tf source	temperature (°C)	**64a** yield (%)	**64b** yield (%)
1	**Tf1**	60	0	0
2	**Tf2**	60	trace	trace
3	**Tf2**	120	37	13

Our next attempt to inhibit the 3-substitution on the pyridine moiety involved simply blocking the 3-position using 2-amidopyrimidine *N*-oxide **66**. It is worth noting that the coupling between 2-aminopyrimidine and the acyl chloride was performed in DCM with pyridine, a weaker base than K_2CO_3, to prevent the deprotonation of the desired secondary amide and successive acylation to the *N*,*N*-diacylated product.[30] Furthermore, oxidation of the 2-amidopyrimidine with mCPBA was

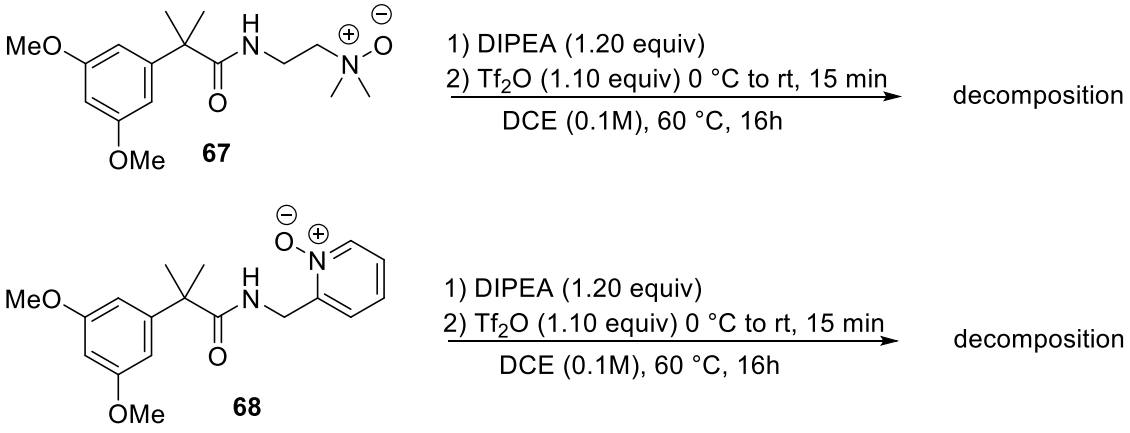
very sluggish affording the *N*-oxide in a very poor yield of 7 % owing to the strong deactivation of the pyrimidine ring. When **66** was subjected to the optimized conditions **66a** was isolated in a good yield of 71 % with no detection of any minor by-products (Scheme 34) indicating the pyrimidine moiety was able to supress 3-substitution.



Scheme 34: Electrophilic Amination of 2-Amidopyrimidine *N*-Oxide **66**.

4.4.2 Attempted Electrophilic Aminations via 6-membered Cyclic Carboximidates.

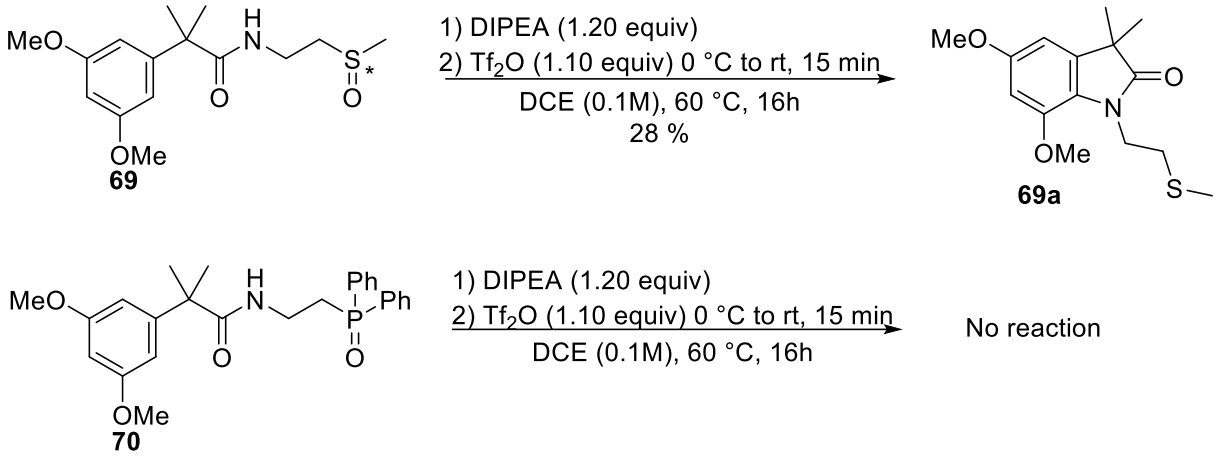
To determine the effect of the carboximidate ring size, substrates **67** and **68** were selected for their two-carbon tether between the amide nitrogen and *N*-oxide nitrogen that would generate a 6-membered carboximidate species. Furthermore, the structure of these substrates would alleviate the formation of 7-membered cyclic by-products encountered above. Compounds **67** and **68** failed to cyclize, and decomposition was observed under the optimal conditions (Scheme 35).



Scheme 35: Attempted Electrophilic Amination of **67** and **68**.

4.5 Electrophilic Aminations of Secondary Amides with Sulfoxide or Phosphine Oxide Tether

With the success of the 2-amido pyridine and pyrimidine *N*-oxides, we chose to investigate secondary amides bearing a sulfoxide **69** or phosphine oxide **70** tether as our last substrates. When **69** endured the optimized conditions *N*-thioether oxindole **69a** was isolated in 28% yield while **70** failed to exhibit any reactivity under the described conditions (Scheme 36). Failure of **70** to elicit any reactivity is likely owing to the poor nucleophilicity of the phosphine oxide toward either the activated electrophilic amide carbon or triflic anhydride.



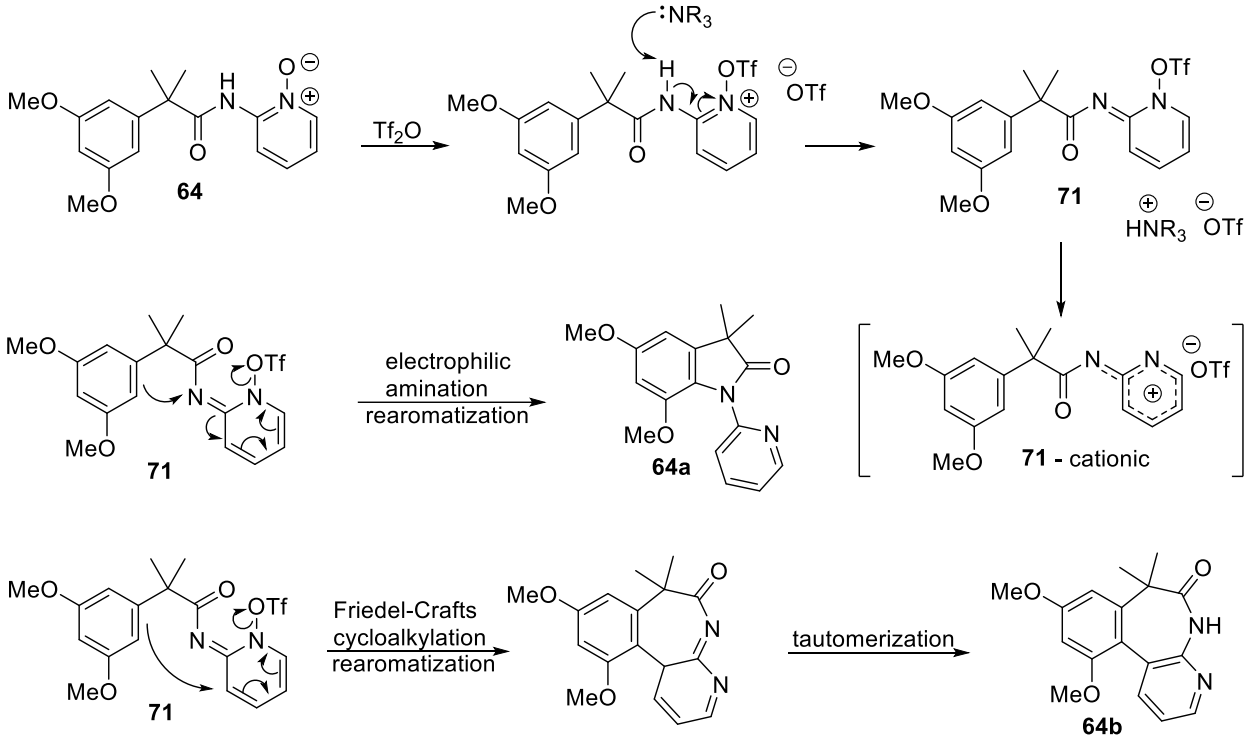
Scheme 36: Attempted Electrophilic Amination of Secondary Amides with Sulfoxide **69** and Phosphine Oxide **70** Tethers.

4.6 Proposed Mechanistic Pathway

After careful analysis of the mixed results obtained for the various secondary amides with *N*-oxide tethers it appeared that the predicted cyclic carboximidate intermediates may not be the electrophilic nitrogen source after all. Notably, the failure of **67** and **68** to form the desired C-N bond indicated that the 2-amidopyridine *N*-oxide structure was a requirement for the reaction. That is, the amide nitrogen must be bound to the 2-position of a pyridine or pyrimidine *N*-oxide for electrophilic amination to take place. Additionally, deprotonation of the amide with a strong base prior to triflation retarded the reaction. If the reaction mechanism did indeed proceed through amide triflation, the amide anion would surely improve the chemoselectivity given the known reactivity of pyridine *N*-oxides with acid anhydride reagents.[31,32] Finally, the ability of the reaction

to proceed at room temperature was indicative of a highly electrophilic nitrogen intermediate – not observed previously during our secondary amide studies (vide supra).

We propose that the electrophilic nitrogen source is intermediate **71** in Scheme 37. To the best of our knowledge, electrophilic nitrogen intermediates of this type are absent in the literature. A mechanism for the formation of **64a** and **64b** is outlined in Scheme 37. Triflation of the *N*-oxide followed by deprotonation of the amide nitrogen proton would afford intermediate **71** in a similar fashion to the Boekelheide reaction of 2-alkylpyridine *N*-oxides with acetic anhydride.[33] Attack of the tethered aryl group onto the electrophilic nitrogen center of **71** would afford **64a**. Whereas **64b** may be realized by attack of the tethered aryl group onto the 3-position of the pyridine ring via a Friedel-Crafts type cycloalkylation followed by tautomerization. Although a concerted neutral mechanism is hypothesized, a stepwise cationic mechanism cannot be ruled out. Intermediates in the Boekelheide reaction that are similar in nature to **71** have been determined by mechanistic experiments to exist as a tight ion pair by elimination of the triflate (**71** – cationic, Scheme 37) and the positive charge may resonate.[34,35] Nucleophilic attack of the aryl group onto the positively charged amide nitrogen center or the positively charged carbon center would likewise provide **64a** and **64b**, respectively.



Scheme 37: Proposed Mechanism for the Formation of **64a** and **64b.**

5. Conclusion

The successful methodology development and optimization for novel electrophilic nitrogen species has been presented. Electrophilic aromatic amination of a secondary *N*-methoxy amide under our conditions afforded the oxindole with N-O bond cleavage in a yield up to 30 %. The novel electrophilic nitrogen species was isolated and characterized by ^{1}H and ^{13}C NMR for an *N*-methoxy amide. Furthermore, 2-amidopyridine *N*-oxides and 2-amidopyrimidine *N*-oxides proved to be excellent sources of electrophilic nitrogen by the simple reagent combination of Tf_2O and DIPEA under mild conditions.

6. Future Work

6.1 Further Exploration of the Reaction Scope

To gain insight on the electrophilicity of the umpoled nitrogen and to determine the scope of the reaction, it would be valuable to alter the π-nucleophilicity on the tethered aryl group. In addition to the 2-amidopyr(im)idine *N*-oxides, 2-amido-3-methylpyridine *N*-oxide (X = CCH_3) may be suitable to hamper the competing 3-substitution. A list of potential substrates is listed in Figure 8.

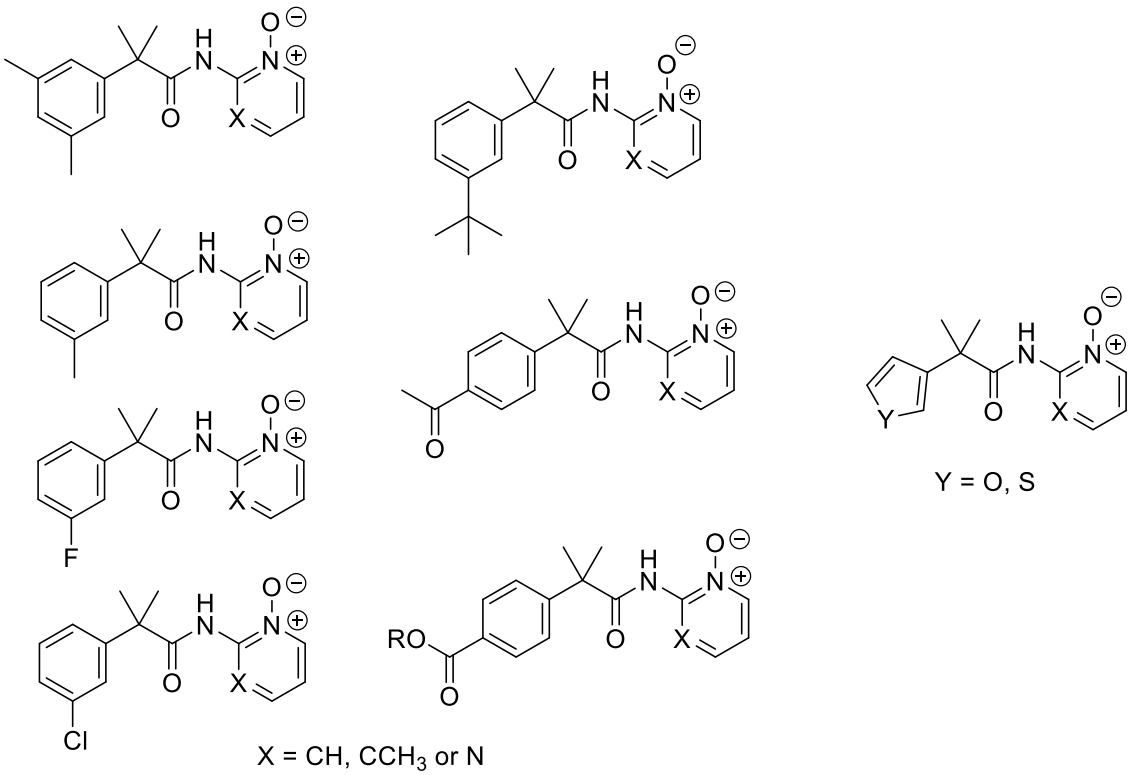
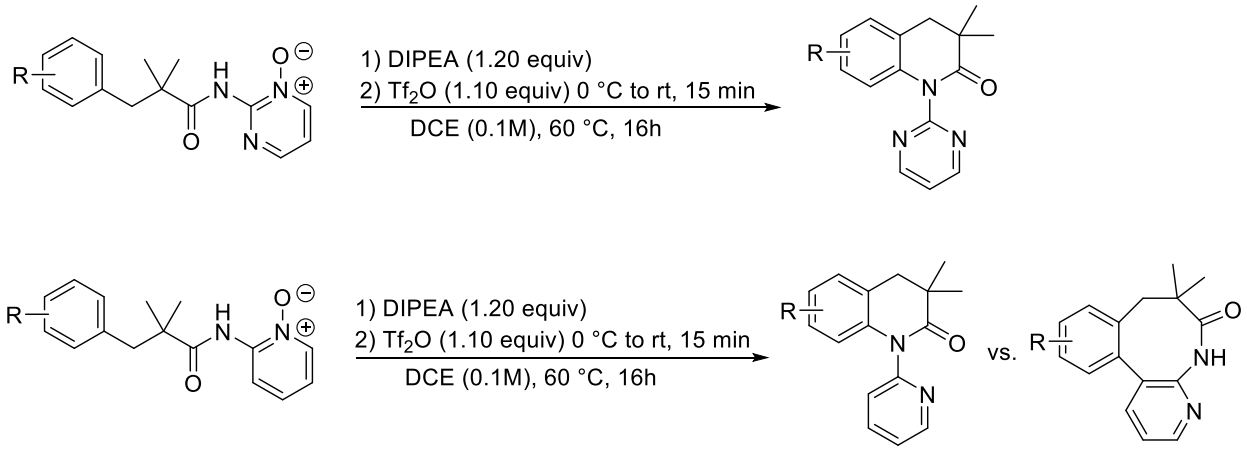


Figure 8: Various π-Nucleophiles.

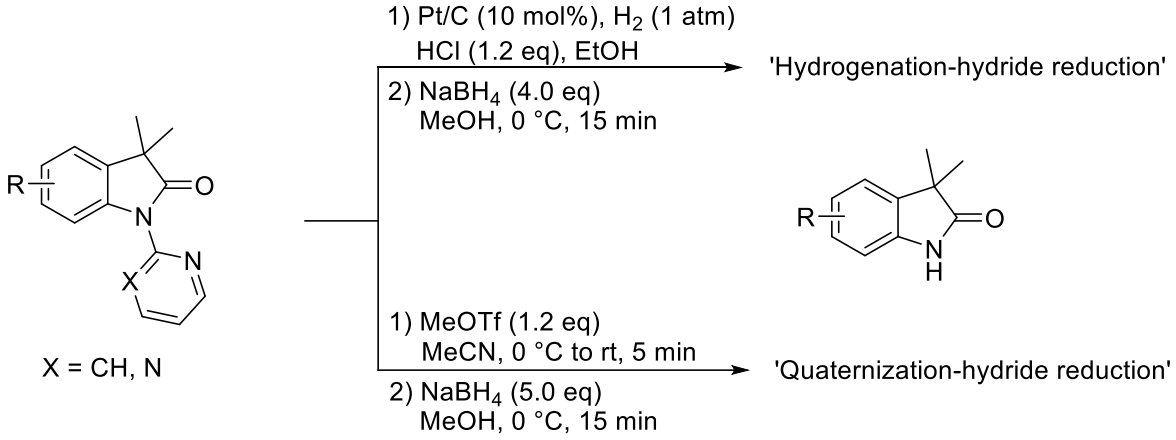
The formation of 6-membered rings from 2-amidopyridine and 2-amidopyrimidine *N*-oxides would additionally be a reasonable next step to determine the potential limitations of this transformation (Scheme 38). Of particular interest would be the 6- vs 8-membered ring formation for the 2-amidopyrimidine *N*-oxide substrate.



Scheme 38: Formation of 6-Membered Rings via Electrophilic Amination.

6.2 Cleavage of Pyri(mi)dyl Group

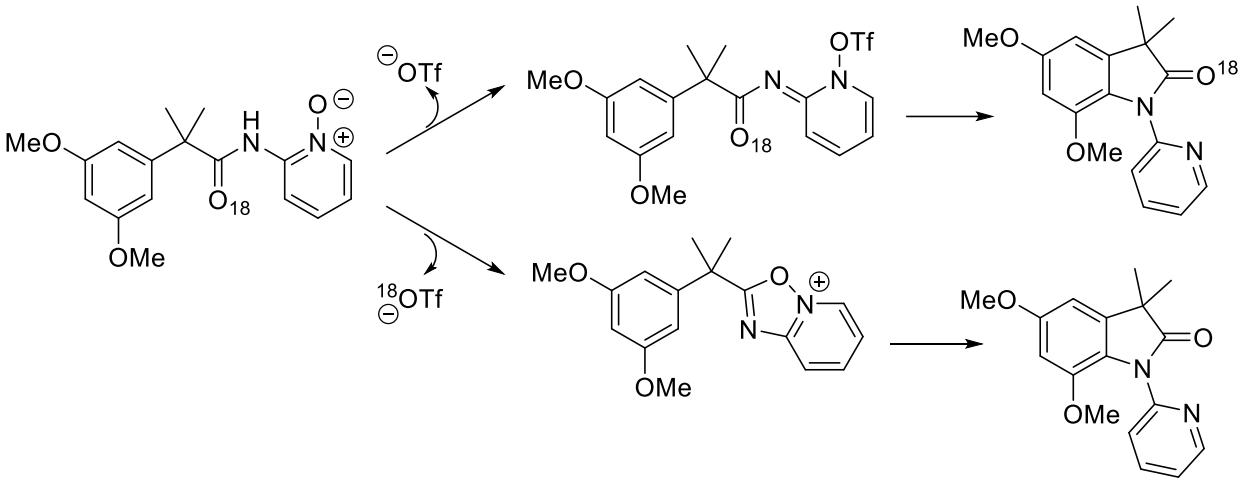
Two strategies for the cleavage of *N*-pyridyl and *N*-pyrimidyl groups has been reported in the literature namely, the 'hydrogenation-hydride reduction' and 'quaternization-hydride reduction' (Scheme 39).[36] Removal of the pyri(mi)dyl moiety through one of these strategies would allow for further synthetic transformations and the pyri(mi)dine *N*-oxide group may be regarded as an activator for the electrophilic amination.



Scheme 39: Removal of Pyri(mi)dyl Groups.

6.3 Mechanistic Studies

Mechanistic insights for the electrophilic aromatic aminations of 2-amidopyridine and 2-amidopyrimidine *N*-oxides could be accomplished by 18-oxygen radiolabelling of the amide carbonyl oxygen (Scheme 40). Erosion of the ^{18}O-label would indicate a cyclic carboximidate type intermediate as initially proposed while preservation of the ^{18}O label would suggest a mechanism as discussed in section 4.6.



Scheme 40: Mechanistic Experiment with ^{18}O-radiolabel.

7. Experimental

General Considerations

All reactions were performed in flame dried glassware under a dry nitrogen atmosphere unless otherwise stated. THF was freshly distilled over sodium/benzophenone ketyl before use. DCM was distilled over CaH_2 and stored in a Schlenk flask under nitrogen. DMF was dried with activated 4 Å Linde molecular sieves. Diisopropylamine, triethylamine, pyridine, and aniline were distilled over CaH_2 and stored in a Schlenk tube under nitrogen. 2-aminopyridine was recrystallized from $CHCl_3$/pet ether. n-BuLi was titrated with N-benzylbenzamide in dry THF at -40 °C.[37] All other solvents and reagents were used as received from commercial sources. Reactions were monitored by thin-layer chromatography on commercially prepared plates and visualized by UV (254 nm) or stained with $KMnO_4$. Flash chromatography was performed using 230-400 mesh silica gel.[38]

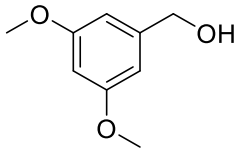
Characterization

Unless otherwise stated, all ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ at 300 and 75 MHz, respectively with a Bruker 300 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) and were calibrated to the solvent residual peak ($CHCl_3$ 7.26 ppm and $CDCl_3$ 77.0 ppm). Abbreviations are as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b). Melting points are uncorrected.

Part 1 – Preparation of Substrates and Reagents

Preparation of Carboxylic Acids

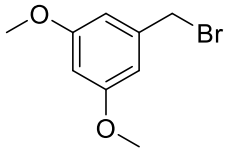
(50) (3,5-Dimethoxyphenyl) methanol[39]



3,5-Dimethoxybenzoic acid (10.1 g, 55.3 mmol, 1.00 equiv) was added portion-wise over 10 minutes to a suspension of lithium aluminum hydride (3.47 g, 91.3 mmol, 1.65 equiv) in dry THF (220 mL) at 0 °C. After complete addition, the reaction mixture was allowed to warm to room

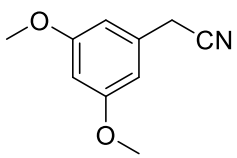
temperature (23 °C) and stirred for 18 hours. The reaction mixture was diluted with diethyl ether (100 mL), cooled to 0 °C and quenched by sequential addition of water (3.5 mL), 15% sodium hydroxide (3.5 mL), and water (10.5 mL). Magnesium sulfate was then added to the mixture and stirred for 15 minutes at room temperature. Filtration of the mixture over a pad of celite washing with diethyl ether, followed by concentration *in vacuo* afforded **50** (9.27 g, 99%) as a white solid. No purification was necessary. MP 46-48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (d, *J* = 2.1 Hz, 2H), 6.39 (t, *J* = 2.1 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 6H) 1.66 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 143.4, 104.6, 99.7, 65.4, 55.4.

(51) 1-(Bromomethyl)-3,5-dimethoxybenzene[40]



Phosphorous tribromide (5.24 mL, 55.1 mmol, 1.00 equiv) was added dropwise to a solution of (3,5-dimethoxyphenyl) methanol **50** (9.27 g, 55.1 mmol, 1.00 equiv) and pyridine (0.242 mL, 2.75 mmol, 0.05 equiv) in dry DCM (80 mL) at 0 °C. The reaction was allowed to warm to room temperature (23 °C) and stirred for 4 hours. Ice water (40 mL) was slowly added to quench the reaction. The phases were partitioned, and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic phases were washed with saturated sodium chloride (40 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford **51** (12.5 g, 98%) as a white solid. No purification was necessary. MP 68-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.1 Hz, 2H), 6.40 (t, *J* = 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 139.8, 107.0, 100.6, 55.4, 33.6.

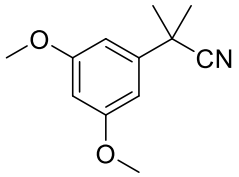
(52) 2-(3,5-Dimethoxyphenyl)acetonitrile[41]



Sodium cyanide (3.98 g, 81.1 mmol, 1.50 equiv) was added in one portion to a solution of 1-(bromomethyl)-3,5-dimethoxybenzene **51** (12.5 g, 54.1 mmol, 1.00 equiv) in dry DMF (120 mL)

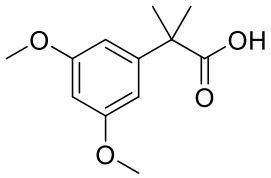
at room temperature (23 °C) and stirred for 4 hours. The reaction was quenched by addition of water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with water (3 x 30 mL), saturated sodium chloride (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford **52** (8.53 g, 89%) as an orange solid. Recrystallization from hot methanol afforded a pale-yellow solid **52** (7.83 g, 83%). MP 50-52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (d, *J* = 2.1 Hz, 2H), 6.41 (t, *J* = 2.1 Hz, 1H), 3.80 (s, 6H), 3.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 131.9, 117.7, 106.1, 99.9, 55.5, 23.8.

(53) 2-(3,5-Dimethoxyphenyl)-2-methylpropanenitrile[42]



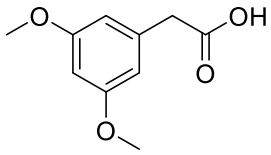
A solution of 2-(3,5-dimethoxyphenyl)acetonitrile **52** (4.47 g, 25.2 mmol, 1.00 equiv) and iodomethane (4.71 mL, 75.6 mmol, 3.00 equiv) in dry DMF (25 mL) was added dropwise to a suspension of sodium hydride [(60 % in mineral oil, washed with pentane) (3.03 g, 75.6 mmol, 3.00 equiv)] and dry DMF (25 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirring was continued for 2 hours. The reaction was diluted with diethyl ether (15 mL) and quenched by slow addition of saturated ammonium chloride (8 mL). The phases were partitioned, and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with water, saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography (1:4, EtOAc:Hexanes) afforded **53** (5.34 g, 99%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (d, *J* = 2.4 Hz, 2H), 6.40 (t, *J* = 2.1 Hz, 1H), 3.81 (s, 6H), 1.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 143.7, 124.3, 103.5, 99.0, 55.3, 37.2, 28.9.

(54) 2-(3,5-Dimethoxyphenyl)-2-methylpropanoic acid[42]



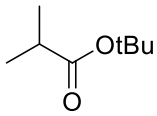
A mixture of 2-(3,5-dimethoxyphenyl)-2-methylpropanenitrile **53** (4.52 g, 22.0 mmol, 1.00 equiv) and sodium hydroxide (2.20 g, 55.1 mmol, 2.50 equiv) in n-butanol (2 mL) and water (1 mL) was refluxed for 16 hours with vigorous stirring. Volatiles were removed under reduced pressure and the residue was acidified with aqueous 10 % hydrochloric acid (until pH ~ 2), diluted with diethyl ether then filtered over a pad of celite. The phases were partitioned, and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic phase was washed with water, saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford **54** (4.30 g, 87%) as a white solid. No purification was necessary. MP 97-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.4 Hz, 2H), 6.37 (t, *J* = 2.4 Hz, 1H), 3.79 (s, 6H), 1.57 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.6, 160.7, 146.2, 104.5, 98.3, 55.3, 46.4, 26.1.

(55) 2-(3,5-Dimethoxyphenyl)acetic acid[42]



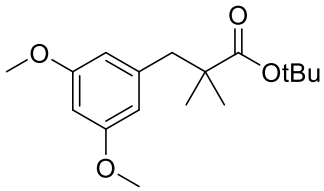
Prepared in the same manner as 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** with 2-(3,5-dimethoxyphenyl)acetonitrile **52** (3.50 g, 19.8 mmol) and sodium hydroxide (1.98 g, 49.5 mmol, 2.50 equiv) in n-butanol (2 mL) and water (1 mL) with refluxing for 16 hours. Afforded **55** (3.43 g, 88%) as a white solid. No purification was necessary. MP 99-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.1 Hz, 2H), 6.37 (t, *J* = 2.1 Hz, 1H), 3.76 (s, 6H), 3.57 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 160.8, 135.2, 107.4, 99.4, 55.3, 41.2.

(56) *tert*-Butyl isobutyrate[43]



Isobutyryl chloride (6.30 mL, 60.0 mmol, 1.00 equiv) was added dropwise to a solution of DMAP (7.70 g, 63.0 mmol, 1.05 equiv) and solid *tert*-butanol (6.67 g, 90.0 mmol, 1.50 equiv) in DCM (43 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was then filtered and concentrated under reduced pressure. The crude residue was dissolved in hexanes and washed with saturated sodium bicarbonate (3x), saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The product was passed through a short alumina pipette column to afford **56** (6.66 g, 77%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (septet, J = 6.9 Hz, 1H), 1.44 (s, 9H), 1.11 (d, J = 6.9 Hz, 6H).

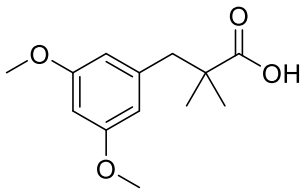
(57) *tert*-Butyl 3-(3,5-dimethoxyphenyl)-2,2-dimethylpropanoate[44]



n-BuLi (2.27 M in hexanes, 9.10 mL, 20.7 mmol, 1.20 equiv) was added dropwise to a solution of diisopropylamine (2.89 mL, 20.7 mmol, 1.20 equiv) in dry THF (20 mL) at 0 °C. After stirring for 15 minutes at 0 °C, the reaction was cooled to -20 °C and **56** (2.98 g, 20.7 mmol, 1.20 equiv) was added dropwise. The resulting solution was stirred for 30 minutes at -20 °C. A solution of **51** (3.97 g, 17.2 mmol, 1.00 equiv) in dry THF (20 mL) pre-cooled to -20 °C was then transferred via a cannula to the lithium enolate solution at -20 °C. The reaction mixture was gradually warmed to room temperature as the cooling bath expired (23 °C) and stirred for 16 hours. The reaction mixture was diluted with diethyl ether (30 mL) and quenched by slow addition of water. The phases were partitioned, and the aqueous phase was extracted with diethyl ether (2x). The combined organic phases were washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography (1:9, EtOAc:Hexanes) afforded **57** (3.48 g, 69%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (bs, 3H), 3.76 (s, 6H), 2.77 (s, 2H), 1.44 (s,

9H), 1.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 160.2, 140.4, 108.4, 98.1, 79.8, 55.0, 46.2, 43.7, 27.9, 25.2.

(58) 3-(3,5-Dimethoxyphenyl)-2,2-dimethylpropanoic acid[44]



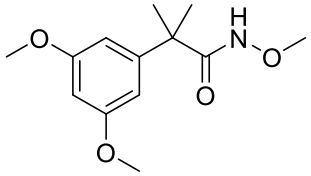
Trifluoroacetic acid (18.0 mL, 247 mmol, 20.1 equiv) was added dropwise to a solution of *tert*-butyl 3-(3,5-dimethoxyphenyl)-2,2-dimethylpropanoate **57** (3.63 g, 12.3 mmol, 1.00 equiv) in dry DCM (48 mL) at room temperature (23 °C) and stirred for 14 hours. The reaction mixture was then washed with 1M hydrochloric acid (2x), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford **58** (2.93 g, quantitative) as a faint brown oil. No further purification was necessary. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34-6.21 (m, 3H), 3.75 (s, 6H), 2.83 (s, 2H), 1.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 160.4, 139.8, 108.3, 98.6, 55.2, 46.1, 43.4, 24.8.

Preparation of Secondary Amides

Coupling of Primary Amines with Carboxylic Acids – General Procedure A[45]

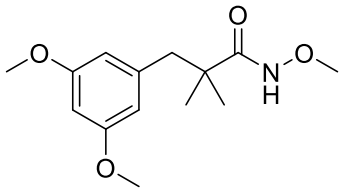
Oxalyl chloride (1.20 equiv) was added dropwise to a solution of carboxylic acid (1.00 equiv) and DMF (2 drops) in dry DCM (0.3M) at 0 °C. The yellow solution was allowed to warm to room temperature (23 °C) and was stirred until bubbling subsided (2-4 hours). The crude acyl chloride was concentrated under reduced pressure, dissolved in dry ethyl acetate (0.1 M) and cooled to 0 °C. Potassium carbonate (2.00 equiv), primary amine (1.00-1.20 equiv) and water (half the volume of ethyl acetate) were then sequentially added to the crude acyl chloride. The reaction mixture was allowed to warm to room temperature and stirred for 12-18 hours. The phases were partitioned, and the aqueous layer was extracted with ethyl acetate (2x). The combined organic phases were washed with saturated sodium bicarbonate (2x), saturated sodium chloride (2x), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude amides were purified by recrystallization or flash chromatography.

(59) 2-(3,5-Dimethoxyphenyl)-*N*-methoxy-2-methylpropanamide



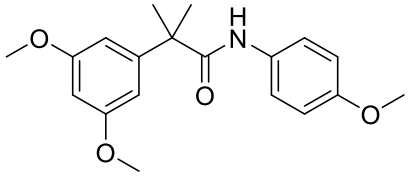
Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (1.00 g, 4.46 mmol, 1.00 equiv) and methoxyamine hydrochloride (0.447 g, 5.35 mmol, 1.20 equiv); secondary amide was purified by recrystallization from hot toluene to give **59** (1.05 g, 93%) as a white solid. MP 71-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (bs, 1H), 6.49 (d, *J* = 1.8 Hz, 2H), 6.38 (t, *J* = 1.8 Hz, 1H), 3.79 (s, 6H), 3.67 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 160.9, 146.2, 104.7, 98.5, 63.9, 55.3, 45.7, 26.7.

(60) 3-(3,5-Dimethoxyphenyl)-*N*-methoxy-2,2-dimethylpropanamide



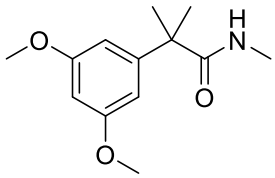
Prepared according to General Procedure A from 3-(3,5-dimethoxyphenyl)-2,2-dimethylpropanoic acid **58** (0.715 g, 3.00 mmol, 1.00 equiv) and methoxyamine hydrochloride (0.301 g, 3.60 mmol, 1.20 equiv); secondary amide was purified by flash chromatography (3:7, EtOAc:Hexanes) to give **60** (0.626 g, 78%) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 6.33 (t, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 2H), 3.75 (s, 6H), 3.68 (s, 3H), 2.79 (s, 2H), 1.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 160.4, 139.8, 108.2, 98.6, 64.2, 55.3, 47.0, 42.6, 24.8.

(61) 2-(3,5-Dimethoxyphenyl)-*N*-(4-methoxyphenyl)-2-methylpropanamide



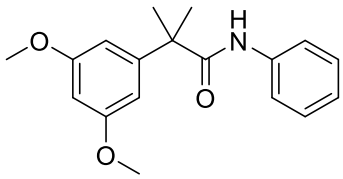
Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (2.00 g, 8.92 mmol, 1.00 equiv) and *p*-anisidine (1.21 g, 9.81 mmol, 1.10 equiv); secondary amide was purified by recrystallization from hot toluene to give **61** (2.20 g, 75%) as a white solid. MP 136-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H), 6.83-6.78 (m, bs, 3H), 6.57 (d, *J* = 2.1 Hz, 2H), 6.40 (t, *J* = 2.1 Hz, 1H), 3.80 (s, 6H), 3.76 (s, 3H), 1.63 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 161.1, 156.3, 147.2, 131.1, 121.6, 114.0, 105.0, 98.7, 55.5, 55.4, 48.0, 26.9.

(62) 2-(3,5-Dimethoxyphenyl)-*N*,2-dimethylpropanamide



Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (1.00 g, 4.46 mmol, 1.00 equiv) and methylamine hydrochloride (0.362 g, 5.35 mmol, 1.20 equiv); secondary amide was purified by recrystallization from hot toluene to give **62** (0.947 g, 89%) as yellow needles. MP 89-92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, *J* = 2.1 Hz, 2H), 6.37 (t, *J* = 2.1 Hz, 1H), 5.21 (bs, 1H), 3.79 (s, 6H), 2.71 (d, *J* = 4.5 Hz, 3H), 1.54 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 160.8, 147.6, 104.9, 98.2, 55.2, 46.9, 26.8, 26.5.

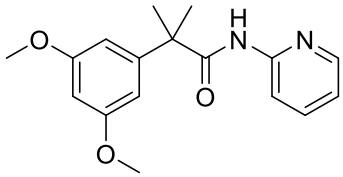
(63) 2-(3,5-Dimethoxyphenyl)-2-methyl-*N*-phenylpropanamide



Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (2.00 g, 8.92 mmol, 1.00 equiv) and aniline (0.82 mL, 8.92 mmol, 1.00 equiv); secondary

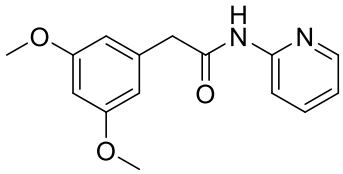
amide was purified by recrystallization from hot toluene to give **63** (2.35 g, 88%) as a pale-yellow solid. MP 140-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (m, 2H), 7.27-7.24 (m, 2H), 7.09-7.03 (t, *J* = 7.2 Hz, 1H), 6.87 (bs, 1H), 6.57 (d, *J* = 2.4 Hz, 2H), 6.41 (t, *J* = 2.4 Hz, 1H), 3.80 (s, 6H), 1.63 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 161.2, 147.0, 138.0, 128.9, 124.1, 119.6, 105.0, 98.7, 55.4, 48.2, 26.9.

2-(3,5-Dimethoxyphenyl)-2-methyl-*N*-(pyridin-2-yl)propanamide



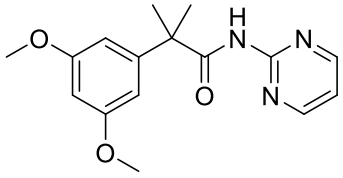
Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (2.00 g, 8.92 mmol, 1.00 equiv) and 2-aminopyridine (1.00 g, 10.7 mmol, 1.20 equiv); secondary amide was purified by flash chromatography (3:7, EtOAc:Hexanes) to give 2-(3,5-dimethoxyphenyl)-2-methyl-*N*-(pyridin-2-yl)propenamide (1.64 g, 61%) as a white solid. MP 93-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (dt, *J* = 8.4, 0.9 Hz, 1H), 8.17 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.70-7.64 (m, 1H), 7.56 (bs, 1H), 6.98 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 2H), 6.39 (t, *J* = 2.1 Hz, 1H), 3.79 (s, 6H), 1.64 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 161.1, 151.4, 147.6, 146.2, 138.1, 119.4, 113.6, 104.8, 98.6, 55.2, 48.1, 26.6.

2-(3,5-Dimethoxyphenyl)-*N*-(pyridin-2-yl)acetamide



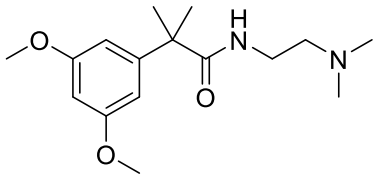
Prepared according to the General Procedure A from 2-(3,5-dimethoxyphenyl)acetic acid **55** (1.00 g, 5.10 mmol, 1.00 equiv) and 2-aminopyridine (0.480 g, 5.10 mmol, 1.00 equiv); crude secondary amide (0.98 g, 70%) was obtained as a yellow oil and used directly in the oxidation step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23-8.20 (m, 2H), 7.87 (bs, 1H), 7.71-7.65 (m, 1H), 7.03-6.99 (m, 1H), 6.47 (d, *J* = 2.1 Hz, 2H), 6.41 (t, *J* = 2.1 Hz, 1H), 3.79 (s, 6H), 3.69 (s, 2H).

2-(3,5-Dimethoxyphenyl)-2-methyl-*N*-(pyrimidin-2-yl)propenamide[30]



Oxalyl chloride (0.320 mL, 3.75 mmol, 1.20 equiv) was added dropwise to a solution of 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (0.700 g, 3.12 mmol, 1.00 equiv) and DMF (2 drops) in dry DCM (10 mL) at 0 °C. The yellow solution was allowed to warm to room temperature (23 °C) and was stirred until bubbling subsided (3 hours). The crude acyl chloride was concentrated under reduced pressure, dissolved in dry DCM (13 mL), and added dropwise to a solution of pyridine (0.760 mL, 9.36 mmol, 3.00 equiv) in dry DCM at 0 °C. After 5 minutes of stirring, a solution of 2-aminopyrimidine (326 mg, 3.43 mmol, 1.10 equiv) in dry DCM (6 mL) was added dropwise over 10 minutes and the resulting mixture was allowed to stir overnight as the cold bath expired. The crude reaction mixture was washed with water, saturated sodium bicarbonate, water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5:95, MeOH:DCM) to give 2-(3,5-dimethoxyphenyl)-2-methyl-*N*-(pyrimidin-2-yl)propenamide (840 mg, 65%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 2H), 6.97 (t, *J* = 4.8 Hz, 1H), 6.57 (d, *J* = 2.1 Hz, 2H), 6.40 (t, *J* = 2.1 Hz, 1H), 3.79 (s, 6H), 1.65 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 161.2, 158.3, 157.6, 146.1, 116.5, 104.9, 99.0, 55.4, 48.8, 26.6.

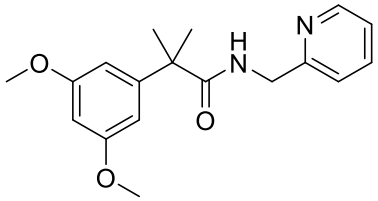
2-(3,5-Dimethoxyphenyl)-*N*-(2-(dimethylamino)ethyl)-2-methylpropanamide



Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (2.00 g, 8.92 mmol, 1.00 equiv) and *N*,*N*-dimethylethylenediamine (1.17 mL, 10.7 mmol, 1.20 equiv); secondary amide was purified by recrystallization from DCM/Hexanes to give 2-(3,5-dimethoxyphenyl)-N-(2-(dimethylamino)ethyl)-2-methylpropanamide (2.08 g, 79%) as a white solid. MP 58-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, *J* = 2.4 Hz, 2H) 6.36 (t, *J* = 2.4 Hz,

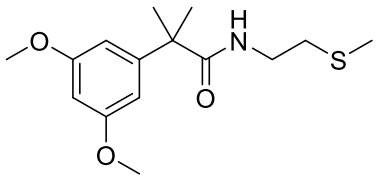
1H), 5.78 (bs, 1H), 3.79 (s, 6H), 3.24 (q, *J* = 5.4 Hz, 2H), 2.28 (t, *J* = 6.3 Hz, 2H), 2.11 (s, 6H), 1.54 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 160.8, 147.8, 104.9, 98.3, 57.8, 55.3, 47.0, 45.1, 37.2, 26.9.

2-(3,5-Dimethoxyphenyl)-2-methyl-*N*-(pyridin-2-ylmethyl)propenamide



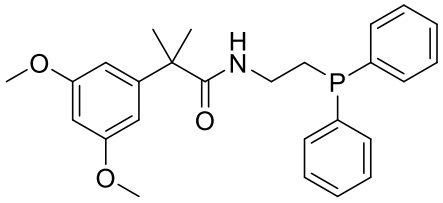
Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (1.00 g, 4.46 mmol, 1.00 equiv) and 2-picolylamine (0.460 mL, 4.46 mmol, 1.00 equiv); crude 2-(3,5-dimethoxyphenyl)-2-methyl-N-(pyridin-2-ylmethyl)propenamide (1.37 g, 98%) was obtained as a yellow oil and used directly in the oxidation step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.19-7.12 (m, 2H), 6.53 (d, *J* = 2.1 Hz, 2H), 6.41 (bs, 1H), 6.36 (t, *J* = 2.1 Hz, 1H), 4.49 (d, *J* = 5.4 Hz, 2H), 3.76 (s, 6H), 1.59 (s, 6H).

2-(3,5-Dimethoxyphenyl)-2-methyl-*N*-(2-(methylthio)ethyl)propenamide



Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (0.850 g, 3.79 mmol, 1.00 equiv) and 2-(methylthio)ethylamine (0.360 mL, 3.79 mmol, 1.00 equiv); crude 2-(3,5-dimethoxyphenyl)-2-methyl-N-(2-(methylthio)ethyl)propenamide (1.04 g, 92%) was obtained as a yellow solid and used directly in the oxidation step without purification. MP 49-51 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, *J* = 2.1 Hz, 2H), 6.37 (t, *J* = 2.1 Hz, 1H), 5.61 (bs, 1H), 3.79 (s, 6H), 3.37 (q, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 6.6 Hz, 2H), 2.03 (s, 3H), 1.55 (s, 6H).

2-(3,5-Dimethoxyphenyl)-*N*-(2-(diphenylphosphaneyl)ethyl)-2-methylpropanamide



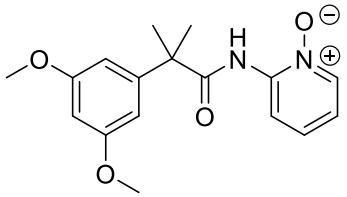
Prepared according to General Procedure A from 2-(3,5-dimethoxyphenyl)-2-methylpropanoic acid **54** (0.876 g, 3.90 mmol, 1.00 equiv) and 2-(diphenylphosphino)ethylamine (0.894 g, 3.90 mmol, 1.00 equiv); crude 2-(3,5-dimethoxyphenyl)-N-(2-(diphenylphosphaneyl)ethyl)-2-methylpropanamide (1.62 g, 95%) was obtained as a yellow solid and used directly in the oxidation step without purification. MP 79-82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (m, 10H), 6.48 (d, *J* = 2.1 Hz, 2H), 6.37 (t, *J* = 2.1 Hz, 1H), 5.45 (bs, 1H), 3.77 (s, 6H), 3.39-3.24 (m, 2H), 2.23-2.18 (m, 2H), 1.50 (s, 6H).

Preparation of Secondary Amides with Oxide Tethers (*N*-Oxides, Sulfoxides and Phosphine Oxides)

Oxidation of Tertiary Amines, Sulfides and Phosphines to Corresponding Oxides – General Procedure B[46]

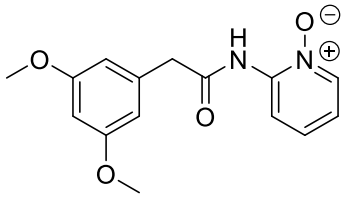
m-CPBA (77% in *m*-chlorobenzoic acid, 1.10 equiv) was added portion-wise over 10 minutes to a solution of secondary amide with tertiary amine, sulfide, or phosphine tether (1.00 equiv) in dry DCM (0.25 M) at 0 °C. The reaction was allowed to warm to room temperature (23 °C) and stirred for 10-16 hours. Aqueous 0.5M sodium hydroxide (1.20 equiv) was added and the phases were partitioned. The aqueous phase was extracted with DCM (2x). The combined organic phases were washed with aqueous 0.5M sodium hydroxide (2x), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude oxides were purified by flash chromatography.

(64) 2-(2-(3,5-Dimethoxyphenyl)-2-methylpropanamido)pyridine 1-oxide



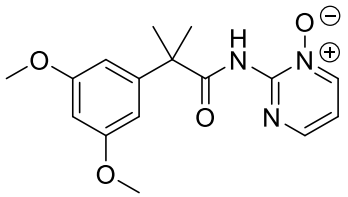
Prepared according to General Procedure B from 2-(3,5-dimethoxyphenyl)-2-methyl-*N*-(pyridin-2-yl)propenamide (1.50 g, 5.00 mmol); N-oxide was purified by flash chromatography (1:1, Me_2CO:Hexanes) to give **64** (1.01 g, 64%) as a yellow solid. MP 103-106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (bs, 1H), 8.41 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.13 (dd, *J* = 6.5, 1.0 Hz, 1H), 7.32-7.26 (m, 1H), 6.92 (ddd, *J* = 7.6, 6.5, 1.9 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 2H), 6.40 (t, *J* = 2.1 Hz, 1H), 3.79 (s, 6H), 1.68 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 161.2, 145.7, 144.4, 136.9, 127.8, 118.3, 114.4, 104.8, 98.8, 55.3, 48.5, 26.4.

(65) 2-(2-(3,5-Dimethoxyphenyl)acetamido)pyridine 1-oxide



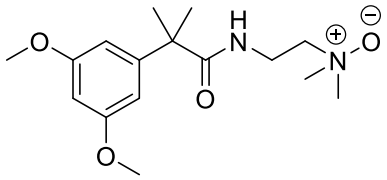
Prepared according to General Procedure B from 2-(3,5-dimethoxyphenyl)-*N*-(pyridin-2-yl)acetamide (0.976 g, 3.58 mmol); *N*-oxide was purified by flash chromatography (3:2, EtOAc:Hexanes) to give **65** (0.430 g, 42%) as a yellow solid. MP 134-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (bs, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 8.18 (d, *J* = 6.1 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.50 (s, 2H), 6.42 (s, 1H), 3.80 (s, 6H), 3.76 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 161.3, 144.1, 137.0, 135.3, 128.0, 118.7, 114.6, 107.4, 99.8, 55.3, 45.3.

(66) 2-(2-(3,5-Dimethoxyphenyl)-2-methylpropanamido)pyrimidine 1-oxide



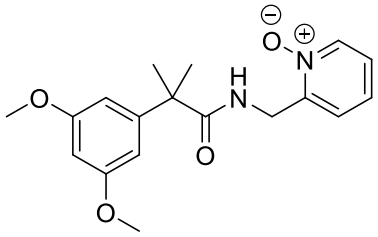
Prepared according to General Procedure B from 2-(3,5-dimethoxyphenyl)-2-methyl-*N*-(pyrimidin-2-yl)propenamide (0.610 g, 2.02 mmol); *N*-oxide was purified by flash chromatography (1:1, Me_2CO:Hexanes) to give **66** (47.2 mg, 7%) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 6.6, 1.8 Hz, 1H), 8.19 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 6.96 (dd, *J* = 6.3 Hz, 4.8 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 2H), 6.40 (t, *J* = 2.4 Hz, 1H), 3.79 (s, 6H), 1.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 161.1, 149.6, 145.2, 144.5, 142.6, 114.6, 104.6, 98.9, 55.2, 48.9, 26.

(67) 1-(2-(3,5-Dimethoxyphenyl)-2-methylpropanamido)-*N*,*N*-dimethylmethanamine oxide



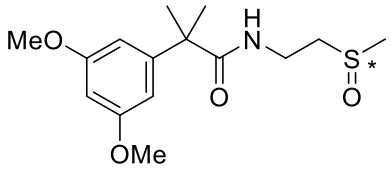
Prepared according to General Procedure B from 2-(3,5-dimethoxyphenyl)-*N*-((dimethylamino)methyl)-2-methylpropanamide (1.47 g, 5.00 mmol); *N*-oxide was purified by flash chromatography (DCM to 1:9, MeOH:DCM) to give **67** (1.18 g, 76%) as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (bs, 1H), 6.52 (d, *J* = 2.1 Hz, 2H), 6.33 (t, *J* = 2.1 Hz, 1H), 3.78 (s, 6H), 3.74 (q, *J* = 6.0 Hz, 2H), 3.38 (t, *J* = 5.7 Hz, 2H), 3.19 (s, 6H), 1.55 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 160.4, 147.6, 104.4, 97.7, 67.5, 59.1, 55.0, 46.3, 35.6, 26.3.

(68) 2-((2-(3,5-Dimethoxyphenyl)-2-methylpropanamido)methyl)pyridine 1-oxide



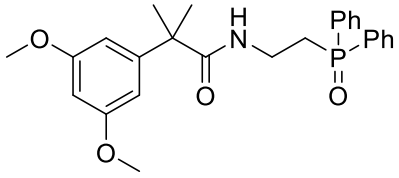
Prepared according to General Procedure B from 2-(3,5-dimethoxyphenyl)-2-methyl-*N*-(pyridin-2-ylmethyl)propenamide (1.37 g, 4.36 mmol); *N*-oxide was purified by flash chromatography (1:1, EtOAc:Hexanes) to give **68** (0.402g, 29%) as a yellow solid. MP 136-139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 5.4 Hz, 1H), 7.36-7.33 (m, 1H), 7.22-7.20 (m, 2H), 6.62 (bs, 1H), 6.44 (d, *J* = 1.8 Hz, 2H), 6.35 (t, *J* = 1.8 Hz, 1H), 4.55 (d, *J* = 6.3 Hz, 2H), 3.75 (s, 6H), 1.52 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 160.8, 147.8, 147.2, 139.3, 125.8, 125.8, 124.7, 104.6, 98.5, 55.2, 47.0, 39.6, 26.7.

(69) 2-(3,5-Dimethoxyphenyl)-2-methyl-*N*-(2-(methylsulfinyl)ethyl)propanamide



Prepared according to General Procedure B from 2-(3,5-dimethoxyphenyl)-2-methyl-*N*-(2-(methylthio)ethyl)propenamide (1.04 g, 3.50 mmol); sulfoxide was purified by flash chromatography (5:95, MeOH:DCM) to give **69** (0.850 g, 78%) as a white solid. MP 96-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (d, *J* = 2.1 Hz, 2H), 6.37 (t, *J* = 2.1 Hz, 1H), 5.96 (bs, 1H), 3.79 (s, 6H), 3.77-3.58 (m, 1H), 3.56-3.53 (m, 1H), 3.06-2.97 (m, 1H), 2.75-2.69 (m, 1H), 2.57 (s, 3H), 1.53 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 160.9, 147.0, 104.8, 98.3, 55.2, 53.5, 46.9, 38.6, 34.3, 26.7, 26.6.

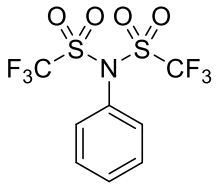
(70) 2-(3,5-Dimethoxyphenyl)-*N*-(2-(diphenylphosphoryl)ethyl)-2-methylpropanamide



Prepared according to General Procedure B from 2-(3,5-dimethoxyphenyl)-*N*-(2-(diphenylphosphaneyl)ethyl)-2-methylpropanamide (1.62 g, 3.72 mmol); phosphine oxide was purified by recrystallization from DCM/Hexanes to give **70** (1.20 g, 71%) as a white solid. MP 141-144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.66 (m, 4H), 7.53-7.46 (m, 6H), 6.46 (d, *J* = 2.1 Hz, 2H), 6.35 (t, *J* = 2.1 Hz, 1H), 6.31 (bs, 1H), 3.76 (s, 6H), 3.58-3.47 (m, 2H), 2.52-2.44 (m, 2H), 1.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 160.8, 147.4, 132.4 (d, $^{1}J_{P\text{-}C}$ = 99 Hz), 131.9 (d, $^{4}J_{P\text{-}C}$ = 2.5 Hz), 130.5 (d, $^{2}J_{P\text{-}C}$ = 9.5 Hz), 128.7 (d, $^{3}J_{P\text{-}C}$ = 12 Hz), 104.7, 98.3, 55.2, 46.7, 34.0 (d, $^{2}J_{P\text{-}C}$ = 3.4 Hz), 29.1 (d, $^{1}J_{P\text{-}C}$ = 70 Hz), 26.6.

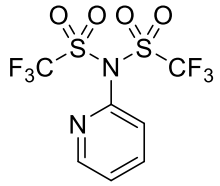
Preparation of Triflating Reagents

(Tf1) 1,1,1-Trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide[47]



Trifluoromethanesulfonic anhydride (0.880 mL, 5.25 mmol, 2.10 equiv) was added dropwise to a solution of aniline (0.230 mL, 2.50 mmol, 1.00 equiv) and triethylamine (0.750 mL, 5.25 mmol, 2.10 equiv) in dry DCM (11 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2 hours, allowed to warm to room temperature (23 °C) and stirred for an additional 16 hours. The reaction was quenched by slow addition of water. The phases were partitioned, and the organic phase was washed with water (2x), aqueous 2M sodium hydroxide (2x), water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a crude white solid (0.824 g, 92%). Crude product was purified by recrystallization from DCM/Hexanes to afford **Tf1** (0.474 g, 53%) as colourless needles. MP 96-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.49 (m, 3H), 7.41 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 132.0, 131.0, 130.0, 119.4 (q, $^{1}J_{F\text{-}C}$ = 325 Hz).

(Tf2) 1,1,1-Trifluoro-*N*-(pyridin-2-yl)-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide[48]



Trifluoromethanesulfonic anhydride (0.880 mL, 5.25 mmol, 2.10 equiv) was added dropwise to a solution of 2-aminopyridine (0.235 g, 2.50 mmol, 1.00 equiv) and pyridine (0.430 mL, 5.25 mmol, 2.10 equiv) in dry DCM (11 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2 hours, allowed to warm to room temperature (23 °C) and stirred for an additional 16 hours. The reaction was quenched by slow addition of cold water. The layers were partitioned, and the aqueous layer was extracted with DCM (4x). The combined organic phases were washed with cold aqueous 10% sodium hydroxide, cold water, brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a crude brown solid (0.858 g, 96%). Crude product was purified by two Kugelrohr distillations (80-85 °C, mmHg unknown) to give **Tf2** (0.618 g, 69%) as a white crystalline solid. MP 39-40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66-8.64 (m, 1H), 7.94 (td, *J* = 7.5, 1.8 Hz, 1H), 7.57-7.52 (m, 1H), 7.47 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 146.0. 139.7, 126.8, 125.5, 119.3 (q, $^{1}J_{F\text{-}C}$ = 325 Hz).

Part 2 – Aromatic Substitutions

General Considerations

All reactions were performed in flame dried Schlenk tubes under a dry nitrogen atmosphere unless otherwise stated. Toluene was freshly distilled over sodium/benzophenone ketyl before use. DCE, DCM, $MeNO_2$, MeCN and PhCl were distilled over CaH_2 and stored in a Schlenk flask under nitrogen. Solvents were degassed via three freeze-pump-thaw cycles. All amine/pyridine bases including: DIPEA, 2-Clpy, 2-Fpy, and 2,4,6-collidine were distilled over CaH_2 and stored in a Schlenk tube under nitrogen. All other reagents were used as received from commercial sources. Reactions were monitored by thin-layer chromatography on commercially prepared plates and visualized by UV (254 nm) or stained with $KMnO_4$. Flash chromatography was performed using 230-400 mesh silica gel.[2]

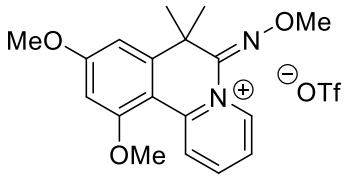
Characterization

Unless otherwise stated, all ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ at 300 and 75 MHz, respectively with a Bruker 300 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) and were calibrated to the solvent residual peak ($CHCl_3$ 7.26 ppm and $CDCl_3$ 77.0 ppm). Abbreviations are as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b). Melting points are uncorrected.

Aromatic Substitutions of Secondary Amides - General Procedure C

Triflic anhydride (37 µL, 0.22 mmol, 1.1 equiv) was added dropwise to a solution of secondary amide (0.20 mmol, 1.0 equiv) and base (0.24 mmol, 1.2 equiv) in DCE (2.0 mL) at 0 °C. After 15 minutes at 0 °C, 2,6-lutidine *N*-oxide (45 µL, 0.40 mmol, 2.0 equiv) was added in one portion and the reaction was stirred for an additional 15 minutes at 0 °C. The reaction mixture was allowed to warm to room temperature (23 °C) over 10 minutes and then heated in an oil bath at 60 °C for 16 hours. The reaction mixture was diluted with DCM and quenched by addition of water. The phases were partitioned, and the aqueous phase was extracted with DCM (2x). The combined organic phases were washed with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

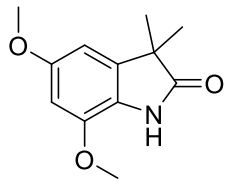
(59a) 9,11-Dimethoxy-6-(methoxyimino)-7,7-dimethyl-6,7-dihydropyrido[2,1-a]isoquinolin-5-ium Trifluoromethanesulfonate



Prepared according to General Procedure C from 2-(3,5-dimethoxyphenyl)-*N*-methoxy-2-methylpropanamide **59** (51 mg, 0.20 mmol, 1.0 equiv) and 2-chloropyridine (23 µL, 0.24 mmol, 1.2 equiv) at 60 °C. Purification by flash chromatography (1:9, MeOH:DCM) gave **59a** (42 mg, 61%) as a bright yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, J = 6.3 Hz, 1H), 8.90 (d, J = 8.7 Hz, 1H), 8.59 (td, J = 7.5 Hz, 1.5 Hz, 1H), 8.06 (td, J = 7.5 Hz, 1.2 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.96 (s, 3H), 1.54 (s, 6H); ^{13}C NMR

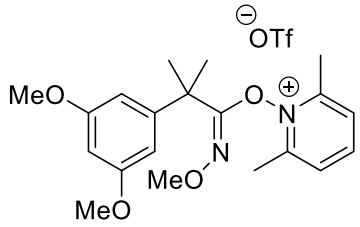
(75 MHz, $CDCl_3$) δ 166.2, 161.5, 147.4, 147.2, 147.0, 144.6, 143.4, 127.4, 123.5, 119.4 (q, $^1J_{F-C}$ = 321 Hz) 105.7, 103.1, 97.6, 64.2, 56.7, 56.2, 40.0 (missing Ar-C-$(CH_3)_2$ quaternary signal).

(59b) 5,7-Dimethoxy-3,3-dimethylindolin-2-one



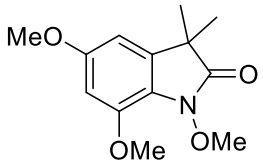
Prepared according to General Procedure C from 2-(3,5-dimethoxyphenyl)-N-methoxy-2-methylpropanamide **59** (51 mg, 0.20 mmol, 1.0 equiv) and diisopropylethylamine (42 µL, 0.24 mmol, 1.2 equiv). Purification by flash chromatography (1:4, EtOAc:Hexanes to 1:1, EtOAc:Hexanes) gave **59b** (13.4 mg, 30%) as a pale yellow solid. MP 162-166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (bs, 1H), 6.40 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.3, 156.9, 144.3, 137.3, 121.6, 100.0, 98.0, 55.9, 55.7, 45.6, 24.3.

(59c) (E)-1-(2-(3,5-Dimethoxyphenyl)-1-(methoxyimino)-2-methylpropoxy)-2,6-dimethylpyridin-1-ium Trifluoromethanesulfonate



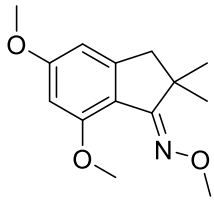
Prepared according to General Procedure C from 2-(3,5-dimethoxyphenyl)-N-methoxy-2-methylpropanamide **59** (51 mg, 0.20 mmol, 1.0 equiv) and diisopropylethylamine (42 µL, 0.24 mmol, 1.2 equiv) at room temperature. Purification by flash chromatography (1:9, MeOH:DCM) gave **59c** (58 mg, 57 %) as a viscous brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (t, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 2.1 Hz, 2H), 6.43 (t, *J* = 2.1 Hz, 1H), 3.83 (s, 6H), 3.50 (s, 3H), 2.53 (s, 6H), 1.72 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 153.0, 148.5, 145.7, 144.2, 127.6, 120.7 (q, $^1J_{F-C}$ = 320 Hz) 104.9, 98.7, 64.3, 55.4, 43.4, 26.4, 17.8.

(59d) 1,5,7-Trimethoxy-3,3-dimethylindolin-2-one[4]



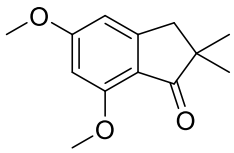
PIDA (77 mg, 0.24 mmol, 1.2 equiv) was added portion wise over 10 minutes to a solution of **59** (51 mg, 0.20 mmol, 1.0 equiv) in MeCN (4 mL) at 0 °C. The mixture was gradually warmed to room temperature as the ice bath expired. After 4 hours, the mixture was poured into a separatory funnel containing saturated sodium bicarbonate (5 mL) and was extracted with ethyl acetate (4 x 2 mL). The combined organic phases were washed with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue purified by flash chromatography (3:7, EtOAc:Hexanes) and gave **59d** (22.4 mg, 45 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 1.36 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 157.5, 145.2, 135.2, 121.0, 100.4, 99.3, 64.5, 56.5, 55.8, 43.1, 24.4.

(60a) (E)-5,7-Dimethoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-one *O*-methyl oxime



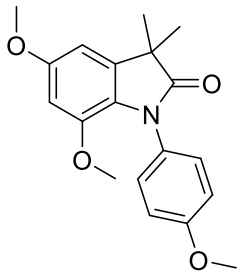
Prepared according to the General Procedure C from 3-(3,5-dimethoxyphenyl)-N-methoxy-2,2-dimethylpropanamide **60** (53 mg, 0.20 mmol, 1.0 equiv) and diisopropylethylamine (42 µL, 0.24 mmol, 1.2 equiv). Purification by flash chromatography (3:7, EtOAc:Hexanes) afforded **60a** (26.5 mg, 53%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32-6.31 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H) 2.83 (s, 2H), 1.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 162.9, 157.7, 149.7, 116.4, 110.7, 97.5, 61.7, 55.7, 55.4, 48.2, 44.4, 26.2.

(60b) 5,7-Dimethoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-one



A mixture of (E)-5,7-dimethoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-one *O*-methyl oxime **60a** (26 mg, 0.10 mmol), 3M HCl (1 mL), and EtOH (1 mL) was heated at 85 °C in a sealed Schlenk tube for 6 hours. After being cooled to room temperature, the reaction mixture was diluted with DCM (2 mL). The phases were partitioned, and the aqueous phase was extracted with DCM (2x). The combined organic phases were washed with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give **60b** (20.3 mg, 83%) as a white solid. No purification was required. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, *J* = 1.5 Hz, 1H), 6.30 (d, *J* = 1.5 Hz), 3.90 (s, 3H), 3.86 (s, 3H), 2.88 (s, 2H), 1.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 167.0, 159.8, 157.1, 117.4, 101.6, 97.4, 55.7, 55.7, 45.7, 42.9, 25.5.

(61a) 5,7-Dimethoxy-1-(4-methoxyphenyl)-3,3-dimethylindolin-2-one

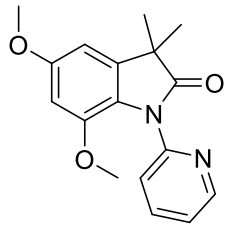


Prepared according to the General Procedure C from 2-(3,5-dimethoxyphenyl)-N-(4-methoxyphenyl)-2-methylpropanamide **61** (66 mg, 0.20 mmol, 1.0 equiv) and diisopropylethylamine (42 µL, 0.24 mmol, 1.2 equiv). Purification by flash chromatography (3:7, EtOAc:Hexanes) afforded **61a** (1.4 mg, 2%) as a white solid. MP undetermined; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.20 (m, 2H), 6.94-6.91 (m, 2H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.52 (s, 3H), 1.45 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 158.5, 156.9, 145.8, 138.1, 129.7, 128.4, 124.0, 113.4, 100.5, 99.5, 56.0, 55.8, 55.4, 44.9, 24.9.

Aromatic Substitutions of Secondary Amides with Oxide Tether - General Procedure D

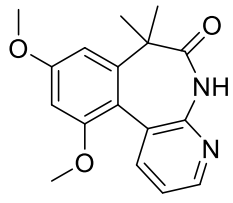
Triflic anhydride (37 µL, 0.22 mmol, 1.1 equiv) was added dropwise to a solution of secondary amide with oxide tether (0.20 mmol, 1.0 equiv) and base (0.24 mmol, 1.20 equiv) in DCE (2.0 mL) at 0 °C. After 15 minutes at 0 °C, the reaction mixture was allowed to warm to room temperature (23 °C) over 10 minutes and then heated in an oil bath at 60 °C for 16 hours. The reaction mixture was diluted with DCM and quenched by addition of water. The phases were partitioned, and the aqueous layer was extracted with DCM (2x). The combined organic phases were washed with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue purified by flash chromatography.

(64a) 5,7-Dimethoxy-3,3-dimethyl-1-(pyridin-2-yl)indolin-2-one



Prepared according to General Procedure D from 2-(2-(3,5-dimethoxyphenyl)-2-methylpropanamido)pyridine 1-oxide **64** (63 mg, 0.20 mmol, 1.0 equiv) and diisopropylethylamine (42 µL, 0.24 mmol, 1.2 equiv). Purification by flash chromatography (1:29:70, TEA:EtOAc:Hexanes) afforded **64a** (26.1 mg, 44%) as a pale-yellow solid. MP 95-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.80 (td, *J* = 7.6, 1.9 Hz), 7.38 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.28-7.24 (m, *J* = 0.9 Hz, 1H), 6.48 (d, *J* = 2.1 Hz, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 3.81 (s, 3H), 3.54 (s, 3H), 1.47 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 157.4, 150.1, 148.5, 146.0, 137.8, 137.4, 123.0, 122.4, 122.0, 100.3, 99.4, 55.9, 55.9, 45.4, 24.9.

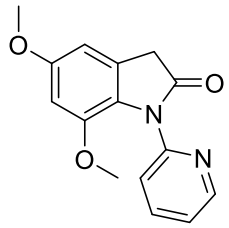
(64b) 9,11-Dimethoxy-7,7-dimethyl-5,7-dihydro-6H-benzo[d]pyrido[2,3-b]azepin-6-one



Isolated as a minor product (12.9 mg, 22%) in above reaction. MP > 250 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (bs, 1H), 8.40 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.08 (dd, *J*

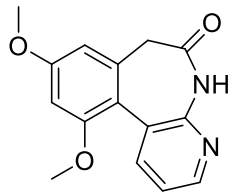
= 7.8, 4.8 Hz, 1H), 6.74 (*d*, *J* = 2.1 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 1.75 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 160.8, 158.0, 148.1, 146.9, 145.5, 140.8, 122.6, 117.9, 115.6, 103.3, 97.8, 55.9, 55.3, 46.5, 26.0, 23.0.

(65a) 5,7-Dimethoxy-1-(pyridin-2-yl)indolin-2-one



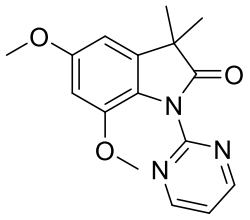
Prepared according to General Procedure D from 2-(2-(3,5-dimethoxyphenyl)acetamido)pyridine 1-oxide **65** (58 mg, 0.20 mmol, 1.0 equiv) and diisopropylethylamine (42 µL, 0.24 mmol, 1.2 equiv). Purification by flash chromatography (1:29:70, TEA:EtOAc:Hexanes) afforded **65a** (17.0 mg, 31%) as a yellow solid. MP 101-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.82 (ddd, *J* = 8.0, 7.5, 1.9 Hz, 1H), 7.38 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.28 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H), 6.54-6.53 (dd, *J* = 2.1, 0.8 Hz, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 2H), 3.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 157.1, 150.0, 148.6, 145.9, 137.6, 126.3, 126.0, 122.7, 122.3, 102.1, 99.8, 55.9, 55.8, 37.2.

(65b) 9,11-Dimethoxy-5,7-dihydro-6H-benzo[d]pyrido[2,3-b]azepin-6-one



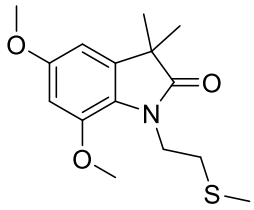
Isolated as a minor product (4.2 mg, 8%) in above reaction. MP > 250 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.35 (bs, 1H), 8.16 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 1H), 3.51 (dd, *J* = 13, 1.8 Hz, 1H), 3.33 (d, *J* = 13 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 161.4, 157.7, 148.3, 147.2, 141.3, 137.0, 122.2, 118.7, 115.2, 104.6, 98.4, 55.7, 55.5, 42.6.

(66a) 5,7-Dimethoxy-3,3-dimethyl-1-(pyrimidin-2-yl)indolin-2-one



Prepared according to General Procedure D from 2-(2-(3,5-dimethoxyphenyl)-2-methylpropanamido)pyrimidine 1-oxide (60 mg, 0.19 mmol, 1.0 equiv), triflic anhydride (35 µL, 0.21 mmol, 1.1 equiv) and diisopropylethylamine (40 µL, 0.23 mmol, 1.2 equiv). Purification by flash chromatography (3:2, EtOAc:Hexanes) afforded **66a** (40 mg, 71%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.8 Hz, 2H), 7.29 (t, *J* = 4.8 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 158.3, 157.6, 156.5, 146.0, 137.5, 122.4, 119.4, 100.2, 99.2, 55.86, 55.82, 45.8, 24.8.

(69a) 5,7-Dimethoxy-3,3-dimethyl-1-(2-(methylthio)ethyl)indolin-2-one



Prepared according to General Procedure D from 2-(3,5-dimethoxyphenyl)-N-(2-(methylsulfinyl)ethyl)acetamide **69** (63 mg, 0.20 mmol, 1.0 equiv) and diisopropylethylamine (42 µL, 0.24 mmol, 1.2 equiv). Purification by flash chromatography (1:29:70, TEA:EtOAc:Hexanes) afforded **69a** (16.6 mg, 28%) as a white solid. MP 111-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.24 (t, *J* = 9.6 Hz, 2H), 3.89 (s, 3H), 3.86 (m, 2H), 3.82 (s, 3H), 2.22 (s, 3H), 1.67 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 161.6, 160.5, 150.5, 115.1, 104.0. 96.8, 67.9, 56.0, 55.2, 54.5, 42.3, 28.5, 18.1.

Bibliography

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