Transition Metal Catalyzed Reactions for the Synthesis of N-heterocycles

BY

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THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Chicago, 2020

Chicago, Illinois

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ACKNOWLEDGEMENTS

I would like to express the deepest appreciation to my committee chair, Prof. Tom Driver who expertly guided me throughout my graduate education and who shared the excitement of six years of research. His unwavering enthusiasm for chemistry kept me constantly engaged with my research, and his personal generosity helped make my time at UIC enjoyable. Without his guidance and persistent help this dissertation would not have been possible.

I would also like to thank my committee members, Prof. Laura Anderson and Prof. Justin Mohr. They have always been good friends to the Driver group. I have learned a lot from both their classes, which helped me grow my knowledge which in turn helped me in my graduate studies. In addition to that, a special thanks to Prof. Laura Anderson for providing insightful suggestions towards the success of my projects. I would also like to thank Prof. Leslie Aldrich for her supportive advice and assistance in my future goals after my graduate studies. Prof. Terry Moore from the College of Pharmacy also provided opportunity to work with them thus extending my knowledge beyond the realm of organic chemistry.

Thanks to all the staff of UIC chemistry department for all their invaluable and innumerable services to keep our research going.

I would also like to thank my current and former lab colleagues. I appreciate Dr Naijing Su, Xinyu Guan, Russel Ford, Tianning Deng, Yuki Yoshinaga, Haoran Zhu for having insightful discussions, which not only motivated me in difficult times but eventually led to the success of our projects. Not only that, thanks to those wonderful time that we had outside the lab exploring almost all the restaurants around UIC, which I will cherish throughout my life.

I would also like to express my deepest gratitude to all my former school, undergraduate, graduate instructors that saw my success before I could see it myself. I would especially like to mention the name of Dr. D.K.Chatterjee and Dr.Ashish Golui who were the reason why I pursued Chemistry as my career. Your contribution towards my success will remain invaluable.

Throughout my journey, I have come across people, who not supported me, but made my life enjoyable in Chicago. I call them “friends for life”. I would like to thank everyone of them especially Rajdeep, Priyanka, Sourav, Indrani, Raktima, Aurobinda, Debajyoti, Neelabja, Tathagata, Srikanth and Shilpa.

Above ground, I am truly indebted to my parents, sister and my extended family, whose value to me only grows with age. Thanks for having faith in me and tolerating my impatience. This journey would not have been possible without

you guys. Finally, I would like to thank and dedicate this to my wife Upasana Banerjee for not only understanding me but also my chemistry. It was fun always to have those discussions after long day of work in the lab. Thanks for being there throughout my journey. I have no valuable words to express my thanks, but my heart is still full of the favors received from every person directly or indirectly.

Contributions of Authors

Chapter 1 represents the introductory chapter which provides a background to my dissertation studies through a review of relevant literature to contextualize the importance of my contributions to the discussed fields of study. Chapter 2 represents a published manuscript for which I was the first author. Dr. Navendu Jana and Bryant T. Thurman assisted me with experiments and substrate scopes. Chapter 3 represents a published manuscript for which Tianning Deng was the first author. I, Dr. Navendu Jana, Russel Ford, Ragda Izar contributed equally to this project. Chapter 4 represents an unpublished manuscript for which I and Yuki Yoshinaga were the first authors. Dana Malo and Darin Hidri assisted us in experiments and synthesizing initial substrates. Chapter 5 is divided into two parts A and B. Part A is a published manuscript in collaboration with UIC College of Pharmacy and Indiana University of Medicine for which Xinyu Guan, I, Dr. Naijing Su, Angie Lockett contributed equally to the project. Part B is an unpublished manuscript which is also another collaboration with UIC College of Pharmacy for which I am the sole author.

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LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bpin	pinacolborane borate
BQ	1,4-benzoquinone
Bz	benzoyl
n-Bu	butyl
t-Bu	*tert*-butyl
Calcd	calculated
cat.	catalytic amount
Cbz	carboxybenyl
COD	1,5-cyclooctadiene
Cond.	condition
Cy	cyclohexyl
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
d	doublet

dba	dibenzylidene acetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DCE	1,2-dichloroethane

LIST OF ABBREVIATIONS (Continued)

DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT	distortionless enhancement by polarization transfer
DFT	Density Functional Theory
DMA	dimethylacetamide
DMB	2,4-dimethoxybenzyl
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMP	Dess–Martin periodinane
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDG	electron-donating group
EE	ethoxyethyl
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
equiv.	molar equivalent
EWG	electron withdrawing group
esp	α, α, α', α'-tetramethyl-1,3-benzenedipropionic acid
G group	Gibbs free energy
g	gram
GC	gas chromatography
h, hrs	hour(s)
HR	high resolution (mass spectrometry)
Hz	Hertz

J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropyl amide
LHMDS	lithium bis(trimethylsilyl)amide

LIST OF ABBREVIATIONS (Continued)

m	multiplet (NMR)
mp	melting point
μ	micro
[M]	metal
M	molar
MS	mass spectrometry
MS	molecular sieves
Me	methyl
Mes	Mesityl
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmol	millimole
mol	mole
MOM	methoxymethyl
MHz	megahertz
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
pfb	perfluorobutyrate, heptafluorobutyrate

Ph	phenyl
Phen	phenanthroline
Piv	pivalyl, trimethylacetyl
PMB	*p*-methoxybenzyl
ppm	parts per million

LIST OF ABBREVIATIONS (Continued)

Pr	propyl
i-Pr	isopropyl
n-Pr	propyl
Py	pyridine
q	quartet (NMR)
quint	quintet (NMR)
rt	room temperature
s	singlet (NMR)
SEM	2-(trimethylsilyl)ethoxymethyl
sept	septet (NMR)
SFC	supercritical fluid chromoatography
t	triplet (NMR)
TBS	*tert*-butyldimethylsilyl
tf	trifluoromethanesulfonyl
TFA	trifluoro acetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tmphen	3,4,7,8-tetramethyl-1,10-phenanthroline
Tol, tol	tolyl
Ts	*p*-toluenesulfonyl
X-Ray	X-radiation

SUMMARY

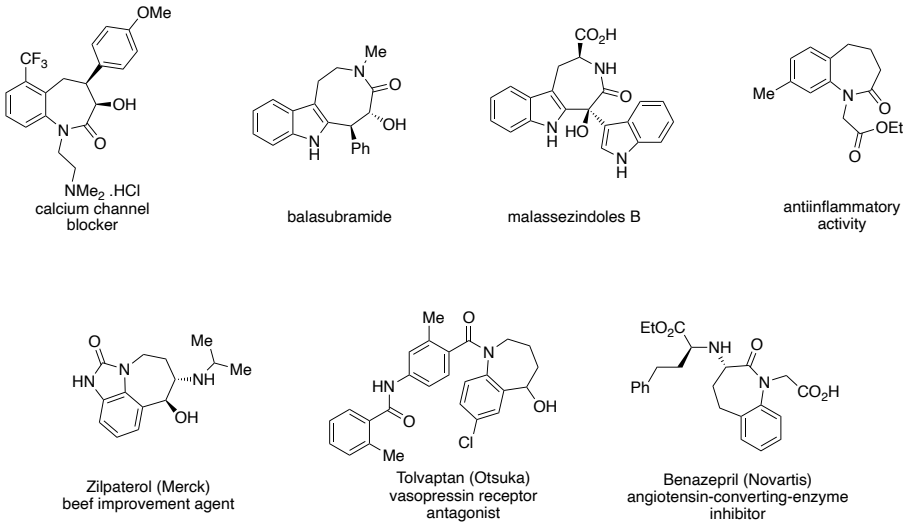
In this thesis, background on classical methods of accessing biologically active medium sized *N*-heterocycles is discussed. Chapter 1 discusses an overview of the successes and limitations of the non-transition and transition metal catalyzed reactions to construct these heterocycles. The Driver group has previously synthesized important *N*-heterocycles through electrocyclization-migration or sp^3 C – H amination strategy. However, they were restricted to only five membered rings.

As an extension of the previous work, I have utilized rhodium (II) carboxylate and Lewis acid catalysts in the synthesis of seven membered *N*-heterocycles using ring expansion strategy starting from aryl azides and aryl anilines respectively. The results of this study are outlined in Chapter 2 and Chapter 3 respectively. Chapter 4 deals with the rhodium (II) catalyzed intermolecular aziridination of olefins using the oxidation of anilines. Chapter 5 is divided into two parts. In Part A, novel NAMPT inhibitors are synthesized for the treatment of Pulmonary arterial hypertension and in Part B, chemical routes to synthesize NAMPT activators are discussed.

Chapter 1. Overview of medium sized *N*-heterocycles

Introduction

Medium-sized nitrogen heterocycles, including seven- and eight membered lactams are structural motifs found in a variety of bioactive compounds and natural products.[1,2] The azepine ring system is present in a wide range of bioactive compounds. This scaffold or closely related variants represent the core structure of many pharmaceutical products. For example, the drugs tolvaptan ™ [3] and benazepril ™,[4] and the beef improvement agent zilpaterol ™,[5] all contain the tetrahydro benzo[*b*]azepine system (Scheme 1.01).

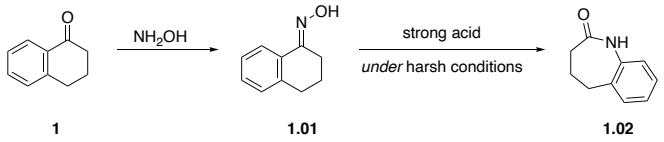


Scheme 1.01 Bioactive compounds, including natural products, with medium-sized nitrogen heterocyclic cores.

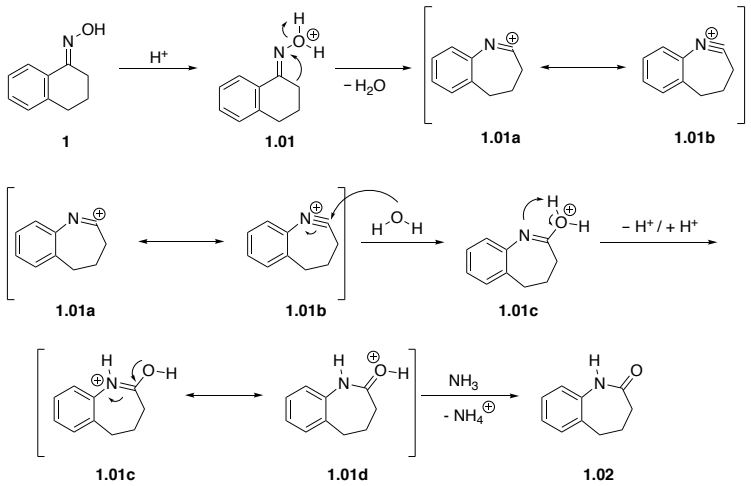
Despite their established pharmaceutical value, azepines and other larger (>6-membered) *N*-heterocyclic rings are underrepresented in drug discovery libraries. This is primarily because of unfavorable enthalpic and entropic barriers in transition states leading to medium-sized rings, which are due to developing Pitzer-[6], Baeyer-[7], and transannular strain.[8] This review summarizes the chemistry of seven-membered heterocycles and puts particular emphasis on new synthetic methods that accesses benzazepine cores. There continues to be strong interest in molecules that contain one-, two- and/or three heteroatoms, particularly those systems fused with aromatic or heteroaromatic rings because of their importance in a variety of natural products with diverse biological activities. Thus, there is a requirement for new transition metal-catalyzed processes for the preparation of aryl or heteroaryl fused seven-membered heterocycles.[9] This review is divided into two parts: the first part focuses on non-transition metal catalyzed reactions and the second part focuses on transition metal catalyzed reactions.

Non-Transition Metal-Catalyzed Reactions

The Beckmann rearrangement,[8,10–15] reported in 1886, is a powerful and atom-economic tool to construct cyclic amides and lactams from their corresponding oximes (Scheme 1.02). This reaction is related to the Hofmann and Schmidt reactions[16–19] and the Curtius rearrangement,[20–25] in that an electrophilic nitrogen is formed that initiates an alkyl migration. Oximes have a high barrier of inversion, and thus this reaction proceeds by protonation of the hydroxyl group of oximes, followed by migration of the alkyl substituent which is *"trans"* to nitrogen to simultaneously cleave the N–O bond through elimination of water (Scheme 1.03).



Scheme 1.02. Classical Beckmann rearrangement

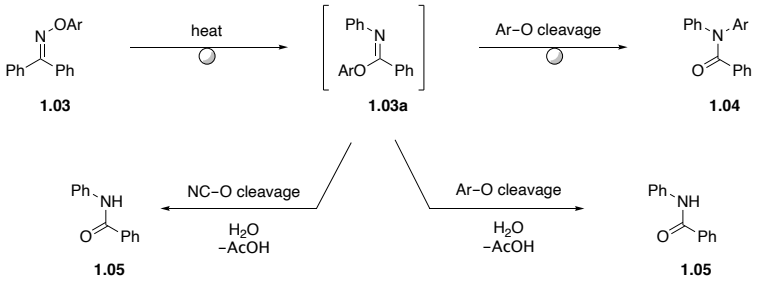


Scheme 1.03. Mechanism of Beckmann rearrangement

While use of Beckmann reaction in the manufacturing of monomers for polymerization of polyamides nylon-6 and nylon-12 is important on a large scale in industrial chemistry, there are significant weaknesses to it that limits its use to produce complex, functionalized *N*-heterocycles.[26–28] Traditionally, this reaction involves harsh conditions such as use of strong acids and high temperatures, [29] as a result of which there are large number of byproducts and compatibility issues with acid-sensitive substrates. Thus, in order to overcome these deficiencies, several organocatalytic methods and Lewis acid catalysis via the activation of the oxime hydroxyl group have been developed in recent years.

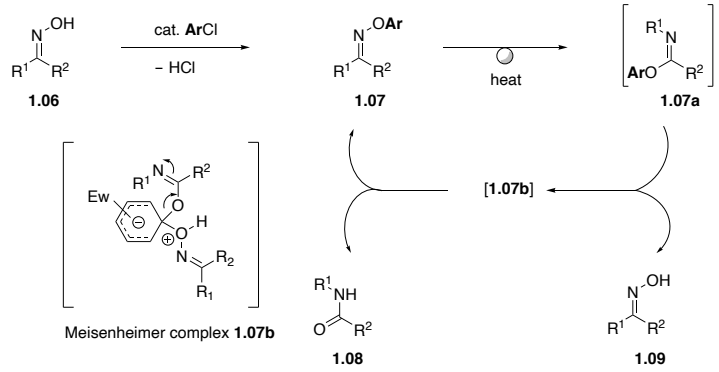
The first example of organocatalytic Beckmann rearrangement was reported by Yamamoto and Ishihara in 2005.[30] They reported that 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) was a highly effective catalyst in Beckmann rearrangement

under reflux in acetonitrile or nitromethane.[31,32] The Beckmann rearrangement of *O*-picrylbenzophenone oxime **1.03** is known to give *N*-picrylbenzanilide **1.04** and benzanilide **1.05**, via a common intermediate, picryl *N*-phenylbenzimidate **1.03a**, under heating conditions in anhydrous and aqueous solvents, respectively (Scheme 1.04). Product **1.04** is formed through a 1,3-shift of the picryl cation of **1.03a** (Ar–O cleavage), while **1.05** is formed through hydrolysis of **1.03a** (Ar–O or NC–O cleavage).



Scheme 1.04. Beckman rearrangement of 1.03 (Ar = 2,4,6-$(NO_2)_3C_6H_2$)

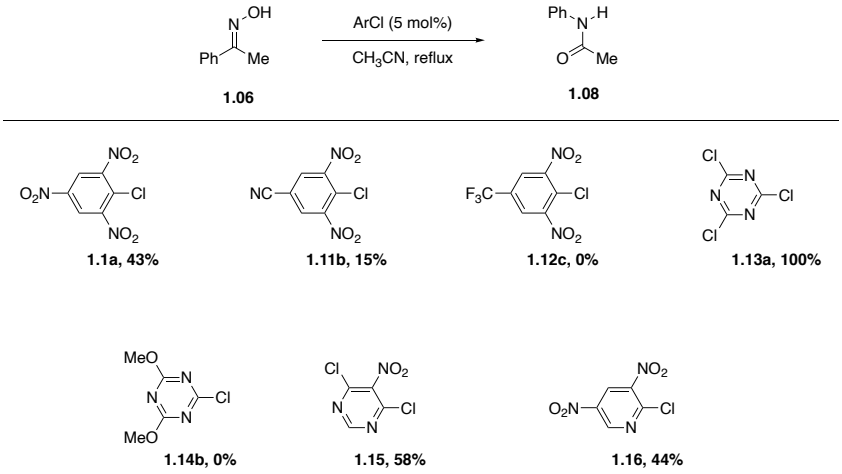
If the rearrangement was performed in the presence of excess benzophenone oxime instead of water, **1.03** may be reproduced with **1.05** through nucleophilic attack of benzophenone oxime to **1.03a**. Thus, based on this assumption, they proposed a new strategy for organocatalyzed rearrangement (Scheme 1.05). They believed that highly electron withdrawing chloroarenes, such as picryl chloride (**1.1a**), might catalytically promote Beckmann rearrangement via the corresponding *O*-aryl ketoxime **1.07**, *O*-aryl imidate intermediate **1.07a**, and Meisenheimer complex **1.07b**.[30]



Scheme 1.05. New strategy for organocatalyzed Beckmann rearrangement

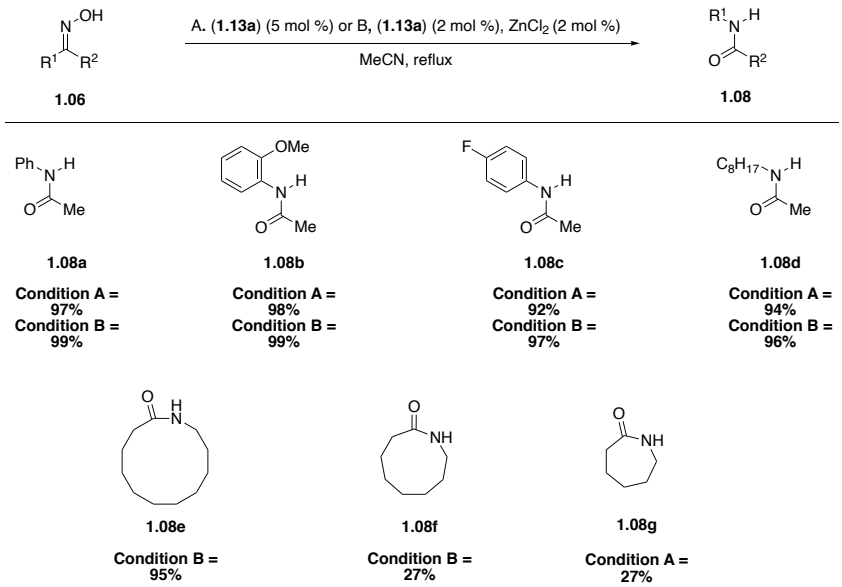
Several chloro-substituted arenes and heteroarenes (5 mol %) were examined as catalysts for the Beckmann rearrangement of oxime in acetonitrile under reflux conditions (Scheme 1.06). The authors found that the use of **1.1a** gave acetanilide in 45% yield. **1.1a** was the most active catalyst among chlorobenzenes bearing electron-withdrawing groups (e.g., **1.11b**, **1.12c)**. Further screening of chloroarenes showed that cyanuric chloride (CNC) (**1.13a**) was much more effective than **1.1a**. **1.14b** was

however inert due to the electron-donating effect of the two methoxy groups. Although they found that **1.15** and **1.16** were as effective as **1.1a**, **1.13a** exhibited the best catalytic activity.



Scheme 1.06. Screening of chloroarenes

Next, several Lewis acids and Bronsted acids were examined as cocatalysts along with CNC to increase its activity. They found that $ZnCl_2$ (as low as 2 mol %) along with CNC (2 mol %) gave the best yield of the amides (Scheme 1.07). To explore the generality and scope, the representative ketoximes were explored by the authors. They found that not only aromatic but also aliphatic ketoximes were smoothly arranged under conditions A and B (**1.08a – d**). Large cycloalkanone oximes were also very reactive and converted to the corresponding lactams (**1.08e**), however, the reaction of six- to eight-membered cycloalkanone oximes gave the desired lactams in poor yields (**1.08f and 1.08g**).



Scheme 1.07. Optimal conditions

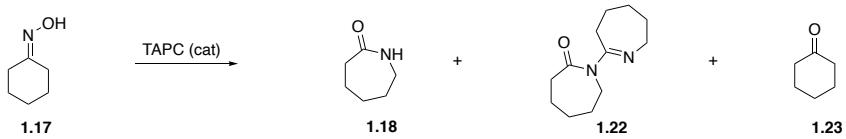
This was the first general organocatalytic Beckmann rearrangement of ketoximes into amides.[30] Though several ketoximes were converted into amides smoothly and in high yields (Scheme 1.07), the rearrangement of cyclohexanone oxime **1.17** to ε-caprolactam **1.18**, which is the most important Beckmann rearrangement in industrial chemistry, only gave yields up to 30 % using 10 mol % of the catalyst.

Ishii and co-workers found that Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam using CNC can be improved by carrying out the reaction in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent.[33] During the course of their study, they wanted to develop a new catalyst other than the Ishihara catalyst,[30] CNC, for Beckmann rearrangement of oximes to lactams under mild conditions. They found triphosphazene, 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC)[33] **1.19a** could efficiently convert ketoximes to lactams. They found TAPC could efficiently transform cyclohexanone oxime to ε-caprolactam which was difficult to achieve by CNC.

The catalytic performance of several catalysts was examined in HFIP and CH_3CN solvent (Scheme 1.08). 1,3,5-Triazo-2,4,6-triphosphorine-2,2,4,4,6,6-fluoride (TAPF) **1.19b**, which is an analogue of TAPC, was found to be inactive. Trichloroisocyanuric acid (TICNA) **1.20** was found to be highly active in HFIP but behaved poorly in CH_3CN. Cyanuric acid (CNA) **1.13a** was inactive, but NBS and NCS showed low activity.[33]

Scheme 1.08. Screening of catalysts

Since TAPC proved to be an efficient catalyst for conversion of several ketoximes to lactams, the most attractive application of TAPC to the Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam was studied (Scheme 1.09). They found that **1.17** was converted to **1.18** and **1.22**. The condensate product **1.22** was hydrolyzed easily to 2 equiv of **1.18** in quantitative yield (98 % isolated yield). This means that **1.17** can be rearranged to **1.18** in an overall yield of 92 %. Thus, in conclusion, they found that TAPC, easily and commercially available, serves as an efficient catalyst for the Beckmann rearrangement.



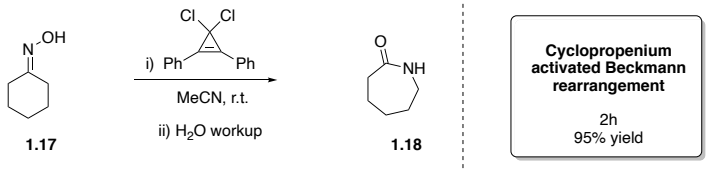
1.17 **1.18** **1.22** **1.23**

entry	catalyst (mol %)	solvent	conv / %[b]	yield / %[b] **1.18**	**1.22**	**1.23**
1	TAPC (1)	HFIP	22	7	3	1
2	TAPC (2)	HFIP	33	13	7	1
3	TAPC (5)	HFIP	88	34	18	2
4[c]	TAPC (5)	HFIP	>99	40	26	trace
5[c]	CNC (5)	HFIP	49	16	7	1
6	TAPC (5)	CH_3CN	39	11	3	5
7[d]	TAPC (5)	CH_3CN	67	20	1	13
8[e]	TAPC (5)	HFIP	56	25	4	8

[a] **1.17** (1.0 mmol) was allowed to react in the presence of catalyst in solvent (2 mL) at 70 °C (bath temperature) for 2 h. [b] By GLC. [c] Reaction time was 4 h. [d] Refluxing temp (ca. 80 °C).[e] H_2O (0.2 mL) was added.

Scheme 1.09. The Beckmann Rearrangement of Cyclohexanone Oxime (1.17) by TAPC or CNC under various conditions [a]

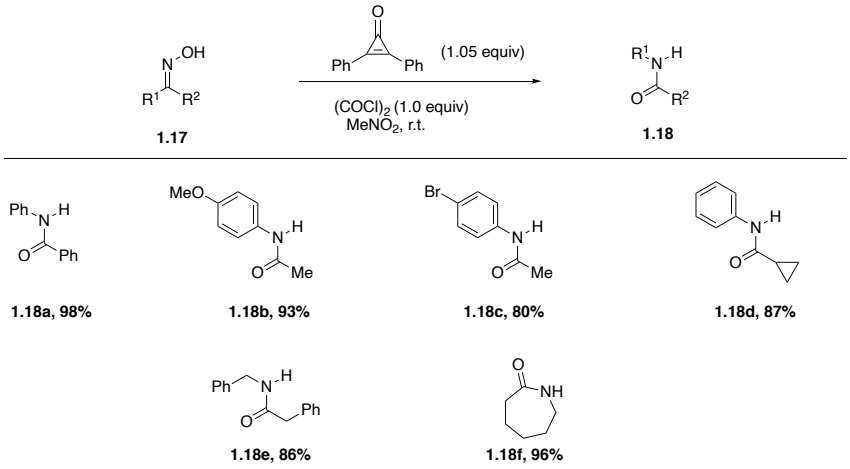
Other notable works on organocatalytic Beckmann rearrangement were done by Lambert and co-workers.[34] In order to see whether cyclopropenium activation was a viable strategy for the promotion of Beckmann rearrangement, they studied the conversion of cyclohexanone oxime (**1.17**) to ε-caprolactam (**1.18**). They found that in fact there was a smooth conversion of the oxime to the lactam in a very good yield (Scheme 1.10).



1.17 **1.18**

Scheme 1.10. Demonstration of cyclopropenium-activated Beckmann rearrangement

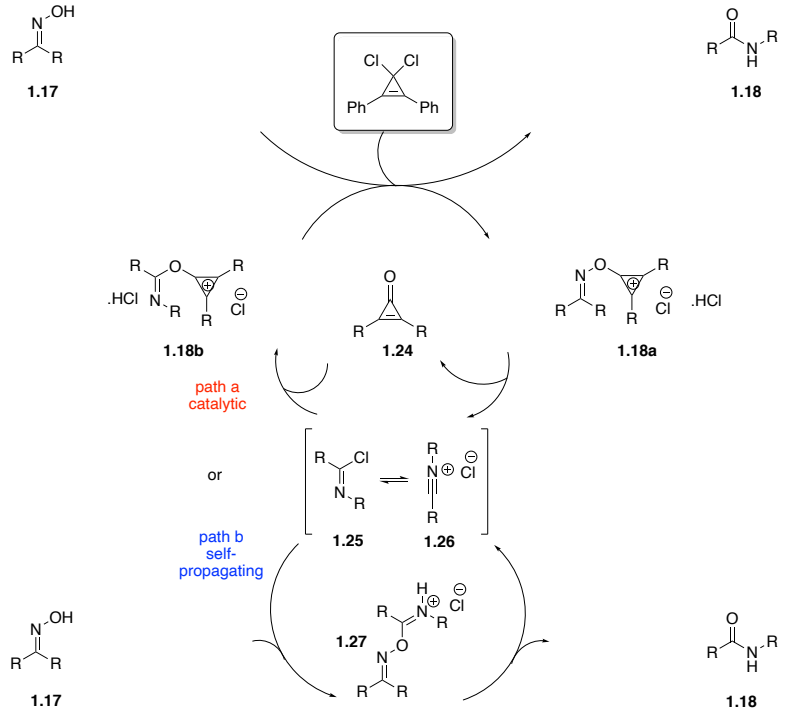
Inspired by the above result, the authors did further optimization studies and investigation of substrate scope revealed high reactivity of cyclopropenium-activated Beckmann rearrangements (Scheme 1.11). Several benzophenones, acetophenones (both electron donating and electron withdrawing), dibenzyl, cyclohexyl oximes smoothly underwent Beckmann rearrangement with high efficiencies.



Scheme 1.11. Scope of cyclopropenium-activated Beckmann rearrangement

With the substrate scope, they envisioned that there were two possibilities by which this mechanism had occurred (Scheme 1.12).[34] First, upon rearrangement of the cyclopropenium oxime **1.18a,** the resulting nitrilium ion **1.26** could alkylate the expelled cyclopropenone **1.24** to produce a cyclopropenium imidate **1.18b**. This imidate could then exchange with another molecule of oxime substrate **1.17** to form the amide **1.18** and thus propagate the catalytic cycle (**path a**). In fact, this was analogous to one first proposed by Ishihara and Yamamoto for their cyanuric chloride-catalyzed protocol.[30]

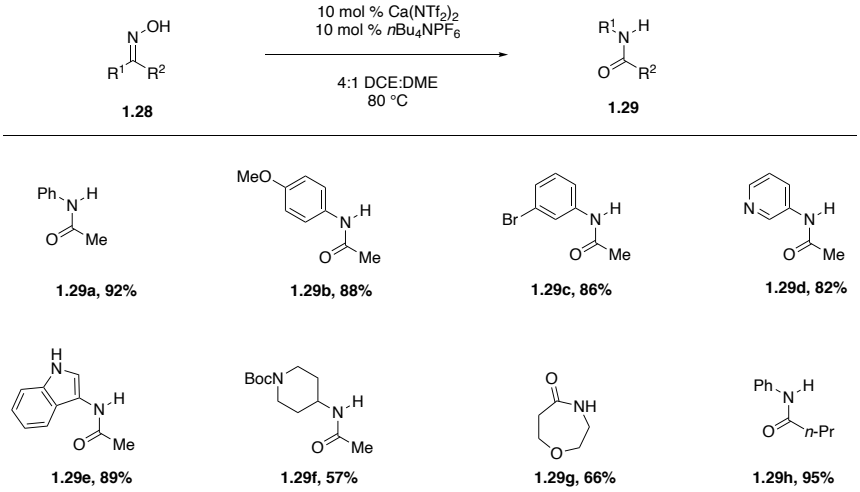
On the other hand, they also recognized another possibility: that nitrilium ion **1.26** (or the imidoyl chloride **1.25**) might alkylate another molecule of oxime **1.17** directly, thus forming intermediate **1.27**, which could then undergo Beckmann rearrangement to produce the amide product and generate nitrilium **1.26** (**path b**). In fact, they found that the self-propagating mechanism (**path b**) was heavily in favor than catalysis (**path a**).[34]



Scheme 1.12. Mechanistic analysis of sub-stoichiometric cyclopropenium-mediated Beckmann rearrangement

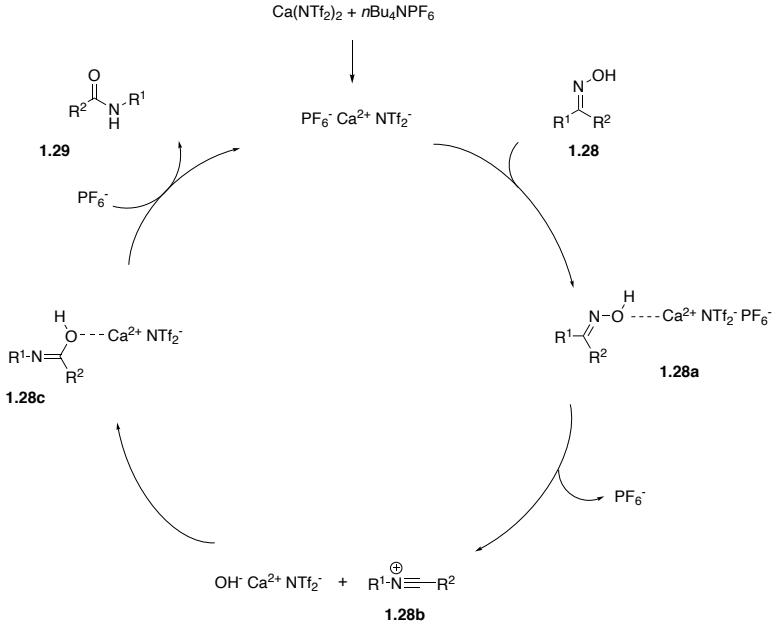
Although all these methodologies provide the amides in good yields and proceed under milder reaction conditions, they still suffer from intolerance to various functional groups. Additionally, many reagents and catalysts conceivably trigger side reactions, thus reducing their use in industry.

McLaughlin and co-workers showed that calcium can be used as a Lewis acid in generating the nitrilium ion which subsequently form the desired amide (Scheme 1.13).[35] They found that 10 mol % of $Ca(NTf_2)_2$ / nBu$_4$NPF$_6$ at room temperature formed the amide in 10% yield. When they heated the reaction to 40 °C, the yield increased to 49%. On further heating the mixture to 80 °C, the desired amide was formed in 93%. They also screened different solvents, but the best yield was obtained in a 4:1 mixture of DCE : DME solvents. With the optimized conditions in hand, the authors studied the scope of the substrates (Scheme 1.13). Though the reaction methodology proved efficient for a variety of functional groups- both electron donating and electron withdrawing groups on aromatic ring, free amines, pyridine, indole, benzimidazole, Boc-protected piperidine, they lacked examples of fused aromatic benzazepinones or in general medium-sized rings.[35]



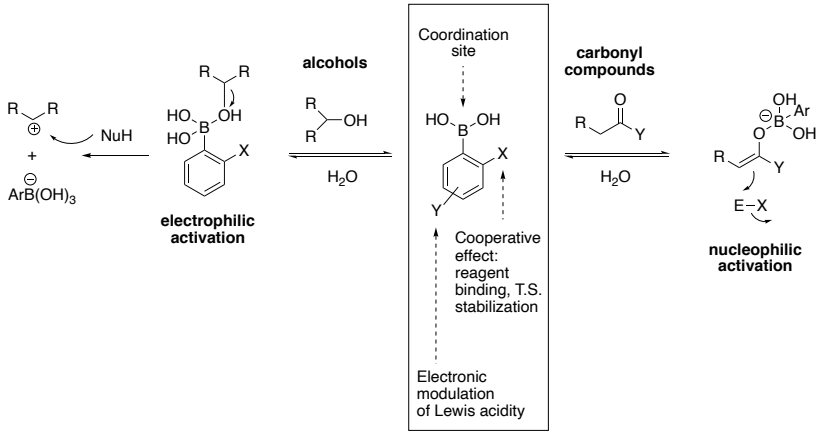
Scheme 1.13. Example of a medium-sized ring lactam

While the mechanism for the Beckmann rearrangements have been the subject of investigation for the past 50 years, [36,37] it is generally accepted that after the oxime is activated and dehydrated, a reactive nitrilium ion is formed. Then this intermediate is attacked by water which upon tautomerization forms the desired amide. In order to understand the true nature of the nucleophile and whether it was preformed water or calcium-oxide type species, they ran the reaction in the presence of 4 Å molecular sieves. They found that full conversion of the oximes to amides took place in 2 hours. Thus, based on this result, the authros suggested a plausible mechanism (Scheme 1.14).[35] Coordination of the hydroxyl group to the calcium catalyst activates the hydroxyl group of oximes which produces transient [OH^- Ca^{2+} PF_6^-]. Elimination from **1.28a** produces nitrilium ion **1.28b** which is then attacked by the calcium hydroxide to form intermediate **1.28c**. The amide **1.29** is then obtained from **1.28c** with the regeneration of the active calcium species through complexation of PF_6^-.



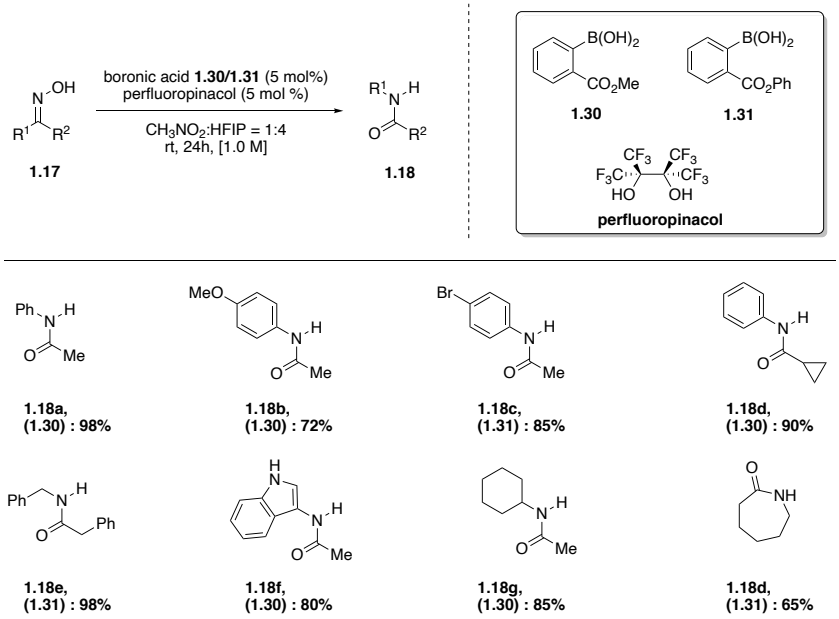
Scheme 1.14. Plausible catalytic pathway

New catalytic methods to activate functional group can unlock new reactivity in organic molecules and lead to new bond forming processes. By applying these to readily available substrates like alcohols and carboxylic acids, efficient and atom-economical processes can be developed that will bypass the use of toxic halide derivatives, Lewis acids or stoichiometric reagents.[38,39] In this regard, the concept of boronic acid catalysis (BAC) that use the Lewis acidity of boronic acids along with their ability to form reversible covalent bonds with hydroxyl functionalities have been used as a mode to activate C–O bonds (Scheme 1.15). Several applications of BAC have been demonstrated by many groups.[40–42] Hall and co-workers have previously reported BAC to substitutions of allylic alcohols[43,44] and Friedel–Crafts alkylation of neutral arenes[45,46] with readily available allylic and benzylic alcohols. In order to expand the scope, they considered direct Beckmann rearrangement of ketoximes to secondary amides.[46]



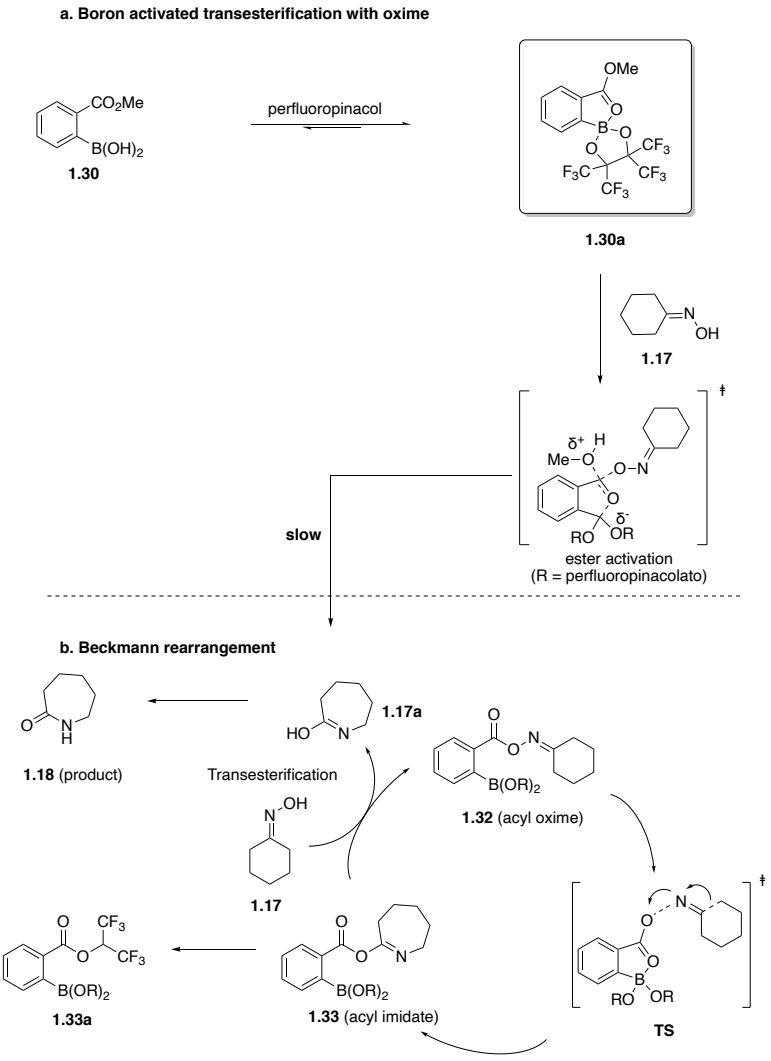
Scheme 1.15. General concept of BAC

After careful optimization, the authors found that 2-methoxy-carbonylphenyl boronic acid provided the significant amount of the amide. They also found that the reaction works best in a solvent mixture of 4:1 hexafluoroisopropanol (HFIP) and nitromethane. HFIP was crucial to the reaction especially for two reasons. It not only provides a polar reaction medium, but also form an electron-poor boronic ester and change the Lewis acidity of the boron atom. To prove their hypothesis, they added a catalytic amount of perfluoropinacol to form a stable cyclic boronic ester. Satisfactorily the target product was formed in excellent yield. Thus, In the presence of perfluoropinacol, boronic acid could be used as low as 5 mol % (Scheme 1.16). Further optimization showed that with the use of phenoxy ester, the reaction time could be shortened, and desired product is formed in a high yield at room temperature. The authors found that several benzophenones, acetophenones (both electron donating and electron withdrawing), dibenzyl, indoles, cyclohexyl oximes smoothly underwent Beckmann rearrangement with high efficiencies.



Scheme 1.16. Substrate scope

The authors proposed the catalytic cycle as shown below (Scheme 1.17).[46] The catalyst reacts with perfluoropinacol to form a more electrophilic boron ester **1.30a**. This mediates the oxime transesterification by activating the carboxyester to form intermediate **1.32**. Carboxyl coordination to the electrophilic boronate turns the benzoyl group into a very reactive leaving group, facilitating bond migration (**TS** in Scheme 1.17 b). The rearranged acyl imidate **1.33** eventually releases the amide product (**1.18)** via exchange with another molecule of oxime.



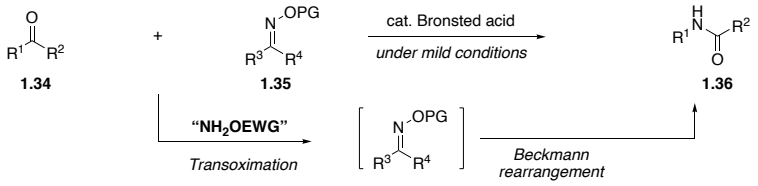
Scheme 1.17. Proposed catalytic cycle of boronic acid catalyzed Beckmann rearrangement

Thus, in summary, they identified boronic acids with catalytic perfluoropinacol as chemoselective organocatalysts for the Beckmann rearrangement under mild conditions at ambient temperature. This operationally simple protocol requires no inert atmosphere or predrying of solvents and displays a broad range oxime substrates and high functional group tolerance. Mechanistic studies not only suggest a novel organocatalytic pathway, but also a true organocatalytic Beckmann rearrangement utilizing the BAC concept.

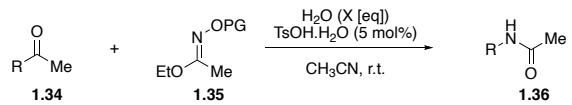
Hyodo and co-workers developed a recent protocol to directly synthesize the amides via Beckmann rearrangement using ketones as the substrate which is a ketoxime precursor (Scheme 1.18).[47] This could be regarded as a formal NH insertion reaction next to the carbonyl carbon of the ketone and would be an attractive method to eliminate both the preparation and tedious purification of oxime isomers.[48]

Direct conversion of ketones to amide have been previously reported by using hydroxylamine salts[49,50] and *O*-(mesitylsulfonyl)hydroxylamine (MSH reagent). However, hydroxylamine is explosive and unstable at high temperature and

needs harsh reaction conditions. While MSH reagent can be used under mild conditions, Al_2O_3/MeOH is needed for the final conversion to the amide after formation of the intermediate *O*-mesitylenesulfonyl ketoxime. Additionally, MSH is explosive and must be handled carefully . [51–53] The transoxamination reaction can be used with more stable oximes instead of unstable hydroxylamine and its derivatives.[54] The authors have previously reported Bronsted acid-catalyzed nitrile synthesis using a similar concept, which showed that an oxime reagent having an electron-withdrawing group on the hydroxyl group acted as a hydroxylamine derivative.[55] Thus, they reported a direct and catalytic synthesis of amide via transoxamination from ketones and Beckmann rearrangement using a bench-stable oxime reagent as an equivalent of MSH.



Scheme 1.18. This work (transoximation)

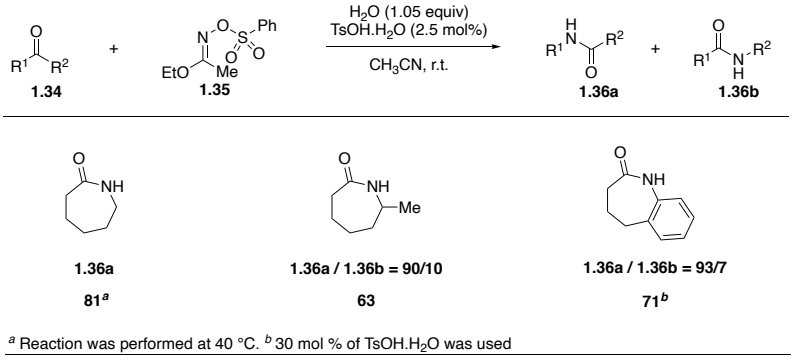


entry[a]	1.35	H_2O (X equiv)	time (h)	yield (%)[c]
1	**1.35a**	0	24	8
2	**1.35a**	0.5	24	49
3	**1.35a**	1.05	8	90
4[c]	**1.35a**	1.05	24	0
5	**1.35b**	1.05	36	95
6	**1.35c**	1.05	24	0
7	**1.35d**	1.05	24	0
8[d]	**1.35a**	1.05	8	91
9[e]	**1.35a**	1.05	24	90

[a] Reaction conditions: **1.34** (0.5 mmol), **1.35** (1.2 equiv), TsOH.H_2O (5 mol %) CH_3CN (1.0 M) at rt. [b] Isolated yield. [c] This reaction was performed without TsOH.H_2O. [d] TsOH.H_2O loading was 2.5 mol %. [e] TsOH.H_2O loading was 0.5 mol % .

Scheme 1.19. Optimization of reaction conditions

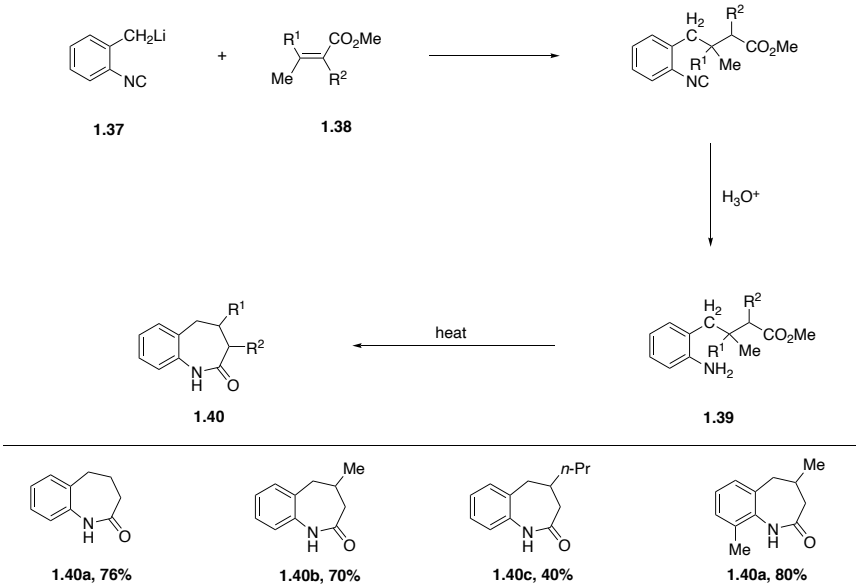
They optimized the reaction conditions for the amide synthesis using 2'-acetophenone **1.34** and oxime **1.35** and found that the reaction works well with TsOH•H_2O as a catalyst in CH_3CN at room temperature (Scheme 1.19). In the absence of H_2O, there was a trace amount of the product. Interestingly, they found that as the loading amount of water was increased, the yield of the desired product also increased. Having optimized conditions in hand, the scope of various substrates was explored (Scheme 1.20). It was found that the more substituted carbon preferentially migrated over the other to give the product in a good ratio > 90 : 10



Scheme 1.20. Substrate scope.

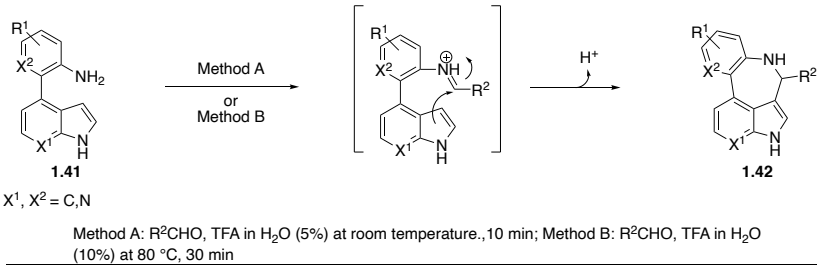
Thus, the authors synthesized several secondary amides and lactams from ketones via the transoximation / Beckmann rearrangement catalyzed by TsOH•H_2O under mild conditions, enabling the use of *O*-protected oximes in place of hydroxylamine salt or MSH reagent .The reaction conditions were not only tolerated by various ketones, but also gave selective amide-migrated products thus making it a powerful synthetic strategy.

Though the preparation of 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-ones has been hitherto performed through Beckmann rearrangements starting with α-tetralone derivatives, Saegusa and co-workers developed a new modular synthetic strategy that involved the construction of the C – N bonds.[56] They used a 1,4-addition reaction of *o*-lithiomethylphenyl isocyanide **1.37** to α,β-unsaturated carboxylic acid esters **1.38** which upon acid hydrolysis gave γ -(o-aminophenyl) butyric acid esters **1.39**, which when heated to 180 °C afforded the benazepinone derivatives **1.40** (Scheme 1.21). This method has a great advantage in that the starting materials because *o*-toluidines and α,β-unsaturated carboxylic acid esters (could use "acrylates" instead), are readily available, and consequently a wide variety of 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-ones can be prepared.

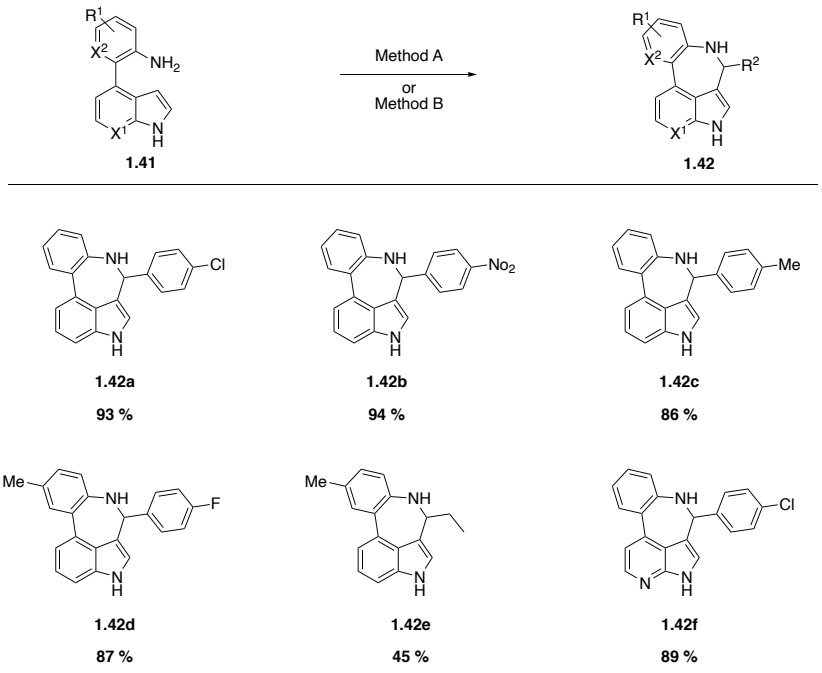


Scheme 1.21. A new synthetic strategy to synthesize 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Kundu and co-workers published an efficient and a versatile method for the synthesis of indole-based polycyclic indolo-benzazepine and its derivatives **1.41** through water-accelerated cationic π-(*7-endo-trig*) cyclization.[57] Their strategy was to condense the arylamine moieties linked to C-4 in indole/azaindole systems **1.42** with arylaldehydes in water containing catalytic amount of Bronsted acids (Scheme 1.22). The formation of C–C bond in water was complete in 10–30 min, whereas in organic solvents in 10–12 h to give the products in excellent yields and purities. Their methodology tolerated electron-donating and electron-withdrawing groups equally (Scheme 1.23).

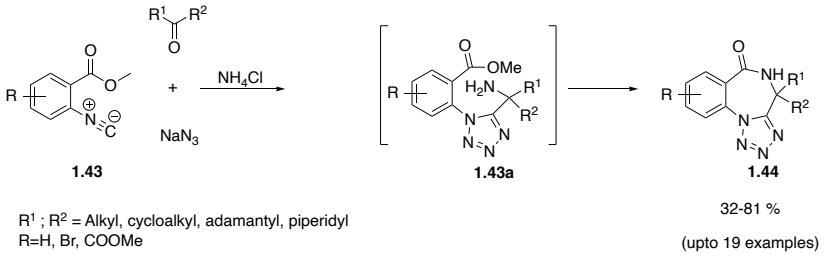


Scheme 1.22. Cationic π-(*7-endo-trig*) cyclization.

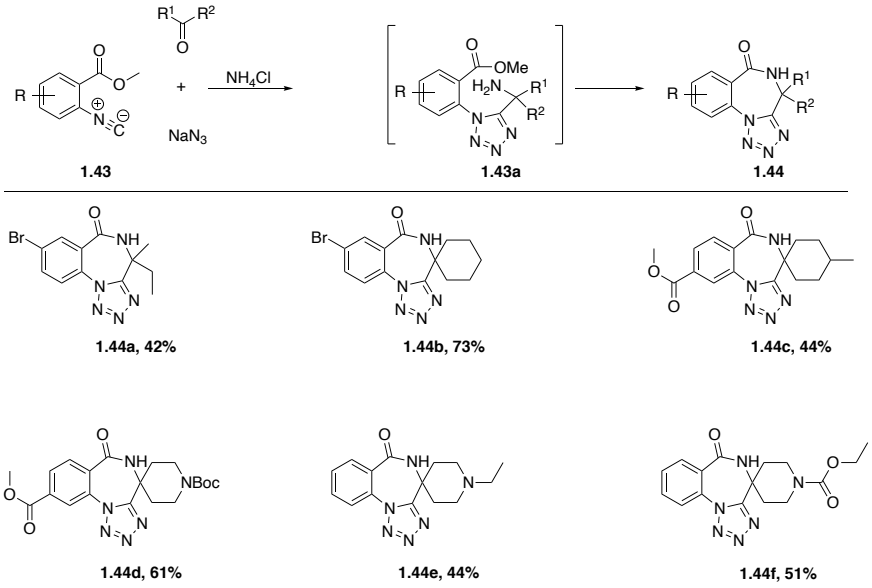


Scheme 1.23. Substrate scope of cationic π-(*7-endo-trig*) cyclization

Among other methods for the synthesis of benzodiazepine derivatives, there is much current interest in isocyanide-based multicomponent reactions because of their modularity and inherent efficiency. Voskressensky and co-workers reported a new azide-Ugi five center four-component reaction of 2-carboxymethyl phenylisocyanide **1.43** with ketones, ammonium chloride and sodium azide afforded amino ester intermediates **1.43a** which spontaneously lactamized into tetrazolo-1,4-benzodiazepines **1.44** (Scheme 1.24).[58] Their methodology tolerated many functional groups as shown below (Scheme 1.25).

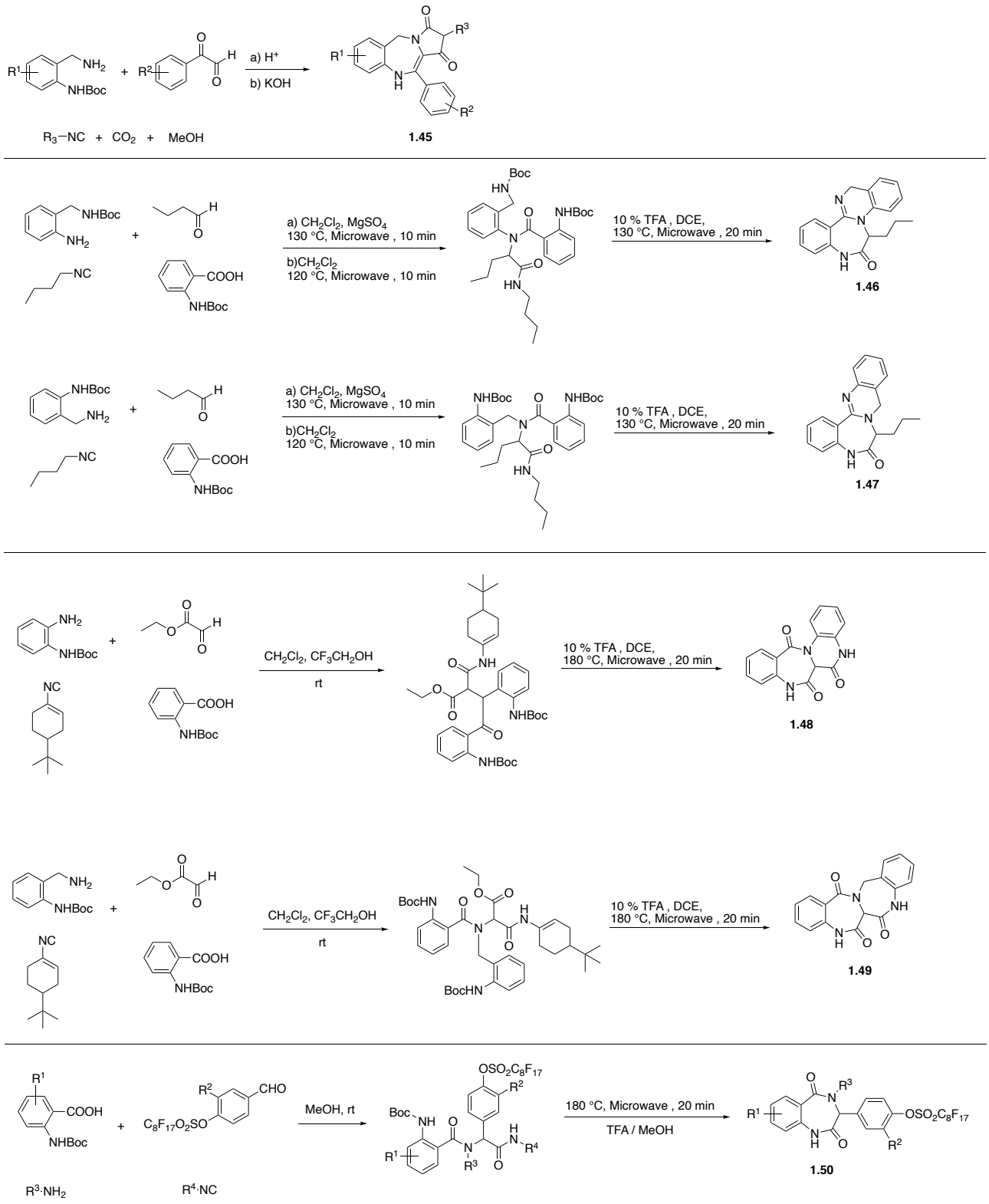


Scheme 1.24. Five center four-component Ugi reaction



Scheme 1.25. Substrate scope of cationic π-(*7-endo-trig*) cyclization

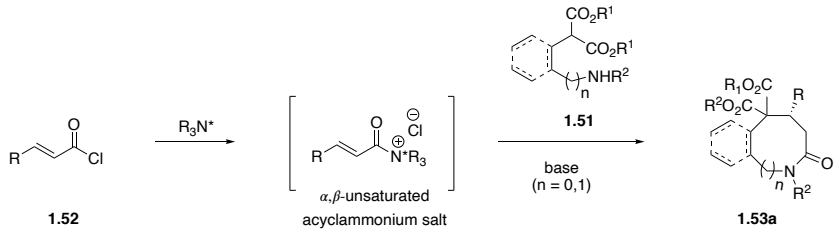
Multicomponent Ugi-type reactions have proved recently to be a common approach to the synthesis of medium-sized *N*-heterocycles (Scheme 1.26). The Ugi five-component carbon-dioxide mediated condensation of ortho-*N*-Boc-amino benzylamines, phenylglyoxyaldehydes, isocyanides and a saturated solution of carbon dioxide in methanol, led to a Boc-protected amine intermediate that was deprotected with TFA promoting cyclization to afford novel fused hydantoin-benzodiazepine derivatives **1.45**.[59] Similar Ugi reactions with aniline or amine Boc-protected 2-aminobenzylamines, aldehydes, isocyanides, and *N*-Boc anthranilic acids followed by deprotection and ring-closure afforded quinazoline-benzodiazepine derivatives **1.46** or **1.47**.[60] Four-component Ugi-deprotection-lactamization reactions of *N*-Boc-1,2-phenylenediamines (or 2-Boc-aminobenzylamines), glyoxylates, isocyanides and *N*-Boc anthranilic acid afforded fused quinoxaline-benzodiazepines **1.48** (or *bis* benzodiazepines **1.49**).[61] Further variations of these multicomponent reactions have been applied to the synthesis of libraries of benzo-1,4-diazepine-2,5-diones **1.50** and benzo-1,5-diazepine-2-ones.[62–64]



Scheme 1.26. Multicomponent Ugi reactions to build various benzazepine cores

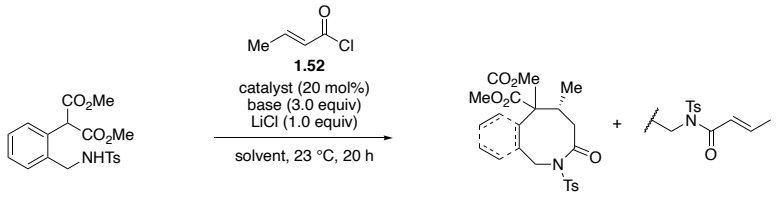
Romo and co-workers recently described a method in which medium-sized heterocycles were enantioselectively synthesized using chiral α,β-unsaturated acylammonium salts. α,β-Unsaturated acylammonium salts have become versatile intermediates for organocatalysis because they are readily available and their divergent reactivity.[1] The authors considered using nucleophile

(Lewis base)-catalyzed Michael addition/proton transfer/lactamization (NCMPL) organocascade to synthesize optically active medium-sized rings, which was previously used to access active γ- and δ-lactams (Scheme 1.27).[65] Thus, they used this strategy to synthesize a large number of heterocycles such as azepanones, benzazepinones, azocanones and benzazocinone in high enantiopurity.



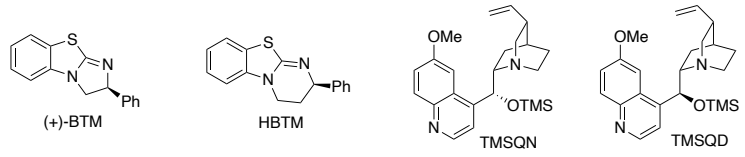
Scheme 1.27. Nucleophile (Lewis base)-catalyzed Michael addition/proton transfer/lactamization (NCMPL) organocascade for the synthesis of medium-sized lactams.

The authors began optimizing conditions towards the synthesis of (+)-benzazocinone (Scheme 1.28). Unfortunately, the previously reported conditions developed for NMPTL employed LiHMDS/DBU as the Bronsted base and TMSQD as the Lewis base catalyst with slow addition of acid chloride did not afford the targeted product.[65] Their optimization investigation, however, identified that enolization under thermodynamic conditions employing Hünig's base and LiCl at ambient temperature gave the desired product in 55% isolated yield with high enantiomeric purity (98:2). Screening of solvents showed that both CH_2Cl_2 and toluene were useful solvents, however the latter gave the best yield (74%). Evaluation of other Bronsted bases with stoichiometric K_2CO_3[66] and other chiral Lewis base catalysts, including BTM and HBTM gave the desired product in trace yields.



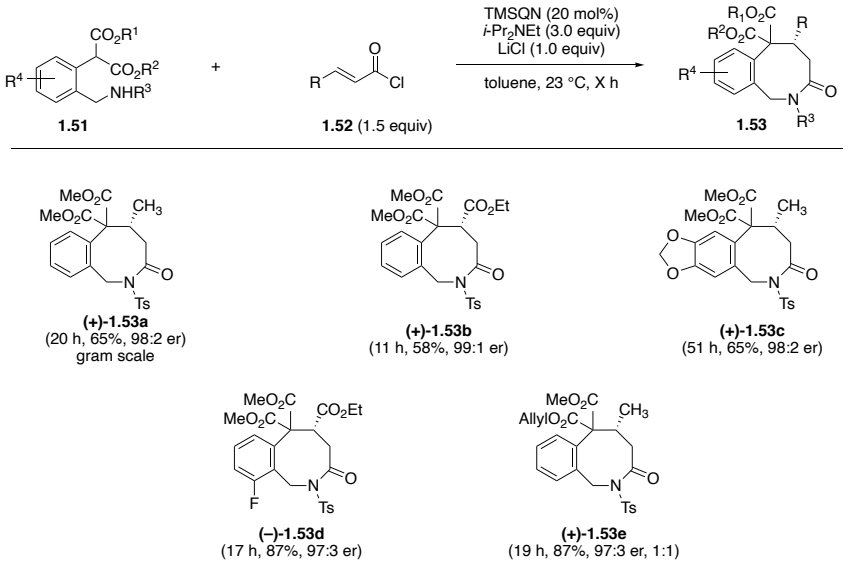
entry[a]	Solvent	Lewis base (equiv)	Bronsted base	yield (%)[b]	er (%)[c]
1[d,e]	THF	TMSQD	LiHMDS with DBU	0	n.d.
2	THF	TMSQN	*i*-Pr_2NEt	55	98:2
3	CH_2Cl_2	TMSQN	*i*-Pr_2NEt	60	98:2
4	toluene	TMSQN	*i*-Pr_2NEt	74	98:2
5	toluene	(+)-BTM	*i*-Pr_2NEt	< 5	n.d.
6	toluene	HBTM	*i*-Pr_2NEt	< 5	n.d.
7[f]	toluene	TMSQD	*i*-Pr_2NEt	71	9:91

[a] Reaction conditions: **1.51** (1.0 equiv), **1.52** (1.5 equiv) and LiCl (1.0 equiv); acid chloride **1.52** was added over 5 h with a syringe pump. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At – 30 °C with 1.05 equiv of LiHMDS and 1.0 equiv of DBU. [e] **1.53a'** was isolated in 4 % yield and 62 % of 1a were recovered. [f] The use of TMSQD gave the enantiomeric bezazocinone (–)-**1.53a**



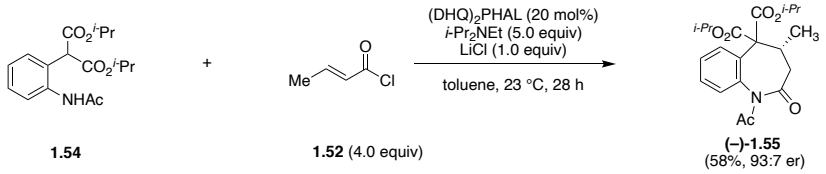
Scheme 1.28. Optimization of the enantioselective Michael addition /proton transfer / lactamization organocascade reaction

With the optimized reaction conditions in hand, the substrate scope with other acid chlorides and variously substituted aryl malonates for the synthesis of benzazocinones were studied (Scheme 1.29).[1] Both electron-donating and withdrawal substituents on the aromatic ring were tolerated, and the authors found that the reaction repeated on a gram scale also gave a comparable yield and enantioselectivity.



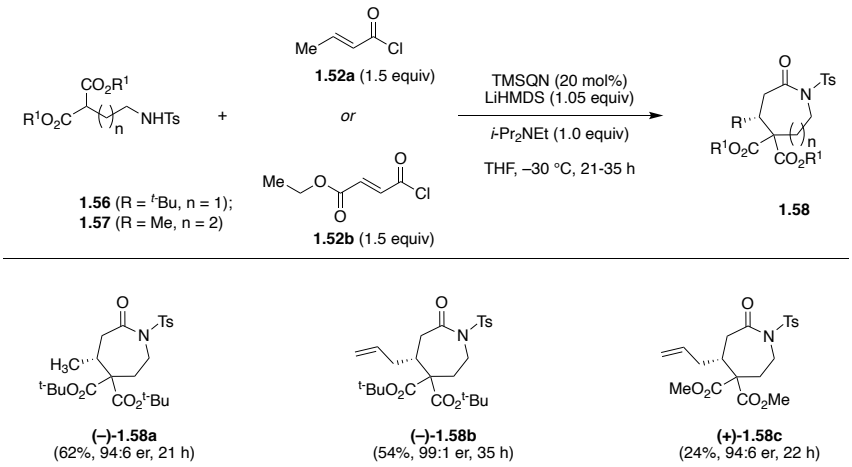
Scheme 1.29. NCMPL organocascade for the synthesis of benzazocinones

The authors also targeted the representative benzazepinone which is a modulator of γ-secretase[67] and serve as longer-acting antihypertensive agents than the often-prescribed diltiazem,[68] which has a benzothiazepine core (Scheme 1.30). They therefore targeted the representative benzo-fused lactam (**1.55**), which they successfully synthesized showing how powerful and efficient their current synthetic strategy it is.



Scheme 1.30. Synthesis of benazepinone

The authors also studied the synthesis of monocyclic lactams through this Michael-addition-initiated organocascade process. A kinetic, strong base , which slowed down the undesired intramolecular *γ*-lactamization, worked best for these substrates and azepanones (–)**-1.58a** and (–)**-1.58b** from tosyl-protected di-*tert*-butyl amino malonates **1.56** as bis-nucleophiles and crotonyl and sorbic chloride respectively. Azocanone (+)**-1.58c** could also be accessed with good optical purity, although in modest yield (Scheme 1.31).[1]



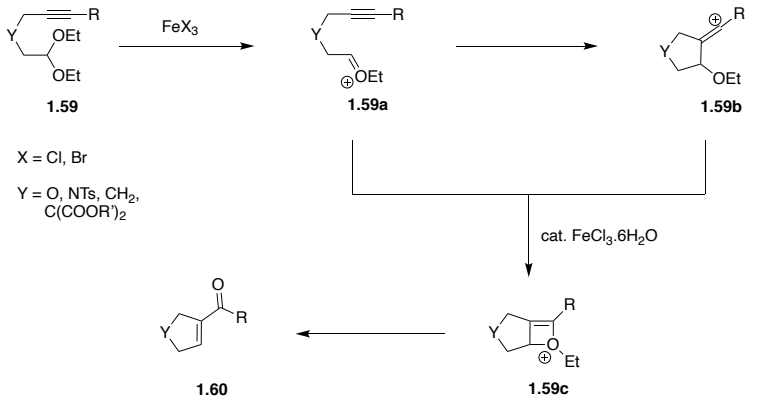
Scheme 1.31. NCMPL for the synthesis of azepanones and azocanones

In conclusion, the authors have developed a direct organocatalytic method for the asymmetric synthesis of medium sized heterocycles, including azepanones, benzazepinones, azocanones and benzazociones. These were prepared from acid chlorides and readily available amino malonates through the formation of α,β-unsaturated acylammonium salts, thus expanding their utility to the synthesis of medium-sized rings which are otherwise difficult to access through conventional methods.

Transition Metal Catalyzed Reactions

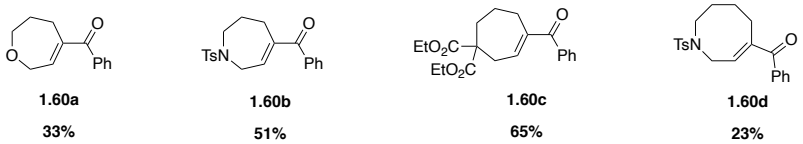
As shown above, medium-sized rings are worth our attention for many reasons; chief among them are their biological activities, and many drugs have medium-sized rings in them. There have been lot of efforts to produce these heterocycles by developing new and efficient synthetic transformations. Among a variety of new synthetic transformations, transition metal-catalyzed reactions have also been reported as an effective strategy to achieve the formation of medium-sized rings. The reason why transition metal catalyzed reactions have been found to be an attractive strategy is because they can directly construct complicated molecules from readily accessible starting materials under mild conditions, thus showing exceptional versatility to access the medium-sized *N*-heterocycles which are otherwise difficult to construct via traditional methods.[69]

Li and co-workers reported Fe (III)-catalyzed Prins cyclization/halogenation of the alkynyl acetals in 2010.[70] The authors anticipated that intramolecular [2+2] cycloaddition of the alkynyl and oxocarbenium moieties in **1.59a** or nucleophilic attack of the ethoxy oxygen in **1.59b** gave **1.59c** which formed **1.60** through eliminative ring-opening pathway (Scheme 1.32).



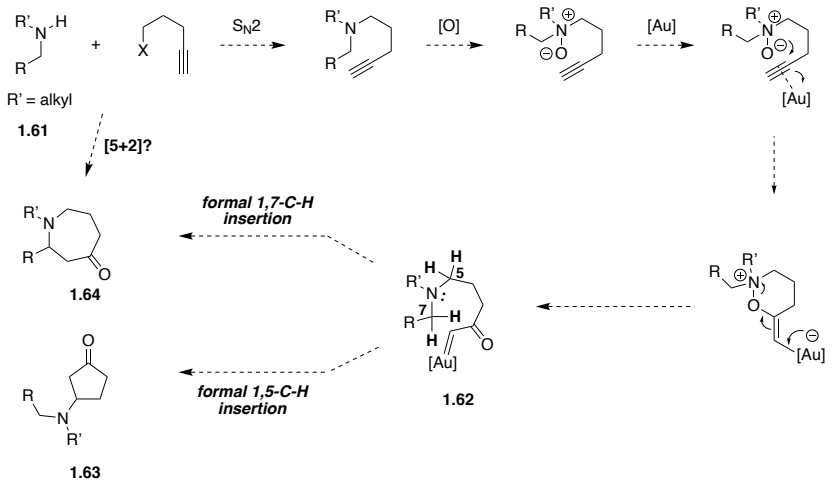
Scheme 1.32. FeX_3-catalyzed cyclization of alkynyl acetals

Careful optimization showed that as low as 5 mol % of $FeCl_3$•$6H_2O$ in DCE or acetone at room temperature or slightly elevated temperatures can form a wide range of medium-sized ring compounds as shown below (Scheme 1.33). The authors found that the reaction was in general good for seven membered rings (**1.60a**, **1.60b, 1.60c**). Heteroatoms were also tolerated. However, the rarer eight-membered ring was formed in low yields (**1.60d**).



Scheme 1.33. FeX_3-catalyzed cyclization of alkynyl acetals

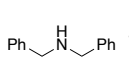
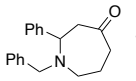
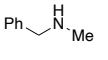
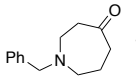
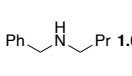
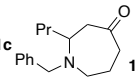
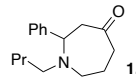
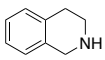
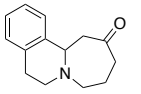
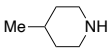
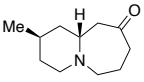
Zhang and co-workers reported a gold-catalyzed synthesis of azepan-4-ones *via* a two-step [5+2] annulation strategy in 2010.[71] The authors have previously reported a two-step synthesis of piperidine-4-ones in a two-step [4+2] mode.[72] Thus, they thought that [5+2] sequence might be possible, which would give azepan-4-ones which are synthetically useful substrates (Scheme 1.34).[73] In this strategy, a gold carbene intermediate **1.62** would form by a gold-catalyzed alkyne oxidation intramolecularly and then a challenging 1,7-C(sp^3)–H insertion by carbene **1.62** over a usual more feasible formal 1,5-C(sp^3)–H insertion during the ring formation step.[74–83]



Scheme 1.34. Two steps formal [5+2] annulation for the synthesis of azepan-4-ones?

The authors studied the scope of the above mentioned chemistry, which involved two steps: 1) *in-situ* generated 5-iodopent-1-yne was alkylated in refluxing MeCN for 12 h using K_2CO_3 as base; 2) *m*-CPBA oxidation followed by (2-biphenyl)$Cy_2PAuNTf_2$ (5 mol%) catalyzed reaction at 0 °C (Scheme 1.35).[71] The authors found that the alkylation step was expectedly efficient and the second step *i.e*. one pot oxidation / gold catalysis was also efficient for the annulation. For symmetric secondary amine (entry 1), the two-step sequence tolerated phenyl groups. For the unsymmetrical secondary amines (entry 2 and 3), the chemistry was sensitive to steric difference and in most cases good to excellent regioselectivities were observed. For example (entry 2), Me group participated highly selectively over a benzyl group. Entry 3 shows that both migrated products were formed, however phenyl migrated product was less than the *n*-propyl group (since phenyl is bigger than *n*-propyl). While the above examples show that sterics outplayed electronics in determining regioselectivity, under similar steric environment, however, electronic difference could provide significant regioselectivity. Thus Entry 4 shows that exclusive formal insertion into its benzylic C – H, yielding **1.64d** in 70% yield. The reaction also showed higher diastereoselectivity in case of 4-methylpiperidine (entry 5). Thus, they discovered a gold-catalyzed efficient synthesis of azepan-4-ones via a two-step [5+2] annulation. The reaction is sensitive to steric differences and is highly regioselective. Good to excellent

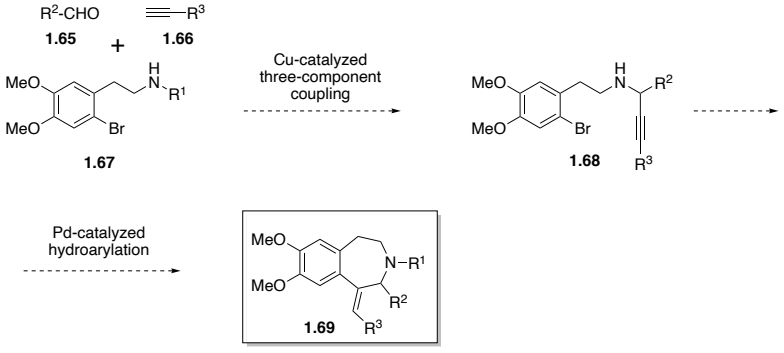
diastereoselectivities were achieved. This chemistry opens an easy, flexible, and efficient route to access various azepane derivatives.[71]

Entry[a]	Substrate	Product[b]	Yield (%) 1st Step	Yield (%) 2nd Step
1	 **1.61a**	 **1.64a**	99	87
2	 **1.61b**	 **1.64b**	85	85
3	 **1.61c**	 **1.64c** 2 :  **1.64c'** 1	93	73[c,d]
4	 **1.61d**	 **1.64d**	80	70
5	 **1.61e**	 **1.64e** d.r. > 20:1	84	76[e]

[a] The reaction concentration was 1 M for the first step and 0.05 M for the second step. [b] Regioselectivity, if not indicated, is > 20:1. [c] Et_3PAuTf_2 (5 mol%) was used instead. [d] Reaction time: 6 h. [h] Reaction time: 3.5 h

Scheme 1.35. Synthesis of azepan-4-ones *via* a two-step, 5 + 2 annulation strategy: scope study

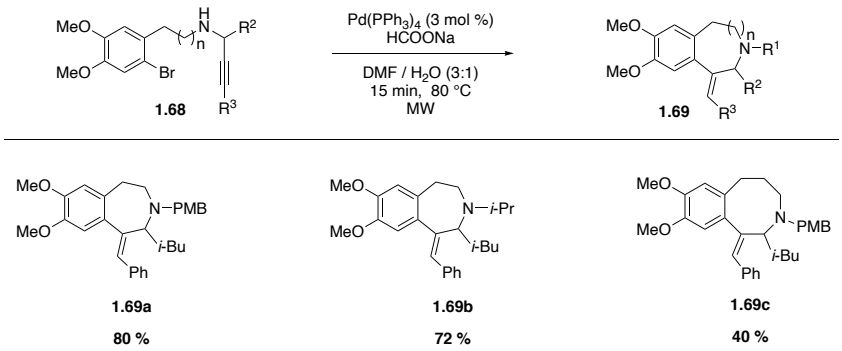
Eycken and co-workers reported a two-step diversity-oriented synthesis of 3-benzazepines **1.69**.[84] Their method consisted of two steps: 1) a three-component coupling between an aldehyde **1.65**, an alkyne **1.66** and an amine **1.67** mediated by Cu^I to form the propargylamines **1.68**,[85–92] 2) intramolecular acetylene hydroarylation reaction mediated by Pd which selectively form the seven-membered 3-benzazepine backbone (Scheme 1.36).



Scheme 1.36. Construction of 3-benzazepine backbone

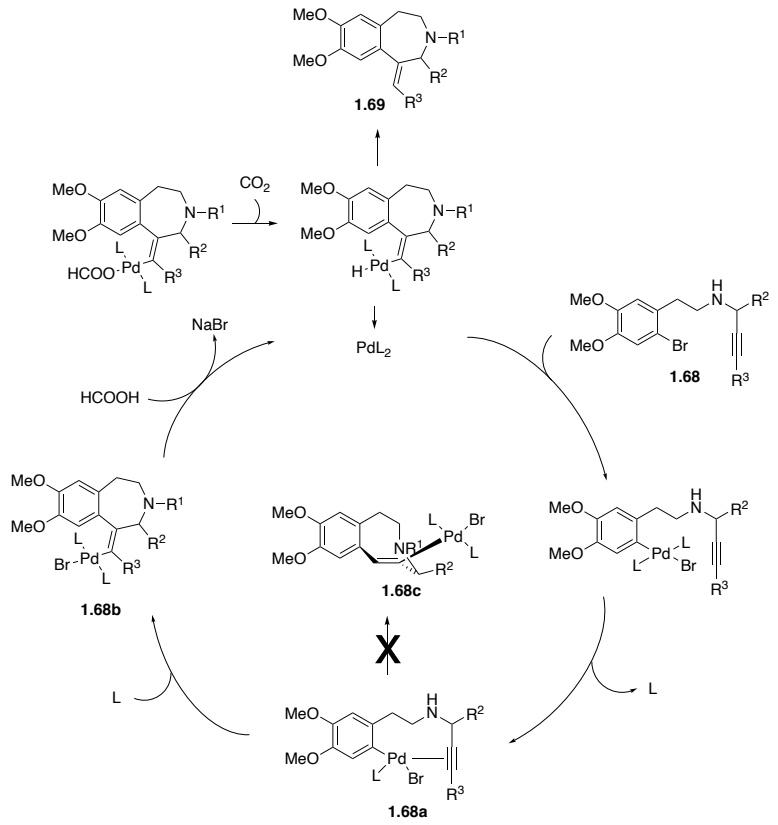
The authors did an optimization study for both the steps. Optimal conditions for the three-component coupling was found to be using CuI (15 mol %) either neat or in PhMe assisted by micro-wave. Then, they studied the Pd-catalyzed intramolecular

reaction and found that $Pd(PPh_3)_4$ (3 mol %), HCOONa in a binary solvent of DMF / H_2O (3:1) gave best yields of the corresponding 3-benzazepine products. The representative scope is shown below (Scheme 1.37). Though the authors developed a two-step protocol for the synthesis of 3-benzazepines, there were less substrate scopes as show below.



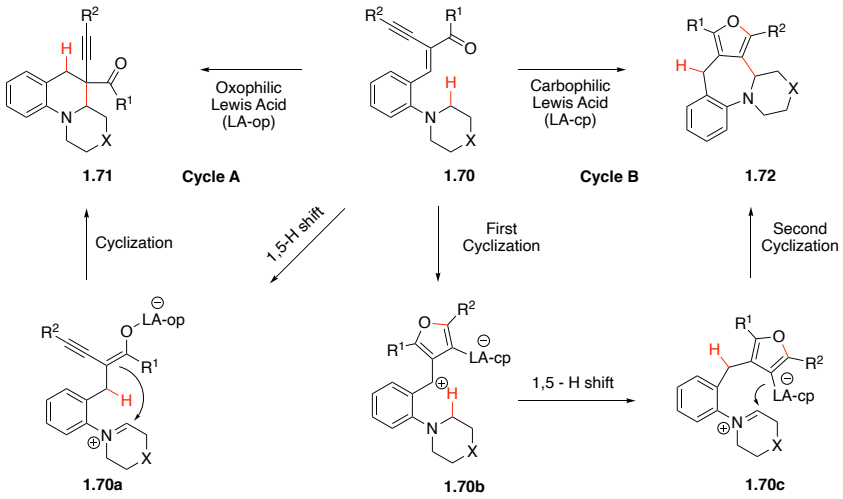
Scheme 1.37. Scope of the reaction

The authors proposed a possible pathway for the Pd-catalyzed intramolecular acetylene hydroarylation (Scheme 1.38).[84] Since *syn*-addition takes place across the triple bond, this strategy exclusively forms compounds **1.69** having Z-configuration of the exocyclic double bond. The authors proposed that the regioselectivity of the reaction and thus the ring size of the generated medium-sized ring, is also governed by the reaction mode. Initially an arylpalladium π-complex **1.68a** is formed which is then transformed into a σ-vinyl palladium complex **1.68b** via simultaneous *syn*-addition to the triple bond. Endocyclization via a hypothetical intermediate **1.68c** is unlikely due to the high strain exerted by the *trans*-geometry around the double bond in the medium-sized ring. Thus only 7- or eight-membered rings are formed.



Scheme 1.38. Proposed mechanism of Pd-catalyzed intramolecular acetylene hydroarylation reaction.

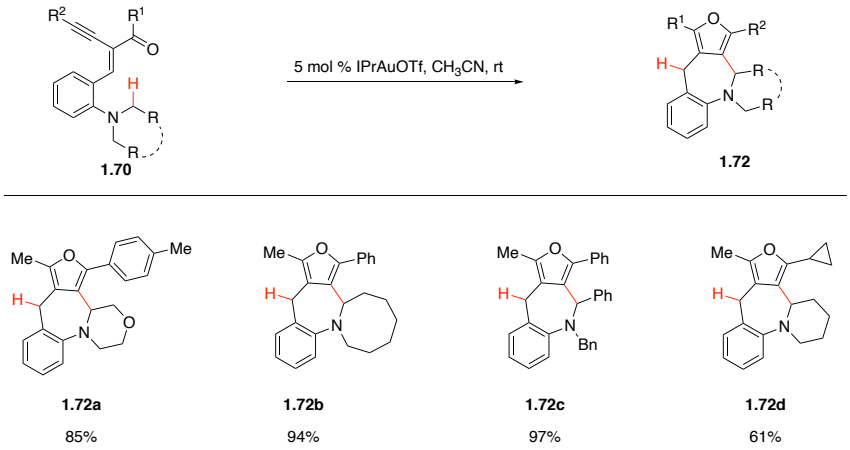
Selective synthesis of ring-fused tetrahydroquinolines and tetrahydroazepines from yne-enones via intramolecular redox reaction was proposed by Zhou and Zhang.[93] In this case the nature of the product was controlled by the nature of the catalyst. Use of oxophilic $Sc(OTf)_3$ selectively gave tetrahydroquinolines and a carbophilic IPrAuOTf gave tetrahydroazepines (Scheme 1.39).



Scheme 1.39. Proposed mechanism

The authors speculated that in the presence of Lewis acid (Scheme 1.39, Cycle A), the reaction would proceed through a zwitterionic intermediate **1.70a** *via* a 1,5-hydride shift,[83,94–96] which in turn would undergo cyclization to give tetrahydroquinolines **1.71**. In this case, the alkyne moiety plays a role as a substituent. However, carbophilic Lewis acid would initiate a heterocyclization (Scheme 31, first cyclization) by activation of the alkyne moiety to generate the furanyl[97–102] intermediate **1.70b** which then undergoes a 1,5-hydride shift to produce intermediate **1.70c** which on subsequent cyclization (Scheme 31, second cyclization) produce tetrahydroazepines **1.72**. This is obviously a novel and alternative strategy to generate a more active hydrogen acceptor **1.70b**, which is quite different from the direct activation of the acceptor by metal.

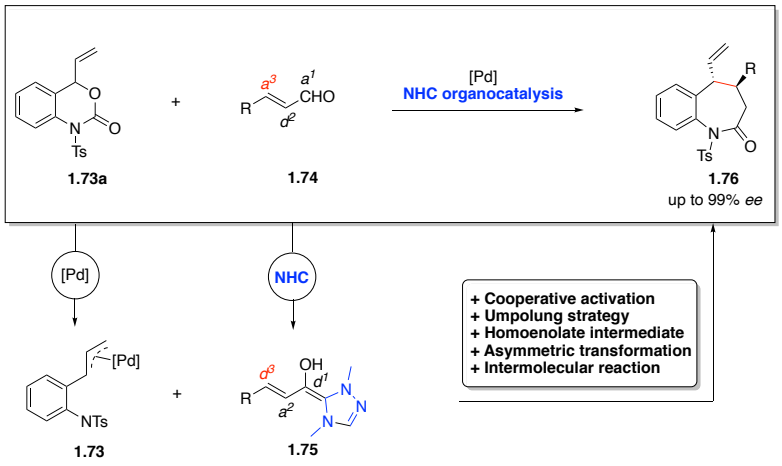
After careful optimization, authors found that the fused tetrahydroazepines can be isolated under the catalysis of carbophilic IPrAuOTf (5 mol %, generated in situ from 1:1 ratio of IPrAuCl and AgOTf) in CH_3CN at room temperature. The scope of some substrates is shown below (Scheme 1.40). The authors found out that that substituent (R^2) on the alkyne moiety plays a significant role. For example, the reaction of aryl substituted substrate (**1.72a**) gave higher yields as compared to cycloalkyl group (**1.72d**), since aryl substituted alkyne is more active to undergo heterocyclization and in turn form the cationic furanyl gold intermediate. The cyclic eight-membered ring (**1.72b**) was also formed in good yield. Starting materials obtained from non-cyclic amine like dibenzyl amine also gave rise to the expected product upon rearrangement (**1.72c**).



Scheme 1.40. Carbophilic Au(I)-catalyzed domino cyclization / 1,5-hydride shift / cyclization reaction.

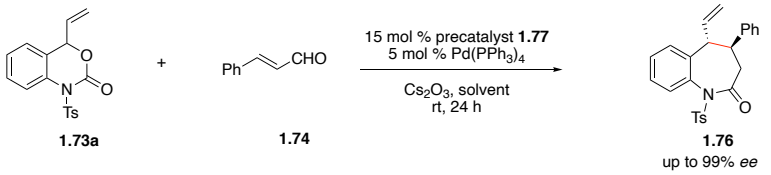
Glorius and co-workers reported a combination of NHC[103] organo-catalysis and transition-metal catalysis giving rise to fundamentally new cooperative reactivity, thus enabling regio- and enantioselective annulation reaction between enals and vinyl benzoxazinanones.[104] The cooperative umpolung annulation[105] eliminates mutual deactivation and leads to a diverse set of benzazepine derivatives in good yield with excellent enantioselectivities (up to 99% ee). Their reaction design involved an allylic alkylation process where an electrophilic allyl-palladium intermediate (**1.73**, Scheme 1.41) is generated upon Pd-mediated decarboxylation of an electrophilic allylic substrate (**1.73a**).[106–108] Meanwhile, the combination of an α,β-unsaturated aldehyde **1.74** and an NHC would lead to the nucleophilic homoenolate equivalent (**1.75**). Subsequent nucleophilic addition of

the NHC-coordinated homoenolate (**1.75**) in an umpolung process onto the allyl-palladium species[109,110] followed by cyclization would provide a powerful route to access enantioenriched benzazepines (**1.76**).



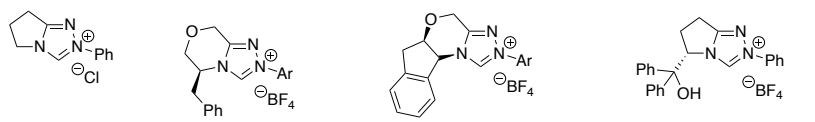
Scheme 1.41. Cooperative enantioselective umpolung annulation.

Based on this synergistic catalyst design, they began optimizing the reaction conditions using vinyl benzoxazinanone **1.73a** and enal **1.74** (Scheme 1.42).[104] They found that precatalyst **1.77a** did not catalyze this reaction. However, chiral triazolium **1.77b** gave the desired product in moderate yield with 63% ee (entry 2). Thus, they screened other chiral triazolium NHC precatalysts and found that precatalyst **1.77c** was the best one to give the product in 86% yield with 99% ee (entry 3).



entry	precat.	solvent	yield (%)[b]	dr of **v** [c]	ee (%)[d]
1	**1.77a**	THF	nr	–	–
2	**1.77b**	THF	38	5:1	63
3	**1.77c**	THF	86	12:1	99
4	**1.77d**	THF	58	14:1	98
5	**1.77e**	THF	nr	–	–
6	**1.77f**	THF	28	7:1	90
7	**1.77c**	toluene	56	12:1	96
8	**1.77c**	$CHCl_3$	29	15:1	94
9	**1.77c**	DME	85	12:1	98

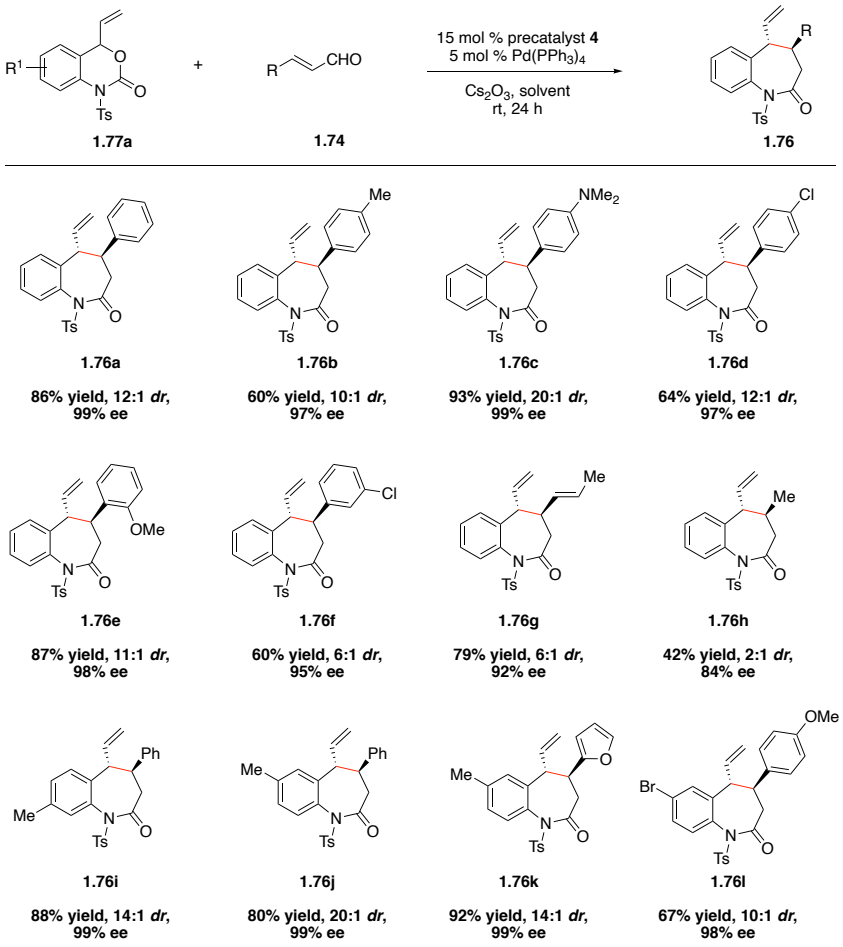
[a] Reactions were conducted with 1.0 equiv of **1.73a** and 2.0 equiv of **1.74**, 24 h. [b] Isolated yields after chromatography. [c] Determined by 1H NMR soectroscopy. [d] Determined by HPLC; nr = no reaction; rt = room temperature.



1.77a | **1.77b**: Ar = 2,4,6-$Me_3C_6H_2$ | **1.77c**: Ar = 2,4,6-$Me_3C_6H_2$, **1.77d**: Ar = 2,6-$Et_2C_6H_3$, **1.77e**: Ar = C_6F_5 | **1.77f** = 2,4,6-$Me_3C_6H_2$

Scheme 1.42. Optimization of reaction conditions[a].

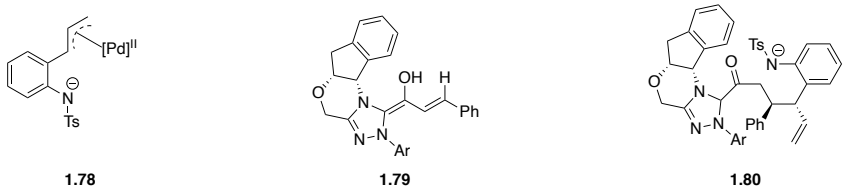
With the optimal conditions in hand, the scope and limitations of enal component as well generality of the reaction with respect to substituents were explored (Scheme 1.43). As shown below, a wide range of electron-donating and withdrawing enals with a variety of functional groups (methyl, chloro, dimethylamine), *β*-alkyl enals gave the products with good to moderate yields and good enantioselectivities. In order to show the generality of the reaction conditions, the substituents on the benzoxazinanone coupling partners were investigated. Both electron-donating and withdrawing groups showed excellent levels of enantioselectivity and gave good yields.[104]



Scheme 1.43. Scope of enal component and vinyl benzoxazinanones.

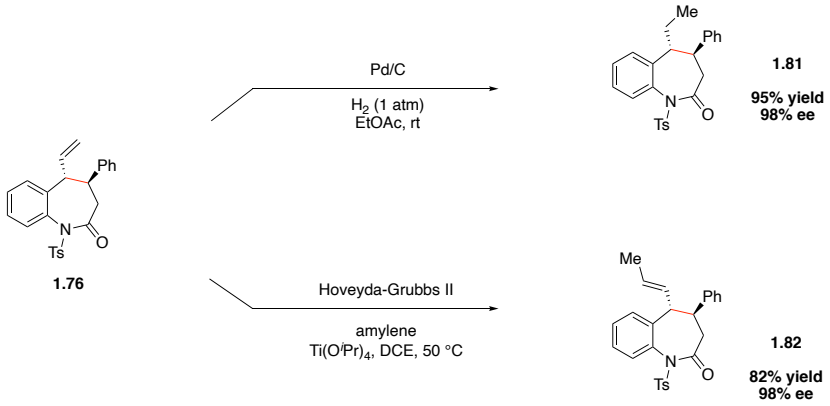
Next, the mechanism was proposed by the authors (Scheme 1.44).[104] The authors proposed that the catalysis was successful due to generation of two reactive species: a nucleophilic NHC-homoenolate (**1.79**) and a highly electrophilic allyl-palladium cation (**1.78**). Catalysis begins with coordination of vinyl benzoxazinanone to the palladium catalyst, followed by formation of the electrophilic allyl-palladium (II) complex (**1.78**) upon decarboxylation. In a parallel organocatalytic cycle, the addition of NHC organo-catalyst to the enal gives rise to the NHC-homoenolate (**1.79**). The NHC homoenolate then undergoes conjugate addition to the in situ formed allyl-palladium (II) complex, presumably promoted by a hydrogen-bonding interaction.

Following carbon-carbon bond formation, palladium catalyst dissociates and tautomerization takes place to form acyl azolium (**1.80**). This then undergoes N-acylation cyclization to form the final benzazepines.



Scheme 1.44. Important intermediates in the catalytic cycle.

The authors also derivatized the optically active benazepine thus showing the potential synthetic utility of the present method (Scheme 1.45). **1.76** could be easily transformed in several ways, highlighting the synthetic potential of the current method. Hydrogenation of **1.76** led to the reduction of olefin and gave **1.81** in excellent yield with no loss of enantiopurity. In addition, the vinyl group in **1.76** underwent cross-metathesis with amylene in the presence of Grubbs-Hoveyda II catalyst to generate **1.82** in good yield.

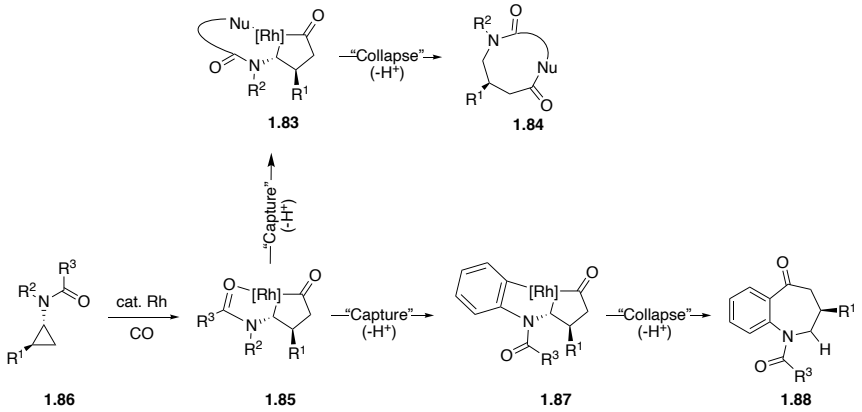


Scheme 1.45. Derivatization of benzazepine 1.76.

Thus, the authors showed that transition metal catalysis can be combined with NHC organo-catalysis in a cooperative process. With the help of cooperative activation of a chiral NHC organo-catalyst with a palladium co-catalyst, asymmetric induction can be observed. The combination of these two processes can thus be used as an important transformation to develop a wide range of stereo-controlled reactions and synthetically useful *N*-heterocycles.

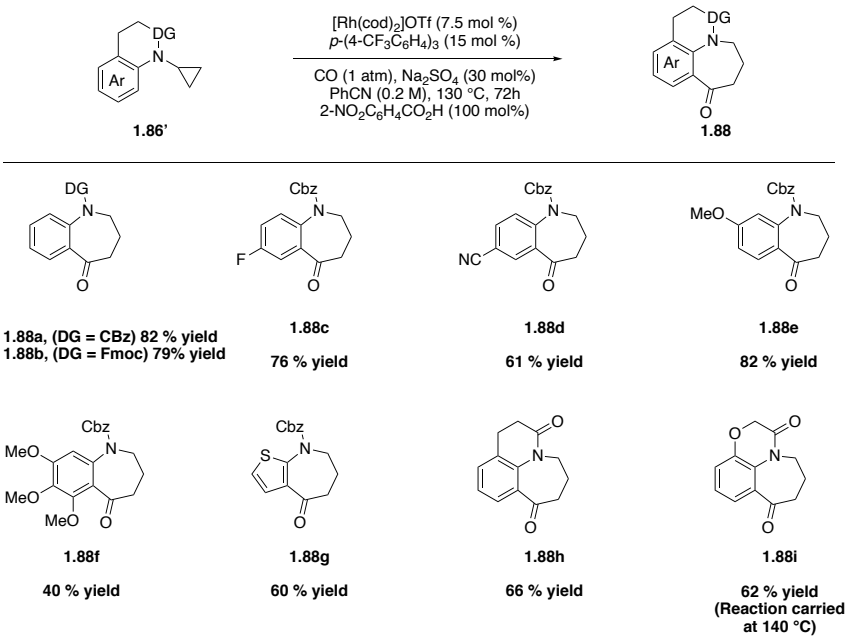
Bower and Wang reported a modular access to azepines by directed carbonylative C–C bond activation of aminocyclopropanes.[111] They proposed an *N*-heterocyclization strategy where "capture" of transient rhodacyclopentanones **1.85** by tethered nucleophiles occurs in advance of C–Nu bond forming "collapse" to the targets (Scheme 1.46).[112–117] This approach is appealing because the strain that is embedded within readily available and stereodefined aminocyclopropanes **1.86**[116] is used for the reaction initiation and achieves otherwise challenging ring closures via the formation of a kinetically accessible bicycles **1.83**. Apart from π-insertion processes, the reactivity of rhodacyclopentanones is relatively unexplored.[118–

[125] However, it is well established that Rh(III)-complexes can promote aryl C–H metalation. Thus, the authors thought that this type of processes might be exploited from **1.85** to provide benzazepines **1.88**.



Scheme 1.46. "Capture-collapse" heterocyclizations.

Their investigation into the optimal conditions identified that using 1 atm CO, the combination of $[Rh(cod)_2]OTf$ (7.5 mol %), *p*-$(4\text{-}CF_3C_6H_4)_3$ (15 mol %), Na_2SO_4 (30 mol %) and $2\text{-}NO_2C_6H_4CO_2H$ (100 mol %) enabled the formation of the corresponding benazepine starting from **1.86'** which was readily prepared in two steps via *N*-arylation of cyclopropylamine and subsequent Cbz protection. With the optimized conditions in hand, scope of aromatic substituents was explored (Scheme 1.47).



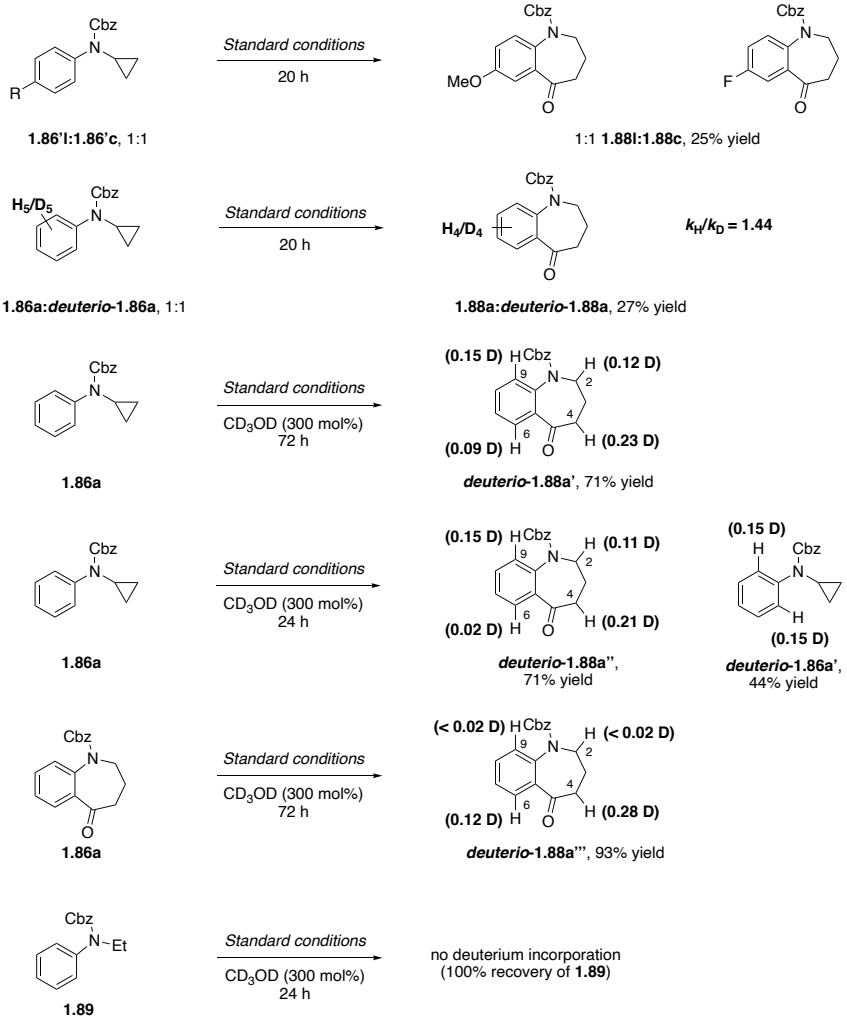
Scheme 1.47. Scope of the aromatic substituents.

As seen from the above scheme, electron-rich, electron poor and heteroaromatic systems were tolerated with same levels of efficiency. For those with *meta*-substituents (**1.88e)**, C–C bond formation is highly regioselective, occurring at the more sterically accessible *ortho*-position. In **1.88f**, where both meta-positions were substituted, cyclization occurred, but with low

yield and a slower process. Other directing group like Fmoc also worked giving the benzazepine (**1.88b**) in very good yield. Cyclic amides can also be used as a directing group giving rise to tricyclic systems **1.88h** and **1.88i** respectively.

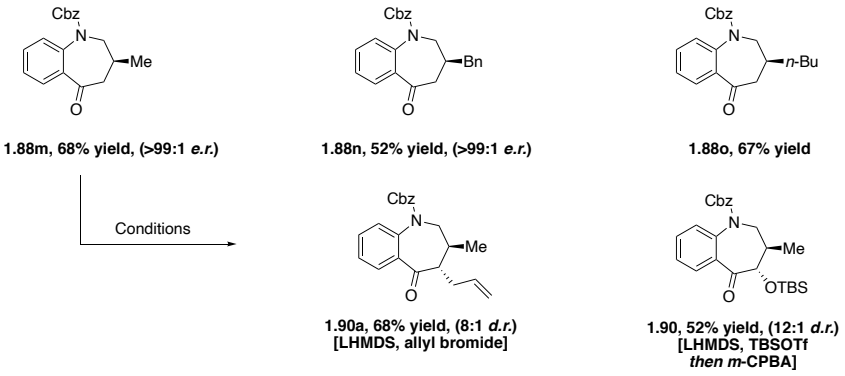
A series of mechanistic experiments were run and proved fundamental in guiding extensions of the approach outlined later (Scheme 1.48).[117] An equimolar mixture of **1.86'l** & **1.86'c** gave a low yield of **1.88l** & **1.88c**. Similarly, competition experiment between **1.86a** & *deuterio*-**1.86a** revealed a relatively small kinetic isotopic effect[126] suggesting that aryl C–H metalation is not turnover limiting. Further insight was obtained by running the reaction in the presence of deuterated methanol. At full conversion, incorporation of deuterium in the product *deuterio*-**1.88a'** was observed at C-2 (12%), C-4 (23%), C-6 (9%), and C-9 (15%). Deuteration at C-2 shows protodemetalation at this position (to **1.88**) after C–C reductive elimination from **1.87**. When reaction was partially run, lower levels of C-6 deuteration were observed, which proves exchange at this position via ketone directed C–H activation of the product.

The key issue as to how deuterium incorporation at C-9 of *deuterio*-**1.88a'/1.88a''** occurred was answered by the following experiments. Equation 5 indicates this was not via C–H activation of **1.86a**. Analysis of recovered starting material in eq 4 revealed 15% deuterium incorporation at the *ortho*-positions (*deuterio*-**1.86a'**); however equation 6 shows that it resulted into no deuterium incorporation in 7, which lacks a cyclopropyl unit, ruling out the exchange pathway involving carbonyl directed C–H activation of **1.86a**. Overall, the collective observations from eqs 3–6 indicate that deuterium exchange at C-9 of *deuterio*-**1.88a'/1.88a''** and at the ortho-C–H bonds of *deuterio*-**1.86a'** does not occur directly from **1.86a** or **1.88a**, but instead via reversible formation of another intermediate, likely bicycle **1.87**.



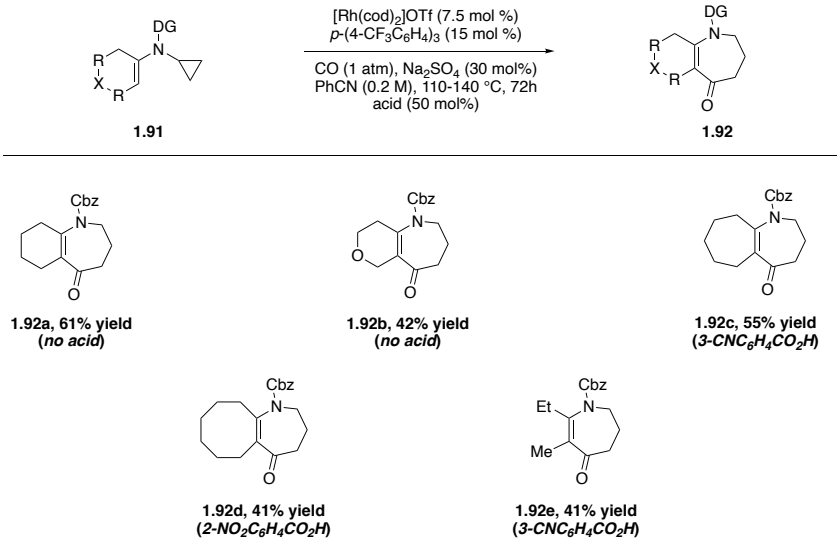
Scheme 1.48. Mechanistic experiments.

The heterocyclizations described by the authors so far used an N-aryl unit as the nucleophilic component, and they questioned whether further classes of the present method might be achieved using other types of π-nucleophile. then synthesized benzazepines bearing stereodefined substituents that might be challenging to install using conventional methods (Scheme 1.49).[117]



Scheme 1.49. Reaction scope and product derivatizations.

After the conclusion of their investigations which identified that the *N*-aryl unit was a competent nucleophilic component for heterocyclizations,[127,128] the authors next wanted to see if other classes of process might be achieved using other types of π-nucleophile. Specifically, they hoped to access non-benzofused azepines by harnessing *N*-vinyl nucleophiles (Scheme 1.50). In the event, they found that **1.91a** and **1.91b** gave the corresponding products **1.92a** and **1.92b** in good yields respectively. They eliminated carboxylic acid additive for these two substrates since it promoted competitive polymerization of **1.91a** and **1.91b**. However, in examples **1.92c – 1.92e**, carboxylic acid derivative was needed for the success of the reaction. From a mechanistic point of view, these processes are important since in principle, carboxylic acid derivative could facilitate CMD-type metalation of the C(sp^2) – H bond (**1.85** to **1.87**), but the formation of **1.92a** and **1.92b** suggests it is not the case. Accordingly, they suggested that, for both N-aryl and N-vinyl systems, C – H metalation occurs by nucleophilic attack of the electron-rich-π-system on the Rh-center of **1.85**, and that the role of the carboxylic acid additive is to facilitate the final protodemetalation step.



Scheme 1.50. Processes using *N*-vinyl carbamates to synthesize non-benzofused azepines

Thus, to conclude, the authors developed a method where rhodacyclopentanones generated by directed carbonylative C–C bond activation are captured by C-based nucleophiles en route to benzazepines and non-benzofused variants.[104,129–135] The methodology uses an atom and step economical manner and using the fundamental mechanistic steps in rhodacyclopentanone-based methodologies, the authors have shown the importance of these processes to access medium-sized rings that are difficult to construct in a modular fashion using conventional approaches.

There has been significant progress in the development of medium-sized rings through non-transition and transition metal catalyzed processes. Despite this progress, we believe that they are still at a nascent stage and with significant challenges remaining. Seven-membered heterocycles will continue to be of interest in biological applications and there appears to be much

opportunity for these ring systems in materials science applications. Innovative strategies to synthesize these scaffolds and applications of existing methods will continue to drive innovation in the discovery of novel medium-sized *N*-heterocycles.

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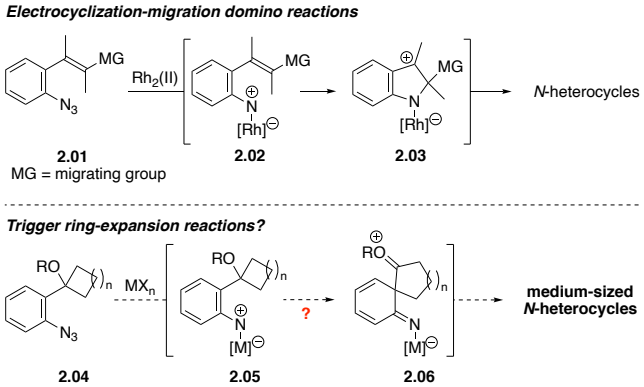
Chapter 2. Rh_2(II)-catalyzed ring expansion of cyclobutanol-substituted aryl azides to access medium-sized *N*-heterocycles. *[1]

The development of processes that tease new reactivity out of catalytic intermediates continues to spur synthetic chemists toward innovative solutions that access *N*-heterocycles.[1] Constructing these scaffolds using metal divalent catalytic intermediates to trigger domino reactions is rare despite the potential of these reactions to dramatically increase the complexity of the substrates.[2] Azides are emerging as valuable precursors for nitrenes in transition metal-catalyzed *N*-atom transfer reactions, but an electron-withdrawing *N*-substituent is generally required for the best outcome.[3,4] Our investigations into the reactivity of rhodium *N*-aryl nitrenes have established them as valuable electrophilic catalytic intermediates for the synthesis of complex indoles from readily accessible styryl azides.[5,6]

During the course of our studies, we were curious if the electrophilicity of **2.01** could be harnessed to participate in other bond-forming reactions instead of initiating electrocyclization-migration- or C–H bond amination reactions. In particular, we wondered if this electrophilicity could trigger the release of the strain embedded in the *ortho*-substituent of aryl azide **2.04** to generate an aza-*ortho*-quinonoid reactive intermediate, such as **2.06**, which could further rearrange.[7-9] If successful, this unprecedented ring expansion might access medium-sized heterocycles, which are challenging to construct with existing metal-catalyzed *N*-atom transfer reactions.[10] Herein, we report our method development and mechanistic experiments to form these important *N*-heterocycles from aryl azides (Scheme 2.01).



Scheme 2.01. Trigger ring-expansion reactions using metal *N*-aryl nitrenes

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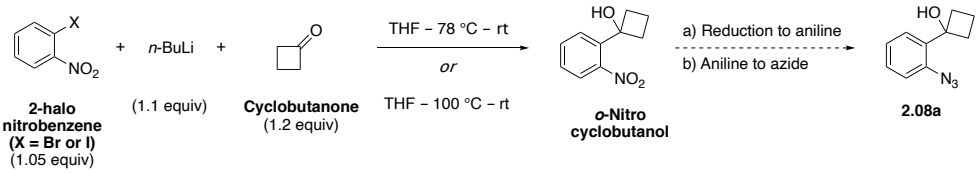
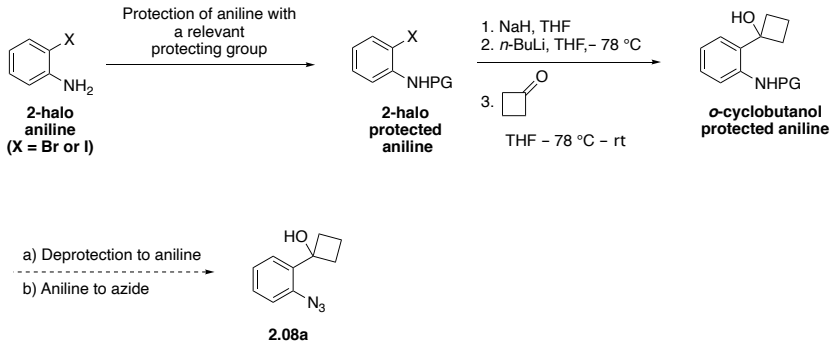
In order to test our hypothesis, I proposed the following strategy to synthesize the *o*-cyclobutanol aryl azides (Scheme 2.02).



Scheme 2.02. **Strategy to synthesize o-cyclobutanol aryl azides**

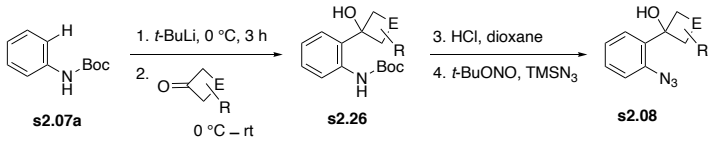
I thought that the commercially available 2-halo nitrobenzene could be lithiated with *n*-BuLi under a very low temperature, which would then be added to cyclobutanone to form *o*-nitrocyclobutanol. The *o*-nitrocyclobutanol then could be reduced to aniline under standard conditions. The so formed aniline then could be converted to the azide using general azidation conditions. However, the first step didn't work initially when I performed the reaction at – 78 °C which led to the decomposition of the starting material leading to formation of mixture of unidentifiable products. The reaction was also performed at – 100 °C but without any success.

After careful survey of literature, the following two strategies were proposed. In method A (Scheme 2.03),[11] I protected the commercially available aryl anilines with relevant protecting groups. The protecting groups that were tested for the reactions were -CHO, -Allyl, -Boc, -Fmoc. None of them worked except the -CHO group which was considered for our reaction. Once the protection was achieved, deprotonation of the protected aniline with NaH, followed by *o*-lithiation with *n*-BuLi and addition to cyclobutanone led to the formation of *o*-cyclobutanol protected aniline. Then the aniline was deprotected under base mediated hydrolysis to reveal the free -NH_2 group which was then converted to azide using general azidation strategies.



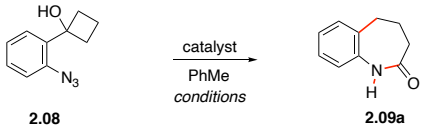
Scheme 2.03. Method A - Modified strategy to synthesize o-cyclobutanol aryl azides

In method B (Scheme 2.04), *N*-phenyl-*tert*-butyl carbamate was *ortho*-lithiated with *t*-Butyl lithium[12] which underwent smooth addition to cyclobutanone to form the Boc protected *o*-cyclobutanol aniline. Then the HCl-mediated Boc deprotection to form the free aniline which was then converted to the azides using *t*-BuONO and Me_3SiN_3.[13]



Scheme 2.04. Method B - Modified strategy to synthesize o-cyclobutanol aryl azides

To test our hypothesis, the reactivity of aryl azide **2.08** towards commercially available transition metal catalysts was examined (Table 2.01). In line with our hypothesis, exposure of aryl azide **2.08** to a Rh_2(II)-carboxylate catalyst triggered a ring-expansion to produce benzazepinone **2.09a**, whose structure was confirmed by X-ray crystallography.[14] The yield of this transformation depended upon the identity of the carboxylate ligand (entries 1 – 6). While poor conversion was observed with electron-rich rhodium carboxylates (entries 2 and 3), perfluorinated complexes were significantly more active (entries 4 and 5). The highest yield of the benzazepinone was obtained using $Rh_2(esp)_2$ (entry 6).[15] The success of $Rh_2(esp)_2$ is attributed to its tetradentate ligands, which confer enhanced thermal stability relative to other rhodium carboxylate complexes.[16] The catalyst loading of $Rh_2(esp)_2$ could be lowered to 1 mol % if the reaction temperature was increased to 120 °C (entry 7). Examination of other established *N*-atom transfer catalysts or Lewis acids revealed the uniqueness of Rh_2(II)-carboxylates to trigger this transformation: no reaction was observed using iron-[17] or copper catalysts,[18] and diminished conversion to benzazepinone **2.09a** was obtained using $RuBr_3$,[19] CoTPP or $[Ir(cod)(OMe)]_2$ complexes (entries 8 – 10).[20,21] Other common Lewis acids like $FeBr_2$ and $FeBr_3$ known to do *N*-atom transfer reactions[17] or trigger semipinacol rearrangements were found to lead to deleterious results.[22] A solvent screen was performed to determine if the yield or catalyst loading could be further reduced. The use of other chlorinated- or ethereal solvents, however, only led to attenuated yields of benzazepinone **2.09a**.[22]



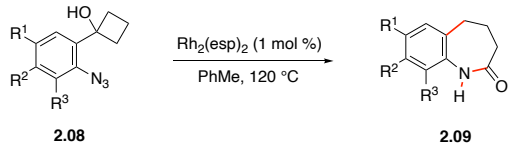
Entry	catalyst	mol %	solvent	T (°C)	**2.09a** yield, %[a]
1	...	...	PhMe	130	trace
2	$Rh_2(O_2CCH_3)_4$	5	PhMe	100	24
3	$Rh_2(O_2CC_7H_{15})_4$	5	PhMe	100	15
4	$Rh_2(O_2CCF_3)_4$	5	PhMe	100	47
5	$Rh_2(O_2CC_3F_7)_4$	5	PhMe	100	66
6	$Rh_2(esp)_2$	5	PhMe	100	80
7	$Rh_2(esp)_2$	5	PhMe	120	71
8	$Rh_2(esp)_2$	1	PhMe	120	82
9	$RuBr_3 \bullet nH_2O$	1	PhMe	120	23

10	Co(TPP)	5	PhMe	120	trace
11	$[Ir(COD)(OMe)]_2$	5	PhMe	120	23
12	$FeBr_2$	20	PhMe	120	…
13	$FeBr_2$	30	CH_2Cl_2	40	…
14	$FeBr_3$	20	PhMe	120	…
15	$FeBr_3$	30	CH_2Cl_2	40	…

[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard.

Table 2.01. Optimization of the ring expansion

The scope and limitations of our $Rh_2(II)$-catalyzed ring-expansion reaction was explored using the optimal conditions (Table 2.02). While our reaction is currently limited to aryl azides,[23] both electron-donating as well as electron-withdrawing R^1- and R^2- substituents on the aryl azide were tolerated without attenuating the benzazepinone yield (**2.09a** – **2.09e**). In contrast to our previously reported aryl azide methods,[5,6] aryl azide **2.08k** could be substituted with an additional *ortho*-substituent and still furnish benzazepinone **2.09k** using the optimal reaction conditions without significant diminishment of the yield.



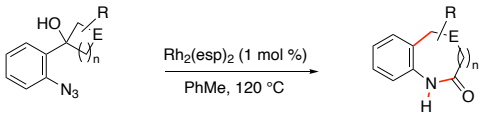
2.08 **2.09**

entry	#	R^1	R^2	R^3	# yield, %[a]
1	a	H	H	H	80
2	b	OMe	H	H	80
3	c	Me	H	H	91[b]
4	d	CF_3	H	H	74
5	e	OCF_3	H	H	71
6	f	H	OMe	H	85
7	g	H	Me	H	80
8	h	H	F	H	78
9	i	H	CF_3	H	86
10	j	Me	F	H	80
11	k	H	H	OMe	74

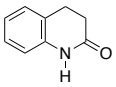
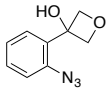
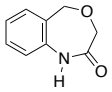
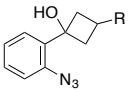
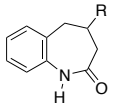
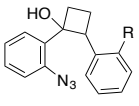
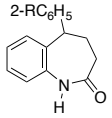
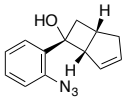
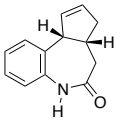
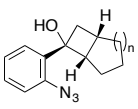
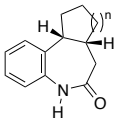
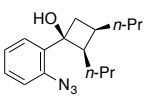
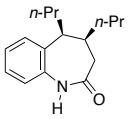
[a] Isolated after silica gel chromatography. [b] Ref. 13, CCDC 1525478.

Table 2.02 Scope and limitations of benzazepinone formation

Next, the identity of the *ortho*-cycloalkanol substituent of the aryl azide was varied to investigate the scope and selectivity of benzazepinone formation (Table 2.03). First, aryl azide **2.10a** established the generality of this phenomenon by revealing that the strain embedded in an *ortho*-cyclopropanol-substituent could be released to access dihydroquinolone **2.11a** (entry 1). Aryl azide **2.10b** revealed that our reaction tolerated the presence of an oxygen heteroatom in the strained *ortho*-substituent to access medium- ring *N*-heterocycle **2.11b**, albeit in a slightly diminished yield (entry 2). The *ortho*-cyclobutanol substituent could be substituted with an alkyl- or aryl substituent to enable access to 4-substituted benzazepinones (entries 3 and 4). The specificity of the [1,2] migration step was investigated with aryl azides **2.10e** – **2.10j** (entries 5 – 10).



2.10 **2.11**

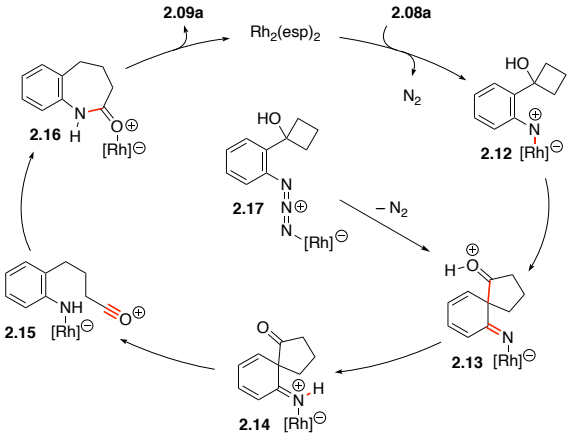
entry	#	aryl azide	*N*-heterocycle	yield, %[a]
1[b]	a			80
2	b			51
3 4	c d			R = *t*-Bu, 66 R = Ph, quant
5 6	e f			R = H, 72 R = Br, 66
7	g			60[b]
8 9	h i			n = 1, 73[b] n = 4, 95[b]
10	j			65[b,c]

[a] Isolated yield of 11 after silica gel chromatography; only product obtained. [b] d.r. >95:5. [c] Diastereoselectivity of the product confirmed by X-ray crystallographic analysis (CCDC 1525486).

Table 2.03. Investigation of the Scope and Selectivity

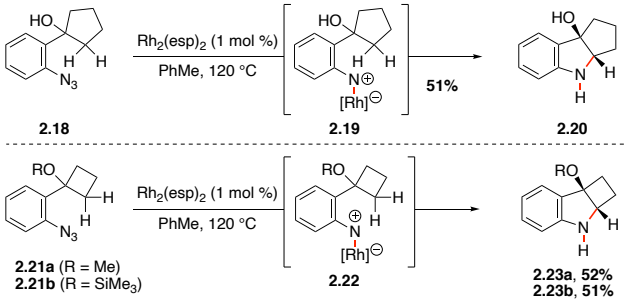
In contrast to related ring-expansion reactions of substituted cyclobutanols containing N_2 as the leaving group,[24] our reaction proved to be selective: each substrate submitted to the reaction conditions produced the medium-ring *N*-heterocycle as a single constitutional isomer. Aryl azides **2.10e** and **2.10f** exhibited exclusive migration of the benzyl carbon over the methylene (entries 5 and 6); while only allyl carbon migration was observed with aryl azide **2.10g** to provide benzazepinone **2.11g** as the only product (entry 7). Our reaction could even differentiate between the methylene- and methine carbons present on the *o*-cyclobutanol substituent: aryl azides **2.10h** and **2.10i** produced only the benzazepinone resulting from migration of cycloalkyl fragment (entries 8 and 9). Finally, the stereospecificity of the [1,2] migration step was established with aryl azide **2.10j** (entry 10). Exposure of the *cis*-substituted **2.10j** to reaction conditions produced benzazepinone **2.11j** as a single diastereomer to suggest that the [1,2] migration is concerted.

The reactivity trends of the *ortho*-cyclobutanol-substituted aryl azides suggest that the benzazepinone product is formed through the catalytic cycle outlined in Scheme 2.05. First, the substrate reacts with the Rh_2(II) carboxylate catalyst to form the metal *N*-aryl nitrene **2.12**.[6,25] Formation of this electrophilic species triggers the selective and stereospecific ring-expansion of the *ortho*-cyclobutanol substituent to produce metallo aza-quinonoid **2.13**.[9,26] After proton transfer to the metalloimine, aromaticity is re-established by generation of acylium ion **2.15**, which is attacked by the proximal nitrogen nucleophile to form **2.16**. Loss of the rhodium carboxylate produces the benzazepinone product. Alternatively, the key [1,2] migration step could occur at the same time as loss of dinitrogen: coordination of the rhodium carboxylate to the γ-nitrogen in **2.17** activates the substrate for a semipinacol ring-expansion with concomitant loss of N_2 to produce **2.13**.[24]



Scheme 2.05. Possible Mechanism for Rh_2(II)-Catalyzed Benzazepinone Formation

Support for a mechanism via a rhodium *N*-aryl nitrene was obtained from the reactivity of aryl azides **2.18** and **2.21** (Scheme 2.06). To assay the importance of ring-strain to the success of the reaction, *ortho*-cyclopentanol-substituted aryl azide **2.18** was constructed from *N*-phenyl-*tert*-butyl carbamate following the route outline in Table 1 using cyclopentanone in place of cyclobutanone. Instead of ring-expansion, submission of **2.18** to the reaction conditions resulted in sp^3-C–H bond amination to produce indoline **2.20** as the only product. The formation of the amination product implicates the intermediacy of rhodium *N*-aryl nitrene **2.19** since these species are established to react with C–H bonds.[6] The reactivity of aryl azides **2.21** revealed the importance of hydroxyl group for ring-expansion process. When it was replaced with either a methyloxy- or trimethylsilyloxy group, C–H bond amination occurred instead to produce indolines **2.23** as the only product. The formation of indolines **2.23** from *ortho*-cyclobutyl-substituted aryl azides **2.21** not only implicate rhodium *N*-aryl nitrene **2.22**, but also show the competitiveness of C–H bond amination to other potential ring-expansion processes.



Scheme 2.06. Mechanistic Support for the Intermediacy of a Rhodium *N*-Aryl Nitrene

A Rh_2(II)-catalyzed reaction of *ortho*-cyclobutanol-substituted aryl azides was discovered to afford medium-ring *N*-heterocycles. This domino reaction is triggered by formation of the rhodium *N*-aryl nitrene, which unravels the *o*-cyclobutanol substituent. Our investigations into the scope of the reaction reveal that the ring-expansion step of the catalytic cycle is both chemoselective and stereospecific to enable predictable formation of a broad range of benzazepinones. Future experiments will be aimed at exploring the reactivity of the strained indoline C–H bond amination product as well as developing domino reaction sequences to access more complex medium-ring *N*-heterocycles.

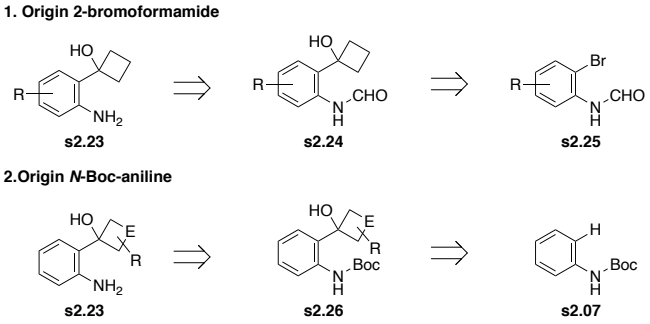
Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was

performed on 0.25 mm silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed using pumps to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware that was oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, methanol, toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[27] Metal salts were stored in a nitrogen atmosphere dry box.

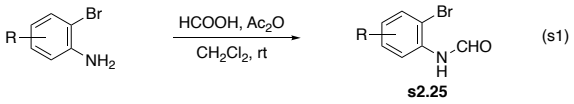
I. Synthesis of *ortho*-Cyclobutanol Anilines

The *ortho*-cyclobutanol anilines for our method development were constructed from either 2-bromoformamide **s2.25** or *N*-Boc aniline **s2.07**



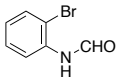
A. General Procedure for Formamide Synthesis

The formamides were prepared following the protocol reported by Takemoto and co-workers.[28]



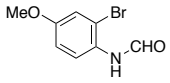
To a mixture of formic acid (3.49 equiv) and acetic anhydride (1.25 equiv) was added a solution of 2-bromoaniline (1.0 equiv) in CH_2Cl_2 and the mixture was stirred at room temperature. After 2 h, the mixture was concentrated under reduced pressure to afford the formamide product as a solid. No additional purification was performed.

B. Characterization Data of Formamides.



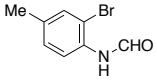
s2.25a

***N*-(2-Bromophenyl)formamide s1a.**[29] The general procedure was followed by using 2.00 g of 2-bromoaniline (11.6 mmol), 1.52 mL of formic acid and 1.36 mL of Ac_2O to give the product, a white solid, as a 2:1 mixture of rotamers (2.03 g, 88%). The spectral data of **s2.25a** matched that reported by Sarvari and Sharghi:[29] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 6.0 Hz, 0.47H), 8.49 (s, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 7.70 (bs, 1H), 7.60 (d, *J* = 8.0 Hz, 0.52H), 7.55 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.34 – 7.30 (m, 1.54H), 7.27 – 7.25 (m, 0.69H), 7.07 (t, *J* = 8.0 Hz, 0.5H), 7.02 – 6.99 (m, 1H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (CH), 158.6 (CH), 134.8 (C), 133.5 (CH), 132.4 (CH), 128.7 (CH), 128.5 (CH), 126.4 (CH), 125.7 (CH), 122.3 (CH), 119.0 (CH), 114.5 (C), 113.0 (C), only visible signals; ATR-FTIR (thin film): 3259, 3106, 2906, 1702, 1665, 1577, 1595, 1521, 1466, 1401, 1293, 1158, 1045, 908, 739 cm^{-1}.



s2.25b

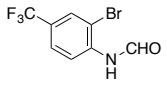
***N*-(2-Bromo-4-methoxyphenyl)formamide s2.25b.** The general procedure was followed by using 2.00 g of 2-bromo-4-methoxy aniline (9.9 mmol), 1.30 mL of formic acid and 1.16 mL of Ac_2O to give the product, a brown solid, as a 2:1 mixture of rotamers (2.03 g, 94%): mp = 115 – 117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 11.5 Hz, 0.46H), 8.43 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.44 (bs, 1H), 7.27 – 7.26 (m, 0.67H), 7.17 – 7.16 (m, 1H), 7.11 – 7.10 (m, 1H), 6.87 (dd, *J* = 9.0 Hz, 2.5 Hz, 1.51H), 3.80 (s, 1.47H), 3.79 (s, 3H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1 (C), 159.0 (CH), 156.7 (C), 128.1 (C), 123.5 (CH), 121.8 (CH), 118.5 (CH), 117.7 (CH), 114.5 (CH), 113.9 (CH), 55.8 (CH_3) 55.7 (CH_3), only visible signals; ATR-FTIR (thin film): 3247, 2891, 1697, 1662, 1581, 1538, 1488, 1403, 1393, 1294, 1223, 1032, 872, 837, 724 cm^{-1}. HRMS (ESI) m/z calcd for $C_8H_9NO_2Br$ $[M + H]^+$: 229.9816, found 229.9817.



s2.25c

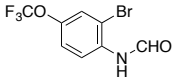
***N*-(2-Bromo-4-methylphenyl)formamide s2.25c.**[30] The general procedure was followed by using 1.00 g of 2-bromo-4-methyl aniline (5.4 mmol), 0.71 mL of formic acid and 0.63 mL of Ac_2O to give the product, a brown solid, as a 2:1 mixture of rotamers (1.2 g, quantitative). The spectral data of **s2.25c** matched that reported by Heinicke and co-workers:[30] ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.62 (d, *J* = 11.5 Hz, 0.49H), 8.46 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.59 (bs, 1H), 7.42 (s, 0.49H), 7.37 (s, 1H), 7.13 (t, *J* = 10.0 Hz, 2H), 2.32 (s, 1.65H), 2.30 (s, 3H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (CH), 158.8 (CH), 136.8 (C), 135.8 (C), 133.8 (CH), 132.6 (CH), 132.5 (C), 132.3 (C), 129.3 (CH), 129.1 (CH), 122.2 (CH), 119.4 (CH), 114.7 (C), 113.0 (C), 20.6 (CH_3), 20.5 (CH_3), only visible signals; ATR-FTIR (thin film): 3242, 2905, 1694, 1666, 1574, 1505, 1399, 1224, 1038, 863, 816, 732, 672 cm^{-1}.



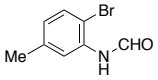
s2.25d

***N*-(2-Bromo-4-trifluoromethylphenyl)formamide s2.25d.** The general procedure was followed by using 0.894 g of 2-bromo-4-trifluoromethyl aniline (5.40 mmol), 0.49 mL of formic acid and 0.43 mL of Ac_2O to give the product, a white solid, as a mixture of rotamers (0.972 g, 97%): mp = 101 – 103 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, *J* = 10.0 Hz, 0.24H), 8.58 (d, *J* = 8.5 Hz, 1H), 8.55 (s, 1H), 7.87 (s, 0.41H), 7.82 (s, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 0.22H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (CH), 158.9 (CH), 137.8 (C), 130.8 (C), 129.5 (q, J_{CF} = 2.9 Hz, CH), 127.4 (q, J_{CF} = 33.4 Hz, C), 125.9 (CH), 125.8 (q, J_{CF} = 2.7 Hz, CH), 125.2 (q, J_{CF} = 270.3 Hz, C), 121.6 (CH), 117.4 (C), 112.4 (C), only visible signals; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.8; ATR-FTIR (thin film): 3278, 1705, 1609, 1525, 1397, 1321, 1265, 1120, 1077, 894, 821, 734, 677 cm^{-1}. HRMS (ESI) m/z calcd for $C_8H_6NOF_3Br$ $[M + H]^+$: 267.9587, found 267.9585.



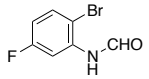
s2.25e

***N*-(2-Bromo-4-trifluoromethoxyphenyl)formamide s2.25e.** The general procedure was followed by using 1.00 g of 2-bromo-4-trifluoromethoxy aniline (3.91 mmol), 0.51 mL of formic acid and 0.46 mL of Ac_2O to give the product, a white solid, as a mixture of rotamers (1.12 g, quantitative): mp = 110 – 112 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 10.5 Hz, 0.26 H), 8.50 (d, *J* = 1.0 Hz, 1H), 8.45 (d, *J* = 9.5 Hz, 1H), 7.69 (bs, 1H), 7.51 (s, 0.26H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 0.26H), 7.21 (d, *J* = 7.5 Hz, 1.3H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (CH), 158.8 (CH), 145.1 (C), 133.8 (C), 126.4 (CH), 125.2 (CH), 122.7 (CH), 122.4 (q, J_{CF} = 256.5 Hz, C), 121.5 (CH), 121.2 (CH), 119.6 (CH), 114.7 (C), 112.9 (C), only visible signals; ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.7; ATR-FTIR (thin film): 3190, 3034, 2894, 1659, 1541, 1482, 1396, 1294, 1197, 1163, 1040, 942, 888, 849, 709 cm^{-1}. HRMS (ESI) m/z calcd for $C_8H_6NO_2BrF3$ $[M + H]^+$: 285.9535, found 285.9534.



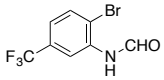
s2.25f

***N*-(2-Bromo-5-methylphenyl)formamide s2.25f.** The general procedure was followed by using 1.00 g of 2-bromo 5-methyl aniline (5.37 mmol), 0.71 mL of formic acid and 0.63 mL of Ac_2O to give the product, a brown solid, as a 2:1 mixture of rotamers (1.24 g, quantitative): mp = 97 – 99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 11.0 Hz, 0.51H), 8.47 (s, 1H), 8.22 (s, 1H), 7.63 (bs, 1.33H), 7.45 (d, *J* = 8.0 Hz, 0.53H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 0.49H), 6.88 (d, *J* = 8.0 Hz, 0.53H), 6.62 (d, *J* = 8.0 Hz, 1H), 2.33 (s, 1.62H), 2.32 (s, 3.34 H) only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (CH), 158.8 (CH), 138.8 (C), 134.4 (C), 133.1 (CH), 131.9 (CH), 127.3 (CH), 126.6 (CH), 122.8 (CH), 119.7 (CH), 109.7 (C), 21.3 (CH_3), 21.1 (CH_3), only visible signals; ATR-FTIR (thin film): 3239, 2922, 1652, 1581, 1526, 1411, 1291, 1195, 1030, 815, 718, 701 cm^{-1}. HRMS (ESI) m/z calcd for C_8H_9NOBr $[M + H]^+$: 213.9870, found 213.9868.



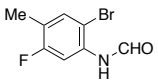
s2.25g

***N*-(2-Bromo-5-fluorophenyl)formamide s2.25g.** The general procedure was followed by using 1.00 g of 2-bromo-5-fluoro aniline (5.30 mmol), 0.70 mL of formic acid and 0.62 mL of Ac_2O to give the product, a white solid, as a 4:1 mixture of rotamers (1.05 g, 88%): mp = 133 – 135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 11.0 Hz, 0.25H), 8.50 (s, 1H), 8.28 (dd, *J* = 10.5 Hz, 2.5 Hz, 1H), 7.70 (bs, 1H), 7.57 – 7.54 (m, 0.29H), 7.50 (dd, *J* = 8.5 Hz, 5.5 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 0.25H), 6.81 (t, *J* = 8.5 Hz, 0.28H), 6.76 (ddd, *J* = 11.0 Hz, 8.5 Hz, 3.0 Hz, 1H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (C), 161. 1 (d, J_{CF} = 31.4 Hz, C), 158.8 (CH), 137.0 (C), 136.0 (d, J_{CF} = 11.4 Hz, C), 134.4 (d, J_{CF} = 9.4 Hz, C), 133.0 (d, J_{CF} = 9.0 Hz, CH), 113.2 (d, J_{CF} = 23.3 HZ, C), 112.6 (d, J_{CF} = 23.4 Hz, CH), 109.7 (d, J_{CF} = 28.3 Hz, CH), 106.7 (d, J_{CF} = 3.6 Hz, C), 106.0 (d, J_{CF} = 27.3 Hz, C), only visible signals; ^{19}F NMR (282 MHz, $CDCl_3$) δ –111.2; ATR-FTIR (thin film): 3261, 3107, 2907, 1668, 1608, 1541, 1427, 1398, 1280, 1133, 1101, 1032, 866, 795, 612 cm^{-1}. HRMS (ESI) m/z calcd for C_7H_6NOFBr $[M + H]^+$: 217.9615, 217.9617 found.



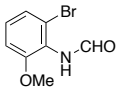
s2.25h

***N*-(2-Bromo-5-trifluoromethylphenyl)formamide) s2.25h.** The general procedure was followed by using 1.00 g of 2-bromo-5-trifluoromethyl aniline (4.20 mmol), 0.56 mL of formic acid and 0.50 mL of Ac_2O to give the product, a white solid, as a mixture of rotamers (0.916 g, 91%): mp = 96 – 98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 0.15H), 8.74 (s, 1H), 8.54 (s, 1H), 7.85 (bs, 1H), 7.74 (d, J = 7.5 Hz, 0.29H), 7.68 (d, J = 8.0 Hz, 1H), 7.50 (s, 0.23H), 7.32 (d, J = 8.0 Hz, 0.24H), 7.25 (d, J = 6.0 Hz, 0.85H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0 (CH), 158.9 (CH), 135.4 (C), 134.2 (CH), 132.9 (CH), 131.0 (q, J_{CF} = 32.6 Hz, C), 123.4 (q, J_{CF} = 269.9 Hz, C), 122.7 (CH), 122.0 (q, J_{CF} = 4.1 Hz, CH), 118.8 (q, J_{CF} = 4.5 Hz, CH), 116.3 (C), 115.1 (CH), only visible signals; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.3; ATR-FTIR (thin film): 3289, 2894, 1677, 1586, 1524, 1427, 1325, 1236, 1169, 1119, 1078, 1029, 894, 819, 737 cm^{-1}. HRMS (ESI) m/z calcd for $C_8H_6NOF_3Br$ $[M + H]^+$: 267.9586, found 267.9585.



s2.25i

***N*-(2-Bromo-5-fluoro-4-methylphenyl)formamide s2.25i.** The general procedure was followed by using 0.900 g of 2-bromo 5-fluoro 4-methyl aniline (4.20 mmol), 0.58 mL of formic acid and 0.52 mL of Ac_2O to give the product, a brown solid, as a mixture of rotamers (1.02 g, quantitative): mp = 108 – 110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 11.0 Hz, 0.29H), 8.45 (d, J = 1.0 Hz, 1H), 8.16 (d, J = 11.5 Hz, 1H), 7.69 (bs, 1H), 7.41 (d, J = 7.5 Hz, 0.28H), 7.34 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 10.0 Hz, 0.28H), 2.23 (s, 1H), 2.21 (d, J = 1.5 Hz, 3.4H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (CH), 160.2 (d, J_{CF} = 243.1 Hz, C), 158.8 (CH), 135.3 (d, J_{CF} = 6.4 Hz, CH), 133.9 (d, J_{CF} = 6.0 Hz, CH), 133.4 (d, J_{CF} = 11.4 Hz, C), 122.6 (d, J_{CF} = 19.1 Hz, C), 109.4 (d, J_{CF} = 30.1 Hz, CH), 106.4 (d, J_{CF} = 3.4 Hz, C), 106.3 (CH), 106.1 (CH), 14.0 (CH_3), 13.9 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –118.7, –115.2; ATR-FTIR (thin film): 3241, 2906, 1697, 1668, 1619, 1514, 1502, 1405, 1294, 1197, 1170, 1120, 877, 772, 749, 602 cm^{-1}. HRMS (ESI) m/z calcd for C_8H_8NOFBr $[M + H]^+$: 231.9776, found 231.9773.



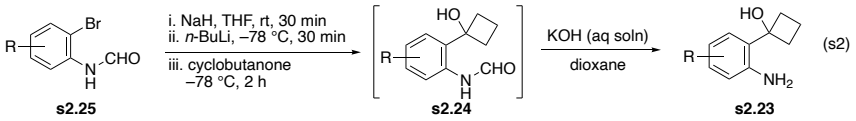
s2.25j

***N*-(2-Bromo-6-methoxyphenyl)formamide s2.25j:** The general procedure was followed by using 1.00 g of 2-bromo 6-methoxy aniline (4.50 mmol), 0.65 mL of formic acid and 0.58 mL of Ac_2O to give the product, a brown solid, as a mixture of rotamers (1.13 g, quantitative): mp = 110 – 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 11.0 Hz, 0.39H), 8.40 (bs,

0.12H), 7.27 – 7.25 (m, 0.15H), 7.22 (d, J = 8.0 Hz, 0.56H), 7.14 (bs, 0.19H), 7.07 (t, J = 9.0 Hz, 0.65H), 7.03 (d, J = 8.5 Hz, 0.50H), 6.92 (d, J = 8.0 Hz, 0.65H), 6.72 (d, J = 8.5 Hz, 0.39H), 6.60 – 6.57 (m, 0.38H), 4.20 (s, 0.67H), 3.85 (d, J = 5.5Hz, 2.96H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (C), 164.0 (C), 150.0 (C), 127.4 (CH), 125.2 (CH), 124.3 (CH), 118.1 (CH), 111.0 (CH), 109.0 (CH), 108.6 (C), 56.2 (CH_3), 55.9 (CH_3); ATR-FTIR (thin film): 3247, 2891, 1697, 1662, 1581, 1538, 1488, 1403, 1393, 1294, 1223, 1032, 872, 837, 724 cm^{-1}. HRMS (ESI) m/z calcd for $C_8H_9NO_2Br$ $[M + H]^+$: 229.9819, found 229.9817.

C. General Procedure for Synthesis of *o*-Cyclobutanol Anilines from 2-Bromoformamides

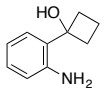
The *o*-cyclobutanol formamides were prepared following the protocol reported by Curtin and co-workers.[11] The formyl group was removed through a base-mediated hydrolysis reaction to provide the *o*-cyclobutanol aniline.



To a slurry of NaH (60% dispersion in mineral oil, 1.83 equiv) in THF (6 mL was added dropwise a solution of *N*-(2-bromophenyl) formamide (1.0 equiv) in 4 mL of tetrahydrofuran. The mixture was stirred at room temperature for 20 minutes, then chilled to – 78 °C. To the cold suspension was added dropwise a 2.5 M solution of *n*-butyllithium in hexanes (1.25 equiv). The mixture was stirred at –78 °C. After 30 minutes, cyclobutanone (1.1 equiv) was added dropwise. The mixture was stirred at –78 °C. After 2 hours, the reactives were quenched by adding 20 mL of a saturated aqueous solution of NH_4Cl. The resulting mixture was warmed to room temperature. The mixture was extracted with 3 × 30 mL of ethyl acetate, and the combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by medium pressure liquid chromatography (MPLC) to give the title compounds as a mixture of rotational isomers, which were submitted to the next step without characterization.

The mixture of *o*-cyclobutanol formamide rotamers was dissolved in dioxane and treated with a 5% aq soln of KOH. The resulting mixture was heated to reflux, and the reaction progress was monitored using thin layer chromatography until the starting material was completely consumed. After the reaction mixture was cooled to room temperature, it was diluted with water. The resulting mixture was extracted with 3 × 10 mL of EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and the filtrate was concentrated under reduced pressure. The resulting residue was purified by MPLC to afford the product.

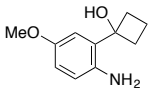
D. Characterization Data of *o*-Cyclobutanol Formamides



s2.23a

***N*-(2-(1-Hydroxycyclobutyl)phenyl)formamide s2.24a.** The general procedure was followed by using 0.653 g (17.0 mmol) of NaH, 2.00 g (9.30 mmol) of **s2.25a**, 4.65 mL (11.6 mmol) of *n*-BuLi and 0.760 mL (10.2 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) provided **s2.24a** as a thick yellow oil (0.50 g, 26%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

***N*-(2-(1-Hydroxycyclobutyl)phenyl)aniline s2.23a.**[11] The general procedure was followed by using 0.200 g (1.23 mmol) of **s2.24a**. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.083 g, 50%): **s2.23a** was previously reported by Curtin and co-workers:[30] R_f = 0.28 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$ with 1% (v/v) TMS) δ 7.23 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.12 – 7.09 (m, 1H), 6.74 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.69 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 4.19 (bs, 2H), 2.70 – 2.65 (m, 2H), 2.39 – 2.33 (m, 2H), 2.04 – 1.96 (m, 1H), 1.69 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$ with 1% (v/v) TMS) δ 145.6 (C), 128.8 (CH), 128.1 (C), 125.3 (CH), 117.7 (CH), 116.8 (CH), 77.6 (C), 35.1 (CH_2), 13.7 (CH_2); ATR-FTIR (thin film): 3341, 2925, 2853, 1608, 1494, 1456, 1303, 1122, 746 cm^{-1}.

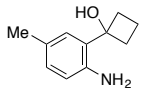


s2.23b

***N*-(2-(1-Hydroxycyclobutyl)-4-methoxyphenyl)formamide s2.24b.** The general procedure was followed by using 0.303 g (7.90 mmol) of NaH, 1.00 g (4.30 mmol) of **s2.25b**, 2.20 mL (5.40 mmol) of *n*-BuLi and 0.350 mL (4.70 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick yellow oil (0.20 g, 21%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

***N*-(2-(1-Hydroxycyclobutyl)-4-methoxyphenyl)aniline s2.23b.** The general procedure was followed by using 0.300 g (1.30 mmol) of **s2.24b**. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.280 g, 78%): R_f = 0.13 (5:1 hexanes:EtOAc); mp = 121 – 123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 – 6.83 (m, 1H), 6.70 – 6.67 (m, 1H), 6.64 – 6.62 (m, 1H), 3.85 – 3.75 (m, 5H), 2.64 – 2.59 (m, 2H), 2.38 – 2.31 (m, 2H), 2.02 – 1.95 (m, 1H), 1.69 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C), 138.9 (C), 130.5 (C), 118.0 (CH), 113.1 (CH), 112.3 (CH), 77.3 (C), 55.9 (CH_3),

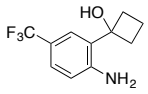
35.1 (CH_2), 13.6 (CH_2); ATR-FTIR (thin film): 3400, 3363, 2935, 1766, 1498, 1428, 1286, 1217, 1128, 1048, 815 cm^{-1}. HRMS (EI) m/z calcd for $C_{11}H_{15}NO_2$: 193.1103, found 193.1094.



s2.23c

***N*-(2-(1-Hydroxycyclobutyl)-4-methylphenyl)formamide s2.24c.** The general procedure was followed by using 0.164 g (4.30 mmol) of NaH, 0.500 g (2.34 mmol) of **s2.25c**, 1.20 mL (2.93 mmol) of *n*-BuLi and 0.200 mL (4.70 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick brown oil (0.10 g, 20%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

***N*-(2-(1-Hydroxycyclobutyl)-4-methylphenyl)aniline s2.23c.** The general procedure was followed by using 0.250 g (1.22 mmol) of **s2.24c**. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.130 g, 60%): R_f = 0.18 (5:1 hexanes:EtOAc); mp = 104 – 106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 3.98 (bs, 2H), 2.67 – 2.62 (m, 2H), 2.36 – 2.31 (m, 2H), 2.27 (s, 3H), 2.02 – 1.97 (m, 1H), 1.68 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142. 9 (C), 129.1 (CH), 128.6 (C), 127.0 (C), 125.9 (CH), 117.1 (CH), 77.5 (C), 35.1 (CH_2), 20.7 (CH_3), 13.8 (CH_2); ATR-FTIR (thin film): 3367, 2983, 2945, 2860, 1502, 1319, 1290, 1130, 909, 815, 760 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{14}NO$ $[M - H]^+$: 176.1073, found 176.1075.

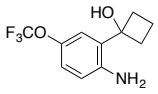


s2.23d

***N*-(2-(1-Hydroxycyclobutyl)-4-trifluoromethylphenyl)formamide s2.24d.** The general procedure was followed by using 0.211 g (5.50 mmol) of NaH, 0.800 g (3.00 mmol) of **s2.25d**, 1.50 mL (3.80 mmol) of *n*-BuLi and 0.250 mL (3.30 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick brown oil (0.20 g, 26%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

***N*-(2-(1-Hydroxycyclobutyl)-4-trifluoromethylphenyl)aniline s2.23d.** The general procedure was followed by using 0.260 g (1.00 mmol) of **s2.24d**. Purification by MPLC (5:1 hexanes:EtOAc) afforded the product as a yellow solid (0.160 g, 70%): R_f = 0.33 (5:1 hexanes:EtOAc), mp = 107 – 109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.16 (bs, 2H), 2.65 – 2.60 (m, 2H), 2.37 – 2.31 (m, 2H), 2.04 – 1.96 (m, 1H), 1.68 – 1.59 (m, 1H); ^{13}C

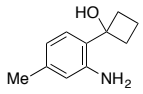
NMR (125 MHz, $CDCl_3$) δ 148.7 (C), 127.3 (C), 126.0 (q, J_{CF} = 4.0 Hz, CH), 124.8 (q, J_{CF} = 268.5 Hz, C), 122.6 (q, J_{CF} = 3.3 Hz, CH), 118.9 (q, J_{CF} = 32.0 Hz, C), 115.9 (CH), 77.3 (C), 34.9 (CH_2), 13.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −61.4 ; ATR-FTIR (thin film): 3374, 3203, 2992, 2954, 1622, 1331, 1263, 1176, 1110, 1082, 904 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{11}NOF_3$ $[M - H]^+$: 230.0799, found 230.0793.



s2.23e

***N*-(2-(1-Hydroxycyclobutyl)-4-trifluoromethoxyphenyl)formamide s2.24e.** The general procedure was followed by using 0.246 g (6.40 mmol) of NaH, 1.00 g (3.50 mmol) of **s2.25e**, 1.80 mL (3.80 mmol) of *n*-BuLi and 0.290 mL (3.30 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick brown oil (0.29 g, 30%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

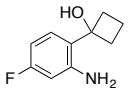
***N*-(2-(1-Hydroxycyclobutyl)-4-trifluoromethoxyphenyl)aniline s2.23e.** The general procedure was followed by using 0.300 g (1.09 mmol) of **s2.24e**. Purification by MPLC (5:1 hexanes:EtOAc) afforded the product as a yellow solid (0.180 g, 65%): R_f = 0.25 (5:1 hexanes:EtOAc); mp = 116 – 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 2.0 Hz, 1H), 6.98 – 6.96 (m, 1H), 6.61 (d, J = 9.0 Hz, 1H), 4.26 (bs, 2H), 2.62 – 2.57 (m, 2H), 2.37 – 2.31 (m, 2H), 2.03 – 1.95 (m, 1H), 1.67 – 1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (C), 140.6 (C), 129.0 (C), 121.6 (CH), 120.7 (q, J_{CF} = 253.6 Hz, C), 118.8 (CH), 117.0 (CH), 77.1 (C), 35.0 (CH_2), 13.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.8; ATR-FTIR (thin film): 3375, 2990, 1625, 1498, 1249, 1215, 1154, 885, 822 cm^{-1}. HRMS (EI) m/z calcd for $C_{11}H_{12}NO_2F_3$: 247.0813, found 247.0820.



s2.23f

***N*-(2-(1-Hydroxycyclobutyl))-5-methylphenyl)formamide s2.24f.** The general procedure was followed by using 0.329 g (8.55 mmol) of NaH, 1.00 g (4.67 mmol) of **s2.25f**, 2.30 mL (5.84 mmol) of *n*-BuLi and 0.390 mL (5.14 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick brown oil (0.20 g, 21%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

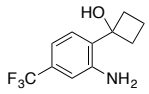
***N*-(2-(1-Hydroxycyclobutyl)-5-methylphenyl)aniline s2.23f.** The general procedure was followed by using 0.180 g (1.02 mmol) of **s2.24f**. Purification by MPLC (5:1 hexanes:EtOAc) afforded the product as a brown solid (0.16 g, 75%): R_f = 0.28 (5:1 hexanes:EtOAc); mp = 96 – 98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 4.12 (bs, 2H), 2.66 – 2.61 (m, 2H), 2.34 (q, *J* = 9.0 Hz, 2H), 2.27 (s, 3H), 2.01 – 1.93 (m, 1H), 1.62 (quin, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5 (C), 138.6 (C), 125. 7 (C), 125.3 (CH), 118.5 (CH), 117.6 (CH), 77.2 (C), 35.1 (CH_2) 21.1 (CH_3), 13.7 (CH_2); ATR-FTIR (thin film): 3418, 3320, 2976, 2934, 2858, 1615, 1510, 1428, 1115, 819, 792 cm^{-1}. HRMS (EI) m/z calcd for $C_{11}H_{15}NO$: 177.11541, found 177.11537.



s2.23g

***N*-(5-Fluoro-2-(1-hydroxycyclobutyl)phenyl)formamide s2.24g.** The general procedure was followed by using 0.288 g (7.50 mmol) of NaH, 0.900 g (4.10 mmol) of **s2.25g**, 2.00 mL (5.10 mmol) of *n*-BuLi and 0.340 mL (4.50 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick brown oil (0.15 g, 18%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

***N*-(5-Fluoro-2-(1-hydroxycyclobutyl)phenyl)aniline s2.23g.** The general procedure was followed by using 0.215 g (1.03 mmol) of **s2.24g**. Purification by MPLC (5:1 hexanes:EtOAc) afforded the product as a brown solid (0.130 g, 68%): R_f = 0.25 (5:1 hexanes:EtOAc); mp = 139 – 141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 8.0 Hz, 6.0 Hz, 1H), 6.38 (dt, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.33 (dd, *J* = 11.0 Hz, 2.5 Hz, 1H), 4.30 (bs, 2H), 2.60 – 2.55 (m, 2H), 2.32 – 2.27 (m, 2H), 2.00 – 1.92 (m, 1H), 1.64 – 1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (d, J_{CF} = 240.8, C), 147.5 (d, J_{CF} = 9.4 Hz, C), 126.7 (d, J_{CF} = 11.0 Hz, CH), 124.0 (C), 103.7 (d, J_{CF} = 20.3 Hz, CH), 103.2 (d, J_{CF} = 24.0 Hz, CH), 77.1 (C), 35.2 (CH_2), 13.7 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –115.2; ATR-FTIR (thin film): 3418, 3326, 3230, 2923, 2852, 1622, 1434, 1332, 1162, 1126, 1104, 870, 804, 740 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{11}NOF$ $[M – H]^+$: 180.0827, found 180.0825.

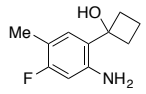


s2.23h

***N*-(2-(1-Hydroxycyclobutyl)-5-trifluoromethylphenyl)formamide s2.24i.** The general procedure was followed by using 0.209 g (5.45 mmol) of NaH, 0.800 g (2.98 mmol) of **s2.25h**, 1.50 mL (3.73 mmol) of *n*-BuLi and 0.250 mL (3.30 mmol) of

cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick brown oil (0.18 g, 23%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

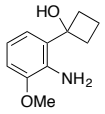
***N*-(2-(1-Hydroxycyclobutyl)-5-trifluoromethylphenyl)aniline s2.23h.** The general procedure was followed by using 0.263 g (1.02 mmol) of **s2.24h**. Purification by MPLC (5:1 hexanes:EtOAc) afforded the product as a yellow solid (0.170 g, 70%): R_f = 0.28 (5:1 hexanes:EtOAc); mp = 102 – 104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 4.40 (s, 2H), 2.64 – 2.59 (m, 2H), 2.37 – 2.31 (m, 2H), 2.02 – 1.96 (m, 1H), 1.65 – 1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0 (C), 131.0 (C), 130.9 (q, J_{CF} = 31.9 Hz, C), 125.7 (CH), 124.1 (q, J_{CF} = 270.5 Hz, C), 114.0 (q, J_{CF} = 4.0 Hz, CH), 112.9 (q, J_{CF} = 3.6 Hz, CH), 77.2 (C), 35.0 (CH_2), 13.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.3; ATR-FTIR (thin film): 3418, 3326, 3230, 2923, 2852, 1622, 1434, 1332, 1162, 1126, 1104, 870, 804, 740 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{11}NOF_3$ $[M – H]^+$: 230.0783, found 230.0793.



s2.23i

***N*-(5-Fluoro-2-(1-hydroxycyclobutyl)-3-methylphenyl)formamide s2.24i.** The general procedure was followed by using 0.174 g (7.10 mmol) of NaH, 0.900 g (3.90 mmol) of **s2.25i**, 1.90 mL (4.88 mmol) of *n*-BuLi and 0.320 mL (4.30 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick brown oil (0.18 g, 21%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

***N*-(5-Fluoro-2-(1-hydroxycyclobutyl)-4-methylphenyl)aniline s2.23i.** The general procedure was followed by using 0.260 g (1.17 mmol) of **s2.24i**. Purification by MPLC (5:1 hexanes:EtOAc) afforded the product as a red solid (0.14 g, 60%) as a mixture of rotamers: R_f = 0.33 (5:1 hexanes:EtOAc); mp = 114 – 116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.5 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 0.26H), 6.35 (d, *J* = 11.0 Hz, 1.21H), 4.13 (s, 2H), 2.82 – 2.76 (m, 0.58H), 2.63 – 2.60 (m, 2H), 2.44 – 2.40 (m, 0.70H), 2.35 – 2.29 (m, 3H), 2.16 (s, 3H), 2.12 (s, 0.90 H), 2.00 – 1.96 (m, 1H), 1.88 – 1.85 (m, 0.37H), 1.66 – 1.57 (m, 1H), 1.27 – 1.24 (m, 0.19H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2 (d, J_{CF} = 241.3 Hz, C), 145.0 (d, J_{CF} = 10.0 Hz, C), 130.3 (d, J_{CF} = 8.1 Hz, CH), 128.1 (d, J_{CF} = 6.9 Hz, CH), 124.0 (C), 112.6 (d, J_{CF} = 17.3 Hz, C), 111.8 (CH), 103.4 (d, J_{CF} = 25.0 Hz, CH), 77.1 (C), 37.1 (d, J_{CF} = 5.6 Hz, CH_2), 35.3 (CH_2), 17.0 (CH_2), 13.8 (CH_3), 13.7 (CH_2), only visible signals; ^{19}F NMR (282 MHz, $CDCl_3$) δ –120.0, –119.2; ATR-FTIR (thin film): 3346, 2948, 2867, 1632, 1587, 1509, 1419, 1310, 1141, 1110, 1044, 1023, 882, 782 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}NOF$ $[M – H]^+$: 194.0979, found 194.0981.

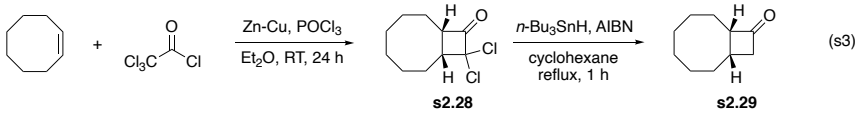


s2.23j

***N*-(2-(1-Hydroxycyclobutyl-6-methoxy)phenyl)formamide s2.24j.** The general procedure was followed by using 0.303 g (7.90 mmol) of NaH, 1 g (4.30 mmol) of **s2.25j**, 2.20 mL (5.40 mmol) of *n*-BuLi and 0.350 mL (4.70 mmol) of cyclobutanone to give the crude material. Purification by MPLC (hexanes:EtOAc 3:1– 1:1) gave the product as a thick yellow oil (0.14 g, 13%), which was submitted to the KOH-mediated hydrolysis step without additional characterization.

***N*-(2-(1-Hydroxycyclobutyl-6-methoxy)phenyl)aniline s2.23j.** The general procedure was followed by using 0.225 g (1.02 mmol) of **s2.24j**. Purification by MPLC (5:1 hexane:EtOAc) afforded the product as a red solid (0.14 g, 70%): R_f = 0.25 (5:1 hexanes:EtOAc); mp = 116 – 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.70 (t, *J* = 8.0 Hz, 1H), 4.36 (s, 2H), 3.86 (s, 3H), 3.85 (s, 1H), 2.70 – 2.65 (m, 2H), 2.40 – 2.31 (m, 2H), 2.02 – 1.95 (m, 1H), 1.68 – 1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8 (C), 135.0 (C), 128.4 (C), 117.6 (CH), 116.7 (CH), 109.9 (CH), 77.6 (C), 55.7 (CH_3), 35.2 (CH_2), 13.8 (CH_2); ATR-FTIR (thin film): 3478, 3389, 3267, 2985, 2942, 2835, 1615, 1568, 1463, 1439, 1284, 1219, 1122, 1048, 954, 837, 734 cm^{-1}. HRMS (EI) m/z calcd for $C_{11}H_{15}NO_2$: 193.10965, found 193.11028.

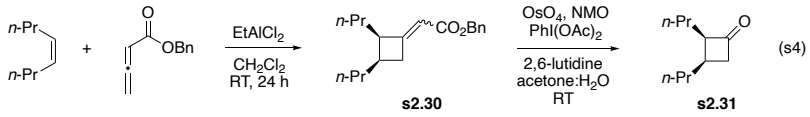
E. General Procedure for Synthesis of Cyclobutanones



(s3)

(1*R*,8*S*)-10,10 dichlorobicyclo[6.2.0]decan-9-one s2.28.[31] The compound was prepared using the procedure developed by Deprés and co-workers.[31] To a stirred mixture of 0.500 g (4.50 mmol) of commercially available cis-cyclooctene and 0.589 g (9.00 mmol) of Zn-Cu couple under argon was added over 1h a solution of 0.64 mL (6.80 mmol) of $POCl_3$ and 0.76 mL (6.80 mmol) of CCl_3COCl in 10 mL dry ether. After the reaction was stirred for 14 h, the ether solution was separated from the excess couple and added to hexane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with cold water, cold aqueous sodium bicarbonate solution, water, and brine, and then dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure afforded **s2.28** as a clear oil (0.460 g, 45%) which was submitted in the next step without further characterization.

(1*S*,8*S*)-[6.2.0]decan-9-one s2.29.[32] Dechlorination was accomplished following the procedure developed by Montaigne and Ghosez.[32] Under an inert atmosphere of argon, 1.60 mL (5.80 mmol) of freshly distilled Bu_3SnH was heated at reflux. To this solution was added, 0.010 g (0.06 mmol) of AIBN and 0.460 g (2.00 mmol) of **s2.28** in cyclohexane quickly in one portion and refluxed for 1h. The solution was cooled, concentrated *in vacuo* and purified using MPLC (25:1 hexanes:EtOAc) to give the product as a colorless oil (0.128 g, 42%): R_f = 0.47 (10:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29 – 3.21 (m, 1H), 3.14 – 3.08 (m, 1H), 2.53 – 2.43 (m, 2H), 1.81 – 1.62 (m, 5H), 1.59 – 1.53 (m, 3H), 1.40 – 1.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2 (C), 62.4 (CH), 52.4 (CH_2), 30.3 (CH_2), 29.8 (CH), 29.7 (CH_2), 28.6 (CH_2), 26.1 (CH_2), 25.4 (CH_2), 22.0 (CH_2); ATR-FTIR (thin film): 2916, 2850, 1773, 1464, 1445, 1208, 1083 cm^{-1}. HRMS (EI) m/z calcd for $C_{10}H_{15}O$: 151.11177, found 151.11230.

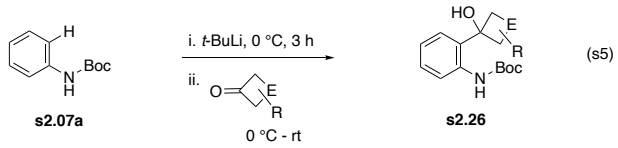


Benzyl 2-(2*R*,3*R*)-2,3-dipropylcyclobutylidene)acetate s2.30.[33] The compound was prepared using the procedure developed by Snider and Spindell. 0.50 mL (3.20 mmol) of commercially available cis-4 octene was added dropwise to a solution of 0.507 g (2.91 mmol) of benzyl buta-2,3 dienoate and 2.65 mL (2.65 mmol) of $EtAlCl_2$ in 6 mL of CH_2Cl_2. The reaction mixture was stirred for 24 h at 25 °C, diluted with ether, and quenched by slow addition of saturated NaH_2PO_4 solution. A 10% aq soln of hydrochloric acid was added to dissolve the precipitated alumina. The two layers were separated and the aqueous layer was washed with three portions of ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (20:1 hexanes:EtOAc) to give **s2.30**, a yellow oil, as 12.5:1 (E:Z) mixture of diastereomers (0.641 g, 77%): R_f = 0.81 (10:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5.66H), 5.70 – 5.59 (m, 1H), 5.63 – 5.62 (m, 0.08H), 5.14 (s, 2.06H), 5.13 (s, 0.20H), 3.16 – 3.10 (m, 1.08H), 3.07 – 3.01 (m, 1.09H), 2.73 – 2.68 (m, 1.14H), 2.45 – 2.38 (m, 1.15H), 1.50 – 1.43 (m, 3.27H), 1.39 – 1.18 (m, 6.07H), 0.93 – 0.88 (m, 6.71H), 0.87 (t, *J* = 7.5 Hz, 0.43H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (C), 166.5 (C), 136.5 (C), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 111.5 (CH), 111.0 (CH), 65.5 (CH_2), 48.4 (CH), 47.3 (CH), 37.8 (CH_2), 37.6 (CH_2), 34.4 (CH), 34.2 (CH), 32.6 (CH_2), 32.1 (CH2), 30.9 (CH_2), 30.0 (CH_2), 22.0 (CH_2), 21.3 (CH_2), 20.7 (CH_2), 14.4 (CH_3), 14.2 (CH_3), 14.2 (CH_3); ATR-FTIR (thin film): 2956, 2927, 2871, 1714, 1670, 1456, 1377, 1336, 1260, 1176, 1004 cm^{-1}. HRMS (EI) m/z calcd for $C_{19}H_{26}O_2$: 286.19366, found 286.19328.

(2*R*,3*R*)-2,3-dipropylcyclobutan-1-one s2.31.[34] The compound was prepared using the procedure developed by Nicolaou and co-workers.[34] To a solution of 0.250 g of cyclobutane **s2.30** (0.87 mmol) in 10:1 acetone:water (0.1 M) were added 0.20 mL of 2,6-lutidine (1.74 mmol), 0.153 g of 4-methylmorpholine *N*-oxide (1.31 mmol) and 0.11 mL of osmium tetroxide (4% in H_2O, 0.02 mmol). The reaction progress was monitored using TLC. When the starting material had been consumed, 0.420 g of $PhI(OAc)_2$ (1.31 mmol) was added. After stirring for 2 h, the reaction was quenched with saturated aqueous sodium thiosulfate (10 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), washed with saturated aqueous copper sulfate (2 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by MPLC (49:1 hexanes:EtOAc) to give **s9** as a clear oil (0.097 g, 72%): R_f = 0.78 (10:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 – 3.22 (m, 1H), 3.14 – 3.08 (m, 1H), 2.51 – 2.39 (m, 2H), 1.61 – 1.54 (m, 1H), 1.46 – 1.19 (m, 7H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0 (C), 61.7 (CH), 50.2 (CH_2), 32.3 (CH_2), 27.4 (CH), 26.4 (CH_2), 21.4 (CH_2), 21.2 (CH_2), 14.1 (CH_3), 14.1 (CH_3); ATR-FTIR (thin film): 2957 , 2928, 2873, 1775, 1465 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{19}O$ $[M + H]^+$: 155.14398, found 155.14360.

F. General Procedure for Synthesis of *o*-Cyclobutanol Carbamates

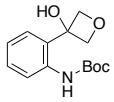
o-Cyclobutanol carbamates were prepared following the protocol reported by Fensome and co-workers.[12]



(s5)

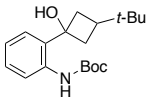
To a cooled (0 °C) 3 M solution of commercially available *N*-Boc aniline (1.0 equiv) in dry Et_2O under an inert atmosphere of argon was dropwise added *t*-butyl lithium (1.9 M in pentane, 2.5 equiv) using a syringe pump. After 3 h, a solution of the cycloalkanone (1.5 equiv) in dry Et_2O was added dropwise. The resulting mixture was allowed to warm to rt. The reactives were quenched through the addition of a saturated aq soln of NH_4Cl. The resulting mixture was diluted with EtOAc. The two layers were separated, and the aqueous layer was extracted 3 additional times with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the filtrate concentrated under reduced pressure. The resulting residue was purified by MPLC to afford the product.

G. Characterization data for *o*-Cyclobutanol Carbamates



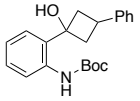
s2.26a

***tert*-Butyl (2-(1-hydroxyoxetane)phenylcarbamate s2.26a.** The general procedure was followed by using 0.800 g of *N*-Boc aniline (4.14 mmol), 5.50 ml of *t*-butyl lithium (10.4 mmol) and 0.360 mL of commercially available 3-oxetanone (6.20 mmol). Purification by MPLC (5:1 hexanes:EtOAc) gave the product as a yellow solid (0.420 g, 38%): R_f = 0.53 (1:1 hexanes:EtOAc); mp = 102 – 104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.18 (s, 1H), 7.14 – 7.08 (m, 2H), 4.96 (d, *J* = 7.0 Hz, 2H), 4.74 (d, *J* = 7.0 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1 (C), 135.6 (C), 133.1 (C), 129.2 (CH), 126.1 (CH), 126.1 (CH), 124.7 (CH), 124.1 (CH), 82.8 (CH_2), 81.1 (C), 75.9 (C), 28.3 (CH_3); ATR-FTIR (thin film): 3360, 2978, 2875, 1698, 1587, 1514, 1450, 1367, 1236, 1155, 1052, 1025, 976, 729 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{19}NO_4Na$ [M + Na]$^+$: 288.1213, found 288.1212.



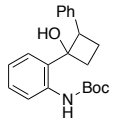
s2.26b

***tert*-Butyl (2-(1-Hydroxy-3-*tert*-butylcyclobutyl)phenylcarbamate s2.26b.** The general procedure was followed by using 0.300 g of *N*-Boc aniline (1.56 mmol), 2.0 mL of *t*-butyl lithium (5.18 mmol) and 0.290 g of 3-*tert*-butylcyclobutanone (2.39 mmol).[35] Purification by MPLC (15:1 hexanes:EtOAc) gave the product as a yellow sticky solid, as a 2:1 mixture of atropisomers (0.17 g, 33%): R_f = 0.78 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 0.93H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 0.41H), 7.53 (s, 0.42H), 7.37 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.29 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.24 (dd, *J* = 8.0 Hz, 2.0 Hz, 0.39 H), 7.18 (dd, *J* = 7.5 Hz, 1.5 Hz, 0.44H), 7.04 – 7.00 (m, 1.43H), 2.56 – 2.47 (m, 2H), 2.26 (d, J = 9.0 Hz, 2H), 2.11 – 2.02 (m, 2H), 1.64 – 1.57 (m, 1H), 1.51 (s, 13.6H), 0.84 (s, 9H), 0.81 (s, 4.51H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5 (C), 153.2 (C), 138.0 (C), 136.6 (C), 135.0 (C), 131.8 (C), 128.6 (CH), 128.4 (CH), 125.3 (CH), 124.8 (CH), 123.1 (CH), 122.4 (CH), 122.3 (CH), 121.9 (CH), 80.3 (C), 80.1 (C), 74.1 (C), 71.8 (C), 40.4 (CH), 36.8 (CH_2), 35.5 (CH_2), 30.9 (C), 30.8 (C), 28.4 (CH_3), 26.6 (CH_3), 26.3 (CH_3) (only visible peaks); ATR-FTIR (thin film): 3356, 2956, 2866, 1729, 1704, 1587, 1520, 1450, 1366, 1304, 1236, 1161, 1025, 755 cm^{-1}. HRMS (ESI) m/z calcd for $C_{19}H_{29}NO_3Na$ [M + Na]$^+$: 342.2040, found 342.2045.



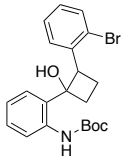
s2.26c

***tert*-Butyl (2-(1-Hydroxy-3-phenylcyclobutyl)phenylcarbamate s2.26c.** The general procedure was followed by using 0.300 g of *N*-Boc aniline (1.56 mmol), 2.30 mL of *t*-butyl lithium (3.89 mmol) and 0.338 g of 3-phenylcyclobutanone (2.33 mmol).[35] Purification by MPLC (15:1 hexanes:EtOAc) gave the product as a white sticky solid, as a 3:1 mixture of atropisomers (0.15 g, 28%): R_f = 0.68 (5:1 hexanes:EtOAc); mp = 153 – 155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1.30H), 7.99 (s, 0.45H), 7.76 (d, *J* = 8.5 Hz, 0.38H), 0.33 (s, 0.43H), 7.49 (dd, *J* = 8.5 Hz, 1.5 Hz, 1.01H), 7.35 – 7.27 (m, 5.81H), 7.24 – 7.18 (m, 2.57H), 7.12 – 7.06 (m, 1.36H), 3.97 (quin, *J* = 8.5 H, 0.40 H), 3.13 – 3.07 (m, 1.82H), 3.04 – 2.97 (m, 1.31H), 2.88 – 2.81 (m, 1.66H), 2.69 – 2.63 (m, 0.86H), 2.57 – 2.51 (m, 1.82H), 1.53 (s, 3.24H), 1.52 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 153.3 (C), 144.7 (C), 144.1 (C), 137.9 (C), 136.3 (C), 135.4 (C), 131.6 (C), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.4 (CH), 126.7 (CH), 126.5 (CH), 126.3 (CH), 126.2 (CH), 125.6 (CH), 124.8 (CH), 123.6 (CH), 122.8 (CH), 122.7 (CH), 122.4 (CH), 80.5 (C), 80.3 (C), 75.0 (C), 72.7 (C), 43.2 (CH2), 42.2 (CH2), 34.2 (CH), 30.7 (CH_3), 28.4 (CH_3) only visible peaks; ATR-FTIR (thin film): 3362, 2977, 2930, 1726, 1703, 1586, 1519, 1450, 1367, 1246, 1155, 1048, 1025, 750, 698 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{25}NO_3Na$ [M + Na]$^+$: 362.1726, found 362.1732.



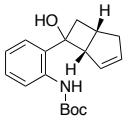
s2.26d

***tert*-Butyl (2-(1-hydroxycyclobutyl)phenylcarbamate s2.26d.** The general procedure was followed by using 0.495 g of *N*-Boc aniline (2.56 mmol), 3.40 mL of *t*-butyl lithium (6.40 mmol) and 0.560 g of 2-phenylcyclobutanone (3.84 mmol).[36] Purification by MPLC (15:1 hexanes:EtOAc) gave the product as a white sticky solid (0.370 g, 43%): R_f = 0.78 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.47 – 7.45 (m, 3H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.05 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 4.20 (m, 1H), 2.56 – 2.45 (m, 3H), 2.29 – 2.22 (m, 1H), 2.07 (d, *J* = 1.0 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C), 138.4 (C), 137.5 (C), 133.3 (C), 128.8 (CH), 128.8 (CH), 128.5 (CH), 127.2 (CH), 125.2 (CH), 122.5 (CH), 121.8 (CH), 80.2 (C), 80.0 (C), 47.8 (CH), 33.6 (CH_2), 28.4 (CH_3), 21.7 (CH_2); ATR-FTIR (thin film): 3374, 2977, 2360, 2341, 1726, 1585, 1522, 1449, 1392, 1305, 1239, 1161, 1048, 753 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{25}NO_3Na$ [M + Na]$^+$: 362.1722, found 362.1732.



s2.26e

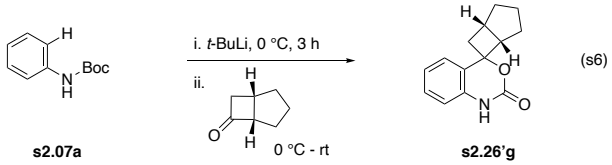
***tert*-Butyl (2-(1-hydroxycyclobutyl)phenylcarbamate s2.26e.** The general procedure was followed by using 0.200 g of *N*-Boc aniline (1.04 mmol), 1.40 mL of *t*-butyl lithium (2.60 mmol) and 0.356 g of 2-(2-bromophenyl)cyclobutanone (1.56 mmol).[37] Purification by MPLC (12:1 hexanes:EtOAc) gave the product as a brown solid (0.200 g, 46%): R_f = 0.53 (5:1 hexanes:EtOAc); mp = 196 – 198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.60 (t, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.56 (t, *J* = 7.5 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.48 – 2.39 (m, 2H), 2.29 – 2.23 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$ δ 153.1 (C), 138.5 (C), 137.3 (C), 133.1 (CH), 132.8 (C), 130.4 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 125.9 (C), 125.7 (CH), 122.6 (CH), 121.7 (CH), 80.8 (C), 80.0 (C), 46.9 (CH), 33.7 (CH_2), 28.3 (CH_3), 22.6 (CH_2); ATR-FTIR (thin film): 3368, 2977, 1704, 1586, 1521, 1448, 1241, 1157, 1048, 1023, 752, 736 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{24}NO_3NaBr$ $[M + Na]^+$: 440.0829, found 440.0837.



s2.26f

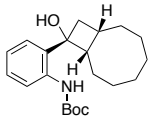
***tert*-Butyl (2-(1-hydroxycyclobutyl)phenylcarbamate s2.26f.** The general procedure was followed by using 0.250 g of *N*-Boc aniline (1.30 mmol), 1.50 mL of *t*-butyl lithium (3.30 mmol) and 0.210 mL of commercially available bicyclo[3.2.0]hept-2-en-6 one (1.95 mmol). Purification by MPLC (12:1 hexanes:EtOAc) gave the product, a brown sticky solid, as a mixture of diastereomers (0.17 g, 43%): R_f = 0.58 (7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 0.10H), 8.27 (d, *J* = 8.0 Hz, 0.11H), 7.85 (d, *J* = 8.0 Hz, 0.86H), 7.49 – 7.48 (m, 0.83H), 7.47 – 7.45 (m, 0.22H), 7.38 – 7.34 (m, 0.27H), 7.32 – 7.25 (m, 2.23H), 7.06 – 7.02 (m, 1H), 7.00 (dd, *J* = 8.0 Hz, 1.5 Hz, 0.10H), 5.99 – 5.95 (m, 1.93H), 5.89 (s, 0.22H), 3.45 – 3.42 (m, 1H), 3.16 – 3.08 (m, 2H), 2.90 (d, *J* = 8.0 Hz, 1H), 2.66 – 2.60 (m, 1H), 2.48 (s, 1H), 2.14 – 2.11 (m, 1H), 1.51 (s, 9H), 1.50 (s, 1.55H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C), 150.9 (C), 139.2 (C), 136.9 (C), 135.6 (CH), 134.4 (CH), 132.7 (CH), 132.4 (CH), 131.9 (CH), 128.4 (CH), 125.3 (CH), 122.9 (CH), 122.7 (CH), 121.0 (CH), 120.4 (CH), 117.1 (CH), 115.8 (CH), 80.5 (C), 80.0 (C), 77.4 (C), 45.7 (CH), 41.9 (CH_2), 39.8 (CH), 33.4 (CH_2), 28.4 (CH_3), 28.3 (CH_3) only visible peaks; ATR-

FTIR (thin film): 3371, 2977, 2928, 1727, 1704, 1585, 1515, 1448, 1238, 1153, 1048, 1024, 748, 726 cm^{-1}. HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_3Na$ $[M + Na]^+$: 324.1571, found 324.1576.



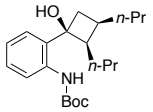
s2.07a **s2.26'g**

Spiro(2-(1-hydroxycyclobutyl)phenylbenzoxazine s2.26'g. The general procedure was followed by using 0.200 g of *N*-Boc aniline (1.04 mmol), 1.32 mL of *t*-butyl lithium (2.50 mmol) and 0.170 g of bicyclo[3.2.0]heptan-6-one (1.50 mmol).[38] Purification by MPLC (5:1 hexanes:EtOAc) gave the product as a orange solid (0.07 g, 30%): R_f = 0.30 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.22 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.10 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 2.90 – 2.86 (m, 1H), 2.77 – 2.72 (m, 1H), 2.65 (quin, *J* = 7.0 Hz, 1H), 2.21 – 2.06 (m, 3H), 1.91 – 1.86 (m, 1H), 1.70 (dd, *J* = 11.5 Hz, 6.0 Hz, 1H), 1.59 – 1.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0 (C), 133.9 (C), 128.5 (CH), 126.4 (C), 123.6 (CH), 122.6 (CH), 114.3 (CH), 80.5 (C), 52.6 (CH), 37.9 (CH_2), 32.6 (CH_2), 31.4 (CH), 26.9 (CH_2), 25.6 (CH_2); ATR-FTIR (thin film): 3245, 2950, 1708, 1597, 1501, 1353, 1250, 1157, 1073, 1019, 751 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$: 230.1176, found 230.1181.



s2.26h

***N*-(2-(1-Hydroxycyclobutyl)phenyl)carbamate s2.26h.** The general procedure was followed by using 0.200 g of *N*-Boc aniline (1.04 mmol), 1.32 mL of *t*-butyl lithium (2.50 mmol) and 0.237 g of bicyclo[6.2.0]decan-9-one (1.50 mmol). Purification by MPLC (15:1 hexanes:EtOAc) gave the product as a white sticky solid (0.12 g, 33%): R_f = 0.54 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.79 (bs, 1H), 7.35 – 7.33 (m, 1H), 7.30 – 7.26 (m, 1H), 7.05 – 7.01 (m, 1H), 2.88 – 2.83 (m, 1H), 2.57 – 2.52 (m, 1H), 2.14 (bs, 1H), 1.99 – 1.83 (m, 4H), 1.82 – 1.71 (m, 2H), 1.59 – 1.42 (m, 13H), 1.32 – 1.17 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C), 137.6 (C), 134.0 (C), 128.3 (CH), 124.4 (CH), 122.6 (CH), 122.4 (CH), 79.9 (C), 75.2 (C), 49.2 (CH), 40.2 (CH_2), 31.5 (CH), 30.2 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 28.4 (CH_3), 25.8 (CH_2), 25.2 (CH_2), 22.6 (CH_2); ATR-FTIR (thin film): 3365, 2975, 2919, 2850, 1729, 1704, 1586, 1519, 1449, 1367, 1245, 1160, 1048, 747 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{31}NO_3Na$ $[M + Na]^+$: 368.2192, found 368.2202.



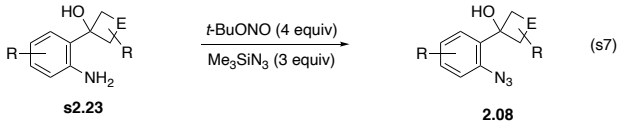
s2.26i

***N*-(2-(1-Hydroxycyclobutyl)phenyl)carbamate s2.26i.** The general procedure was followed by using 0.200 g of *N*-Boc aniline (1.04 mmol), 1.32 mL of *t*-butyl lithium (2.50 mmol) and 0.240 g of (2*S*,3*S*)-2,3-dipropylcyclobutan-1-one (1.50 mmol). Purification by MPLC (15:1 hexanes:EtOAc) gave the product as a white sticky solid (0.14 g, 40%): R_f = 0.78 (10:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.93 (s, 1H), 7.31 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.00 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 2.72 – 2.64 (m, 2H), 2.25 (bs, 1H), 2.03 – 1.93 (m, 2H), 1.71 – 1.54 (m, 2H), 1.51 (s, 9H), 1.48 – 1.40 (m, 4H), 1.34 – 1.25 (m, 1H), 1.22 – 1.12 (m, 1H), 1.00 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C), 137.6 (C), 133.6 (C), 128.3 (CH), 124.7 (CH), 122.4 (CH), 121.9 (CH), 79.9 (C), 75.9 (C), 46.2 (CH), 39.4 (CH_2), 32.6 (CH_2), 30.4 (CH), 28.4 (CH_3), 27.4 (CH_2), 23.4 (CH_2), 20.8 (CH_2), 14.8 (CH_3), 14.3 (CH_3); ATR-FTIR (thin film): 3365, 2975, 2919, 2850, 1729, 1704, 1586, 1519, 1449, 1367, 1245, 1160, 1048, 747 cm^{-1}. HRMS (EI) m/z calcd for $C_{21}H_{33}NO_3$: 347.24507, found 347.24605.

II. Synthesis of *o*-Cyclobutanol Aryl Azides

A. General Procedure

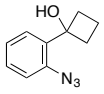
The *o*-cyclobutanol aryl azides were prepared following the protocol reported by Moses and co-workers.[39]



s2.23 **2.08**

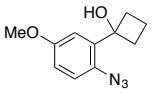
To a cooled solution (0 °C) of o-cyclobutanol aniline **s2.23** in MeCN (0.2 M), was added dropwise *t*-BuONO (4.0 equiv), Me_3SiN_3 (3.0 equiv). The resulting solution was warmed to room temperature. After 1.5 h, the reaction mixture was concentrated in vacuo. The residue was purified by MPLC (10:1 – 7:1 hexanes:EtOAc) to afford the *ortho*-cyclobutanol aryl azide.

B. Characterization Data for *o*-Cyclobutanol Azides



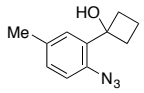
2.08a

***o*-Cyclobutanol aryl azide 2.08a.** The general procedure was followed by using 0.155 g of aniline **s2.23a** (0.950 mmol), 0.450 mL of *t*-BuONO (3.80 mmol), 0.37 mL Me_3SiN_3 (2.85 mmol) in 4.8 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil (0.150 g, 82%): R_f = 0.52 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.31 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.17 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.12 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 3.24 (s, 1H), 2.58 – 2.52 (m, 2H), 2.40 – 2.34 (m, 2H), 2.15 – 2.08 (m, 1H), 1.70 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4 (C), 136.2 (C), 128.8 (CH), 126.4 (CH), 124.7 (CH), 118.8 (CH), 76.8 (C), 35.2 (CH_2), 14.5 (CH_2); ATR-FTIR (thin film): 3397, 2946, 2125, 2087, 1486, 1444, 1293, 1131, 751 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{12}NO$ [M + H – N_2]$^+$: 162.0923, found 162.0919.



2.08b

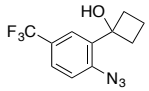
***o*-Cyclobutanol aryl azide 2.08b.** The general procedure was followed by using 0.152 g of aniline **s2.23b** (0.790 mmol), 0.380 mL of *t*-BuONO (3.16 mmol), 0.310 mL of Me_3SiN_3 (2.37 mmol) in 3.9 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil (0.160 g, 94%): R_f = 0.40 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 1.0 Hz, 1H), 6.84 (dd, *J* = 8.5 Hz, 1.0 Hz, 1H), 3.81 (s, 3H), 3.16 (bs, 1H), 2.55 – 2.50 (m, 2H), 2.39 – 2.34 (m, 2H), 2.14 – 2.07 (m, 1H), 1.72 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8 (C), 137.6 (C), 129.6 (C), 119.8 (CH), 113.1 (CH), 113.0 (CH), 76.7 (C), 55.7 (CH_3), 35.2 (CH_2), 14.3 (CH_2); ATR-FTIR (thin film): 3513, 2941, 2836, 2108, 1579, 1485, 1312, 1237, 1038, 803 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_3O_2Na$ [M + Na]$^+$: 242.0899, found 242.0905.



2.08c

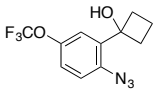
***o*-Cyclobutanol aryl azide 2.08c.** The general procedure was followed by using 0.150 g of aniline **s2.23c** (0.84 mmol), 0.40 mL of *t*-BuONO (3.16 mmol), 0.33 mL of Me_3SiN_3 (2.37 mmol) in 3.5 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil (0.122 g, 72%): R_f = 0.55 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.12 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 3.09 (s, 1H), 2.57 – 2.52 (m, 2H), 2.39 – 2.36 (m, 2H), 2.35 (s, 3H), 2.15 – 2.08 (m, 1H), 1.72 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (C), 134.5 (C), 134.4 (C), 129.2 (CH), 127.1 (CH),

118.7 (CH), 76.8 (C), 35.2 (CH_2), 21.0 (CH_3), 14.5 (CH_2); ATR-FTIR (thin film): 3417, 2947, 2114, 1492, 1300, 1157, 1137, 910, 807 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{14}NO$ $[M + H - N_2]^+$: 176.1077, found 176.1075.



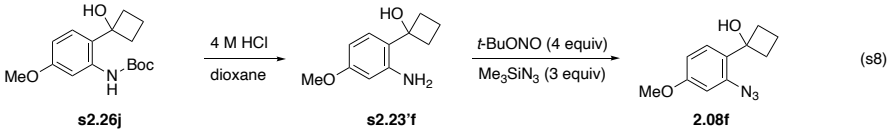
2.08d

***o*-Cyclobutanol aryl azide 2.08d.** The general procedure was followed by using 0.232 g of aniline **s2.23d** (1.00 mmol), 0.480 mL of *t*-BuONO (3.16 mmol), 0.400 mL of Me_3SiN_3 (2.37 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil (0.210 g, 80%): R_f = 0.55 (5:1 hexanes:EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 3.06 (s, 1H), 2.59 – 2.54 (m, 2H), 2.42 – 2.37 (m, 2H), 2.21 – 2.12 (m, 1H), 1.76 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1 (C), 136.8 (C), 126.8 (q, J_{CF} = 32.5 Hz, C), 125.8 (q, J_{CF} = 3.8 Hz, CH), 123.9 (q, J_{CF} = 269.9 Hz, C), 123.6 (q, J_{CF} = 3.9 Hz, CH), 119.0 (CH), 76.5 (C), 35.0 (CH_2), 14.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.3 ; ATR-FTIR (thin film): 3383, 2952, 2109, 1614, 1496, 1293, 1272, 1119, 1081, 903, 822 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{11}NOF_3$ $[M + H - N_2]^+$: 230.0790, found 230.0792.



2.08e

***o*-Cyclobutanol aryl azide 2.08e.** The general procedure was followed by using 0.114 g of aniline **s2.23e** (0.460 mmol), 0.220 mL of *t*-BuONO (1.84 mmol), 0.180 mL of Me_3SiN_3 (1.38 mmol) in 2.31 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil (0.090 g, 70%): R_f = 0.54 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.16 (m, 3H), 3.14 (s, 1H), 2.55 – 2.49 (m, 2H), 2.40 – 2.35 (m, 2H), 2.17 – 2.09 (m, 1H), 1.74 – 1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8 (C), 138.1 (C), 136.1 (C), 121.2 (CH), 120.5 (q, J_{CF} = 255.4 Hz, C), 119.8 (CH), 119.7 (CH), 76.4 (C), 35.1 (CH_2), 14.3 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.5 ; ATR-FTIR (thin film): 3390, 2953, 2118, 1483, 1249, 1208, 1158, 890, 817 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{11}NO_2F_3$ $[M + H - N_2]^+$: 246.0742, found 246.0742.

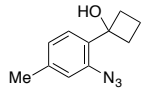


s2.26j s2.23'f 2.08f (s8)

***tert*-Butyl (2-(1-hydroxycyclobutyl)phenylcarbamate s2.26j.** The compound was prepared by slightly modifying the original procedure. 1.000 g of commercially available *tert*-butyl (2-bromo-5-methoxyphenyl) carbamate (3.31 mmol) was dissolved in dry THF under an inert atmosphere of argon and the solution was cooled to – 78 °C. 4.36 mL of *t*-butyl lithium (1.9 M in pentane, 8.28 mmol) was added dropwise using a syringe pump and the mixture was stirred at – 78 °C for 2 h. 0.37 mL of cyclobutanone (4.97 mmol) was added dropwise and the mixture was allowed to warm to rt. The reactives were quenched through the addition of a saturated aq soln of NH_4Cl. The resulting mixture was diluted with EtOAc. The two layers were separated, and the aqueous layer was extracted 3 additional times with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the filtrate concentrated under reduced pressure. The resulting residue was purified by MPLC (10:1 hexanes:EtOAc) to afford the product as a white sticky solid (0.296 g, 24%): R_f = 0.48 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (bs, 1H), 7.60 (d, *J* = 3.0 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.53 (dd, *J* = 8.5 Hz, 3.0 Hz, 1H), 3.80 (s, 3H), 2.59 – 2.53 (m, 2H), 2.40 (s, 1H), 2.39 – 2.31 (m, 2H), 2.05 – 1.97 (m, 1H), 1.67 – 1.59 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (C), 153.1 (C), 138.6 (C), 125.8 (CH), 124.9 (C), 108.3 (CH), 107.0 (CH), 80.2 (C), 77.1 (C), 55.4 (CH_3), 35.6 (CH_2), 28.4 (CH_3), 13.8 (CH_2); ATR-FTIR (thin film): 3346, 2978, 2360, 1727, 1703, 1616, 1528, 1239, 876 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{23}NO_4Na$ $[M + Na]^+$: 316.1517, found 316.1515.

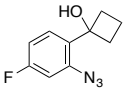
***N*-(2-(1-Hydroxy-3-*tert*-butylcyclobutyl)phenyl)aniline s2.23'f.** The compound was prepared using 0.500 g of **s2.26b** (1.34 mmol), 4 mL of HCl (4M in dioxane) to give **s2.23'f** as a yellow solid (0.219 g, 60%) which was submitted to the next step without further characterization.

***o*-Cyclobutanol aryl azide 2.08f.** The general procedure was followed by using 0.280 g of aniline **s2.23'f** (1.03 mmol), 0.490 mL of *t*-BuONO (4.12 mmol), 0.410 mL of Me_3SiN_3 (3.09 mmol) in 5.2 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil (0.243 g, 79%): R_f = 0.52 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 6.66 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.83 (s, 3H), 2.96 (s, 1H), 2.55 – 2.50 (m, 2H), 2.38 – 2.33 (m, 2H), 2.13 – 2.04 (m, 1H), 1.69 – 1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9 (C), 138.5 (C), 128.9 (C), 127.3 (CH), 109.4 (CH), 105.2 (CH), 76.4 (C), 55.5 (CH_3), 35.4 (CH_2), 14.4 (CH_2); ATR-FTIR (thin film): 3400, 2915, 2110, 2107, 1608, 1502, 1315, 1229, 1123, 830 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_3O_2Na$ $[M + Na]^+$: 242.0898, found 242.0904.



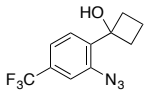
2.08g

***o*-Cyclobutanol aryl azide 2.08g.** The general procedure was followed by using 0.178 g of aniline **s2.23f** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.00 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil (0.170 g, 80%): R_f = 0.55 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 6.95 – 6.93 (m, 1H), 3.06 (s, 1H), 2.39 – 2.34 (m, 5H), 2.13 – 2.05 (m, 1H), 1.70 – 1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9 (C), 137.1 (C), 133.4 (C), 126.2 (CH), 125.5 (CH), 119.4 (CH), 76.6 (C), 35.3 (CH_2), 21.1 (CH_3), 14.4 (CH_2); ATR-FTIR (thin film): 3417, 2947, 2114, 1492, 1300, 1157, 1137, 910, 807 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{14}NO$ $[M + H - N_2]^+$: 176.1074, found 176.1075.



2.08h

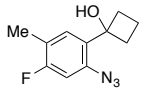
***o*-Cyclobutanol aryl azide 2.08h.** The general procedure was followed by using 0.183 g of aniline **s2.23g** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a yellow oil (0.180 g, 85%): R_f = 0.53 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.5 Hz, 6.5 Hz, 1H), 6.88 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H), 6.81 (dt, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.03 (s, 1H), 2.54 – 2.48 (m, 2H), 2.38 – 2.33 (m, 2H), 2.15 – 2.07 (m, 1H), 1.70 – 1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5 (d, J_{CF} = 247.6 Hz, C), 139.1 (d, J_{CF} = 9.1 Hz, C), 132.3 (d, J_{CF} = 3.3 Hz, C), 127.8 (d, J_{CF} = 9.0 Hz, CH), 111.3 (d, J_{CF} = 20.3 Hz, CH), 106.3 (d, J_{CF} = 24.1 Hz, CH), 76.4 (C), 35.3 (CH_2), 14.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –112.9; ATR-FTIR (thin film): 3394, 2950, 2109, 1593, 1498, 1412, 1292, 1230, 1140, 959, 842, 666 cm^{-1}. HRMS (CI) m/z calcd for $C_{10}H_{11}N_3OF$ $[M + H]^+$: 208.0884, found 208.0886.



2.08i

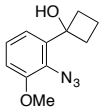
***o*-Cyclobutanol aryl azide 2.08i.** The general procedure was followed by using 0.233 g of aniline **s2.23h** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1

hexanes:EtOAc) gave the product as a yellow oil (0.210 g, 80%): R_f = 0.55 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 3.5 Hz, 2H), 3.2 (s, 1H), 2.58 – 2.52 (m, 2H), 2.42 – 2.36 (m, 2H), 2.19 – 2.10 (m, 1H), 1.74 – 1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7 (C), 138.5 (C), 131.2 (q, J_{CF} = 33.1 Hz, C), 127.0 (CH), 123.5 (q, J_{CF} = 270.3 Hz, C), 121.5 (q, J_{CF} = 3.9 Hz, CH), 115.6 (q, J_{CF} = 3.9 Hz, CH), 76. 5 (C), 35.1 (CH_2), 14.4 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.2; ATR-FTIR (thin film): 3490, 2924, 2107, 1417, 1328, 1274, 1123, 1086, 902, 871, 834, 656 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{11}NOF_3$ $[M + H - N_2]^+$: 230.0791, found 230.0793.



2.08j

***o*-Cyclobutanol aryl azide 2.08j.** The general procedure was followed by using 0.197 g of aniline **s2.23i** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a yellow oil (0.190 g, 85%) as a mixture of rotamers: R_f = 0.56 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 8.5 Hz, 1H), 7.1 (t, J = 8.0 Hz, 0.19H), 6.84 (d, J = 9.5 Hz, 1H), 6.84 (s, 0.11H), 2.97 (s, 1H), 2.69 – 2.65 (m, 0.39H), 2.54 – 2.48 (m, 2H), 2.47 – 2.43 (m, 0.38H), 2.38 – 2.32 (m, 2H), 2.24 (d, J = 1.5 Hz, 3H), 2.21 (d, J = 2.5 Hz, 0.56H), 2.15 – 2.08 (m, 1H), 1.88 – 1.81 (m, 0.20H), 1.71 – 1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6 (d, J_{CF} = 244.1 Hz, C), 159.6 (d, J_{CF} = 246.1 Hz, C), 136.2 (d, J_{CF} = 7.3 Hz, C), 131.9 (d, J_{CF} = 2.9 Hz, C), 130.4 (d, J_{CF} = 5.9 Hz, CH), 129.3 (d, J_{CF} = 5.6 Hz, CH), 120.9 (d, J_{CF} = 18.1 Hz, C), 113.9 (d, J_{CF} = 3.5 Hz, CH), 106.0 (d, J_{CF} = 25.8 Hz, CH), 76.4 (C), 37.3 (d, J_{CF} = 4.1 Hz, CH_2), 35.4 (CH_2), 29.7 (C), 17.6 (CH_2), 14.5 (CH_2), 14.4 (d, J_{CF} = 5.4 Hz, CH_2), 14.1 (d, J_{CF} = 3.6 Hz, CH_3), only visible signals; ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.4, −116.7 ; ATR-FTIR (thin film): 3353, 2949, 2106, 1588, 1504, 1313, 1239, 1164, 1134, 1091, 889, 839 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}NOF$ $[M + H - N_2]^+$: 194.0980, found 194.0981.



2.08k

***o*-Cyclobutanol aryl azide 2.08k.** The general procedure was followed by using 0.195 g of aniline **s2.23j** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a orange oil (0.180 g, 80%): R_f = 0.53 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$)

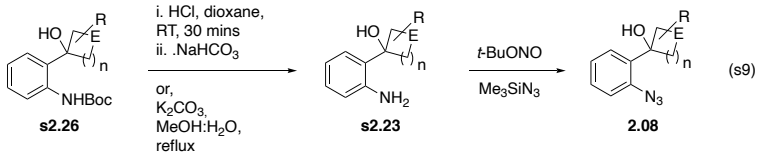
δ 7.10 – 7.06 (m, 1H), 6.94 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 6.84 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 3.90 (s, 3H), 3.31 (s, 1H), 2.57 – 2.51 (m, 2H), 2.41 – 2.35 (m, 2H), 2.15 – 2.07 (m, 1H), 1.71 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5 (C), 138.1 (C), 125.3 (C), 125.2 (CH), 118.1 (CH), 111.3 (CH), 77.1 (C), 56.1 (CH_3), 35.4 (CH_2), 14.5 (CH_2); ATR-FTIR (thin film): 3543, 2941, 2146, 2118, 2096, 1579, 1455, 1439, 1310, 1261, 1033, 734 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_3O_2Na$ [M + Na]$^+$: 242.0899, found 242.0905.

2.08l

***o*-Cyclopropanol aryl azide 2.08l.** The general procedure was followed by using 0.0400 g of aniline **s2.23l** (0.270 mmol),[40] 0.130 mL of *t*-BuONO (1.08 mmol), 0.110 mL of Me_3SiN_3 (0.810 mmol) in 2.0 mL of MeCN. Purification by MPLC (5:1 hexanes:EtOAc) gave the product as a yellow oil (0.03 g, 65%): R_f = 0.56 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.20 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.11 – 7.07 (m, 1H), 3.18 (s, 1H), 1.16 – 1.13 (m, 2H), 0.94 – 0.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5 (C), 133.2 (C), 129.1 (CH), 128.8 (CH), 124.8 (CH), 118.3 (CH), 55.2 (C), 13.9 (CH_2); ATR-FTIR (thin film): 3391, 2926, 2853, 2360, 2127, 2093, 1491, 1445, 1293, 1225, 753 cm^{-1}. HRMS (ESI) m/z calcd for $C_9H_9N_3ONa$ [M + Na]$^+$: 198.0644, found 198.0646.

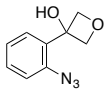
C. General Procedure for Synthesis of *o*-Cyclobutanol Azides from *o*-Cyclobutanol Carbamates

Deprotection of the *N*-Boc carbamate was accomplished following two different strategies reported by Hruby and co-workers and Harigaya and co-workers.[41]



Method A.[41a] The original procedure described by Hruby and co-workers was slightly modified. The *o*-cyclobutanol carbamate was dissolved in 1 mL of dioxane. To the stirred solution was added dropwise a 4 M solution of HCl in dioxane. The reaction progress was monitored by TLC. When the starting material was consumed, the mixture was neutralized by adding a saturated solution of $NaHCO_3$ (until effervescence stopped). The solution was extracted 3 × 10 mL of EtOAc. The organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The resulting aniline was submitted to the next step without further characterization or purification.

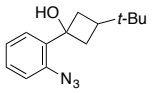
Method B.[41b] The original procedure developed by Harigaya and co-workers was slightly modified. The *o*-cyclobutanol carbamate was dissolved in a 3:1 v:v solution of MeOH and H_2O (1 mL / mmol). To the resulting solution was added K_2CO_3 (3.0 equiv), and the mixture was heated to reflux. The reaction progress was monitored using TLC. Once starting material was consumed, the reaction mixture was cooled to room temperature and was concentrated i*in vacuo*. The resulting mixture was diluted with EtOAc. The organic layer was seperated, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* and submitted to the next step without further characterization or purification.



2.08m

***N*-(2-(1-Hydroxyoxetane)phenyl)aniline s2.23m. Method B** was followed using 0.460 g of **s2.26a** (1.74 mmol), 0.721 g of K_2CO_3 (5.22 mmol) to give **s2.23m** as a yellow solid (0.167 g, 58%) which was submitted to the next step without further characterization or purification.

***o*-Oxetane aryl azide 2.08m.** The general procedure was followed by using 0.167 g of aniline **s2.23m** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (5:1 hexanes:EtOAc) gave the product as a yellow oil (0.120 g, 62%): R_f = 0.47 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dt, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.22 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.18 – 7.14 (m, 2H), 5.05 (d, *J* = 7.5 Hz, 2H), 4.81 (d, *J* = 7.5 Hz, 2H), 3.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4 (C), 132.4 (C), 129.9 (CH), 127.0 (CH), 125.1 (CH), 118.7 (CH), 82.8 (CH_2), 75.7 (C); ATR-FTIR (thin film): 3352, 2947, 2875, 2121, 2089, 1489, 1287, 972 752 cm^{-1}. HRMS (ESI) m/z calcd for $C_9H_9N_3O_2Na$ $[M + Na]^+$: 214.0593, found 214.0595.

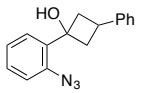


2.08n

***N*-(2-(1-Hydroxy-3-*tert*-butylcyclobutyl)phenyl)aniline s2.23n. Method A** was followed using 0.500 g of **s2.26b** (1.56 mmol), 4 mL of HCl (4 M in dioxane) to give **s2.23n** as a yellow solid (0.220 g, 64%) which was submitted to the next step without further characterization or purification.

***o*-Cyclobutanol aryl azide 2.08n.** The general procedure was followed by using 0.220 g of aniline **s2.23n** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product, a yellow oil, as a mixture of atropisomers (0.160 g, 63%): R_f = 0.57 (5:1 hexanes:EtOAc);

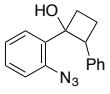
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.5 Hz, 1.5 Hz, 0.76H), 7.36 (dt, *J* = 7.5 Hz, 1.5 Hz, 0.78H), 7.31 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.26 – 7.21 (m, 1.88H), 7.18 – 7.15 (m, 1.75H), 7.12 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 3.45 (s, 0.70H), 2.76 (s, 0.88H), 2.64 – 2.57 (m, 0.94H), 2.52 – 2.47 (m, 1.56H), 2.32 – 2.27 (m, 2H), 2.22 – 2.17 (m, 2H), 2.16 – 2.10 (m, 1.64H), 1.63 – 1.55 (m, 0.88H), 0.85 (s, 7.05H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9 (C), 137.1 (C), 137.0 (C), 135.7 (C), 128.8 (CH), 128.7 (CH), 126.5 (CH), 126.2 (CH), 124.8 (CH), 124.7 (CH), 119.0 (CH), 118.6 (CH), 73.0 (C), 70.8 (C), 40.7 (CH), 36.8 (CH), 36.5 (CH_2), 35.9 (CH_2), 30.9 (C), 30.9 (CH), 26.6 (CH_3), 26.3 (CH_3); ATR-FTIR (thin film): 3393, 2953, 2865, 2125, 2088, 1486, 1293, 1235, 750 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{20}NO$ $[M + H - N_2]^+$: 218.1540, found 218.1545.



2.08o

***N*-(2-(1-Hydroxy-3-phenylcyclobutyl)phenyl)aniline s2.23o. Method A** was followed using 0.500 g of **s2.26c** (1.47 mmol), 4 mL of HCl (4 M in dioxane) to give **s2.23o** as a yellow solid (0.230 g, 68%) which was submitted to the next step without further characterization or purification.

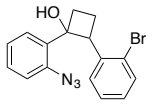
***o*-Cyclobutanol aryl azide 2.08o.** The general procedure was followed by using 0.230 g of aniline **s2.23o** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product, a yellow oil, as a mixture of atopisomers (0.220 g, 86%): R_f = 0.30 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 0.58H), 7.42 (t, *J* = 7.5 Hz, 0.60H), 7.36 – 7.27 (m, 6.77H), 7.26 – 7.19 (m, 4.84H), 7.15 (t, *J* = 7.5 Hz, 1H), 4.00 (quin, *J* = 9.0 Hz, 0.93H), 3.61 (s, 0.54H), 3.11 – 3.04 (m, 1.71H), 3.00 (s, 1H), 2.92 – 2.87 (m, 1.94H), 2.66 – 2.57 (m, 3.15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1 (C), 144.5 (C), 138.0 (C), 137.2 (C), 136.6 (C), 135.1 (C), 129.1 (CH), 129.0 (CH), 128.4 (CH), 128.4 (CH), 126.8 (CH), 126.6 (CH), 126.5 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 124.9 (CH), 124.9 (CH), 119.1 (CH), 118.7 (CH), 74.1 (C), 71.9 (C), 43.1 (CH_2), 42.4 (CH_2), 34.4 (CH), 30.8 (CH); ATR-FTIR (thin film): 3393, 3025, 2981, 2933, 2122, 2092, 1579, 1486, 1445, 1279, 747, 697 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{16}NO$ $[M + H - N_2]^+$: 238.1229, found 238.1232.



2.08p

***N*-(2-(1-Hydroxy-2-phenylcyclobutyl)phenyl)aniline s2.23p. Method A** was followed using 0.500 g of **s2.26d** (1.47 mmol), 4 mL of HCl (4 M in dioxane) to give **s2.23p** as a yellow solid (0.242 g, 72%) which was submitted to the next step without further characterization or purification.

***o*-Cyclobutanol aryl azide 2.08p.** The general procedure was followed by using 0.242 g of aniline **s2.23p** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a yellow oil, (0.180 g, 71%): R_f = 0.61 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.41 – 7.36 (m, 4H), 7.34 – 7.31 (m, 1H), 7.29 – 7.25 (m, 1H), 7.17 – 7.13 (m, 2H), 3.95 (t, *J* = 9.0 Hz, 1H), 2.80 (d, *J* = 1.0 Hz, 1H), 2.72 – 2.66 (m, 1H), 2.62 – 2.54 (m, 1H), 2.38 – 2.33 (m, 1H), 2.29 – 2.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4 (C), 137.1 (C), 136.8 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 126.8 (CH), 126.8 (CH), 124.8 (CH), 119.0 (CH), 79.6 (C), 49.5 (CH), 32.3 (CH_2), 22.5 (CH_2); ATR-FTIR (thin film): 3542, 2948, 2123, 2089, 1577, 1484, 1444, 1290, 1021, 901, 751, 699 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{16}NO$ [M + H – N_2]$^+$: 238.1242, found 238.1232.

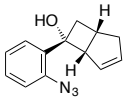


2.08q

***N*-(2-(1-Hydroxy-2-arylcyclobutyl)phenyl)aniline s2.23q. Method A** was followed using 0.500 g of **s2.26e** (1.20 mmol), 4 mL of HCl (4 M in dioxane) to give **s2.23q** as a brown solid (0.229 g, 60%) which was submitted to the next step without further characterization or purification.

***o*-Cyclobutanol aryl azide 2.08q.** The general procedure was followed by using 0.321 g of aniline **s2.23q** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product, a yellow oil, as a mixture of atropisomers (0.240 g, 68%): R_f = 0.56 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.67 (dd, *J* = 7.5 Hz, 1.5 Hz, 0.23H), 7.59 (dd, *J* = 8.0 Hz, 1.5 Hz, 1.19H), 7.54 – 7.50 (m, 0.53H), 7.44 – 7.41 (m, 1.23H), 7.40 – 7.35 (m, 1.27H), 7.31 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.15 – 7.09 (m, 3H), 6.32 – 6.29 (m, 0.22H), 4.32 – 4.28 (m, 1H), 3.18 (t, *J* = 7.5 Hz, 0.46H), 3.10 (d, *J* = 2.0 Hz, 0.92H), 2.85 – 2.79 (m, 1H), 2.56 (quin, *J* = 10.0 Hz, 1H), 2.37 – 2.29 (m, 0.49H), 2.27 – 2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0 (C), 137.2 (C), 136.3 (C), 133.2 (CH), 132.6 (CH), 131.0 (C), 130.8 (CH), 130.4 (CH), 130.2 (CH), 128.8 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 126.8 (CH), 126.6 (CH), 125.9 (CH), 124.9 (CH), 124.8 (CH), 119.2 (C), 119.1 (CH), 118.7 (CH), 82.9 (C), 80.6 (C), 49.0 (CH), 38.7 (CH_2), 30.4 (CH_2), 28.4 (CH_2), 22.9 (CH_2) only visible peaks;

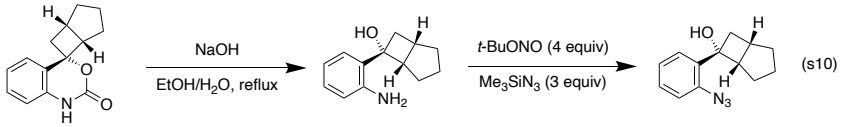
ATR-FTIR (thin film): 3459, 2956, 2924, 2854, 2125, 2093, 1637, 1485, 1281, 751 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{15}NOBr$ $[M + H - N_2]^+$: 316.0346, found 316.0337.



2.08r

***N*-(2-(1-Hydroxycyclobutyl)phenyl)aniline s2.23r. Method A** was followed using 0.500 g of **s2.26f** (1.66 mmol), 4 mL of HCl (4 M in dioxane) to give **s2.23r** as a brown solid (0.233 g, 70%) which was submitted to the next step without further characterization or purification.

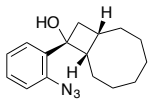
***o*-Cyclobutanol aryl azide 2.08r.** The general procedure was followed by using 0.297 g of aniline **s2.23r** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a yellow oil, (0.120 g, 38%): R_f= 0.54 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 1H), 7.35 – 7.30 (m, 1H), 7.20 – 7.13 (m, 2H), 5.95 – 5.92 (m, 2H), 3.38 – 3.34 (m, 1H), 3.12 – 3.06 (m, 2H), 3.00 – 2.95 (m, 1H), 2.68 (s, 1H), 2.64 – 2.57 (m, 1H), 2.15 – 2.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3 (C), 137.1 (C), 134.8 (CH), 132.9 (CH), 128.7 (CH), 127.0 (CH), 124.7 (CH), 119.0 (CH), 76.0 (C), 46.6 (CH), 41.3 (CH_2), 39.8 (CH), 33.5 (CH_2); ATR-FTIR (thin film): 3459, 3050, 2923, 2123.4, 2089, 1668, 1485, 1292, 1078, 750 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{14}NO$ $[M + H - N_2]^+$: 200.1082, found 200.1075.



s2.26'g **s2.23s** **2.08s**

***N*-(2-(1-Hydroxycyclobutyl)phenyl)aniline s2.23s:** The compound was prepared by using the procedure developed by Bali and co-workers.[42] To a solution of 0.500 g of **s2.26'g** (2.12 mmol) in 8 mL of EtOH was added 4 mL of a 10% aq soln of NaOH. The resulting mixture was heated to reflux, and the reaction progress was monitored using TLC. Once the starting material was consumed, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting mixture was diluted with water and extracted with 3 × 10 mL of EtOAc. The combined organic phases were washed with saturated brine, dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to give **s2.23s** as a yellow solid (0.301 g, 70%) which was submitted to the next step without further characterization or purification.

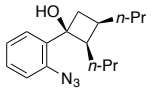
***o*-Cyclobutanol aryl azide 2.08s.** The general procedure was followed by using 0.205 g of aniline **s2.23s** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (10:1 Hex:EtOAc) gave the product as a yellow oil, (0.150 g, 65%): R_f = 0.52 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.23 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.18 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.12 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 3.15 (s, 1H), 3.06 – 3.01 (m, 1H), 2.99 – 2.95 (m, 1H), 2.32 – 2.27 (m, 1H), 2.22 (dd, *J* = 13.0 Hz, 6.5 Hz, 1H), 1.60 – 1.41 (m, 4H), 1.38 – 1.27 (m, 1H), 1.11 (dd, *J* = 12.5 Hz, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4 (C), 133.4 (C), 128.8 (CH), 127.4 (CH), 124.8 (CH), 118.4 (CH), 77.1 (C), 53.1 (CH), 34.2 (CH_2), 32.8 (CH), 32.4 (CH_2), 28.6 (CH_2), 24.8 (CH_2); ATR-FTIR (thin film): 3400, 2944, 2853, 2123, 2085, 1484, 1446, 1277, 1022, 752 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{16}NO$ $[M + H - N_2]^+$: 202.1229, found 202.1232.



2.08t

***N*-(2-(1-Hydroxycyclobutyl)phenyl)aniline s2.23t. Method A** was followed using 0.150 g of **s2.26h** (0.43 mmol), 2 mL of HCl (4 M in dioxane) to give **s2.23t** as a brown solid (0.063 g, 60%) which was submitted to the next step without further characterization or purification.

***o*-Cyclobutanol aryl azide 2.08t.** The general procedure was followed using 0.248 g of aniline **s2.23t** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (20:1 Hex:EtOAc) gave the product as a yellow oil, (0.164 g, 60%): R_f = 0.54 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.32 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.20 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.14 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 3.07 (s, 1H), 2.82 – 2.77 (m, 1H), 2.49 – 2.44 (m, 1H), 2.01 – 1.74 (m, 6H), 1.56 – 1.46 (m, 4H), 1.39 – 1.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3 (C), 134.0 (C), 128.7 (CH), 127.6 (CH), 125.0 (CH), 118.1 (CH), 79.1 (C), 54.0 (CH), 35.3 (CH_2), 32.9 (CH), 31.1 (CH_2), 28.9 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 25.2 (CH_2); ATR-FTIR (thin film): 2918, 2849, 2124, 1623, 1485, 1464, 1445, 1277, 1156, 1051, cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{20}NO$ $[M - H - N_2]^+$: 242.1536, found 242.1545.



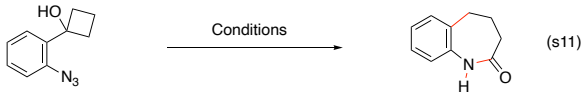
2.08u

***N*-(2-(1-Hydroxycyclobutyl)phenyl)aniline s2.23u. Method A** was followed using 0.150 g of **s2.26i** (0.43 mmol), 2 mL of HCl (4 M in dioxane) to give **s2.23u** as a yellow solid (0.074 g, 70%) which was submitted to the next step without further characterization or purification.

***o*-Cyclobutanol aryl azide 2.08u.** The general procedure was followed using 0.250 g of aniline **s2.23u** (1.01 mmol), 0.480 mL of *t*-BuONO (4.04 mmol), 0.400 mL of Me_3SiN_3 (3.03 mmol) in 5.0 mL of MeCN. Purification by MPLC (20:1 Hex:EtOAc) gave the product as a yellow oil, (0.182 g, 66%): R_f = 0.55 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.19 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.16 – 7.11 (m, 2H), 3.38 (br s, 1H), 2.89 – 2.80 (m, 1H), 2.56 – 2.51 (m, 1H), 2.28 – 2.18 (m, 2H), 1.47 – 1.40 (m, 1H), 1.33 – 1.19 (m, 4H), 1.14 – 1.05 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.87 – 0.81 (m, 1H), 0.78 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4 (C), 134.2 (C), 128.7 (CH), 127.6 (CH), 124.9 (CH), 118.1 (CH), 78.2 (C), 51.0 (CH), 35.2 (CH_2), 32.8 (CH_2), 32.7 (CH), 29.6 (CH_2), 21.7 (CH_2), 20.6 (CH_2), 14.4 (CH_3), 14.3 (CH_3); ATR-FTIR (thin film): 3556, 2956, 2929, 2871, 2125, 1627, 1485, 1278, 751 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{22}N$ [M – H – N_2O]$^+$: 228.1744, found 228.1752.

III. Rh_2(II)-Catalyzed Benzazepine-2-one Formation

A. General Procedure for the Screening of Reaction Conditions



2.08a **2.09a**

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.10 mmol of azide followed by the metal salt (1 – 5 mol %) in 1.0 mL of solvent. The Schlenk tube was sealed and heated for 16 h. The reaction mixture was then cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the crude mixture was analyzed using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

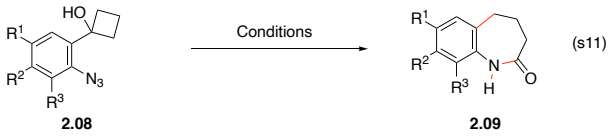
Table s1. Screen of catalyst, catalyst loading, solvent and reaction temperature.

Entry	catalyst	mol %	solvent	T (°C)	**9a** yield, %[a]
1	...	...	PhMe	130	trace
2	$Rh_2(O_2CCH_3)_4$	5	PhMe	100	24
3	$Rh_2(O_2CC_7H_{15})_4$	5	PhMe	100	15

4	$Rh_2(O_2CCF_3)_4$	5	PhMe	100	47
5	$Rh_2(O_2CC_3F_7)_4$	5	PhMe	100	66
6	$Rh_2(esp)_2$	5	PhMe	100	80
7	$Rh_2(esp)_2$	5	PhMe	120	71
8	$Rh_2(esp)_2$	1	PhMe	120	82
9	$RuBr_3•nH_2O$	1	PhMe	120	23
10	Co(TPP)	5	PhMe	120	trace
11	$[Ir(COD)(OMe)]_2$	5	PhMe	120	23
12	$FeBr_2$	20	PhMe	120	…
13	$FeBr_2$	30	CH_2Cl_2	40	…
14	$FeBr_3$	20	PhMe	120	…
15	$FeBr_3$	30	CH_2Cl_2	40	…

[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard.

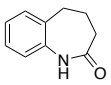
B. Optimized Procedure



2.08 **2.09** (s11)

To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.10 mmol of azide followed by 0.001 mmol of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. The Schlenk tube was sealed and heated at 120 °C for 16 h. The reaction mixture was then cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the crude mixture was purified by MPLC (7:1 – 3:1 hexanes:EtOAc) to afford the benzazepinone product.

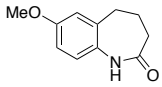
C. Characterization Data for Benzazepine-2-one



2.09a

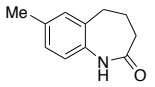
Benzazepine-2-one 2.09a.[43] The optimized procedure was followed using 0.019 g of azide **2.08a (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.0129 g, 80%). The spectral data of **2.09a** matched that reported by Chen and Gilman:[43] ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.26 – 7.22 (m, 2H), 7.14 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.24 (quin, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0 (C), 137.7 (C), 134.4 (C), 129.9 (CH), 127.5 (CH), 125.8 (CH), 121.8 (CH), 32.7 (CH_2), 30.4 (CH_2), 28.4 (CH_2); ATR-FTIR (thin film): 3184, 3061, 2934, 1656, 1490, 1383, 1155, 787 cm^{-1}.

The diastereomeric identity of the product was confirmed using X-Ray crystallography.[44]



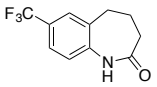
2.09b

Benzazepine-2-one 2.09b.[45] The optimized procedure was followed using 0.030 g of azide **2.08b (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded product as an orange solid (0.0205 g, 80%). The spectral data of **2.09b** matched that reported by Crosby and co–workers:[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.76 – 6.74 (m, 2H), 3.79 (s, 3H), 2.76 (t, *J* = 7.0 Hz, 2H), 2.32 (t, *J* = 7.0 Hz, 2H), 2.21 (quin, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (C), 157.4 (C), 135.9 (C), 130.8 (CH), 123.1 (C), 115.2 (CH), 112.2 (CH), 55.5 (CH_3), 32.5 (CH_2), 30.5 (CH_2), 28.2 (CH_2); ATR-FTIR (thin film): 3172, 2935, 1661, 1621, 1498, 1381, 1282, 1164, 1050, 890, 737 cm^{-1}.



2.09c

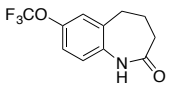
Benzazepine-2-one 2.09c.[46] The optimized procedure was followed using 0.029 g of azide **2.08c** (0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded the product as a white solid (0.016 g, 91%). Benzazepinone **2.09c** was previously reported by Huanming and co–workers:[46] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (bs, 1H), 7.04 – 7.03 (m, 2H), 6.86 – 6.84 (m, 1H), 2.76 (t, *J* = 7.0 Hz, 2H), 2.36 – 2.33 (m, 5H), 2.21 (quin, *J* = 7.0 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0 (C), 135.5 (C), 135.1 (C), 134.2 (C), 130.5 (CH), 127.9 (CH), 121.7 (CH), 32.7 (CH_2), 30.3 (CH_2), 28.4 (CH_2), 20.9 (CH_3); ATR-FTIR (thin film): 3178, 3041, 2933, 1656, 1504, 1386, 1160, 825 cm^{-1}.



2.09d

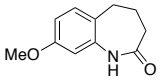
Benzazepine-2-one 2.09d.[47] The optimized procedure was followed using 0.026 g of azide **2.08d (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded the product as a white solid (0.0169 g, 74%). Benzazepinone **2.09d** was previously reported by Hoyt and co-workers:[47] ^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.37 (s, 1H), 7.51 – 7.46 (m, 2H), 7.09 (d, J = 8.0 Hz, 1H), 2.87 (t, J = 7.0 Hz, 2H), 2.40 (t, J = 7.5 Hz, 2H), 2.28 (quin, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1 (C), 141.1 (C), 134.7 (C), 127.6 (q, J_{CF} = 32.1 Hz, C), 127.1 (q, J_{CF} = 4.5 Hz, CH), 126.1 (q, J_{CF} = 269.4 Hz, C), 124.7 (q, J_{CF} = 3.6 Hz, CH), 121.8 (CH), 32.9 (CH_2), 30.5 (CH_2), 28.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.6; ATR-FTIR (thin film): 3186, 2949, 1670, 1348, 1259, 1158, 1124, 1078, 932, 846 cm^{-1}.



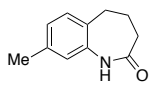
2.09e

Benzazepine-2-one 2.09e.[47] The optimized procedure was followed using 0.027 g of azide **2.08e (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.0174 g, 71%). Benzazepinone **2.09e** was previously reported by Hoyt and co-workers:[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.10 – 7.08 (m, 2H), 7.04 – 7.01 (m, 1H), 2.81 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 2.25 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1 (C), 146.4 (C), 136.5 (C), 136.2 (C), 123.0 (CH), 122.5 (CH), 120.4 (q, J_{CF} = 255.3 Hz, C), 120.0 (CH), 32.7 (CH_2), 30.4 (CH_2), 28.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.4; ATR-FTIR (thin film): 3170, 3074, 2943, 1683, 1496, 1380, 1283, 1231, 1205, 1165, 894, 814, 738 cm^{-1}.



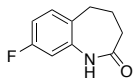
2.09f

Benzazepine-2-one 2.09f.[48] The optimized procedure was followed using 0.030 g of azide **2.08f (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded product as a brown solid (0.0229 g, 85%). Benzazepinone **2.09f** was previously reported by Takashi and co-workers:[48] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 6.52 (d, J = 2.5 Hz, 1H), 3.79 (s, 3H), 2.74 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.19 (quin, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0 (C), 159.0 (C), 138.5 (C), 130.5 (CH), 126.4 (C), 111.0 (CH), 107.8 (CH), 55.5 (CH_3), 32.8 (CH_2), 29.5 (CH_2), 28.5 (CH_2); ATR-FTIR (thin film): 3209, 2935, 1667, 1615, 1509, 1378, 1279, 1162, 1038, 858 cm^{-1}.



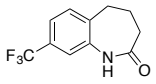
2.09g

Benzazepine-2-one 2.09g.[49] The optimized procedure was followed using 0.020 g of azide **2.08g (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded product as a light orange solid (0.0136 g, 80%). Benzazepinone **2.09g** was previously reported by Huisgen.[49] R_f = 0.56 (1:1 hexanes:EtOAc); mp = 152 – 154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.80 (s, 1H), 2.76 (t, *J* = 7.0 Hz, 2H), 2.37 – 2.33 (m, 5H), 2.33 (s, 3H), 2.21 (quin, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (C), 137.6 (C), 137.4 (C), 131.2 (C), 129.7 (CH), 126.4 (CH), 122.4 (CH), 32.8 (CH_2), 29.9 (CH_2), 28.5 (CH_2), 21.0 (CH_3); ATR-FTIR (thin film): 3172, 3077, 2940, 1684, 1662, 1512, 1383, 1159, 799 cm^{-1}.



2.09h

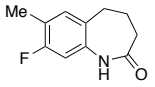
Benzazepine-2-one 2.09h.[50] The optimized procedure was followed using 0.021 g of azide **2.08h (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.0136 g, 78%). Benzazepinone **2.09h** was previously reported by Altenbach and co-workers:[50] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.16 (dd, *J* = 8.5 Hz, 6.0 Hz, 1H), 6.83 (dt, *J* = 8.0 Hz, 2.5 Hz, 1H), 6.73 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.20 (quin, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C), 161.8 (d, J_{CF} = 244.1 Hz, C), 139.1 (d, *J* = 9.9 Hz, C), 130.9 (d, J_{CF} = 8.9 Hz, CH), 129.9 (C), 112.3 (d, J_{CF} = 20.8 Hz, CH), 109.1 (d, J_{CF} = 23.3 Hz, CH), 32.8 (CH_2), 29.7 (CH_2), 28.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −115.3; ATR-FTIR (thin film): 3187, 3102, 2951, 1663, 1605, 1507, 1483, 1260, 1161, 1151, 998, 834, 705 cm^{-1}.



2.09i

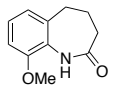
Benzazepine-2-one 2.09i. The optimized procedure was followed using 0.026 g of azide **2.08i (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded the product as a white solid (0.0197 g, 86%): R_f = 0.30 (1:1 hexanes:EtOAc); mp = 146 – 148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 2.87 (t, *J* = 7.0 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.27 (quin, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0 (C), 138.4 (C), 138.3 (C), 130.5 (CH), 130.1 (q, J_{CF} = 32.8 Hz, C), 123.7 (q, J_{CF} = 270.3 Hz, C), 122.4 (q, J_{CF} = 3.8 Hz, CH), 118.7 (q, J_{CF} = 3.8 Hz, CH), 32.7 (CH_2), 30.4 (CH_2), 28.2 (CH_2); ^{19}F NMR

(282 MHz, $CDCl_3$) δ –62.9; ATR-FTIR (thin film): 3190, 2925, 1675, 1327, 1166, 1115, 1076, 987, 828, 672 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{11}NOF_3$ $[M + H]^+$: 230.0794, found 230.0793.



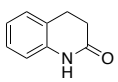
2.09j

Benzazepine-2-one 2.09j. The optimized procedure was followed using 0.022 g of azide **2.08j (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.0155 g, 80%): R_f = 0.48 (1:1 hexanes:EtOAc); mp = 142 – 144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 10.0 Hz, 1H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.26 – 2.17 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C), 159.9 (d, J_{CF} = 242.5 Hz, C), 136.4 (d, J_{CF} = 9.8 Hz, C), 132.3 (d, J_{CF} = 6.0 Hz, CH), 129.7 (d, J_{CF} = 2.9 Hz, C), 129.0 (d, J_{CF} = 5.9 Hz, C), 121.9 (d, J_{CF} = 16.5 Hz, C), 108.9 (d, J_{CF} = 23.4 Hz, CH), 32.8 (CH_2), 29.6 (CH_2), 28.5 (CH_2), 14.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –119.3; ATR-FTIR (thin film): 3192, 2951, 2869, 1667, 1625, 1509, 1495, 1376, 1102, 881, 759 cm^{-1} HRMS (ESI) m/z calcd for $C_{11}H_{13}NOF$ $[M + H]^+$: 194.0983, found 194.0981.



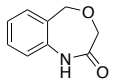
2.09k

Benzazepine-2-one 2.09k. The optimized procedure was followed using 0.022 g of azide **2.08k (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded product as a light orange solid (0.0142 g, 74%): R_f = 0.14 (5:1 hexanes:EtOAc); mp = 160 – 162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.80 (t, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.23 (quin, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3 (C), 150.1 (C), 134.8 (C), 126.8 (C), 125.5 (CH), 121.7 (CH), 109.1 (CH), 55.6 (CH_3), 33.3 (CH_2), 30.4 (CH_2), 28.5 (CH_2); ATR-FTIR (thin film): 3198, 2968, 2935, 1652, 1602, 1455, 1288, 1084, 787, 771 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{14}NO_2$ $[M + H]^+$: 192.1019, found 192.1025.



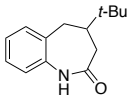
2.09l

Quinolinone 2.09l.[51] The optimized procedure was followed using 0.018 g of azide **2.08l (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (7:1 – 3:1 hexanes:EtOAc) afforded product as a white solid (0.0118 g, 80%). The spectral data of **2.09l** matched that reported by Liu and Hu:[51] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.19 – 7.1 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C), 137.2 (C), 128.0 (CH), 127.6 (CH), 123.7 (C), 123.2 (CH), 115.3 (CH), 29.7 (CH_2), 25.4 (CH_2); ATR-FTIR (thin film): 3197, 2975, 2914, 1682, 1595, 1492, 1439, 1386, 1282, 1246, 1033, 817, 749 cm^{-1}.



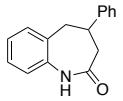
2.09m

Benzazepine-2-one 2.09m.[52] The optimized procedure was followed using 0.019 g of azide **2.08m (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 1:1 hexanes:EtOAc) afforded product as a white solid (0.0083 g, 51%). The spectral data of **2.08m** matched that reported by Ashweek and co–workers:[52] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.74 (s, 2H), 4.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (C), 135.8 (C), 129.2 (CH), 128.7 (C), 128.6 (CH), 123.8 (CH), 119.2 (CH), 73.5 (CH_2), 72.9 (CH_2); ATR-FTIR (thin film): 3192, 3058, 2992, 1657, 1592, 1495, 1447, 1402, 1133, 944, 839 cm^{-1}.



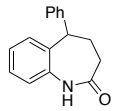
2.09n

Benzazepine-2-one 2.09n. The optimized procedure was followed using 0.024 g of azide **2.08n (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a white solid (0.0143 g, 66 %): R_f = 0.29 (3:1 Hexane:EtOAc); mp = 178 – 180 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.24 – 7.19 (m, 2H), 7.10 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.95 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 2.84 – 2.78 (m, 2H), 2.43 – 2.34 (m, 2H), 2.20 (quin, *J* = 7.0 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4 (C), 137.8 (C), 134.1 (C), 130.9 (CH), 127.3 (CH), 125.3 (CH), 121.2 (CH), 51.4 (CH), 34.8 (CH_2), 34.4 (C), 32.4 (CH_2), 27.7 (CH_3); ATR-FTIR (thin film): 3056, 2962, 2360, 1663, 1586, 1491, 1264, 733 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{20}NO$ $[M + H]^+$: 218.1543, found 218.1545.



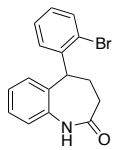
2.09o

Benzazepine-2-one 2.09o.[53] The optimized procedure was followed using 0.025 g of azide **2.08o (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a white solid (0.0237 g, quantitative). The spectral data of **2.09o** matched that reported by Hudson and co–workers:[53] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.33 – 7.28 (m, 5H), 7.26 – 7.22 (m, 2H), 7.17 (t, *J* = 7.0 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 3.71 (quin, *J* = 7.5 Hz, 1H), 3.20 (dd, *J* = 14.0 Hz, 7.0 Hz, 1H), 2.91 (dd, *J* = 13.5 Hz, 6.5 Hz, 1H), 2.69 – 2.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1 (C), 145.0 (C), 137.8 (C), 133.0 (C), 130.7 (CH), 128.7 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 125.7 (CH), 121.8 (CH), 46.7 (CH), 39.6 (CH_2), 38.8 (CH_2); ATR-FTIR (thin film): 3195, 3059, 2918, 1664, 1584, 1492, 1380, 1158, 756 cm^{-1}.



2.09p

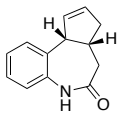
Benzazepine-2-one 2.09p.[54] The optimized procedure was followed using 0.025 g of azide **2.08p (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a white solid (0.0161 g, 72%). The spectral data of **2.09p** matched that reported by Ikeda and co–workers:[54] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.28 (m, 3H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* =7.5 Hz, 1H), 4.43 – 4.39 (m, 1H), 2.60 – 2.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6 (C), 140.9 (C), 137.1 (C), 137.0 (C), 128.9 (CH), 128.8 (CH), 128.6 (CH), 127.3 (CH), 127.1 (CH), 125.8 (CH), 121.8 (CH), 45.1 (CH), 33.6 (CH_2), 32.7 (CH_2); ATR-FTIR (thin film): 3198, 3060, 2924, 1665, 1484, 1381, 759, 735 cm^{-1}.



2.09q

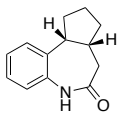
Benzazepine-2-one 2.09q. The optimized procedure was followed using 0.034 g of azide **2.08q (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a brown solid

(0.0209 g, 66%). R_f = 0.27 (1:1 hexanes:EtOAc); mp = 160 – 162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.24 – 7.16 (m, 2H), 7.04 – 6.97 (m, 2H), 6.59 (d, *J* = 7.5 Hz, 1H), 4.79 – 4.73 (m, 1H), 2.57 – 2.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3 (C), 140.2 (C), 137.2 (C), 135.6 (C), 133.6 (CH), 129.2 (CH), 128.6 (CH), 128.0 (CH), 127.9 (C), 127.4 (CH), 126.0 (CH), 125.9 (CH), 121.8 (CH), 44.3 (CH), 32.7 (CH_2), 32.6 (CH_2); ATR-FTIR (thin film): 3197, 3060, 2924, 1667, 1486, 1470, 1379, 757, 738 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{15}NOBr$ $[M + H]^+$: 316.0331, found 316.0337.



2.09r

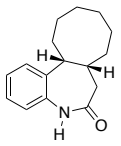
Benzazepine-2-one 2.09r. The optimized procedure was followed using 0.032 g of azide **2.08r (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a brown solid (0.0175 g, 60%): R_f = 0.24 (1:1 hexanes:EtOAc); mp = 158 – 160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.27 – 7.22 (m, 2H), 7.13 (t, *J* = 7.0 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.90 – 5.89 (m, 1H), 5.78 – 5.76 (m, 1H), 3.68 – 3.58 (m, 2H), 2.74 – 2.61 (m, 3H), 2.27 – 2.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (C), 137.0 (C), 136.7 (C), 132.2 (CH), 131.4 (CH), 131.0 (CH), 127.6 (CH), 125.5 (CH), 122.9 (CH), 52.1 (CH), 45.2 (CH), 39.9 (CH_2), 37.8 (CH_2); ATR-FTIR (thin film): 3197, 3050, 2920, 1666, 1583, 1489, 1433, 1391, 1169, 752, 732, 706 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{14}NO$ $[M + H]^+$: 200.1072, found 200.1075.



2.09s

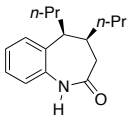
Benzazepine-2-one 2.09s. The optimized procedure was followed using 0.023 g of azide **2.08s (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a brown solid (0.0147 g, 73%): R_f = 0.12 (3:1 hexanes:EtOAc); mp = 164 – 166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.24 – 7.20 (m, 2H), 7.12 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.96 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 3.29 (q, *J* = 7.5 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.52 (dd, *J* = 12.5 Hz, 7.5 Hz, 1H), 2.14 (dd, *J* = 12.5 Hz, 7.5 Hz, 1H), 2.05 – 1.96 (m, 2H), 1.95 – 1.85 (m, 2H), 1.67 – 1.57 (m, 1H), 1.57 – 1.49 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C), 137.1 (C), 136.0 (C), 129.6 (CH), 127.2 (CH), 125.4 (CH), 122.5 (CH), 46.3 (CH), 44.5 (CH), 38.4 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 25.0 (CH_2); ATR-FTIR (thin film): 3197,

3056, 2925, 1668, 1580, 1491, 1430, 1390, 1169, 754, 705 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{16}NO$ $[M + H]^+$: 202.1229, found 200.1232.



2.09t

Benzazepine-2-one 2.09t. The optimized procedure was followed using 0.024 g of azide **2.08t (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a white solid (0.0205 g, 95%): R_f = 0.23 (1:1 hexanes:EtOAc); mp = 173 – 175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.30 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.24 – 7.17 (m, 2H), 6.98 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 3.10 – 3.05 (m, 1H), 2.89 – 2.82 (m, 1H), 2.33 – 2.29 (m, 1H), 2.19 – 2.11 (m, 1H), 1.91 (t, *J* = 12.0 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.75 – 1.58 (m, 6H), 1.56 – 1.46 (m, 3H), 1.14 – 1.09 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9 (C), 137.7 (C), 137.1 (C), 127.5 (CH), 126.9 (CH), 125.5 (CH), 121.7 (CH), 42.8 (CH), 42.3 (CH_2), 41.0 (CH), 29.7 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 25.3 (CH_2); ATR-FTIR (thin film): 3191, 2918, 2853, 2359, 1667, 1582, 1481, 1443, 1373, 757, 730 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{22}NO$ $[M + H]^+$: 244.1697, found 244.1701.



2.09u

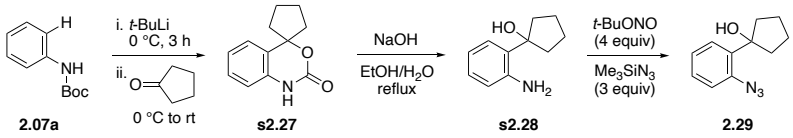
Benzazepine-2-one 2.09u. The optimized procedure was followed using 0.027 g of azide **2.08u (**0.10 mmol) and 0.0080 g of $Rh_2(esp)_2$ (1 mol %) in 1.0 mL of toluene. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded product as a brown solid (0.0160 g, 65%): R_f = 0.27 (2:1 hexanes:EtOAc); mp = 170 – 172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.24 – 7.16 (m, 3H), 7.01 – 6.99 (m, 1H), 3.09 (q, *J* = 6.5 Hz, 1H), 2.54 – 2.42 (m, 2H), 1.83 – 1.64 (m, 3H), 1.48 – 1.41 (m, 1H), 1.33 – 1.21 (m, 3H), 1.13 – 1.04 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.90 – 0.80 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5 (C), 137.8 (C), 135.1 (C), 127.5 (CH), 126.8 (CH), 125.3 (CH), 121.8 (CH), 42.7 (CH), 41.8 (CH), 39.5 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 20.8 (CH_2), 19.5 (CH_2), 14.4 (CH_3), 14.1 (CH_3); ATR-FTIR (thin film): 3196, 2955, 2929, 2870, 1665, 1378, 756 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{23}NO$: 245.17819, found 245.17797.

The diastereomeric identity of the product was confirmed using X-Ray crystallography.[55]

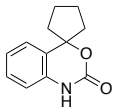
VI. Mechanistic Experiments

A. Synthesis of Mechanism Probes.

The *ortho*-cyclopentanol aryl azide was constructed following the sequence below.



Scheme s12. Synthesis of *ortho*-cyclopentanol aryl azide.



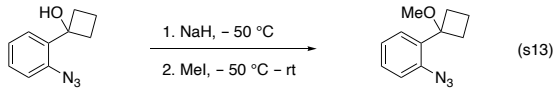
s2.27

Spiro[4*H*-3,1-benzoxazine-4,1'-cyclopentan]-2(1*H*)-one s2.27.[56] To a cooled (0 °C) 3 M solution of *N*-Boc aniline (0.800 g, 4.14 mmol) in 1.4 mL of dry Et_2O under an inert atmosphere of argon was dropwise added 5.45 mL of a 1.9 M solution of *t*-butyl lithium in pentane using a syringe pump. After 3 h, a solution of the 0.550 mL of cyclopentanone (6.21 mmol) in 2.0 mL dry Et_2O was added dropwise. The resulting mixture was allowed to warm to rt. The reactives were quenched through the addition of a saturated aq soln of NH_4Cl. The resulting mixture was diluted with EtOAc. The two layers were separated, and the aqueous layer was extracted 3 additional times with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the filtrate concentrated under reduced pressure. The resulting residue was purified by MPLC (2:1 hexanes:EtOAc) to afford the product as a white solid (0.33 g, 40%). The spectral data of **s2.27'** matched that reported by Puwen and Jeffrey:[56] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (bs, 1H), 7.22 – 7.19 (m, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 2.37 – 2.31 (m, 2H), 2.11 – 1.99 (m, 4H), 1.88 – 1.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4 (C), 134.8 (C), 128.8 (CH), 124.6 (C), 123.3 (CH), 122.9 (CH), 114.6 (CH), 93.2 (C), 39.7 (CH_2), 23.7 (CH_2); ATR-FTIR (thin film): 3096, 2927, 1702, 1596, 1493, 1372, 1262, 1047, 762 cm^{-1}.

1-(2-Aminophenyl) cyclopentanol s2.28. To a solution of 0.330 g of **s2.27** (1.63 mmol) in 6.0 mL of EtOH was added 3.0 mL of a 10% aq soln of NaOH. The resulting mixture was heated to reflux, and the reaction progress was monitored using TLC. Once the starting material was consumed, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting mixture was diluted with water and extracted with 3 × 10 mL of EtOAc. The combined organic phases

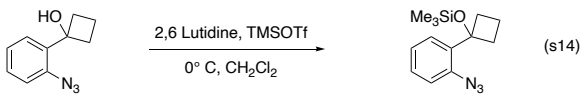
were washed with saturated brine, dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo* to give **s2.28** as a yellow solid (0.230 g, 80%) which was submitted to the next step without further characterization or purification.

1-(2-Azidophenyl) cyclopentanol 2.29. To a cooled solution (0 °C) of 0.092 g of 1-(*o*-aminophenyl) cyclopentanol **s2.28** (0.52 mmol)) in 2.6 mL of MeCN, was added dropwise 0.250 mL of *t*-BuONO (2.08 mmol) and 0.210 mL of Me_3SiN_3 (1.56 mmol). The resulting solution was warmed to room temperature. After 1.5 h, the reaction mixture was concentrated in vacuo. The residue was purified by MPLC (10:1 hexanes:EtOAc) to afford the product as a yellow oil (0.085 g, 80%): $R_f = 0.70$ (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.31 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 7.19 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.11 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 2.99 (s, 1H), 2.11 – 2.04 (m, 4H), 2.01 – 1.92 (m, 2H), 1.82 – 1.74 (m, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2 (C), 137.1 (C), 128.4 (CH), 126.6 (CH), 124.8 (CH), 118.9 (CH), 82.6 (C), 39.6 (CH_2), 23.5 (CH_2); ATR-FTIR (thin film): 3423, 2951, 2871, 2120, 2084, 1576, 1484, 1443, 1284, 1000, 750 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_3ONa$ $[M + Na]^+$: 226.0957, found 226.0959.



s2.08a **s2.30a** (s13)

1-Azido-2-(1-methoxycyclobutyl)benzene s2.30a. A solution of azide alcohol **s2.08a** (0.100 g, 0.53 mmol) in THF (2 mL) was added to a cold (– 50 °C) stirred suspension of 60% NaH (0.030 g, 0.78 mmol) in THF (3 mL). After stirring for 10 min, methyl iodide (0.050 mL, 0.78 mmol) was added. The mixture was allowed to warm to room temperature overnight and the reactives were quenched through the addition of water. The resulting mixture was extracted with dichloromethane, dried over anhydrous magnesium sulfate, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC (15:1 hexanes:EtOAc) to provide the compound as a yellow oil (0.054 g, 50%): $R_f = 0.66$ (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 2.93 (s, 3H), 2.54 – 2.42 (m, 4H), 2.10 – 2.01 (m, 1H), 1.72 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6 (C), 132.7 (C), 129.1 (CH), 129.0 (CH), 123.9 (CH), 119.2 (CH), 81.8 (C), 50.6 (CH_3), 32.4 (CH_2), 14.9 (CH_2) ; ATR-FTIR (thin film): 2983, 2940, 2819, 2121, 2085, 1485, 1443, 1295, 1130, 752 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_3ONa$ $[M + Na]^+$: 226.0956, found 226.0958.

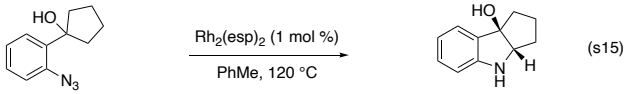


s2.08a **s2.30b** (s14)

(1-(2-Azidophenyl)cyclobutoxy)trimethylsilane s2.30b. To a cooled solution (0 °C) of 0.162 g of aryl azide **s2.08a** (0.86 mmol) in 8 mL of CH_2Cl_2 under an Ar atmosphere was added 1.00 mL of 2,6-lutidine (8.60 mmol) followed by the dropwise

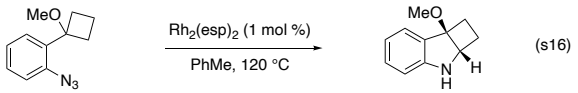
addition of 0.780 mL of Me_3SiOTf (4.30 mmol). After 3 h, the reaction mixture was passed through a short silica gel column using Et_2O as the eluent, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC (20:1 hexanes:EtOAc) to give the product as a yellow oil (0.170 g, 75%): R_f = 0.47 (10:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 2.67 – 2.62 (m, 2H), 2.46 – 2.40 (m, 2H), 1.95 – 1.87 (m, 1H), 1.53 – 1.43 (m, 1H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2 (C), 135.3 (C), 128.9 (CH), 127.2 (CH), 124.1 (CH), 119.6 (CH), 77.6 (C), 37.3 (CH_2), 14.0 (CH_2), 1.3 (CH_3); ATR-FTIR (thin film): 2953, 2123, 2090, 1487, 1444, 1294, 1249, 1135, 987, 839 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{19}N_3OSiNa$ $[M + Na]^+$: 284.1195, found 284.1196.

B. Mechanistic experiments



2.29 **2.31** (s15)

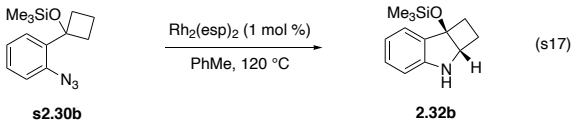
Tetrahydrocyclopenta indol-ol 2.31. To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.020 g of azide **2.29** (0.10 mmol) followed by 0.080 g of $Rh_2(esp)_2$ (0.001 mmol) in 1.0 mL of toluene. The Schlenk tube was sealed and heated at 120 °C for 16 h. The reaction mixture was then cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the crude mixture was purified by MPLC (5:1 – 3:1 hexanes:EtOAc) to afford the product as a brown liquid (0.009 g, 52%): R_f = 0.18 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.26 (m, 1H), 7.13 – 7.10 (m, 1H), 6.76 (t, *J* = 7.0 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 4.01 – 3.99 (m, 1H), 3.91 (br s, 1H), 2.15 – 2.04 (m, 4H), 1.81 – 1.76 (m, 1H), 1.69 – 1.64 (m, 1H), 1.59 – 1.48 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9 (C), 132.7 (C), 129.6 (CH), 123.9 (CH), 118.8 (CH), 109.6 (CH), 90.7 (C), 71.2 (CH), 41.3 (CH_2), 35.6 (CH_2), 24.7 (CH_2); ATR-FTIR (thin film): 3243, 2946, 2923, 2854, 1713, 1606, 1464, 1314, 1295, 1067, 1056, 756 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{14}NO$ $[M + H]^+$: 176.1074, found 176.1075.



s2.30a **2.32a** (s16)

Methoxy-tetrahydrocyclobuta indole 2.32a. To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.020 g of azide **s2.30a** (0.10 mmol) followed by 0.080 g of $Rh_2(esp)_2$ (0.001 mmol) in 1.0 mL of toluene. The Schlenk tube was sealed and heated at 120 °C for 16 h. The reaction mixture was then cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the crude mixture was purified by MPLC (5:1 – 3:1 hexanes:EtOAc) to afford the product as a brown liquid (0.009 g, 52%): R_f = 0.41 (5:1 hexanes:EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.29 (m,

1H), 7.19 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 6.88 – 6.85 (dt, J = 7.5 Hz, 1H), 6.76 – 6.74 (m, 1H), 4.20 (t, J = 6.5 Hz, 1H), 4.03 (bs, 1H), 3.05 (s, 3H), 2.48 – 2.35 (m, 2H), 2.24 – 2.17 (m, 1H), 1.47 – 1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2 (C), 130.3 (C), 129.7 (CH), 125.1 (CH), 119.7 (CH), 111.9 (CH), 86.3 (C), 59.2 (CH_3), 51.2 (CH), 31.9 (CH_2), 22.5 (CH_2); ATR-FTIR (thin film): 3359, 2922, 2852, 1607, 1464, 1310, 1172, 746 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{14}NO$ $[M + H]^+$: 176.1075, found 176.1075.



s2.30b **2.32b** (s17)

Trimethylsilyloxytetrahydrocyclobutaindole 2.32b. To a 10 mL Schlenk tube, under a nitrogen atmosphere, was added 0.026 g of azide **s2.30b** (0.10 mmol) followed by 0.080 g of $Rh_2(esp)_2$ (0.001 mmol) in 1.0 mL of toluene. The Schlenk tube was sealed and heated at 120 °C for 16 h. The reaction mixture was then cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*, and the crude mixture was purified by MPLC using neutral alumina (15:1 hexanes:EtOAc) to afford the product as a brown liquid (0.012 g, 52%): R_f = 0.84 (10:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.82 (t, J = 7.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 4.09 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 4.04 (bs, 1H), 2.45 (dd, J = 10.0 Hz, 7.0 Hz, 2H), 2.17 – 2.11 (m, 1H), 1.38 – 1.30 (m, 1H), – 0.04 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0 (C), 134.4 (C), 129.4 (CH), 125.4 (CH), 119.5 (CH), 112.0 (CH), 82.4 (C), 63.7 (CH), 35.1 (CH_2), 22.2 (CH_2), 1.26 (CH_3); ATR-FTIR (thin film): 3368, 2953, 2360, 2124, 1608, 1478, 1465, 1250, 1168, 1128, 841 cm^{-1}. HRMS (EI) m/z calcd for $C_{13}H_{20}NOSi$ $[M + H]^+$: 234.1314, found 234.1314.

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Chapter 3. Oxidation of Non-Activated Anilines to Generate *N*-Aryl Nitrenoids.*[2]

The creation of C–N bonds by harnessing the reactivity of nitrenes has spurred considerable research because it promises to simplify the construction of complex molecules.[1] Historically nitrenes have been generated by pyrolysis or photolysis of azides.[2,3] These harsh reaction conditions, however, lead to the formation of tars and other undesired by-products.[4] In the 1980s, researchers determined that iminoiodinanes can be prepared by the oxidation of sulfonamides and that nitrenes can be transferred from iminoiodinanes to transition metal complexes.[5] A canonical report from Breslow and Gellman in 1983 disclosed that metal nitrenes can trigger a C–H bond amination process to produce *N*-heterocycles (Scheme 3.01A).[5a] This approach to nitrene formation was significantly advanced by Du Bois and co-workers in 2001,[6] with the discovery that iminoiodinanes could be generated in situ from either sulfonamides or carbamates to produce either a 6-membered- or five-membered *N*-heterocycles through C–H bond amination. While many elegant studies have advanced this approach to oxidative nitrene transfer reactions for use in complex molecule synthesis,[7] all of these methods require a strong electron-withdrawing group on nitrogen to access productive C–N bond-forming reactivity.[8] Despite the ubiquitous nature of the *N*-aryl group in synthetic targets and established practical processes for the oxidation of phenols,[9] oxidative methods that form *N*-aryl nitrenes from anilines to produce C–NAr bonds have lagged behind sulfonamides and carbamates.[10] Current methods require the presence of a strong electron-withdrawing group on the nitrogen and have been limited to the formation of planar *N*-heterocycles (Scheme 3.01B).[10b,c,e] For example, Antonchick and co-workers reported that carbazoles could be formed from the oxidation of biarylamines **3.07** only if an *N*-acetyl group was present; no *N*-heterocycle formation was observed in its absence or if it was replaced with a benzyl group.[10b] We were curious if *N*-aryl nitrenoid intermediates generated from unattenuated anilines might engage in alternative C–NAr bond forming reaction when generated under compatible oxidative conditions.

Non-planar *N*-heterocycles, *3H*-indole and benzazepinones, are common motifs in synthetic targets and clinical candidates. Typically these scaffolds are constructed from substrates with pre-existing C–NAr bonds (Scheme 3.01C).[11,12] For example, the quaternary center in the 3*H*-indole portion of the *Aspidosperma* alkaloids has been set through alkylation of indole **3.10**.[13] Further, there exist few methods to access C4,C5-disubstituted benzazepinones despite their established important biological activity.[14] Glorius's recent report where vinyl *N*-tosyl benzoxazinones **3.12** were transformed into benzazepinones **3.13** also

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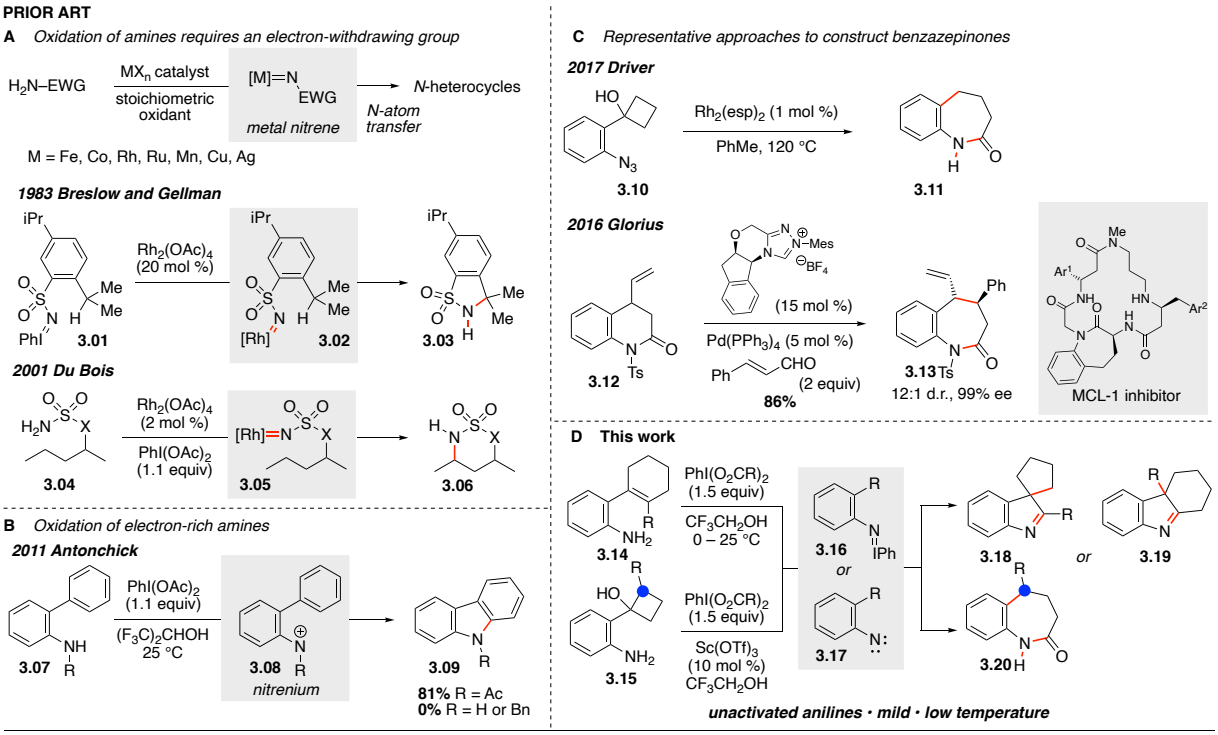
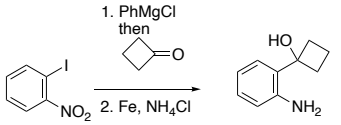
follows this strategy of employing substrates with the C–NAr bond pre-installed.[14c] If *N*-aryl nitrenes could be generated using mild oxidative conditions and their reactivity harnessed to construct C–NAr bonds in 3*H*-indoles and benzazepinones through a cyclization-migration cascade reaction, then the synthesis of these important *N*-heterocyclic scaffolds could be eased dramatically. This route would avoid the requirement of a pre-existing *N*-heterocycle, circumvent the step inefficient functional group interconversion, and enable access to a broad range of 3*H*-indoles or benzazepinones by simply changing the identity of the aniline substituent. Herein we report that *N*-aryl nitrenoids can be generated at or below room temperature from free anilines under conditions that allow them to engage in productive C–NAr bond forming processes. Formation of these nitrenoids in the presence of suitable *ortho*-substituents triggers pericyclic reaction sequences to access 3*H*-indoles or benzazepinones through a selective and stereospecific processes.



Scheme 3.01. A. Prior art in the oxidation of amines to afford nitrenes for N-atom transfer processes; B. Aniline oxidation requires a second *N*-electron-withdrawing substituent to afford a nitrenium ion; C. Current routes to non-planar *N*-heterocycles modify a *N*-heterocyclic substrate with a pre-existing C–NAr bond; D. The development of mild, protecting group-free oxidation of 2-substituted anilines to afford 3*H*-indoles or benzazepinones.

To examine if nitrenoid formation from anilines could be used to create medium-ring *N*-heterocycles, 2-cyclobutanol-substituted anilines were examined as potential substrates (Scheme 3.02). The anilines for this study were synthesized through a short sequence: metalation of the 2-iodonitroarene using PhMgCl produced 2-magnesium nitroarene in situ that was added

to cyclobutanone, and the resulting 2-cyclobutanol nitroarene was reduced using iron to produce aniline **3.22**. Optimization conditions were then developed which is summarized below (Table 3.1).



3.22a – 3.22s

Scheme 3.02. Preparation of the substrate

We began optimization by performing the reaction in the presence of oxidant (PIFA) in CH_2Cl_2 and TFE which gave moderate yield of the desired benzazepinone product (entries 1 & 2). We found that in these cases, a considerable amount of aniline still did not react. In order to make the aniline go to completion, we introduced Lewis acids and additives. To our delight we found that *o*-substituted cyclobutanol anilines were smoothly converted to benzazepinone in >99% yield in the presence of $Sc(OTf)_3$ and *p*-TsOH in CH_2Cl_2 and TFE (entries 3 & 4). We anticipated that *p*-TsOH used in combination with $Sc(OTf)_3$ might rescue the yield of the transformation by facilitating the substitution of the trifluoroacetoxy substituent with aniline resulting in a faster formation of the iminoiodinane intermediate. Other solvents were then screened (entries 5 – 8) which showed that the reaction works mostly for non-nucleophilic protic solvent or polar solvent. The reaction did not work well in ethereal, non-polar and polar protic solvents. Further, lowering the catalyst loading to 10 mol % did not attenuate the yield of the corresponding benzazepinone (entries 9 & 10). Lowering the catalyst loading to as low as 5 mol % decreased the yield considerably (entry 11). Further optimization showed that the reaction works well in the absence of *p*-TsOH as well (entry 14). In contrast to $Sc(OTf)_3$, other Lewis acids screened (entries 25 – 30) gave either low or moderate yields of the benzazepinone. Thus the optimal condition for our transformation was using 10 mol % of $Sc(OTf)_3$, 1.5 equiv of PIFA in TFE (0.1M) (entry 16).

3.22a **3.23a**

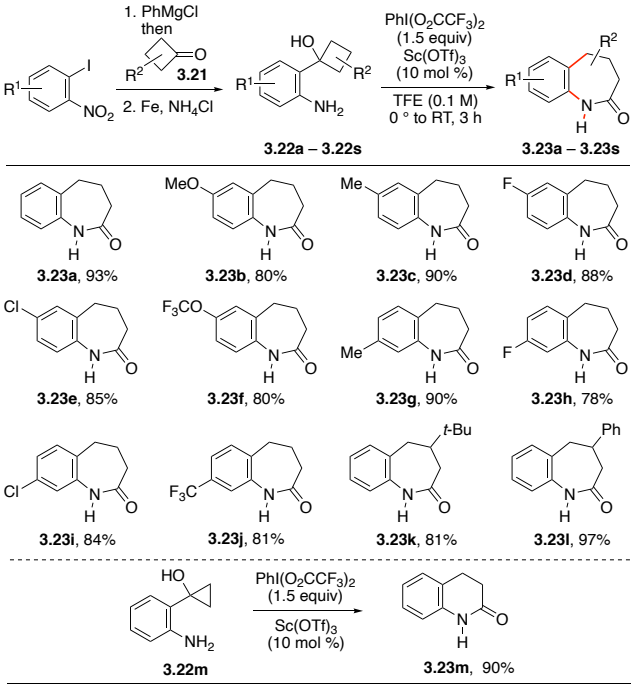
Table 3.01. Screen of catalyst, catalyst loading, additives, additives loading, oxidant and solvent.

Entry	catalyst (mol %)	additives (mol %)	oxidant (equiv)	solvent (M)	**3.23** yield, %[a]
1	...	...	PIFA (2.0)	CH_2Cl_2 (0.1)	42
2	…	…	PIFA (2.0)	TFE (0.1)	45
3	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	CH_2Cl_2 (0.1)	99

4	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	99
5	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	1,2 DCE (0.1)	77[b]
6	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	PhMe (0.1)	44[b]
7	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	1,4 dioxane (0.1)	37[b]
8	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	MeOH (0.1)	…
9	$Sc(OTf)_3$ (10)	*p*TsOH (20)	PIFA (2.0)	CH_2Cl_2 (0.1)	93
10	$Sc(OTf)_3$ (10)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	99
11	$Sc(OTf)_3$ (5)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	80
12	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	99
13	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (1.5)	TFE (0.1)	99
14	$Sc(OTf)_3$ (20)	…	PIFA (2.0)	TFE (0.1)	99
15	$Sc(OTf)_3$ (20)	…	PIFA (1.5)	TFE (0.1)	95
16	**$Sc(OTf)_3$ (10)**	**…**	**PIFA (1.5)**	**TFE (0.1)**	**93**
17	$Sc(OTf)_3$ (5)	…	PIFA (1.5)	TFE (0.1)	80
18	$Sc(OTf)_3$ (2)	…	PIFA (1.5)	TFE (0.1)	60
19	$Sc(OTf)_3$ (20)	…	PIFA (1.5)	HFIP (0.05)	20
20	$Sc(OTf)_3$ (20)	…	PIFA (1.5)	TFE (0.05)	69
21	$Sc(OTf)_3$ (10)	…	PIFA (1.2)	TFE (0.1)	75[c]
22	$Bi(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	42
23	$Sc(OTf)_3$ (10)	…	PIFA (1.5)	iPrOAc (0.1)	35
24	$Sc(OTf)_3$ (10)	…	PIDA (1.5)	TFE (0.1)	57
25	$Rh_2(esp)_2$ (10)	…	PIFA (1.5)	TFE (0.1)	53
26	$ScCl_3$ (10)	…	PIFA (1.5)	TFE (0.1)	39
27	$Y(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	53
28	$Mg(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	63
29	$Ag(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	57

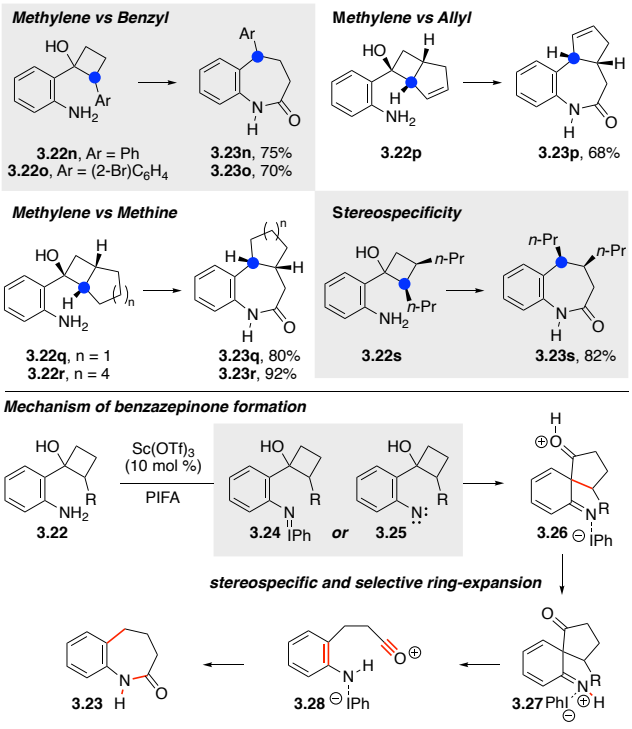
[a] Isolated yield, [b] PIFA was added in one portion to the reaction mixture, [c] Reaction run overnight. PIFA = [bis(trifluoroacetoxy)iodo]benzene, PIDA = (diacetoxyiodo)benzene, TFE = 2,2,2-trifluoroethanol, 1,2 DCE = 1,2-dichloroethene, HFIP =1,1,1,3,3,3-hexafluoro-2-propanol, *p*TsOH = *p*-toluenesulfonic acid,monohydrate.

Using these conditions, the scope of the reaction was interrogated (Scheme 3.03). We found the yield of benzazepinone **3.23** was unaffected if the aniline was electron-rich or electron-poor to afford high yields of **3.23a** – **3.23j**. Substrates containing an *ortho*-cyclobutanol with a *t*-Bu- or Ph group could also be smoothly converted into benzazepinones **3.23k** and **3.23l**. The effect of ring-strain on the reaction outcome was also investigated: while substrates with an *ortho*-cyclopentanol decomposed under the oxidative reaction conditions,[15] submission of *o*-cyclopropanol aniline **3.22m** to reaction conditions afforded quinolinone **3.23m**.



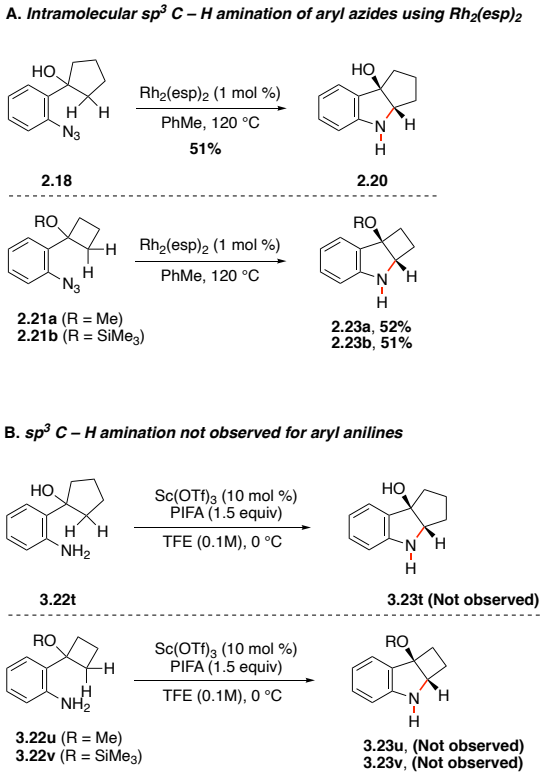
Scheme 3.03. Construction of benzazepinones from 2-cyclobutanol-substituted anilines.

Our examination of substituted *o*-cyclobutanol **3.22n** – **3.22s** enabled us to draw conclusions into both the selectivity of migration as well as the mechanism of the migration step (Scheme 3.04). Substrates **3.22n** and **3.22o** showed that benzyl migration was preferred over methylene migration to afford exclusively benzazepinones **3.23n** and **3.23o**. Submission of **3.22p** to reaction conditions afforded only **3.23p** revealing that allylic migration as preferred over methylene migration. Remarkably the migration distinguished between methine- and methylene migration affording solely **3.23q** – **3.23s** irrespective of whether the methine carbon was part of a five-membered ring, eight-membered ring or was acyclic.



Scheme 3.04. **Investigation of the migratorial aptitude in benzazepinone formation.**

The outcome of the latter substrate revealed that the migration step was stereospecific because the *cis*-stereochemistry embedded in the cyclobutanol was translated into the benzazepinone product without any loss of stereochemical integrity. The migratorial aptitude trends suggests a mechanism for benzazepinone formation (Scheme 3.04). Oxidation of the aniline produces iminoiodinane **3.24** (or nitrene **3.25** if PhI dissociates). Formation of the electrophilic *N*-aryl reactive intermediate triggers a Pinacol-like ring expansion to produce spirocycle aza-quinoid **3.26**.[16] This 1,2 shift is stereospecific, and migration of the more substituted carbon is strongly preferred. A proton shift from the oxocarbenium ion to the nitrogen triggers a fragmentation to re-establish aromaticity and produce acylium ion **3.28**, which is trapped by the Lewis basic nitrogen to form the benzazepinone.



Scheme 3.05. Reactivity differences between aryl azides and aryl anilines

To assay the importance of the ring strain to the success of the reaction, *o*-cyclopentanol-substituted aryl aniline **3.22t** was constructed by the route explained in **Scheme 3** using cyclopentanone in place of cyclobutanone. Instead of ring expansion, decomposition was observed. This was in contrast to our previously reported methodology, where *o*-cyclopentanol-substituted aryl azide **2.18** formed the corresponding sp^3 C – H amination product **2.20** (Scheme 3.05). This result along with the present result indicates that we do not see "nitrene" formation for our present oxidative process. The reactivity of aryl anilines **3.22u and 3.22v** revealed the importance of the hydroxyl group for ring-expansion processes. When it was replaced with either a methoxy or trimethylsilyloxy group, the ring-expansion did not occur but led to decomposition. Thus, we can conclude that both ring-size and hydroxyl group was an absolute necessity for the success of the reaction outcome.

CONCLUSION

We have developed a low temperature iodine(III) oxidation of unactivated anilines that generates an electrophilic *N*-aryl nitrogen species, which can be trapped intramolecularly to construct benzazepinones. Changing the identity of the *ortho*-substituent to a cyclobutanol enables access to benzazepinones through a selective and stereospecific ring-expansion reaction to produce a spirocycle aza-dienone, which upon fragmentation produces an acylium ion that is trapped to produce a benazazepinone. Our results prove that the oxidation of anilines does not require activation by an electron-withdrawing group

and that functionalized 3*H*-indoles or benzazepinones can be constructed by accessing the unique reactivity patterns embedded in *N*-aryl nitrene reactive intermediates.

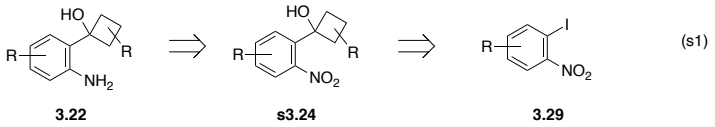
EXPERIMENTALS

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Infrared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[17] Metal salts were stored in a nitrogen atmosphere dry box.

I. Synthesis of *ortho*-substituted aniline.

A. Substrate synthesis overview.

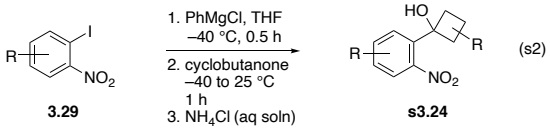
The *ortho*-cyclobutanol anilines substrates for our method development were constructed from 1-iodo-2-nitrobenzenes (Scheme s1).



Scheme s1. Strategy to construct the *ortho*-cyclobutanol aniline precursors

B. Synthesis of 2-nitro *o*-cyclobutanols from 1-iodo-2-nitrobenzenes.

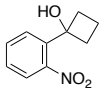
1. 2-Nitro *o*-cyclobutanols were prepared following the protocol reported by Knochel and co-workers (Scheme s2).[18]



Scheme s2. Synthesis of 2-nitro *o*-cyclobutanols

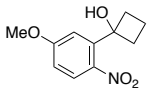
A dry and argon-flushed 100 mL flask equipped with a magnetic stirrer and a septum was charged with 1-iodo-2-nitrobenzene (1.0 equiv). Dry THF was added to create a 0.2 M solution, and the mixture was cooled to –40 °C. PhMgCl (1.1 equiv, 2.0 M in THF) was added dropwise and the reaction mixture was stirred at –40 °C for 0.5 h. Cyclobutanone (1.2 equiv) dissolved in 2 mL of THF was added dropwise, and the reaction mixture was stirred for 1 hour at –40 °C. The cooling bath was removed, and the mixture was stirred for an additional 1 hour at room temperature. The reaction mixture was quenched by adding 10 mL of a saturated aq soln of NH_4Cl. The resulting mixture was poured into water, and the phases were separated. The aqueous phase was extracted with 2 × 40 mL of ethyl acetate. The combined organic phases were washed with brine (30 mL), and dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by medium pressure liquid chromatography (MPLC) to give the title compounds as a pure product or submitted to the next step without characterization.

2. Characterization Data of 2-Nitro *o*-Cyclobutanols.



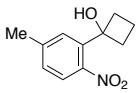
s3.24a

2-Nitro *o*-cyclobutanol s3.24a. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol). Purification by MPLC (10:1 – 5:1 hexanes:EtOAc) gave the product as a brown oil (0.420 g, 54%): R_f = 0.30 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.5 Hz,1H), 7.40 (t, *J* = 7.5 Hz, 1H), 3.66 (s, 1H), 2.49 – 2.37 (m, 4H), 2.25 – 2.16 (m, 1H), 1.74 – 1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7 (C), 140.2 (C), 133.2 (CH), 128.4 (CH), 128.3 (CH), 124.7 (CH), 75.8 (C), 34.6 (CH_2), 14.6 (CH_2); ATR-FTIR (thin film): 3550, 3418, 2993, 2950, 1520, 1355, 1130, 1090 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{10}NO_2$ $[M - H]^+$: 176.0712, found 176.0712.



s3.24b

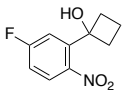
2-Nitro *o*-cyclobutanol s3.24b. The general procedure was followed by using 1.12 g of 2-iodo-4-methoxy-1-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol). Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) gave the product as a brown oil (0.601 g, 67%): R_f = 0.18 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 9.0 Hz, 1H), 6.91– 6.90 (m, 1H), 6.82 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 3.96 (s, 1H), 3.86 (s, 3H), 2.42 – 2.38 (m, 4H), 2.21 – 2.12 (m, 1H), 1.70 – 1.62 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4 (C), 143.2 (C), 141.5 (C), 127.9 (CH), 113.9 (CH), 112.4 (CH), 76.0 (C), 55.9 (CH_3), 34.5 (CH_2), 14.5 (CH_2); ATR-FTIR (thin film): 3554, 3422, 2991, 2950, 2874, 1515, 1348, 1156 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{13}NO_4$: 223.08446 , found 223.08361.



s3.24c

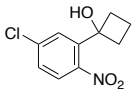
2-Nitro *o*-Cyclobutanol s3.24c. The general procedure was followed by using 1.06 g of 2-iodo-4-methyl-1-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol). Purification by MPLC (10:1 – 5:1 hexanes:EtOAc) gave the product as a brown oil (0.633 g, 76%): R_f = 0.33 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 7.12 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 3.79 (s, 1H), 2.42 – 2.08 (m, 7H), 2.18 – 2.08 (m, 1H), 1.67 – 1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4 (C), 144.4 (C), 140.1 (C), 128.8 (CH), 128.7 (CH), 124.9 (CH), 75.8 (C), 34.6 (CH_2), 21.5 (CH_3), 14.5 (CH_2); ATR-FTIR (thin film): 3544, 3086, 2943, 2841, 1603, 1577, 1510, 1333, 1316, 1292, 1231, 1138, 1029 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{12}NO_2$ $[M - H]^+$: 190.0868, found 190.0866.



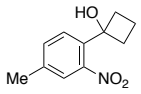
s3.24d

2-Nitro *o*-Cyclobutanol s3.24d. The general procedure was followed by using 1.07 g of 4-fluoro-2-iodo-1-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol) giving the product as a brown oil (0.560 g, 76%), which was taken to the next step without any additional purification or characterization.



s3.24e

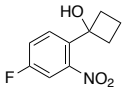
2-Nitro *o*-Cyclobutanol s3.24e. The general procedure was followed by using 1.14 g of 4-chloro-2-iodo-1-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol). Purification by MPLC (10:1 – 5:1 hexanes:EtOAc) gave the product as a brown oil (0.549 g, 60%): R_f = 0.36 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.34 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.69 (s, 1H), 2.45 – 2.34 (m, 4H), 2.23 – 2.15 (m, 1H), 1.73 – 1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9 (C), 142.0 (C), 139.4 (C), 128.5 (CH), 128.4 (CH), 126.2 (CH), 75.6 (C), 34.7 (CH_2), 14.4 (CH_2); ATR-FTIR (thin film): 3548, 3406, 3101, 2993, 2952, 2876, 1600, 1567, 1522, 1351, 1136 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{11}NO_3Cl$ $[M + H]^+$: 228.04275, found 228.04245.



s3.24f

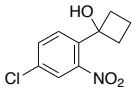
2-Nitro *o*-Cyclobutanol s3.24f. The general procedure was followed by using 1.06 g of 1-iodo-4-methyl-2-Nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of commercially available cyclobutanone (4.82 mmol): Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) gave the product as a brown oil (0.558 g, 67%): R_f = 0.30 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.37 – 7.33 (m, 2H), 3.65 (s, 1H), 2.44 – 2.32 (m, 7H), 2.20 – 2.11 (m, 1H), 1.69 – 1.61 (m,

1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 (C), 138.9 (C), 137.3 (C), 133.8 (CH), 128.1 (CH), 124.9 (CH), 75.6 (C), 34.7 (CH_2), 20.7 (CH_3), 14.5 (CH_2); ATR-FTIR (thin film): 3555, 3422, 2990, 2950, 2874, 1525, 1351, 1174, 1135 cm^{-1}. HRMS (ESI) m/z calcd for $C_{11}H_{12}NO_2$ $[M - H]^+$: 190.0868, found 190.0862.



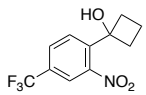
s3.24g

2-Nitro *o*-Cyclobutanol s3.24g. The general procedure was followed by using 1.07 g of 4-fluoro-1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol) giving the crude product as a brown oil (0.654 g, 77%), which was taken to the next step without any additional purification or characterization.



s3.24h

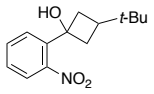
2-Nitro *o*-Cyclobutanol s3.24h. The general procedure was followed by using 1.14 g of 4-chloro-1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol): Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a brown oil, as a 4.2:1 mixture of rotamers (0.558 g, 67%): R_f= 0.27 (5:1 hexanes:EtOAc); **Major rotamer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.70 (m, 1H), 7.55 – 7.52 (m, 1H), 7.43 – 7.40 (m, 1H), 3.54 (s, 1H), 2.46 – 2.34 (m, 4H), 2.25 – 2.16 (m, 1H), 1.75 – 1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0 (C), 138.7 (C), 133.9 (C), 133.1 (CH), 129.6 (CH), 124.7 (CH), 75.5 (C), 34.7 (CH_2), 14.5(CH_2); **Diagnostic Peaks for minor rotamer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 1H), 7.36 – 7.33 (m, 1H), 7.27 – 7.24 (m, 1H), 3.53 (s, 1H), 2.57 – 2.52 (m, 4H), 2.04 – 1.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.4 (CH), 127.2 (CH), 124.9 (CH), 36.8 (CH_2), 13.0 (CH_2); ATR-FTIR (thin film): 3500, 3108, 2870, 2943, 2990, 1542, 1350, 1260, 1157 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{11}NO_3Cl$ $[M + H]^+$: 228.04275, found 228.04299.



s3.24i

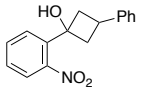
2-Nitro *o*-Cyclobutanol s3.24i. The general procedure was followed by using 1.27 g of 1-iodo-2-nitro-4-(trifluoromethyl)benzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.36 mL of cyclobutanone (4.82 mmol) giving

the crude product as a brown oil (0.654 g, 77%), which was taken to the next step without any additional purification or characterization.



s3.24j

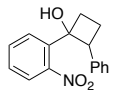
2-Nitro *o*-Cyclobutanol s3.24j. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.608 g of 3-*tert*-butylcyclobutanone (4.82 mmol).[19] Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) gave the product as a brown oil, as a 3:1 mixture of diastereomers (0.531 g, 53%): R_f = 0.39 (5:1 hexanes:EtOAc); **Major diastereomer**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 8.0 Hz, 3.0 Hz, 1H), 7.68 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.45 – 7.41 (m, 1H), 3.80 (s, 1H), 2.50 – 2.46 (m, 2H), 2.22 – 2.17 (m, 2H), 1.60 – 1.52 (m, 1H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0 (C), 139.1 (C), 133.0 (CH), 128.6 (CH), 128.1 (CH), 125.3 (CH), 70.4 (C), 36.9 (CH), 36.6 (CH_2), 30.9 (C), 26.5 (CH_3); **Diagnostic Peaks for minor diastereomer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 8.0 Hz, 2.5 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.45 – 7.41 (m, 1H), 7.40 – 7.37 (m, 1H), 3.63 (s, 1H), 2.60 – 2.53 (m, 1H), 2.33 – 2.28 (m, 2H), 2.06 – 2.02 (m, 2H), 0.75 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3 (C), 140.7 (C), 133.3 (CH), 128.5 (CH), 128.3 (CH), 124.4 (CH), 71.6 (C), 40.1 (CH_2), 35.1 (CH), 30.8 (C), 26.2 (CH_3); ATR-FTIR (thin film): 3551, 3423, 2954, 2903, 2866, 1524, 1473, 1363, 1238, 1165 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{20}NO_3$ $[M + H]^+$: 249.1400, found 249.1402.



s3.24k

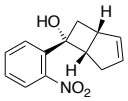
2-Nitro *o*-Cyclobutanol s3.24k. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.705 g of 3-phenylcyclobutanone (4.82 mmol).[19] Purification by MPLC (10:1 – 5:1 hexanes:EtOAc) gave the product as a brown oil, as a 8:1 mixture of diastereomers (0.725 g, 67%): R_f = 0.24 (5:1 hexanes:EtOAc); **Major diastereomer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.79 – 7.76 (m, 1H), 7.69 – 7.66 (m, 1H), 7.49 (dt, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.36 – 7.28 (m, 4H), 7.26 – 7.20 (1H), 3.94 (s, 1H), 3.10 – 3.05 (m, 2H), 3.04 – 3.00 (m, 1H), 2.68 – 2.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9 (C), 144.2 (C), 138.7 (C), 133.3 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 126.7 (CH), 126.3 (CH), 125.5 (CH), 71.7 (C), 43.2 (CH), 33.6 (CH_2); **Diagnostic Peaks for minor diastereomer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.42 (dt, *J* =

7.5 Hz, 1.0 Hz, 1H), 7.26 – 7.17 (m, 5H), 3.82 (s, 1H), 2.96 – 2.92 (m, 1H), 2.54 – 2.48 (m, 1H), only visible peaks; ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5 (C), 133.5 (CH), 131.0 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 126.3 (CH), 126.2 (C), 124.8 (CH), 124.6 (C), 72.7 (C), 41.5 (CH), 30.6 (CH_2); ATR-FTIR (thin film): 3544, 3410, 3061, 3026, 2984, 2938, 1521, 1495, 1347, 1165, 954 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{15}NO_3Na$ $[M + Na]^+$: 292.0950, found 292.0944.



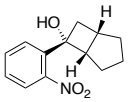
s3.24l

2-Nitro *o*-Cyclobutanol s3.24l. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.705 g of 2-phenylcyclobutanone (4.82 mmol).[20] Purification by MPLC (20:1 – 15:1 hexanes:EtOAc) gave the product as a brown oil, as a single diastereomer (0.238 g, 22%): R_f = 0.39 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (t, J = 8.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.38 (m, 3H), 7.31 (t, *J* = 7.0 Hz, 1H), 4.05 (t, *J* = 9.0 Hz, 1H), 3.13 (s, 1H), 2.58 (quin, *J* = 10.0 Hz, 1H), 2.48 – 2.44 (m, 2H), 2.33 – 2.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2 (C), 140.1 (C), 138.7 (C), 132.6 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 127.2 (CH), 124.5 (CH), 78.5 (C), 48.5 (CH), 34.0 (CH_2), 23.3 (CH_2); ATR-FTIR (thin film): 3545, 3062, 3025, 2995, 2951, 1525, 1496, 1359, 1270, 1191, 1146, 903 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{14}NO_2$ $[M – H]^+$: 252.1025, found 252.1025.



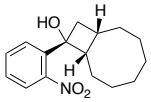
s3.24m

2-Nitro *o*-Cyclobutanol s3.24m. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.521 g of commercially available bicyclo[3.2.0]hept-2-en-6 one (4.82 mmol). Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) gave the product as a brown oil, as a single diastereomer (0.474 g, 51%): R_f = 0.33 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.40 – 7.36 (m, 1H), 5.89 – 5.87 (m, 1H), 5.83 – 5.80 (m, 1H), 3.32 – 3.28 (m, 1H), 3.25 (s, 1H), 3.07 – 3.02 (m, 1H), 2.92 – 2.85 (m, 2H), 2.57 – 2.50 (m, 1H), 2.18 (dd, *J* = 13.0 Hz, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1 (C), 140.6 (C), 133.8 (CH), 132.9 (CH), 132.8 (CH), 128.8 (CH), 128.3 (CH), 124.4 (CH), 74.7 (C), 45.9 (CH), 41.8 (CH_2), 39.1 (CH), 33.6 (CH_2); ATR-FTIR (thin film): 3551, 3048, 2923, 2847, 1520, 1440, 1349, 1103, 1008, 909 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{13}NO_3$: 231.08955, found 231.08918.



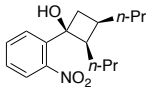
s3.24n

2-Nitro *o*-Cyclobutanol s3.24n. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.531 g of bicyclo[3.2.0]heptan-6 one (4.82 mmol).[22] Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) gave the product as a brown oil, as a single diastereomer (0.535 g, 57%): R_f = 0.39 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 3.36 (s, 1H), 2.89 – 2.81 (m, 2H), 2.37 (quin, *J* = 7.0 Hz, 1H), 2.08 (dd, *J* = 13.5 Hz, 7.0 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.88 (dd, *J* = 13.5 Hz, 6.5 Hz, 1H), 1.80 – 1.74 (m, 1H), 1.58 – 1.49 (m, 2H), 1.48 – 1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5 (C), 141.1 (C), 132.9 (CH), 128.3 (CH), 128.3 (CH), 124.9 (CH), 71.9 (C), 49.0 (CH), 38.6 (CH_2), 32.8 (CH_2), 30.7 (CH), 27.4 (CH_2), 25.8 (CH_2); ATR-FTIR (thin film): 3552, 2947, 2853, 1521, 1353, 1249, 1130, 1013 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{16}NO_3$ $[M + H]^+$: 234.11302, found 234.11368.



s3.24o

2-Nitro *o*-Cyclobutanol s3.24o. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.772 g of bicyclo[6.2.0]decan-9 one (4.82 mmol).[23] Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) gave the product as a brown oil (0.421 g, 38%): R_f = 0.46 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 3.34 (s, 1H), 2.73 – 2.68 (m, 1H), 2.58 – 2.53 (m, 1H), 2.01 – 1.82 (m, 5H), 1.79 – 1.73 (m, 1H), 1.57 – 1.48 (m, 2H), 1.45 – 1.39 (m, 3H), 1.35 – 1.26 (m, 2H), 1.25 – 1.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4 (C), 140.6 (C), 132.9 (CH), 128.3 (CH), 127.8 (CH), 125.0 (CH), 74.0 (C), 48.9 (CH), 40.6 (CH_2), 32.5 (CH), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 22.3 (CH_2); ATR-FTIR (thin film): 3563, 2916, 2848, 2694, 1765, 1523, 1464, 1360, 1204, 1057, 1001 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{21}NO_3$: 275.15215, found 275.15291.

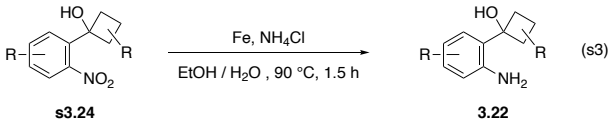


s3.24p

2-Nitro *o*-Cyclobutanol s3.24p. The general procedure was followed by using 1.00 g of 1-iodo-2-nitrobenzene (4.02 mmol), 2.21 mL of PhMgCl (4.42 mmol) and 0.744 g of (2*S*,3*S*)-2,3-dipropylcyclobutan-1-one (4.82 mmol).[23] Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) gave the product as a brown oil, as a single diastereomer (0.569 g, 51%): R_f = 0.58 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.57 (m, 2H), 7.41 – 7.36 (m, 1H), 3.41 (s, 1H), 2.78 – 2.74 (m, 1H), 2.51 – 2.47 (m, 1H), 2.08 – 1.99 (m, 2H), 1.78 – 1.65 (m, 2H), 1.62 – 1.56 (m, 1H), 1.54 – 1.48 (m, 1H), 1.43 – 1.29 (m, 3H), 1.18 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3 (C), 140.9 (C), 132.9 (CH), 128.2 (CH), 128.0 (CH), 124.8 (CH), 74.9 (C), 45.9 (CH), 39.2 (CH_2), 32.6 (CH_2), 31.2 (CH), 27.0 (CH_2), 21.8 (CH_2), 20.5 (CH_2), 14.5 (CH_3), 14.3 (CH_3); ATR-FTIR (thin film): 3564, 2956, 2929, 2870, 1575, 1524, 1355, 1133, 999 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{22}NO_2$ $[M - H]^+$: 260.1651, found 260.1645.

C. Synthesis of *o*-cyclobutanol anilines from 2-nitro *o*-cyclobutanols. (Scheme s3)

1. General procedures

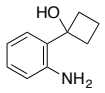


s3.24 **3.22**

Scheme s3. Synthesis of *o*-cyclobutanol anilines

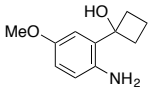
To a 0.4 M solution of 2-nitro *o*-cyclobutanols in a 1.5:1 mixture of ethanol and H_2O was added Fe powder (5.0 equiv) and NH_4Cl (4.0 equiv). The resulting mixture was heated at 90 °C. After 1.5 h, mixture was cooled to room temperature and filtered through a plug of silica gel. The plug of silica gel was eluted with an additional 2 × 5 mL of ethanol. The solvent was then concentrated in vacuo, and the residue extracted with 2 × 20 mL of ethyl acetate. The combined organic phases were washed with 30 mL of brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by medium pressure liquid chromatography (MPLC) to give the title compounds as a pure product.

2. Characterization data of *o*-cyclobutanol anilines.



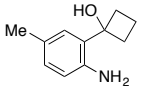
3.22a

***o*-Cyclobutanol Aniline 3.22a.**[23] The general procedure was followed by using 0.386 g of **s3.24a** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a yellow solid (0.229 g, 70%). The spectral data of **3.22a** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.75 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.13 (br s, 2H), 2.67 – 2.61 (m, 2H), 2.35 – 2.29 (m, 2H), 2.02 – 1.94 (m, 1H), 1.67 – 1.58 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6 (C), 128.7 (CH), 128.3 (C), 125.3 (CH), 117.7 (CH), 116.8 (CH), 77.4 (C), 35.0 (CH_2), 13.7 (CH_2). ATR-FTIR (thin film): 3341, 2925, 2853, 1608, 1494, 1456, 1303, 1122, 746 cm^{-1}.



3.22b

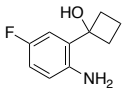
***o*-Cyclobutanol Aniline 3.22b.**[23] The general procedure was followed by using 0.448 g of **s3.24b** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a yellow solid (0.198 g, 51%). The spectral data of **3.22b** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, J = 8.0 Hz, 1H), 6.71 – 6.68 (m, 1H), 6.65 (dd, J = 8.5 Hz, 1.0 Hz, 1H), 3.85 (br s, 2H), 3.76 (s, 3H), 2.65 – 2.60 (m, 2H), 2.38 – 2.32 (m, 2H), 2.04 – 1.96 (m, 1H), 1.69 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4 (C), 138.9 (C), 130.5 (C), 118.1 (CH), 113.2 (CH), 112.3 (CH), 77.4 (C), 55.9 (CH_3), 35.1 (CH_2), 13.6 (CH_2). ATR-FTIR (thin film): 3400, 3363, 2935, 1766, 1498, 1428, 1286, 1217, 1128, 1048, 815 cm^{-1}.



3.22c

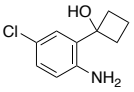
***o*-Cyclobutanol Aniline 3.22c.**[23] The general procedure was followed by using 0.414 g of **s3.24c** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by

MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a white solid (0.191 g, 54%). The spectral data of **3.22c** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.92 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.00 (br s, 2H), 2.65 – 2.60 (m, 2H), 2.35 – 2.28 (m, 5H), 2.03 – 1.95 (m, 1H), 1.68 – 1.59 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142. 9 (C), 129.1 (CH), 128.7 (C), 126.9 (C), 125.9 (CH), 117.1 (CH), 77.4 (C), 35.1 (CH_2), 20.7 (CH_3), 13.8 (CH_2). ATR-FTIR (thin film): 3367, 2983, 2945, 2860, 1502, 1319, 1290, 1130, 909, 815, 760 cm^{-1}.



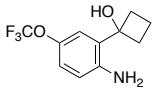
3.22d

***o*-Cyclobutanol Aniline 3.22d.** The general procedure was followed by using 0.422 g of **s3.24d** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g (8.00 mmol) of NH_4Cl in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a white solid (0.246 g, 68%): R_f = 0.06 (5:1 hexanes:EtOAc), mp = 118 – 120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (td, *J* = 4.5 Hz, 2.0 Hz, 1H), 6.79 (tt, *J* = 4.5 Hz, 2.5 Hz, 1H), 6.56 (dd, *J* = 9.0 Hz, 5.0 Hz, 1H), 4.00 (br s, 2H), 2.92 (br s, 1H), 2.57 – 2.52 (m, 2H), 2.32 – 2.26 (m, 2H), 1.99 – 1.91 (m, 1H), 1.64 – 1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9 (d, J_{CF} = 233.9 Hz, C), 141.4 (C), 130.0 (d, J_{CF} = 5.5 Hz, C), 117.7 (d, J_{CF} = 7.5 Hz, CH), 114.7 (d, J_{CF} = 21.9 Hz, CH), 112.3 (d, J_{CF} = 23.1 Hz, CH), 76.9 (C), 35.0 (CH_2), 13.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ; ATR-FTIR (thin film): 3389, 3317, 3184, 2996, 2947, 1590, 1493, 1433, 1274, 1244, 1197, 1170, 1139 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{12}NOF$: 181.09029, found 181.09043.



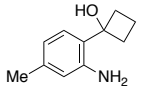
3.22e

***o*-Cyclobutanol Aniline 3.22e.** The general procedure was followed by using 0.455 g of **s3.24e** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a white solid (0.281 g, 71%): R_f = 0.10 (5:1 hexanes:EtOAc), mp = 110 – 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 2.5 Hz, 1H), 7.03 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 4.14 (br s, 2H), 2.90 (br s, 1H), 2.55 – 2.49 (m, 2H), 2.28 – 2.21 (m, 2H), 2.00 – 1.90 (m, 1H), 1.63 – 1.55 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1 (C), 129.8 (C), 128.3 (CH), 125.4 (CH), 122.4 (C), 117.9 (CH), 77.0 (C), 35.0 (CH_2), 13.6 (CH_2); ATR-FTIR (thin film): 3365, 3199, 2994, 2949, 1606, 1487, 1416, 1270, 1244, 1129, 1103 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{12}NOCl$: 197.06074, found 197.06114.



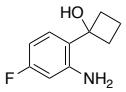
3.22f

***o*-Cyclobutanol Aniline 3.22f.**[23] The following compound was prepared using the procedure previously reported by Driver and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 2.5 Hz, 1H), 6.96 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 6.57 (d, J = 9.0 Hz, 1H), 4.22 (br s, 2H), 2.79 (br s, 1H), 2.59 – 2.52 (m, 2H), 2.33 – 2.26 (m, 2H), 2.02 – 1.92 (m, 1H), 1.64 – 1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (C), 140.6 (C), 129.1 (C), 121.5 (CH), 120.7 (q, J_{CF} = 253.5 Hz, C), 118.8 (CH), 117.0 (CH), 76.9 (C), 35.0 (CH_2), 13.5 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.8; ATR-FTIR (thin film): 3375, 2990, 1625, 1498, 1249, 1215, 1154, 885, 882 cm^{-1}.



3.22g

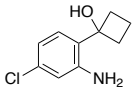
***o*-Cyclobutanol Aniline 3.22g.**[23] The general procedure was followed by using 0.414 g of **s3.24f** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a white solid (0.177 g, 50%). The spectral data of **3.22g** matched that reported by Driver and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 7.5 Hz, 1H), 6.52 (s, 1H), 4.14 (br s, 2H), 2.67 – 2.61 (m, 2H), 2.37 – 2.32 (m, 2H), 2.26 (s, 3H), 2.16 (br s, 1H), 2.02 – 1.94 (m, 1H), 1.67 – 1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145. 5 (C), 138.7 (C), 125.5 (C), 125.3 (CH), 118.4 (CH), 117.5 (CH), 77.4 (C), 35.1 (CH_2), 21.1 (CH_3), 13.7 (CH_2). ATR-FTIR (thin film): 3418, 3320, 2976, 2934, 2858, 1615, 1510, 1428, 1115, 819, 792 cm^{-1}.



3.22h

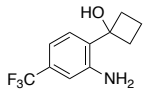
***o*-Cyclobutanol Aniline 3.22h.**[23] The general procedure was followed by using 0.422 g of **s3.24g** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a white solid (0.196 g, 54%) as a 17:1 mixture of rotamers. The spectral data of **3.22h** matched that reported by Driver and co-workers:[24] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (dd, J =

8.5 Hz, 6.0 Hz, 0.06H, 7.12 (dd, J = 8.5 Hz, 6.0 Hz, 1H), 7.08 (dd, J = 8.5 Hz, 6.6 Hz, 0.06H), 6.51 (dt, J = 8.5 Hz, 2.5 Hz, 0.06H), 6.39 (dt, J = 8.5 Hz, 2.5 Hz, 0.99H), 6.33 (dd, J = 10.5 Hz, 2.5 Hz, 1.01H), 6.29 (dd, J = 8.5 Hz, 2.5 Hz, 0.06H), 6.24 (dd, J = 10.5 Hz, 2.5 Hz, 0.06H), 6.20 (dd, J = 12.0 Hz, 2.5 Hz, 0.07H), 4.46 (br s, 0.18H), 4.30 (br s, 1.97H), 2.76 – 2.69 (m, 0.19H), 2.60 – 2.55 (m, 2.30H), 2.50 (br s, 0.97H), 2.39 – 2.34 (m, 0.26H), 2.32 – 2.26 (m, 2.18H), 2.10 – 2.01 (m, 0.16H), 1.99 – 1.92 (m, 1.16H), 1.69 – 1.64 (m, 0.06H), 1.62 – 1.55 (m, 1.04H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2 (d, J_{CF} = 241.8 Hz, C), 147.4 (d, J_{CF} = 10.9 Hz, C), 128.4 (d, J_{CF} = 9.9 Hz, C), 126.7 (d, J_{CF} = 10.1 Hz, CH), 126.2 (d, J_{CF} = 10.0 Hz, CH), 123.9 (C), 104.4 (d, J_{CF} = 20.9 Hz, CH), 103.7 (d, J_{CF} = 21.1 Hz, CH), 103.1 (d, J_{CF} = 24.3 Hz, CH), 102.7 (d, J_{CF} = 21.5 Hz, CH), 101.4 (d, J_{CF} = 26.3 Hz, CH), 77.6 (C), 77.1 (C), 35.4 (CH_2), 35.2 (CH_2), 34.2 (CH_2), 15.4 (CH_2), 14.1 (CH_2), 13.7 (CH_2), only visible signals. ^{19}F NMR (282 MHz, $CDCl_3$) δ –115.2; ATR-FTIR (thin film): 3418, 3326, 3230, 2923, 2852, 1622, 1434, 1332, 1162, 1126, 1104, 870, 804, 740 cm^{-1}.



3.22i

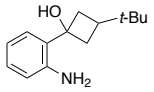
***o*-Cyclobutanol Aniline 3.22i.** The general procedure was followed by using 0.455 g of **s3.24h** (2.00 mmol) 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a white solid (0.253 g, 64%): R_f = 0.15 (5:1 hexanes:EtOAc), mp = 110 – 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, J = 8.0 Hz, 1H), 6.67 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 4.27 (bs, 2H), 2.60 – 2.54 (m, 2H), 2.41 (s, 1H), 2.33 – 2.26 (m, 2H), 2.00 – 1.92 (m, 1H), 1.64 – 1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9 (C), 134.1 (C), 126.5 (CH), 126.4 (C), 117.3 (CH), 116.2 (CH), 77.1 (C), 35.1 (CH_2), 13.6 (CH_2). ATR-FTIR (thin film): 3370, 2986, 2949, 2871, 1614, 1568, 1492, 1246, 1120, 1024, 907 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{12}NOCl$: 197.06074, found 197.06111.



3.22j

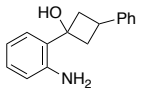
***o*-Cyclobutanol Aniline 3.22j.**[23] The general procedure was followed by using 0.462 g of **s3.24i** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a white solid (0.287 g, 62%). The spectral data of **3.22j** matched that reported by Driver and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.88 (s,

1H), 4.41 (br s, 2H), 2.66 – 2.58 (m, 2H), 2.39 – 2.26 (m, 3H), 2.04 – 1.94 (m, 1H), 1.67 – 1.56 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0 (C), 130.9 (q, J_{CF} = 24.1 Hz, C), 130.6 (C), 125.7 (CH), 124.1 (q, J_{CF} = 270.3 Hz, C), 114.0 (q, J_{CF} = 4.3 Hz, CH), 112.9 (q, J_{CF} = 3.6 Hz, CH), 77.2 (C), 35.0 (CH_2), 13.5 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ – 63.3; ATR-FTIR (thin film): 3418, 3326, 3230, 2923, 2852, 1622, 1434, 1332, 1162, 1126, 1104, 870, 804, 740 cm^{-1}.



3.22k

***o*-Cyclobutanol Aniline 3.22k.** The general procedure was followed by using 0.498 g of **s3.24j** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (7:1 – 5:1 hexanes:EtOAc) afforded the product, a white solid, as a 3:1 mixture of diastereomers (0.215 g, 49%): R_f = 0.22 (5:1 hexanes:EtOAc); mp = 76 – 78 °C; **Major diastereomer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.28 (m, 1H), 7.15 – 7.11 (m, 1H), 6.78 – 6.74 (m, 1H), 6.69 – 6.67 (m, 1H), 4.11 (br s, 2H), 2.60 – 2.56 (m, 2H), 2.06 – 2.01 (m, 2H), 1.66 – 1.58 (m, 1H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9 (C), 128.8 (CH), 127.7 (C), 125.3 (CH), 117.6 (CH), 116.9 (CH), 71.7 (C), 37.0 (CH), 36.2 (CH_2), 30.9 (C), 26.7 (CH_3); **Diagnostic Peaks for minor diastereomer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 – 7.07 (m, 2H), 6.73 – 6.71 (m, 1H), 6.63 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 2.60 – 2.56 (m, 2H), 2.31 – 2.22 (m, 5H), 0.84 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3 (C), 130.1 (C), 128.6 (CH), 125.6 (CH), 117.9 (CH), 116.7 (CH), 74.4 (C), 40.5 (CH), 35.3 (CH_2), 31.0 (C), 26.4 (CH_3); ATR-FTIR (thin film): 3371, 2952, 2901, 2864, 1617, 1580, 1495, 1456, 1364, 1269, 1157, 1088, 986 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{21}NO$: 219.16232, found 219.16289.



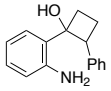
3.22l

***o*-Cyclobutanol Aniline 3.22l.** The general procedure was followed by using 0.539 g of **s3.24k** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (10:1 – 5:1 hexanes:EtOAc) afforded the product, a yellow oil, as a 4:1 mixture of diastereomers (0.321 g, 67%): R_f = 0.28 (5:1 hexanes:EtOAc); **Major diastereomer** : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 1H), 7.34 (q, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.20 – 7.17 (m, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.77 – 6.73 (m, 1H), 4.19 (bs, 2H), 3.19 – 3.15 (m, 2H), 3.05 – 2.98 (m, 1H), 2.52 – 2.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0 (C), 144.6 (C), 129.1 (CH), 128.4 (CH), 127.0 (C), 126.7 (CH), 126.1 (CH), 125.3 (CH), 117.8 (CH), 117.0 (CH), 72.8 (C), 42.7 (CH_2), 30.8 (CH);

Diagnostic Peaks for minor diastereomer : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 7.13 – 7.10 (m, 2H), 6.67 (d, *J* = 8.5 Hz, 1H), 3.98 (quin, *J* = 9.0 Hz, 2H), 2.88 – 2.83 (m, 2H), 2.74 – 2.69 (m, 2H), only visible signals; ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3 (C), 145.0 (C), 129.7 (C), 128.9 (CH), 128.4 (CH), 126.5 (CH), 126.1 (CH), 125.6 (CH), 118.0 (CH), 116.8 (CH), 75.6 (C), 41.9 (CH_2), 34.1 (CH); ATR-FTIR (thin film): 3338, 3053, 3028, 2984, 1615, 1603, 1495, 1455, 1302, 1264, 1155, 1065, 953 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{17}NO$: 239.13102, found 239.13063.

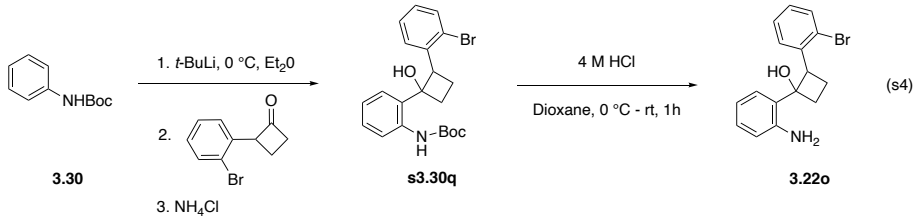
3.22m

***o*-Cyclopropanol Aniline 3.22m.** The following compound was prepared using the procedure previously reported by Egan and co-workers:[24] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.10 (m, 2H), 6.72 – 6.69 (m, 2H), 3.30 (br s, 3H), 1.15 – 1.13 (m, 2H), 0.95 – 0.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (C), 129.1 (CH), 128.1 (CH), 126.2 (C), 117.9 (CH), 115.6 (CH), 56.0 (C), 13.1 (CH_2). ATR-FTIR (thin film): 3484, 2920, 2916, 2849, 2342, 1650, 1250 cm^{-1}.



3.22n

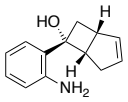
***o*-Cyclobutanol Aniline 3.22n.** The general procedure was followed by using 0.539 g of **s3.24l** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (10:1 – 5:1 hexanes:EtOAc) afforded the product, a yellow oil, as a 3:1 mixture of diastereomers (0.235 g, 49%): R_f = 0.28 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 0.07H), 7.57 – 7.53 (m, 0.10H), 7.48 (d, *J* = 7.5 Hz, 2.01H), 7.45 – 7.43 (m, 0.11H), 7.41 – 7.36 (m, 3.13H), 7.31 – 7.28 (m, 1.06H), 7.10 (dt, *J* = 7.5 Hz, 1.5 Hz, 1.01H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.22 (t, *J* = 8.5 Hz, 1.34H), 4.16 (br s, 1.64H), 3.96 (t, *J* = 7.5 Hz, 0.09H), 3.73 (s, 0.49H), 3.54 (d, *J* = 7.5 Hz, 0.16H), 2.57 – 2.48 (m, 3.14H), 2.33 – 2.23 (m, 1.21H), 2.17 (br s, 0.74H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7 (C), 139.3 (C), 133.3 (CH), 133.0 (CH), 129.6 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 126.9 (CH), 125.7 (CH), 125.3 (CH), 117.7 (CH), 116.9 (CH), 80.8 (C), 52.8 (CH), 52.2 (CH), 47.5 (CH), 33.0 (CH_2), 32.3 (CH_2), 22.1 (CH_2), only visible signals. ATR-FTIR (thin film): 3466, 3346, 3063, 3032, 2999, 2948, 2922, 2854, 1753, 1646, 1581, 1484, 1451, 1277, 1145 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ $[M - H - O]^{+}$: 222.1283, found 222.1283.



***tert*-Butyl (2-(1-hydroxycyclobutyl)phenylcarbamate s3.30q.**[23] To a cooled (0 °C) 3 M solution of 0.200 g of N-Boc aniline (1.04 mmol) in 10 mL of dry Et_2O under an inert atmosphere of argon was dropwise added 1.40 mL of *t*-butyl lithium (1.9 M solution in pentane, 2.60 mmol) using a syringe pump. The reaction mixture was stirred at 0 °C. After 3 h, a solution of 0.356 g of 2-(2-bromophenyl)cyclobutanone in 2.0 mL of dry Et_2O was added dropwise. The reaction mixture was stirred at 0 °C for 30 mins and then warmed to room temperature and stirred for another 30 mins. The reactives were quenched through addition of a saturated aqueous solution of NH_4Cl. The resulting mixture was diluted with 15 mL of EtOAc. The two layers were separated, and the aqueous layer was extracted with 3 × 15 mL of EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and the filtrate concentrated under reduced pressure to give the crude product. Purification by MPLC (12:1 hexanes:EtOAc) gave the product as a brown solid (0.200 g, 46%). The spectral data of **s3.30q** matched that reported by Driver and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.60 (t, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.56 (t, *J* = 7.5 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.48 – 2.39 (m, 2H), 2.29 – 2.23 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C), 138.5 (C), 137.3 (C), 133.1 (CH), 132.8 (C), 130.4 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 125.9 (C), 125.7 (CH), 122.6 (CH), 121.7 (CH), 80.8 (C), 80.0 (C), 46.9 (CH), 33.7 (CH_2), 28.3 (CH_2), 22.6 (CH_3); ATR-FTIR (thin film): 3368, 2977, 1704, 1586, 1521, 1448, 1241, 1157, 1048, 1023, 752, 736 cm^{-1}.

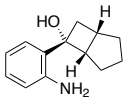
***o*-Cyclobutanol Aniline 3.22o.** To a cooled (0 °C) solution of 0.200 g of **s3.30q** (0.48 mmol) in 1 mL of dioxane was added dropwise 2 mL of a 4 M solution of HCl in dioxane. The reaction was stirred at 0 °C for 20 mins and then warmed to room temperature. The reaction progress was monitored using thin layer chromatography, and when the starting material was consumed, the mixture was neutralized by adding a saturated solution of $NaHCO_3$ until effervescence stopped. The resulting mixture was extracted with 3 × 10 mL EtOAc. The organic layers were combined and washed with 20 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by MPLC (10:1 hexanes:EtOAc) gave the product as a yellow oil (0.122 g, 80%): R_f = 0.16 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.14 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.10 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 4.58 (t, *J* = 8.0 Hz, 1H), 3.98 (br s, 2H), 2.63 – 2.57 (m, 1H), 2.48 – 2.42 (m, 1H), 2.41 – 2.35 (m, 1H), 2.30 – 2.24 (m, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 145.3 (C), 139.2 (C), 133.0 (CH), 130.5 (CH), 129.4 (C), 128.7 (CH), 128.3 (CH), 127.4 (CH), 126.0 (CH), 125.7 (C), 118.1 (CH), 117.2 (CH), 81.0 (C), 47.0 (CH), 33.1 (CH_2), 22.7 (CH_2). ATR-FTIR (thin film): 3445, 3381, 3061, 3023, 2988, 2947, 2866, 1616, 1494, 1453, 1437, 1304, 1126 898 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{14}NOBr$ [M – H_2]$^+$: 315.02587, found 315.02477.



3.22p

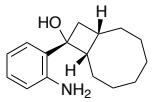
***o*-Cyclobutanol Aniline 3.22p.** The general procedure was followed by using 0.463 g of **s3.24m** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (7:1 – 5:1 hexanes:EtOAc) afforded the product as a black oil (0.246 g, 61%): R_f = 0.28 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.10 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.99 – 5.95 (m, 2H), 4.06 (br s, 2H), 3.54 – 3.50 (m, 1H), 3.15 – 3.08 (m, 2H), 2.87 (dd, *J* = 7.0 Hz, 3.0 Hz, 1H), 2.67 – 2.62 (m, 1H), 2.33 (s, 1H), 2.17 – 2.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4 (C), 135.5 (CH), 132.7 (CH), 129.7 (C), 128.6 (CH), 125.7 (CH), 117.8 (CH), 116.9 (CH), 77.2 (C), 45.0 (CH), 42.0 (CH_2), 39.7 (CH), 33.6 (CH_2). ATR-FTIR (thin film): 3444, 3368, 3045, 2975, 2920, 2841, 1616, 1579, 1493, 1455, 1348, 1303, 1071, 948 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{15}NO$: 201.11537, found 201.11592.



3.22q

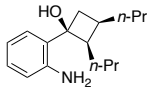
***o*-Cyclobutanol Aniline 3.22q.** The general procedure was followed by using 0.467 g of **s3.24n** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (7:1 – 5:1 hexanes:EtOAc) afforded the product as a yellow solid (0.210 g, 52%): R_f = 0.28 (5:1 hexanes:EtOAc); mp = 55 – 57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.11 (br s, 2H), 3.12 – 3.08 (m, 1H), 2.97 – 2.92 (m, 1H), 2.45 (quin, *J* = 7.5 Hz, 1H), 2.30 (bsr , 1H), 2.15 (dd, *J* = 13.5 Hz, 7.5 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.89 (q, *J* = 7.0 Hz, 1H), 1.76 (dd, *J* = 13.0 Hz, 6.5 Hz, 1H), 1.66 – 1.60 (m, 2H), 1.58 – 1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5 (C), 130.2 (C), 128.5 (CH), 124.9 (CH), 117.7 (CH), 117.1 (CH), 72.9 (C), 48.0 (CH), 37.8 (CH_2), 32.7 (CH_2), 31.2 (CH), 26.7 (CH_2), 26.1 (CH_2). ATR-FTIR (thin film): 3372, 3077,

2947, 2852, 1707, 1615, 1494, 1455, 1361, 1222, 1181, 1065 cm^{-1}. HRMS (ESI) m/z calcd for $C_{13}H_{17}NO$: 203.13102, found 203.13106.



3.22r

***o*-Cyclobutanol Aniline 3.22r.** The general procedure was followed by using 0.551 g of **s3.24o** (2.00 mmol), 0.559 g of Fe powder (10.00 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (10:1 – 7:1 hexanes:EtOAc) afforded the product as a brown oil (0.245 g, 50%): R_f = 0.75 (5:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.02 (br s, 1H), 2.84 – 2.80 (m, 1H), 2.68 (t, *J* = 10.0 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.90 – 1.74 (m, 5H), 1.61 – 1.48 (m, 4H), 1.40 – 1.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7 (C), 129.5 (C), 128.5 (CH), 125.0 (CH), 117.7 (CH), 117.0 (CH), 75.5 (C), 47.8 (CH), 40.2 (CH_2), 32.0 (CH), 30.0 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 22.8 (CH_2). ATR-FTIR (thin film): 3433, 3326, 3276, 3020, 2918, 2850, 1605, 1581, 1495, 1446, 1275, 1162, 984 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{22}NO$ $[M - H]^+$: 244.17014, found 244.16974.

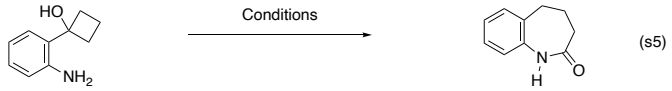


3.22s

***o*-Cyclobutanol Aniline 3.22s.** The general procedure was followed by using 0.549 g of **s3.24p** (2.00 mmol), 0.559 g of Fe powder (10.0 mmol) and 0.428 g of NH_4Cl (8.00 mmol) in 5 mL of a 1.5:1 mixture of EtOH and H_2O (0.4 M). Purification by MPLC (10:1 hexanes:EtOAc) afforded the product as a brown oil (0.312 g, 63%): R_f = 0.44 (5:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.73 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.14 (bs, 2H), 2.89 – 2.84 (m, 1H), 2.68 – 2.62 (m, 1H), 2.08 – 2.01 (m, 2H), 1.69 – 1.58 (m, 2H), 1.52 – 1.48 (m, 2H), 1.42 (quin, *J* = 7.5 Hz, 2H), 1.37 – 1.27 (m, 1H), 1.23 – 1.13 (m, 1H), 1.00 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7 (C), 129.6 (C), 128.5 (CH), 125.3 (CH), 117.6 (CH), 116.9 (CH), 76.5 (C), 44.7 (CH), 39.1 (CH_2), 32.8 (CH_2), 30.9 (CH), 27.3 (CH_2), 22.2 (CH_2), 20.8 (CH_2), 14.7 (CH_3), 14.3 (CH_3). ATR-FTIR (thin film): 3573, 3452, 2958, 2930, 2871, 1617, 1494, 1456, 1264, 931 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{25}NO$: 247.19362, found 247.19324.

III. Sc(III)-Catalyzed Benzazepine-2-one Formation

A. General Procedure for the Screening of Reaction Conditions



3.22 3.23 (s5)

To a 20 mL scintillation vial containing PIFA (1.2 – 2.0 equiv) was added 1.0 mL of TFE. Dissolution was achieved by warming the mixture while gently agitating it. Upon dissolution, the solution was cooled to room temperature. In a separate 10 mL flask equipped with a magnetic bar, *o*-cyclobutanol aniline **3.22a** (1.0 equiv), metal catalysts (2 – 20 mol %), additives (20 – 40 mol %) and 1.0 mL of TFE were added. The reaction mixture was cooled to 0 °C. After 10 mins, the pre-prepared PIFA solution was added slowly. Two hours after the addition was complete, the reaction warmed to room temperature, and the reaction progress was monitored by thin layer chromatography. Once all the starting material was consumed, the reaction mixture was diluted with CH_2Cl_2, concentrated in vacuo and purified by MPLC (5:1 – 2:1 hexanes:EtOAC) to afford the product.

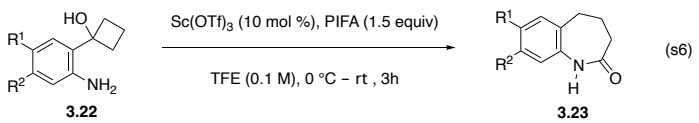
Table s3.03. Screen of catalyst, catalyst loading, additives, additives loading, oxidant and solvent.

Entry	catalyst (mol %)	additives (mol %)	oxidant (equiv)	solvent (M)	**3.23** yield, %[a]
1	...	...	PIFA (2.0)	CH_2Cl_2 (0.1)	42
2	…	…	PIFA (2.0)	TFE (0.1)	45
3	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	CH_2Cl_2 (0.1)	99
4	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	99
5	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	1,2 DCE (0.1)	77[b]
6	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	PhMe (0.1)	44[b]
7	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	1,4 dioxane (0.1)	37[b]
8	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	MeOH (0.1)	…
9	$Sc(OTf)_3$ (10)	*p*TsOH (20)	PIFA (2.0)	CH_2Cl_2 (0.1)	93
10	$Sc(OTf)_3$ (10)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	99
11	$Sc(OTf)_3$ (5)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	80
12	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (2.0)	TFE (0.1)	99

13	$Sc(OTf)_3$ (20)	*p*TsOH (40)	PIFA (1.5)	TFE (0.1)	99
14	$Sc(OTf)_3$ (20)	…	PIFA (2.0)	TFE (0.1)	99
15	$Sc(OTf)_3$ (20)	…	PIFA (1.5)	TFE (0.1)	95
16	**$Sc(OTf)_3$ (10)**	**…**	**PIFA (1.5)**	**TFE (0.1)**	**93**
17	$Sc(OTf)_3$ (5)	…	PIFA (1.5)	TFE (0.1)	80
18	$Sc(OTf)_3$ (2)	…	PIFA (1.5)	TFE (0.1)	60
19	$Sc(OTf)_3$ (20)	…	PIFA (1.5)	HFIP (0.05)	20
20	$Sc(OTf)_3$ (20)	…	PIFA (1.5)	TFE (0.05)	69
21	…	…	PIFA (1.5)	TFE (0.1)	45
22	…	…	PIFA (1.2)	TFE (0.1)	47[c]
23	$Sc(OTf)_3$ (10)	…	PIFA (1.2)	TFE (0.1)	75[c]
24	$Bi(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	42
25	$Sc(OTf)_3$ (10)	…	PIFA (1.5)	iPrOAc (0.1)	35
26	$Sc(OTf)_3$ (10)	…	PIDA (1.5)	TFE (0.1)	57
27	$Rh_2(esp)_2$ (10)	…	PIFA (1.5)	TFE (0.1)	53
28	$ScCl_3$ (10)	…	PIFA (1.5)	TFE (0.1)	39
29	$ScCl_3$ (10)	$AgNTf_2$ (30)	PIFA (1.5)	TFE (0.1)	55
30	$ScCl_3$ (10)	AgF (30)	PIFA (1.5)	TFE (0.1)	68
31	$ScCl_3$ (10)	$AgNTf_2$ (30)	PIFA (1.5)	TFE (0.1)	78
32	$Y(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	53
33	$Mg(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	63
34	$Ag(OTf)_3$ (10)	…	PIFA (1.5)	TFE (0.1)	57

[a] Isolated yield, [b] PIFA was added in one portion to the reaction mixture, [c] Reaction run overnight. PIFA = [bis(trifluoroacetoxy)iodo]benzene, PIDA = (diacetoxyiodo)benzene, TFE = 2,2,2-trifluoroethanol, 1,2 DCE = 1,2-dichloroethene, HFIP =1,1,1,3,3,3-hexafluoro-2-propanol, *p*TsOH = *p*-toluenesulfonic acid,monohydrate.

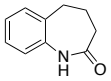
B. Optimized Procedure



(s6)

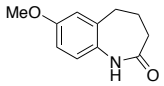
To a 20 mL scintillation vial containing PIFA (1.5 equiv) was added 1.0 mL of TFE. Dissolution was achieved by warming the mixture with a heat gun while gently agitating it. Upon dissolution, the solution was cooled to room temperature. In a separate 10 mL flask equipped with a magnetic bar, *o*-cyclobutanol aniline (1.0 equiv), $Sc(OTf)_3$ (10 mol %) and 1.0 mL of TFE were added. were weighed. This mixture was cooled to 0 °C. After 10 min, the PIFA solution was added slowly. Two hours after addition was complete, the reaction mixture warmed to room temperature, and the reaction progress was monitored using thin layer chromatography. Once all the starting material was consumed, the reaction mixture was diluted with CH_2Cl_2, concentrated in vacuo and purified by MPLC.

A. Characterization Data for Benzazepine-2-ones



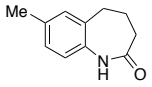
3.23a

Benzazepine-2-one 3.23a.[25] The optimized procedure was followed using 0.0326 g of aniline **3.22a (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0300 g, 93%). The spectral data of **3.23a** matched that reported by Chen and Gilman:[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.25 – 7.21 (m, 2H), 7.13 (dt, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 2.24 (quin, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5 (C), 137.7 (C), 134.4 (C), 129.9 (CH), 127.5 (CH), 125.8 (CH), 121.9 (CH), 32.8 (CH_2), 30.3 (CH_2), 28.5 (CH_2); ATR-FTIR (thin film): 3184, 3061, 2934, 1656, 1490, 1383, 1155, 787 cm^{-1}.



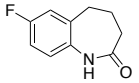
3.23b

Benzazepine-2-one 3.23b.[26] The optimized procedure was followed using 0.0388 g of aniline **3.22b (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0308 g, 80%). The spectral data of **3.23b** matched that reported by Crosby and co-workers:[26] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.75 – 6.73 (m, 2H), 3.79 (s, 3H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.0 Hz, 2H), 2.20 (quin, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5 (C), 157.3 (C), 135.9 (C), 130.9 (C), 123.1 (CH), 115.2 (CH), 112.2 (CH), 55.5 (CH_3), 32.6 (CH_2), 30.5 (CH_2), 28.3 (CH_2); ATR-FTIR (thin film): 3172, 2935, 1661, 1621, 1498, 1381, 1282, 1164, 1050, 890, 737 cm^{-1}.



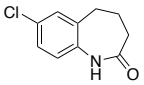
3.23c

Benzazepine-2-one 3.23c.[27] The optimized procedure was followed using 0.0354 g of aniline **3.22c (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0314 g, 90%). The spectral data of **3.23c** matched that reported by Huanming and co–workers:[27] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.04 – 7.02 (m, 2H), 6.87 (dd, J = 6.0 Hz, 3.0 Hz, 1H), 2.76 (t, J = 7.0 Hz, 2H), 2.35 – 2.29 (m, 5H), 2.21 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (C), 135.4 (C), 135.2 (C), 134.2 (C), 130.5 (CH), 127.9 (CH), 121.7 (CH), 32.7 (CH_2), 30.3 (CH_2), 28.4 (CH_2), 20.9 (CH_3). ATR-FTIR (thin film): 3178, 3041, 2933, 1656, 1504, 1386, 1160, 825 cm^{-1}.



3.23d

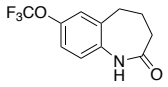
Benzazepine-2-one 3.23d.[28] The optimized procedure was followed using 0.0358 g of aniline **3.22d (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0315 g, 88%).The spectral data of **3.23d** matched that reported by Hoyt and co-workers:[28] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (br s, 1H), 6.97 – 6.92 (m, 3H), 2.79 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.0 Hz, 2H), 2.23 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5 (C), 160.2 (d, J_{CF} = 243.4 Hz, C), 136.5 (d, J_{CF} = 7.8 Hz, C), 133.9 (C), 123.4 (d, J_{CF} = 8.6 Hz, CH), 116.5 (d, J_{CF} = 21.6 Hz, CH), 114.0 (d, J_{CF} = 22.5 Hz, CH), 32.6 (CH_2), 30.4 (CH_2), 28.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ – 117.4; ATR-FTIR (thin film): 3187, 2980, 2966, 2942, 2880, 2852, 1755, 1658, 1494, 1282, 1161, 1020, 800 cm^{-1}.



3.23e

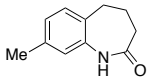
Benzazepine-2-one 3.23e.[25] The optimized procedure was followed using 0.0391 g of aniline **3.22e (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0332 g, 85%). The spectral data of **3.23e** matched that reported by Gilman and co-workers:[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 7.20 – 7.17 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 2.76 (t, J = 7.0 Hz,

2H), 2.35 (t, J = 7.5 Hz, 2H), 2.23 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6 (C), 136.6 (C), 136.0 (C), 130.7 (C), 129.7 (CH), 127.4 (CH), 123.1 (CH), 32.7 (CH_2), 30.3 (CH_2), 28.3 (CH_2). ATR-FTIR (thin film): 3168, 3063, 3044, 2939, 2865, 1674, 1456, 1438, 1169, 1034 cm^{-1}.



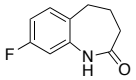
3.23f

Benzazepine-2-one 3.23f.[28] The optimized procedure was followed using 0.0490 g of aniline **3.22f (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0392 g, 80%). The spectral data of **3.23f** matched that reported by Hoyt and co-workers:[28] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.10 – 7.09 (m, 2H), 7.02 – 7.01 (m, 1H), 2.81 (t, J = 7.0 Hz, 2H), 2.38 (t, J = 7.0 Hz, 2H), 2.26 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C), 146.5 (C), 136.4 (C), 136.2 (C), 123.5 (CH), 123.0 (CH), 120.4 (q, J_{CF} = 255.1 Hz, C), 120.0 (CH), 32.6 (CH_2), 30.4 (CH_2), 28.1 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ –58.4; ATR-FTIR (thin film): 3170, 3074, 2943, 1683, 1496, 1380, 1283, 1231, 1205, 1165, 894, 814, 738 cm^{-1}.



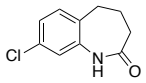
3.23g

Benzazepine-2-one 3.23g.[29] The optimized procedure was followed using 0.0350 g of aniline **3.22g (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0315 g, 90%). Benzazepinone **3.23g** was previously reported by Huisgen.[29] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.82 (s, 1H), 2.76 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.32 (s, 3H), 2.21 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6 (C), 137.7 (C), 137.4 (C), 131.2 (C), 129.6 (CH), 126.3 (CH), 122.4 (CH), 32.9 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 21.0 (CH_3). ATR-FTIR (thin film): 3172, 3077, 2940, 1684, 1662, 1512, 1383, 1159, 799 cm^{-1}.



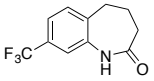
3.23h

Benzazepine-2-one 3.23h.[30] The optimized procedure was followed using 0.0358 g of aniline **3.22h (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0326 g, 78%). Benzazepinone **3.23h** was previously reported by Altenbach and co-workers:[30] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.17 (d, J = 7.5 Hz, 1H), 6.87 – 6.82 (m, 1H), 6.74 (d, J = 9.0 Hz, 1H), 2.77 (t, J = 7.0 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 2.22 (quin, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5 (C), 161.8 (d, J_{CF} = 244.3 Hz, C), 138.9 (d, J_{CF} = 9.4 Hz, C), 130.9 (d, J_{CF} = 8.8 Hz, CH), 130.0 (C), 112.4 (d, J_{CF} = 20.8 Hz, CH), 109.2 (d, J_{CF} = 23.4 Hz, CH), 32.7 (CH_2), 29.7 (CH_2), 28.5 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ –115.3; ATR-FTIR (thin film): 3187, 3102, 2951, 1663, 1605, 1507, 1483, 1260, 1161, 1151, 998, 834, 705 cm^{-1}.



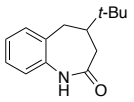
3.23i

Benzazepine-2-one 3.23i.[25] The optimized procedure was followed using 0.0391 g of aniline **3.22i (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0330 g, 84%). The spectral data of **3.23i** matched that reported by Gilman and co-workers:[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 7.15 – 7.09 (m, 2H), 7.03 (s, 1H), 2.77 (t, J = 7.0 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.23 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6 (C), 139.0 (C), 132.8 (C), 132.7 (C), 130.9 (CH), 125.7 (CH), 122.0 (CH), 32.8 (CH_2), 29.9 (CH_2), 28.3 (CH_2). ATR-FTIR (thin film): 3174, 3081, 2944, 2873, 1666, 1600, 1576, 1488, 1380, 1323, 1248, 1162, 984 cm^{-1}.



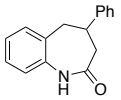
3.23j

Benzazepine-2-one 3.23j.[23] The optimized procedure was followed using 0.0458 g of aniline **3.22j (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0371 g, 81%). The spectral data of **3.23j** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (br s, 1H), 7.38 – 7.32 (m, 2H), 7.28 (s, 1H), 2.86 (t, J = 7.0 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 2.27 (quin, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7 (C), 138.6 (C), 138.3 (C), 130.4 (CH), 130.0 (q, J_{CF} = 32.4 Hz, C), 123.8 (q, J_{CF} = 270.1 Hz, C), 122.3 (q, J_{CF} = 3.9 Hz, CH), 118.8 (q, J_{CF} = 4.1 Hz, CH), 32.7 (CH_2), 30.4 (CH_2), 28.3 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.9; ATR-FTIR (thin film): 3190, 2925, 1675, 1327, 1166, 1115, 1076, 987, 828, 672 cm^{-1}.



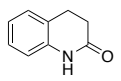
3.23k

Benzazepine-2-one 3.23k.[23] The optimized procedure was followed using 0.0435 g of aniline **3.22k (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.0330 g, 76%). The spectral data of **3.23k** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 7.23 – 7.18 (m, 2H), 7.10 – 7.07 (m, 1H), 6.98 (d, J = 7.5 Hz, 1H), 2.79 (dd, J = 7.5 Hz, 2.5 Hz, 2H), 2.43 – 2.34 (m, 2H), 2.20 (quin, J = 7.5 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9 (C), 138.0 (C), 134.0 (C), 130.8 (CH), 127.3 (CH), 125.2 (CH), 121.3 (CH), 51.5 (CH), 34.9 (CH_2), 34.4 (C), 32.4 (CH_2), 27.7 (CH_3); ATR-FTIR (thin film): 3056, 2962, 2360, 1663, 1586, 1491, 1264, 733 cm^{-1}.



3.23l

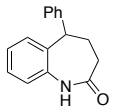
Benzazepine-2-one 3.23l.[31] The optimized procedure was followed using 0.0479 g of aniline **3.22l (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 3:1 hexanes:EtOAc) afforded the product as a brown solid (0.0461 g, 97%). The spectral data of **3.23l** matched that reported by Hudson and co-workers:[31] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.34 – 7.29 (m, 5H), 7.27 – 7.25 (m, 1H), 7.22 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 3.73 (quin, J = 7.0 Hz, 1H), 3.20 (dd, J = 14.0 Hz, 7.0 Hz, 1H), 2.91 (dd, J = 14.0 Hz, 7.0 Hz, 1H), 2.71 – 2.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6 (C), 145.0 (C), 138.0 (C), 132.9 (C), 130.6 (CH), 128.7 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 125.7 (CH), 121.9 (CH), 46.8 (CH), 39.7 (CH_2), 38.8 (CH_2). ATR-FTIR (thin film): 3195, 3059, 2918, 1664, 1584, 1492, 1380, 1158, 756 cm^{-1}.



3.23m

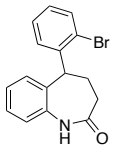
Quinolinone 3.23m.[32] The optimized procedure was followed using 0.0298 g of aniline **3.22m (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 1:1 hexanes:EtOAc) afforded the product as a brown solid (0.0265 g, 90%). The spectral data of **3.23m** matched that reported by Liu and Hu:[32] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (br s, 1H), 7.19 – 7.15 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 2.97 (t, J =

7.5 Hz, 2H), 2.65 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9 (C), 137.3 (C), 128.0 (CH), 127.5 (CH), 123.7 (C), 123.1 (CH), 115.4 (CH), 30.8 (CH_2), 25.4 (CH_2). ATR-FTIR (thin film): 3197, 2975, 2914, 1682, 1595, 1492, 1386, 1282, 1246, 1033, 817, 749 cm^{-1}.



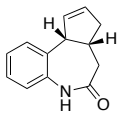
3.23n

Benzazepine-2-one 3.23n.[33] The optimized procedure was followed using 0.0479 g of aniline **3.22n (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0356 g, 75%). The spectral data of **3.23n** matched that reported by Ikeda and co-workers:[33] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (bs, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.32 – 7.26 (m, 3H), 7.21 (t, J = 7.5 Hz, 1H), 7.06 – 7.00 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 4.42 – 4.38 (m, 1H), 2.62 – 2.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2 (C), 140.7 (C), 136.9 (C), 136.6 (C), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.4 (CH), 127.2 (CH), 126.2 (CH), 122.1 (CH), 45.0 (CH), 33.7 (CH_2), 32.5 (CH_2); ATR-FTIR (thin film): 3198, 3060, 2924, 1665, 1484, 1381, 759, 735 cm^{-1}.



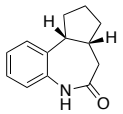
3.23o

Benzazepine-2-one 3.23o.[23] The optimized procedure was followed using 0.0479 g of aniline **3.22o (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0443 g, 70%). The spectral data of **3.23o** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.04 – 7.00 (m, 2H), 6.58 (d, J = 7.5 Hz, 1H), 4.79 – 4.76 (m, 1H), 2.55 – 2.52 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8 (C), 140.3 (C), 137.4 (C), 135.5 (C), 133.6 (CH), 129.3 (CH), 128.6 (CH), 128.0 (CH), 127.4 (CH), 126.0 (C), 125.8 (CH), 121.9 (CH), 44.3 (CH), 32.8 (CH_2), 32.7 (CH_2), (only visible signals). ATR-FTIR (thin film): 3197, 3060, 2924, 1667, 1486, 1379, 757, 738 cm^{-1}.



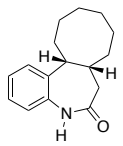
3.23p

Benzazepine-2-one 3.23p.[23] The optimized procedure was followed using 0.0403 g of aniline **3.22p (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0271g, 68%). The spectral data of **3.23p** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 7.27 – 7.22 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 5.89 – 5.88 (m, 1H), 5.77 – 5.75 (m, 1H), 3.65 (q, *J* = 9.0 Hz, 1H), 3.60 – 3.57 (m, 1H), 2.74 – 2.60 (m, 3H), 2.27 – 2.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C), 137.0 (C), 136.7 (C), 132.1 (CH), 131.3 (CH), 131.0 (CH), 127.6 (CH), 125.6 (CH), 123.1 (CH), 52.3 (CH), 45.2 (CH), 40.0 (CH_2), 37.8 (CH_2). ATR-FTIR (thin film): 3197, 3050, 2920, 1666, 1583, 1489, 1433, 1391, 1169, 752, 738 cm^{-1}.



3.23q

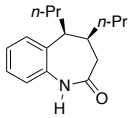
Benzazepine-2-one 3.23q.[23] The optimized procedure was followed using 0.0405 g of aniline **3.22q (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0321 g, 80%). The spectral data of **3.23q** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.23 – 7.19 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 3.27 (q, *J* = 7.5 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.51 (dd, *J* = 12.5 Hz, 5.0 Hz, 1H), 2.14 (dd, *J* = 12.5 Hz, 7.0 Hz, 1H), 2.04 – 1.96 (m, 2H), 1.94 – 1.84 (m, 2H), 1.66 – 1.59 (m, 1H), 1.57 – 1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8 (C), 137.1 (C), 136.0 (C), 129.6 (CH), 127.3 (CH), 125.4 (CH), 122.6 (CH), 46.3 (CH), 44.7 (CH), 38.4 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 25.0 (CH_2). ATR-FTIR (thin film): 3199, 3055, 2953, 1662, 1583, 1488, 1394, 1164, 756, 733 cm^{-1}.



3.23r

Benzazepine-2-one 3.23r.[23] The optimized procedure was followed using 0.0489 g of aniline **3.22r (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc)

afforded the product as a brown solid (0.0356 g, 92%). The spectral data of **3.23r** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.23 – 7.19 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 3.08 – 3.03 (m, 1H), 2.89 – 2.83 (m, 1H), 2.33 (dd, *J* = 12.5 Hz, 6.5 Hz, 1H), 2.15 (q, *J* = 12.5 Hz, 1H), 1.92 (t, *J* = 12.0 Hz, 1H), 1.88 – 1.82 (m, 1H), 1.75 – 1.58 (m, 6H), 1.53 – 1.48 (m, 3H), 1.15 – 1.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6 (C), 137.3 (C), 137.1 (C), 127.5 (CH), 126.9 (CH), 125.8 (CH), 121.8 (CH), 42.8 (CH), 42.1 (CH_2), 41.2 (CH), 29.7 (CH_2), 28.3 (CH_2), 28.2 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 25.3 (CH_2). ATR-FTIR (thin film): 3191, 2918, 2853, 2359, 1667, 1582, 1481, 1443, 1373, 757, 730 cm^{-1}.



3.23s

Benzazepine-2-one 3.23s.[23] The optimized procedure was followed using 0.050 g of aniline **3.22s (**0.20 mmol), 0.0098 g of $Sc(OTf)_3$ (10 mol %) and 0.130 g of PIFA (0.30 mmol) in 2.0 mL of TFE. Purification by MPLC (5:1 – 2:1 hexanes:EtOAc) afforded the product as a brown solid (0.0402 g, 82%). The spectral data of **3.23s** matched that reported by Driver and co-workers:[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (bs, 1H), 7.25 – 7.18 (m, 3H), 7.01 (d, *J* = 7.5 Hz, 1H), 3.07 (q, *J* = 7.0 Hz, 1H), 2.56 – 2.50 (m, 1H), 2.48 – 2.44 (m, 1H), 1.83 – 1.73 (m, 2H), 1.73 – 1.65 (m, 1H), 1.48 – 1.42 (m, 1H), 1.33 – 1.20 (m, 3H), 1.03 – 1.06 (m, 1H), 0.93 (q, *J* = 7.0 Hz, 3H), 0.90 – 0.82 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2 (C), 137.5 (C), 135.1 (C), 127.6 (CH), 126.9 (CH), 125.6 (CH), 121.9 (CH), 42.9 (CH), 41.8 (CH), 39.3 (CH_2), 31.2 (CH_2), 30.8 (CH_2), 20.8 (CH_2), 19.5 (CH_2), 14.3 (CH_3), 14.1 (CH_3). ATR-FTIR (thin film): 3196, 2955, 2929, 2870, 1665, 1378, 756 cm^{-1}.

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(15) Refer to the Supporting Information for more details.

(16) The inability of $PhI(OAc)_2$ to convert biphenyl amine to carbazole as reported by Antonchick and co-workers in ref 10b could be attributed to the instability of a reactive intermediate or the N-H carbazole to the oxidation conditions.

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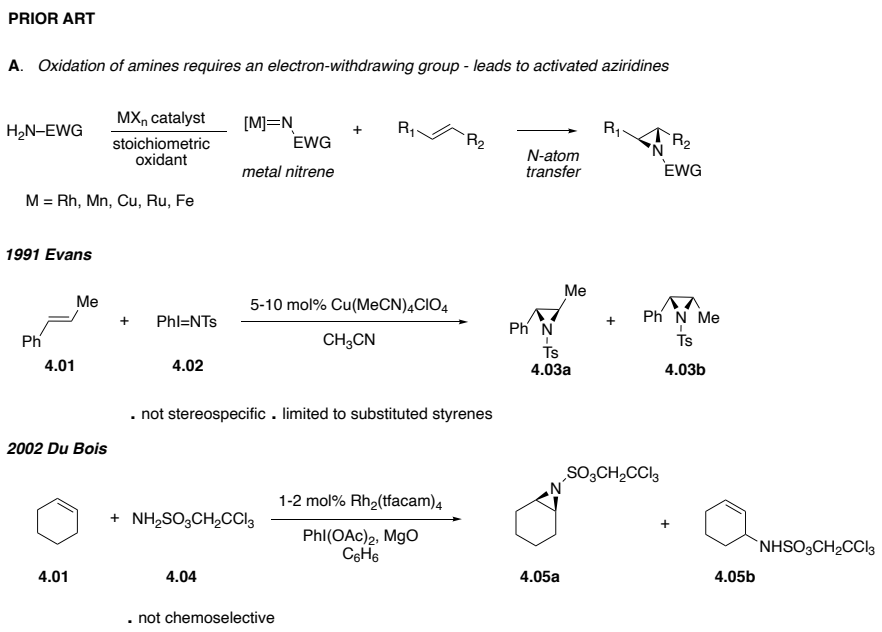
Chapter 4. Intermolecular aziridination of unactivated olefins

Aziridines are three-membered, comparably highly strained nitrogen analogues of epoxides. They are important building blocks en route to structurally complex molecules because of their versatility in a wide variety of regio- and stereoselective transformations (ring openings and expansions, as well as rearrangements).[2–6] The aziridine structural motif also appears in biologically active natural products (e.g., azinomycins and mitomycins).[1] As a result, intense research has been done for the past 25 years for the synthesis and chemistry of aziridines.

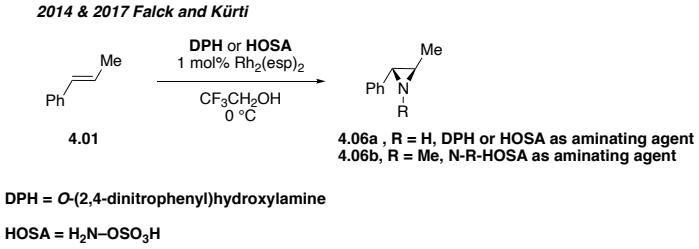
In the 1980s, researchers have shown that iminoiodinanes can be prepared by the oxidation of sulfonamides and that the nitrenes can be transferred from iminoiodinanes to transition metal complexes.[1,7–19] A report from Evans work in 1991 disclosed that the metal nitrenium species can be reacted with olefins to produce corresponding aziridines (Scheme 4.01A).[15] However, a limitation of their methodology was that the reactions were not stereospecific and were limited to substituted styrenes. This approach to nitrene formation was significantly advanced by Du Bois and co-workers in 2002,[16] with the discovery that iminoiodinanes could be generated in situ from either sulfonamides or carbamates which could form aziridines on reacting with olefins (4.01A). Though their method worked well for a wide variety of alkenes, the reaction was not chemoselective for cyclohexene and resulted in a mixture of 1:1 ratio of undesired allylic C – H amination and aziridination.

Based on the electronic properties of the nitrogen atom, aziridines can be classified as activated (for example, *N*-Ts, *N*-Ns) and unactivated (*N*-H, *N*-alkyl, *N*-aryl). For more than two decades, lot of efforts have been invested by synthetic organic chemists for the development of practical methods for the efficient preparation of aziridines. Although significant progress has been made, the majority of these methods are still limited to the synthesis of activated aziridines (Scheme 4.01)[7–9,13–18] that almost invariably require the removal of the activating groups in order to obtain the final target compounds. The need to remove these activating groups from the aziridine nitrogen atom (for example, $–SO_2R$ or $–CO_2R$) often causes additional synthetic challenges as they often use harsh reaction conditions to cleave the strong *N*-sulfonyl and *N*-acyl bonds.



Scheme 4.01. Preparation of activated aziridines

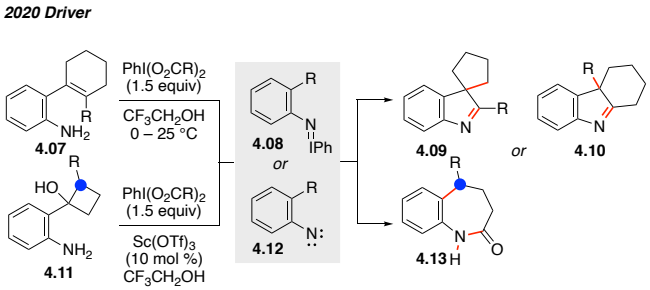
Clearly, the direct synthesis would alleviate such problems. Reports by Falck and Kürti in 2014 and 2017 have shown that a more direct and stereospecific method towards the synthesis of unprotected *N*-H and *N*-Me aziridines could be accomplished (Scheme 4.02),[10,11] which is not only a first general reported method of aziridination of unactivated olefins, but also a mild and simple approach that has wide utility in the preparation of functional-group-rich intermediates as well as the synthesis and modification of structurally complex molecules.



Scheme 4.02. Synthesis of N-H and N-Me Aziridines

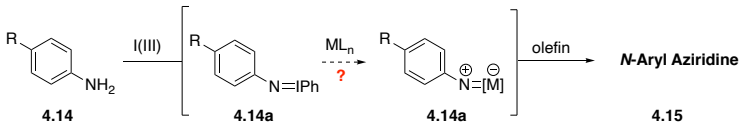
Recently we have developed a reaction to synthesize non-planar *N*-heterocycles (for example, *3H*-indoles, benzazepinones) through an oxidative strategy (Scheme 4.03).[21] We reported that *N*-aryl nitrenoid intermediates can be generated at or below room temperature from unattenuated anilines under conditions that allow them to engage in productive C−NAr bond-forming processes. The formation of these nitrenoids in the presence of suitable *ortho*-substituents triggers pericyclic reaction sequences

to access *3H*-indoles or benzazepinones through selective and stereospecific processes which are common motifs in synthetic targets and clinical candidates.



Scheme 4.03. Mild and low temperature oxidation of unactivated anilines

We were curious to see if this oxidative strategy could be extended to synthesize aziridines which are not only important heterocycles but are also difficult to handle and synthesize. Here, we report an operationally simple, inherently safe, chemoselective and stereospecific conversion of a wide range of unactivated olefins to the corresponding *N*-Aryl aziridines which are otherwise difficult to synthesize requiring multiple steps, often suffering with low yields and undesired ring open products.[22,23] Herein we report a one-step synthesis of *N*-Aryl aziridines from commercially available anilines and olefins via a rhodium-catalyzed pathway in the presence of external oxidant (Scheme 4.04).



Scheme 4.04. Intermolecular aziridination of unactivated anilines

Results and discussion.

Optimization of the reaction conditions began by taking commercially available *p*-Nitro aniline as the aniline source and *cis*-Cyclooctene as an olefin partner. We selected *cis*-cyclooctene because it has potentially two different sites for functionalization *i.e*. olefinic double bonds and allylic C–H bonds.

Table 4.01 shows the optimization conditions. In entry 1, there was no product obtained when the reaction was done with PIFA (2.0 equiv) in the presence of TFE as a solvent. In entry 2, 20 mol % of $Sc(OTf)_3$ was added, mimicking our previously developed reaction conditions, which didn't lead to the desired product. However, when a transition metal catalyst which is known to do nitrene transfer reaction like $Rh_2(OAc)_4$ was introduced, to our delight, we saw the formation of the desired product (entry 3) in 20 % yield. We rationalized the low yield of the desired aziridine due to the fact that they tend to undergo

ring opening in the presence of Lewis acids.[5,6] Since, $Sc(OTf)_3$ is a strong Lewis acid, the result was not a surprise. So, when $Sc(OTf)_3$ was removed from the reaction mixture, in the presence of $Rh_2(OAc)_4$ (10 mol %) and 3.3 equiv of MgO (to quench trifluoroacetic acid formed in the reaction mixture) , the yield of the aziridine increased to 67 % (entry 4). Entry 5 shows that other iodine(III) oxidant like PIDA also gave moderate yield of the product. Entry 6 – 12 shows that other known transition metal catalysts (Cu(I) and Cu(II)) which are well established in aziridination of olefins gave only low to moderate yields. Other Rh_2(II) catalysts were also screened (entries 13 – 15, 19, 25 & 27), which gave no yield or low yields. Other transition metals like Fe, Mn, Ir, Ni, Ru were also screened but without success. Though the yield was modest with $Rh_2(OAc)_4$, the compound was never isolated in pure form (always contaminated with the ring-opened product when column chromatography was performed in silica gel). Further, we hypothesized that since commercially available silica gel is also slightly acidic in nature, that might be a potential reason explaining the contamination of ring-opened product along with the desired aziridine. Thus, in entry 20 and 21, the reaction was performed, and product was isolated on neutral Al_2O_3 column. To our delight we found that the aziridine could in fact be isolated in its pure form in 75% and 78% yield respectively in the presence of 10 mol % of $Rh_2(OAc)_4$ or 10 mol % of $Rh_2(O_2CC_3F_7)_4$ respectively. Other solvents were also screened (entry 28 – 34), however the reaction didn't work in polar aprotic, polar protic or non-polar solvents. Thus, after careful screening, we found that the optimal conditions for our methodology was using 10 mol % of $Rh_2(OAc)_4$ or $Rh_2(O_2CC_3F_7)$, 2.0 equiv of PIFA, 3.3 equiv of MgO in 0.2M TFE using 1.0 equiv of *p*-Nitro aniline and 15.0 – 20.0 equiv of cyclooctene.

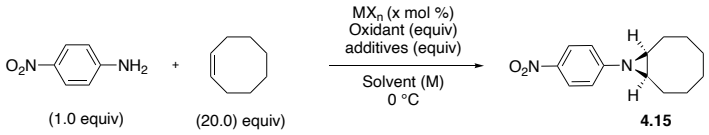


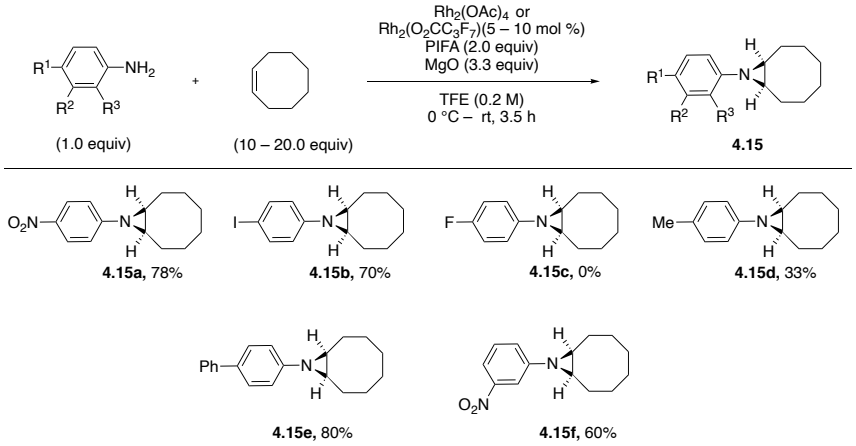
Table 4.01. Development of optimal conditions

Entry	catalyst (mol %)	additive (3.3 equiv)	oxidant (equiv)	solvent (0.2M)	**4.15** yield, %[a]
1	...	...	PIFA (2.0)	TFE	0
2	$Sc(OTf)_3$	…	PIFA (2.0)	TFE	0
3	$Sc(OTf)_3$ (20), $Rh_2(OAc)_4$ (10)	*p*TsOH[b]	PIFA (2.0)	TFE	20
4	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	TFE	67
5	$Rh_2(OAc)_4$ (10)	MgO	PIDA (2.0)	TFE	62
6	CuCl (10)	MgO	PIFA (2.0)	TFE	40
7	CuBr (10)	MgO	PIFA (2.0)	TFE	42
8	CuI (10)	MgO	PIFA (2.0)	TFE	21
9	$Cu(OTf)_2$ (10)	MgO	PIFA (2.0)	TFE	42
10	Cu(I)OTf•PhH (10)	MgO	PIFA (2.0)	TFE	40
11	Cu(I)OTf•PhMe (10)	MgO	PIFA (2.0)	TFE	48

12	$Cu(C_5H_4F_3O_2)_2$ (10)	MgO	PIFA (2.0)	TFE	30
13	$Rh_2(oct)_4$ (10)	MgO	PIFA (1.5)	TFE	0
14	$Rh_2(TFA)_4$ (10)	MgO	PIFA (2.0)	TFE	0
15	$Rh_2(TPA)_4$ (10)	MgO	PIFA (2.0)	TFE	0
16	FeOEP (10)	MgO	PIFA (2.0)	TFE	0
17	Mn(TPP)Cl (10)	MgO	PIFA (2.0)	TFE	0
18	$[Ir(OMe)(1,5\text{-cod})]_2$ (10)	MgO	PIFA (2.0)	TFE	0
19	$RhCl_3$ (10)	MgO	PIFA (2.0)	TFE	0
20	**$Rh_2(OAc)_4$ (10)**	**MgO**	**PIFA (2.0)**	**TFE**	**75[c]**
21	**$Rh_2(O_2CC_3F_7)_4$ (10)**	**MgO**	**PIFA (2.0)**	**TFE**	**78[c]**
22	FeF_3 (10)	MgO	PIFA (2.0)	TFE	0
23	$FeCl_3$ (10)	MgO	PIFA (2.0)	TFE	0
24	$Ni(cod)_2$ (10)	MgO	PIFA (2.0)	TFE	0
25	$Rh_2(cap)_4$ (10)	MgO	PIFA (2.0)	TFE	45
26	RuTPP(CO) (10)	MgO	PIFA (2.0)	TFE	0
27	$Rh_2(esp)_2$ (10)	MgO	PIFA (2.0)	TFE	40
28	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	CH_2Cl_2	0
29	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	CH_3CN	0
30	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	HFIP	0
31	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	PhH	0
32	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	PhMe	0
33	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	MeOH	0
34	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	iPrOAc	0

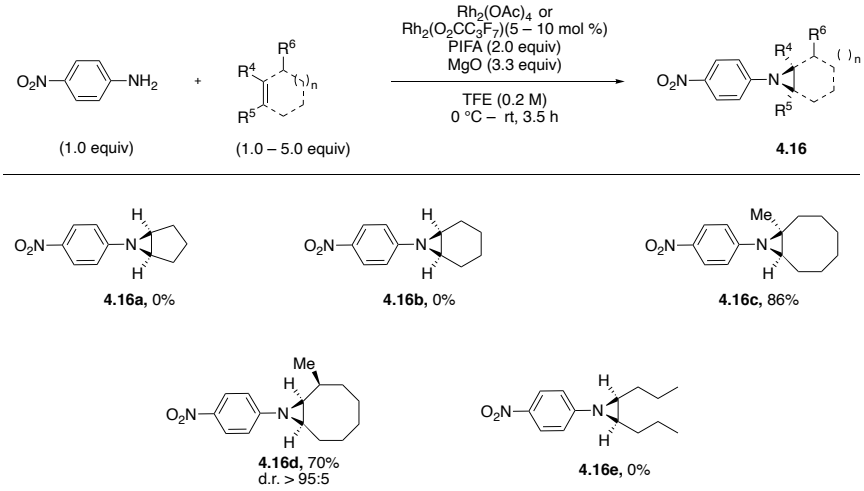
[a] Isolated yield, [b] 40 mol % of *p*-TsOH was used, [c] Isolated on neutral Al_2O_3 PIFA = [bis(trifluoroacetoxy)iodo]benzene, PIDA = (diacetoxyiodo)benzene, TFE = 2,2,2-trifluoroethanol, HFIP =1,1,1,3,3,3-hexafluoro-2-propanol, *p*TsOH = *p*-toluenesulfonic acid,monohydrate.

After careful optimization (Entry 20 and 21), we chose to study the scope of substituents on the aromatic ring (Scheme 4.05). We found that the reaction in general was good for electron withdrawing groups (**4.15a, 4.15b, 4.15e**). Unexpectedly, a *p*-fluoro-substituent was not tolerated (**4.15c**) under these reaction conditions. The reaction was not well suited in particular for electron donating groups. A low yield (33 %) was observed when *p*-methyl group was present (**4.15d**). This could be due to the fact that the methyl group contains a potentially reactive benzylic C–H which might be oxidized under these reaction conditions.[25–27] Consistent with this trend, I found that 3-nitroaniline was a competent N-atom source to provide a decent yield (60%) of the corresponding aziridine (**4.15f**).



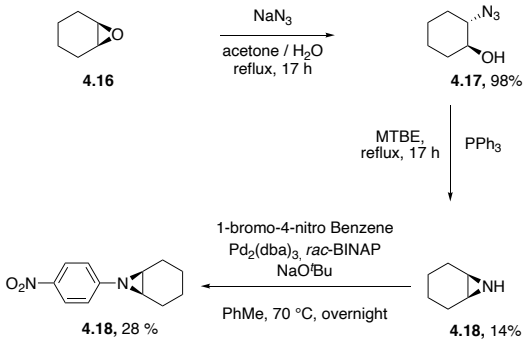
Scheme 4.05. Substrate scopes of aromatic ring

With these results, we further explored our oxidative strategy for the scope of the alkenes (Scheme 4.06). The reaction worked well for 1-substituted cyclooctene giving an yield of 86 % (**4.16c**). Stereoselectivity was demonstrated using 3-substituted cyclooctene (**4.16d**), which also gave a very good yield of the aziridine (70%) with a d.r > 95:5. When the reaction was performed with other unactivated olefins (**4.16a, 4.16b, 4.16e**), surprisingly the reaction did not give the desired aziridines and led to formation of unidentified decomposition products. Unfortunately, these conditions proved not to be general in accessing the unactivated aziridines.



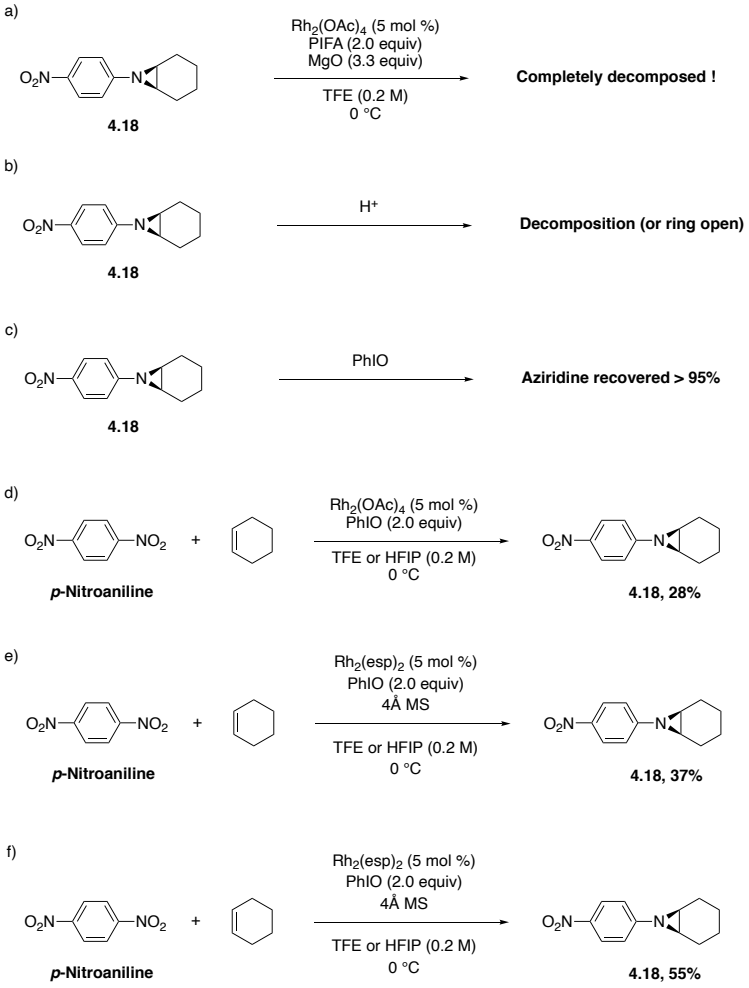
Scheme 4.06. Scope of alkenes

To rationalize these results, we hypothesized that *N*-atom transfer to unactivated olefins like cyclopentene or cyclohexene was successful, but they were getting decomposed under the reaction conditions. To test this hypothesis, we wanted to test the stability of cyclohexene- or cyclopentene aziridine to our reaction conditions. Towards this end, I independently synthesized the *N*-aryl cyclohexene aziridine according to the existing literature (Scheme 4.07).[23]



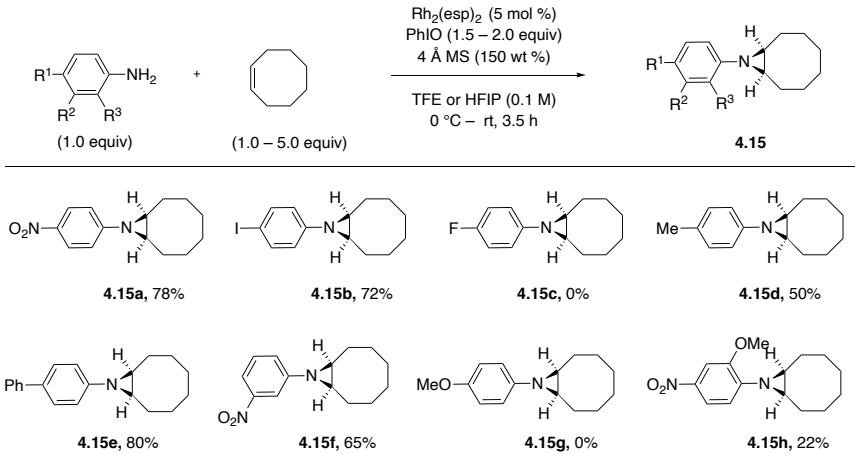
Scheme 4.07. Literature reported synthesis of *N*-aryl cyclohexene aziridine.

Once *N*-aryl cyclohexene aziridine (**4.18**) was synthesized, a series of experiments were performed (Scheme 4.08). In the first experiment (a), **4.18** was subjected to the optimal reaction conditions and found that it underwent complete decomposition and the starting aziridine could not be isolated. In the second experiment (b), when **4.18** was subjected to trifluoroacetic acid (one of the by-products formed when aniline gets oxidized by PIFA), and decomposition was observed as well. The results from these control experiments motivated us to examine other iodine(III) oxidants whose byproduct was not an acid. One such iodine(III) oxidant that does not form acid by-product is the commercially available PhIO. Iodosobenzene instead forms H_2O as a by-product which we anticipated would not open the ring and could be easily removed from the reaction mixture by adding molecular sieves. In line with our hypothesis, we found that when **4.18** was treated with PhIO that the aziridine did not decompose but could be isolated in a yield of > 95 %. Next, we were delighted to see that iodosobenzene was a competent oxidant to enable the formation of the aziridine in 28% when 4-nitroaniline was used as the N-atom precursor. When the catalyst was changed from $Rh_2(OAc)_4$ to $Rh_2(esp)_2$ and molecular sieves were introduced, the yield of the aziridine increased to 37%. Diluting the reaction mixture to 0.1 M further improved the yield to 55%.



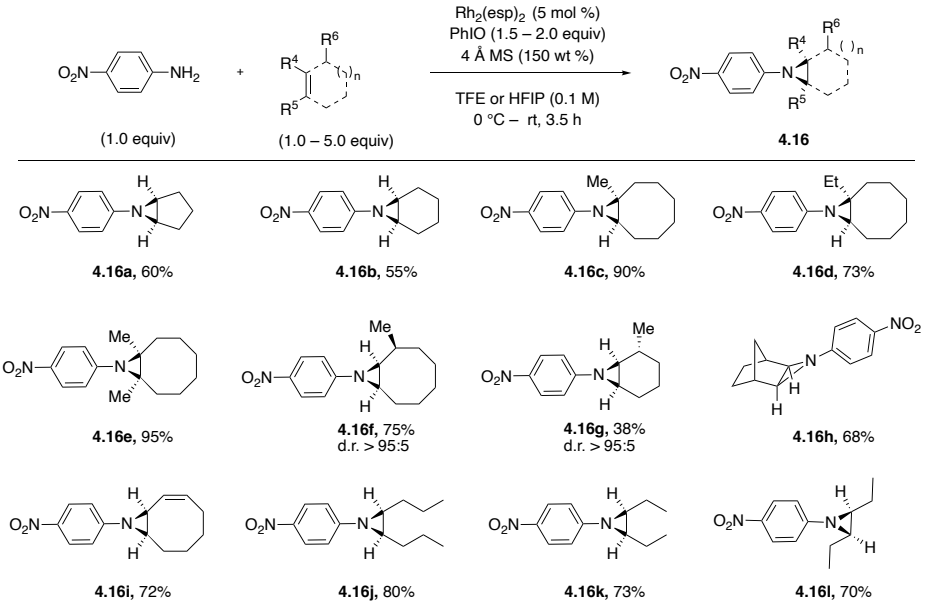
Scheme 4.08. Experiments performed to understand the reactivity of the aziridines

With the optimized conditions in hand, the substrate scope was investigated (Scheme 4.09). The reaction worked well for electron withdrawing groups on the *para*-position on the aniline to afford the *N*-aryl aziridine in good yields (72 – 80%) (**4.15a**, **4.15b**, **4.15e**). As before, *p*-fluoro (**4.15c**) was not tolerated as a substituent on the aniline. Toluidine (**4.15d**) worked better than the first-generation conditions to afford 50% of aziridine **4.15d**. Unfortunately, successful aziridination could not be achieved using *p*-OMe aniline (**4.15g**). As before, 3-nitroaniline was a potent N-atom transfer precursor to afford *N*-aryl aziridine **4.15f** in a good yield (**4.15f**). To our surprise, the detrimental effect of the methoxy group on aziridination could be overcome if a nitro-group was also present on the aniline: exposure of 2-methoxy-4-nitroaniline to reaction conditions produced aziridine **4.15h** in 22%.



Scheme 4.09. Scope of substituents on the aromatic ring

Next, the scope of the alkenes was investigated (Scheme 4.10). Cyclopentene and cyclohexene were effectively converted to aziridines **4.16a** and **4.16b** as the only *N*-atom transfer product observed. The reaction also worked well for tri- and tetrasubstituted alkenes (**4.16c**, **4.16d** and **4.16e**), showing that the reaction is not affected by steric bulk of the substituents on the alkene moiety. Stereoselectivity of the reaction was shown by the substrates **4.16f**, **4.16g** and **4.16h** which afforded only one diastereomer (identities of the correct diastereomers were found by nOe experiments and/or literature reports) exclusively. **4.16i** shows that the reaction was also well tolerated for conjugated alkenes giving rise to the product in a good yield. Substrates **4.16j**, **4.16k** and **4.16l** shows that the reaction was stereospecific. Exposure of *cis*-octene or *cis*-hexene to the reaction afforded only *cis*-substituted aziridines **4.16j** and **4.16k**. Analogously, *trans*-hexene gave only *trans* aziridine **4.16l**. These results clearly indicate that the cycloaddition reaction is concerted.



Scheme 4.10. Scope of alkenes

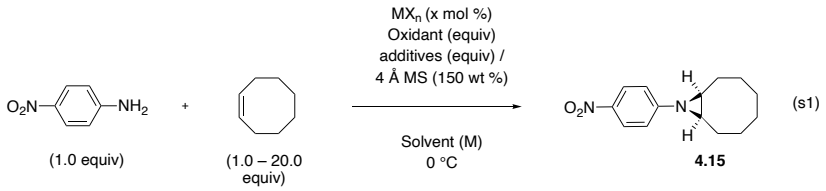
We have developed an one step, low temperature iodine(III) oxidation of unactivated anilines that generates an electrophilic *N*-aryl nitrogen species, which can be trapped intermolecularly by an olefin to form aziridines. The reaction is mild, operationally simple and use commercially available substrates. Our results prove that the oxidation of anilines does not require the presence of an *N*-electron-withdrawing group and that aziridines could be constructed by accessing the unique reactivity pattern embedded in *N*-aryl nitrene species. Our reaction also well tolerated a wide variety of substrates and is chemoselective, stereoselective and stereospecific. Future experiments will be aimed at exploring how this strategy could be used in asymmetric aziridination reactions and other C−H bond amination process.

Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed using pumps to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware that was oven dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, methanol, toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[3] Metal salts were stored in a nitrogen atmosphere dry box.

I) Rh_2(II)-catalyzed intermolecular aziridination

A. General procedure for the screening of reaction conditions



[3] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

To an oven dried 10 mL round bottomed flask equipped with a magnetic stir bar was weighed *p*-Nitro aniline (1.0 equiv), additives (3.3 equiv) and / or 4 Å MS (150 wt %) outside the glove box. The flask was then stoppered with a septum and taken inside the glove box. The metal salts (5 – 20 mol %) were weighed inside the glove box. Once it was taken outside, an Argon balloon was attached .1 mL of solvent and *cis*-Cyclooctene (1.0 – 20.0 equiv) was added and purged for 2 mins. The reaction mixture was cooled to 0 °C and stirred for 10 mins. In a separate oven dried 20 mL scintillation vial, the oxidant (1.5 – 2.0 equiv) was weighed and dissolved in 1 mL of the solvent to give a clear solution. After 10 mins, the oxidant was then added to the reaction mixture with a help of syringe pump over a period of 1.5 h – 3 h. Once the addition was complete, the reaction was stirred at 0 °C for 30 mins. The ice bath was then removed, and the reaction was stirred for an additional 30 mins (TLC taken to confirm the disappearance of the aniline). Then the solvent was removed in *vacuo* to give the crude product which was purified by MPLC on neutral Al_2O_3 using (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine.

Note: PIFA is insoluble in TFE. So, it was slightly warmed with a heat gun and swirled to dissolve to give a clear solution. Once it dissolved, it was cooled to rt before adding to the reaction mixture. PIDA is freely soluble in TFE at rt. PhIO is also freely soluble in HFIP at rt.

Table 4.01. Screening of catalyst, catalyst loading, oxidant and solvent

Entry	catalyst (mol %)	additives (3.3equiv)	oxidant (equiv)	solvent (0.2M)	**4.15** yield, %[a]
1	...	...	PIFA (2.0)	TFE	0
2	$Sc(OTf)_3$	…	PIFA (2.0)	TFE	0
3	$Sc(OTf)_3$ (20), $Rh_2(OAc)_4$ (10)	*p*TsOH[b]	PIFA (2.0)	TFE	20
4	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	TFE	67
5	$Rh_2(OAc)_4$ (10)	MgO	PIDA (2.0)	TFE	62
6	CuCl (10)	MgO	PIFA (2.0)	TFE	40
7	CuBr (10)	MgO	PIFA (2.0)	TFE	42
8	CuI (10)	MgO	PIFA (2.0)	TFE	21
9	$Cu(OTf)_2$ (10)	MgO	PIFA (2.0)	TFE	42
10	Cu(I)OTf. PhH (10)	MgO	PIFA (2.0)	TFE	40
11	Cu(I)OTf. PhMe (10)	MgO	PIFA (2.0)	TFE	48
12	$Cu(C_5H_4F_3O_2)_2$ (10)	MgO	PIFA (2.0)	TFE	30
13	$Rh_2(oct)_4$ (10)	MgO	PIFA (1.5)	TFE	0
14	$Rh_2(TFA)_4$ (10)	MgO	PIFA (2.0)	TFE	0
15	$Rh_2(TPA)_4$ (10)	MgO	PIFA (2.0)	TFE	0
16	Fe(OEP)Cl (10)	MgO	PIFA (2.0)	TFE	0
17	Mn(TPP)Cl (10)	MgO	PIFA (2.0)	TFE	0
18	$[Ir(OMe)(1,5\text{-cod})]_2$ (10)	MgO	PIFA (2.0)	TFE	0
19	$RhCl_3$ (10)	MgO	PIFA (2.0)	TFE	0
20	**$Rh_2(OAc)_4$ (10)**	**MgO**	**PIFA (2.0)**	**TFE**	**75**[c]

21	**$Rh_2(O_2CC_3F_7)_4$ (10)**	**MgO**	**PIFA (2.0)**	**TFE**	**78**[c]
22	FeF_3 (10)	MgO	PIFA (2.0)	TFE	0
23	$FeCl_3$ (10)	MgO	PIFA (2.0)	TFE	0
24	$Ni(cod)_2$ (10)	MgO	PIFA (2.0)	TFE	0
25	$Rh_2(cap)_4$ (10)	MgO	PIFA (2.0)	TFE	45
26	RuTPP(CO) (10)	MgO	PIFA (2.0)	TFE	0
27	$Rh_2(esp)_2$ (10)	MgO	PIFA (2.0)	TFE	40
28	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	CH_2Cl_2	0
29	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	CH_3CN	0
30	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	HFIP	0
31	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	PhH	0
32	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	PhMe	0
33	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	MeOH	0
34	$Rh_2(OAc)_4$ (10)	MgO	PIFA (2.0)	iPrOAc	0

[a] Isolated yield, [b] 40 mol % of *p*TsOH was used, [c] Isolated on neutral Al_2O_3 PIFA = [bis(trifluoroacetoxy)iodo]benzene, PIDA = (diacetoxyiodo)benzene, TFE = 2,2,2-trifluoroethanol, HFIP =1,1,1,3,3,3-hexafluoro-2-propanol, *p*TsOH = *p*-toluenesulfonic acid,monohydrate, TFA = trifluoroacetate, TPA = triphenylacetate, OEP = 2,3,7,8,12,13,17,18-octaethylporphyrinato, TPP = 2,3,7,8,12,13,17,18- octaethyl-21*H*, 23*H*-porphine, cod = 1,5 cyclooctadiene, cap = caprolactamate, esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid.

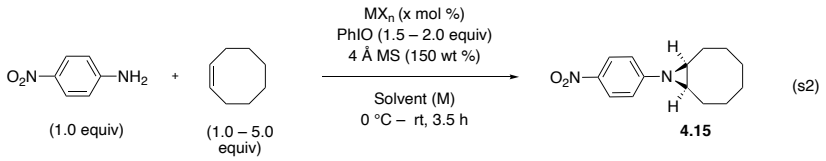
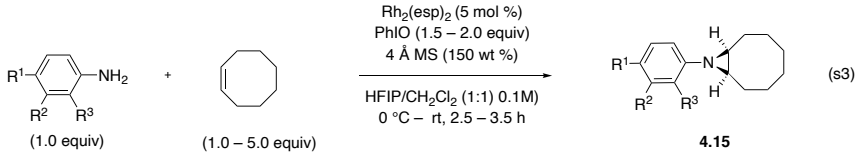


Table 4.02. Development of final optimal conditions

Entry	MX_n (x mol %)	solvent (0.1M)	**4.15** yield, %[a]
1	$Rh_2(esp)_2$ (5)	TFE	85
2	$Rh_2(esp)_2$ (5)	HFIP	90
3	$Rh_2(esp)_2$ (5)	HFIP/CH_2Cl_2(1:1)	90[b]
4	$Rh_2(esp)_2$ (5)	CH_2Cl_2	0
5	$Rh_2(esp)_2$ (5)	PhH	0
6	$Rh_2(esp)_2$ (5)	MeOH	0
7	$Rh_2(OAc)_4$ (5)	HFIP/CH_2Cl_2(1:1)	85
8	$Rh_2(cap)_4$ (5)	HFIP/CH_2Cl_2(1:1)	50
9	Fe(OEP)Cl (5)	HFIP/CH_2Cl_2(1:1)	0
10	$Cu(OTf)_2$ (5)	HFIP/CH_2Cl_2(1:1)	25
11	Co(TPP) (5)	HFIP/CH_2Cl_2(1:1)	0

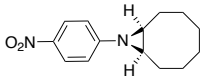
[a] Isolated yield, [b] yield doesn't diminish when the alkene was used as low as 1.0 equiv.

B. Optimized procedure



To an oven dried 10 mL round bottomed flask equipped with a magnetic stir bar was weighed *p*-Nitro aniline (1.0 equiv), and 4 Å MS (150 wt %) outside the glove box. The flask was then stoppered with a septum and taken inside the glove box. $Rh_2(esp)_2$ (5 mol %) was weighed inside the glove box. Once it was taken outside, an Argon balloon was attached. 1 mL of HFIP / CH_2Cl_2 and *cis*-Cyclooctene (1.0 –5.0 equiv) was added and purged for 2 mins. The reaction mixture was cooled to 0 °C and stirred for 10 mins. In a separate oven dried 20 mL scintillation vial, PhIO (1.5 – 2.0 equiv) was weighed and dissolved in 1 mL of HFIP / CH_2Cl_2 to give a clear solution. After 10 mins, the solution was then added to the reaction mixture with a help of syringe pump over a period of 1.5 h – 3 h. Once the addition was complete, the reaction was stirred at 0 °C for 30 mins. The ice bath was then removed, and the reaction was stirred for an additional 30 mins (TLC taken to confirm the disappearance of the aniline). Then the solvent was removed in *vacuo* to give the crude product which was purified by MPLC on neutral Al_2O_3 using (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine.

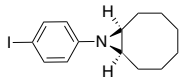
C. Characterization data for aziridines.



4.15a

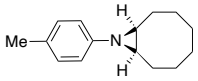
Aziridine 4.15a. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 163 µL of commercially available *cis*-Cyclooctene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine as a white solid (0.048 g, 78%). The spectral data of **4.15a** matched that reported by Cenini and co-workers.[4] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 2.31 (d, J = 13.0 Hz, 2H), 2.21 (d, J = 10.0 Hz, 2H), 1.70 – 1.66 (m, 2H), 1.63 – 1.56 (m, 2H), 1.53 – 1.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (C), 142.2 (C), 125.2 (CH), 120.2 (CH), 44.3 (CH), 27.0 (CH_2), 26.9 (CH_2), 26.4 (CH_2).

[4] Caselli, A.; Gallo, E.; Fantauzzi, S.; Morlacchi, S.; Ragaini, F.; Cenini, S. *Eur. J. Inorg. Chem.* **2008**, 19, 3009.



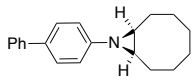
4.15b

Aziridine 4.15b. The optimized procedure was followed using 0.0547 g of commercially available *p*-Iodo aniline (0.25 mmol), 163 μL of commercially available *cis*-Cyclooctene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.137 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) afforded the aziridine **4.15b** as a brown oil (0.059 g, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 2.32 – 2.29 (m, 2H), 2.07 (d, *J* = 9.5 Hz, 2H), 1.69 – 1.57 (m, 4H), 1.53 – 1.38 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4 (C), 137.6 (CH), 122.6 (CH), 84.4 (C), 43.8 (CH), 27.1 (CH_2), 27.0 (CH_2), 26.4 (CH_2).



4.15d

Aziridine 4.15d. The optimized procedure was followed using 0.0270 g of commercially available *p*-Methyl aniline (0.25 mmol), 163 μL of commercially available *cis*-Cyclooctene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.068 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine as a brown solid (0.027 g, 50%). The spectral data of **4.15d** matched that reported by Jenkins and Cramer.[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 2.32 – 2.30 (m, 2H), 2.28 (s, 3H), 2.06 (d, *J* = 9.5 Hz, 2H), 1.70 – 1.55 (m, 4H), 1.52 – 1.37 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C), 131.1 (C), 130.0 (CH), 121.0 (CH), 43.8 (CH), 27.1 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 21.0 (CH_3).

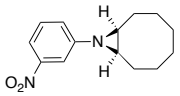


4.15e

Aziridine 4.15e. The optimized procedure was followed using 0.042 g of commercially available *p*-Phenyl aniline (0.25 mmol), 163 μL of commercially available *cis*-Cyclooctene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.105 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 –

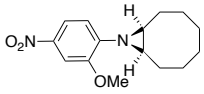
[5] Cramer, S. A.; Jenkins, D. M. *J. Am. Chem. Soc.* **2011**, *133*, 19342.

10:1 hexanes:EtOAc) to afford the aziridine as a brown solid (0.027 g, 50%). The spectral data of **4.15e** matched that reported by Che and co-workers.[6] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 2H), 7.49 – 7.47 (m, 2H), 7.45 – 7.42 (m, 2H), 7.33 – 7.30 (m, 1H), 7.07 – 7.06 (m, 2H), 2.38 – 2.35 (m, 2H), 2.18 – 2.14 (m, 2H), 1.73 – 1.61 (m, 4H), 1.58 – 1.43 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9 (C), 141.0 (C), 134.8 (C), 128.7 (CH), 127.5 (CH), 126.7 (CH), 126.6 (CH), 120.6 (CH), 43.8 (CH), 27.3 (CH_2), 27.1 (CH_2), 26.5 (CH_2).



4.15f

Aziridine 4.15f. The optimized procedure was followed using 0.0345 g of commercially available *m*-Nitro aniline (0.25 mmol), 163 μL of commercially available *cis*-Cyclooctene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.15f** as a yellow solid (0.027 g, 50%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.79 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.29 (m, 1H), 2.39 – 2.36 (m, 2H), 2.22 – 2.20 (m, 2H), 1.74 – 1.68 (m, 2H), 1.66 – 1.58 (m, 2H), 1.57 – 1.42 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5 (C), 148.7 (C), 129.5 (CH), 126.7 (CH), 116.8 (CH), 115.0 (CH), 44.3 (CH), 27.0 (CH_2), 26.9 (CH_2), 26.4 (CH_2).

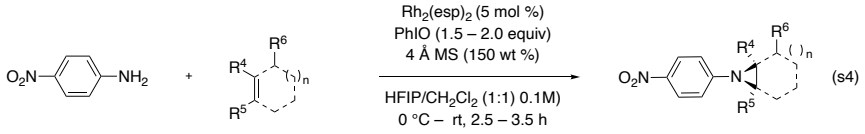


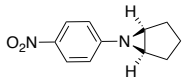
4.15h

Aziridine 4.15h. The optimized procedure was followed using 0.042 g of commercially available 2-methoxy-4-nitro aniline (0.25 mmol), 163 μL of commercially available *cis*-Cyclooctene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.105 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.15g** as a yellow solid (0.027 g, 50%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.69 (d, *J* = 2.5 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 3.97 (s, 3H), 2.41 – 2.38 (m, 2H), 2.19 –

[6] Law, S. M.; Chen, D.; Chan, S. L. F.; Guan, X.; Tsui, W. M.; Huang, J. S.; Zhu, N.; Che, C. M. *Chem. - A Eur. J.* **2014**, *20*, 11035.

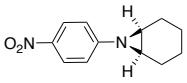
2.15 (m, 2H), 1.74 – 1.67 (m, 2H), 1.66 – 1.59 (m, 2H), 1.57 – 1.43 (m, 6H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2 (C), 150.7 (C), 142.6 (C), 119.2 (CH), 117.4 (CH), 105.9 (CH), 56.1 (CH_3), 44.8 (CH), 26.9 (CH_2), 26.6 (CH_2), 26.5 (CH_2).





4.16a

Aziridine 4.16a. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 110 μL of commercially available Cyclopentene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16a** as a yellow solid (0.031 g, 60%). The spectral data of **4.16a** matched that reported by Cenini and co-workers.[7] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 2.90 (s, 2H), 2.13 – 2.09 (m, 2H), 1.73 – 1.65 (m, 3H), 1.28 – 1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1 (C), 142.0 (C), 125.2 (CH), 120.3 (CH), 45.9 (CH), 27.1 (CH_2), 20.5 (CH_2).



4.16b

Aziridine 4.16b. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 127 μL of commercially available Cyclohexene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16b** as a yellow solid (0.030 g, 55%). The spectral data of **4.16b** matched that reported by Sriraghavan and Ramakrishnan.[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 2.43 (s, 2H), 2.08 – 2.03 (m, 2H), 1.95 – 1.92 (m, 2H), 1.56 – 1.47 (m, 2H), 1.36 – 1.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1 (C), 142.2 (C), 125.1 (CH), 120.3 (CH), 39.5 (CH), 24.3 (CH_2), 20.1 (CH_2).

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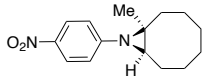
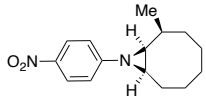
[7] Caselli, A.; Gallo, E.; Fantauzzi, S.; Morlacchi, S.; Ragaini, F.; Cenini, S. *Eur. J. Inorg. Chem.* **2008**, 19, 3009.

[8] Sriraghavan, K.; Ramakrishnan, V. T. *Synth. Commun.* **2001**, *31*, 1105.



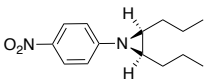
4.16c

Aziridine 4.16c. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 192 μL of *Z*-1-Methylcyclooctene (1.25 mmol),[9] 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16c** as a yellow solid (0.059 g, 90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 2.31 (dd, *J* = 14.0 Hz, 2.5 Hz, 1H), 2.04 – 1.99 (m, 2H), 1.69 – 1.66 (m, 1H), 1.59 – 1.42 (m, 9H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9 (C), 141.9 (C), 125.1 (CH), 120.2 (CH), 50.5 (CH), 46.4 (C), 33.4 (CH_2), 27.9 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 19.1 (CH_3).



4.16d

Aziridine 4.16d. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 192 μL of 3-Methylcyclooctene (1.25 mmol),[10] 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16d** as a yellow solid (0.049 g, 75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 2.38 – 2.35 (m, 1H), 2.28 – 2.25 (m, 1H), 1.92 – 1.89 (m, 1H), 1.73 – 1.66 (m, 2H), 1.65 – 1.58 (m, 3H), 1.48 – 1.42 (m, 2H), 1.38 – 1.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (C), 142.3 (C), 125.2 (CH), 120.2 (CH), 50.6 (CH), 45.2 (CH), 35.9 (CH_2), 31.6 (CH), 28.3 (CH_2), 27.2 (CH_2), 26.7 (CH_2), 26.2 (CH), 21.3 (CH_3).

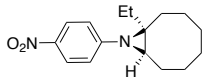


4.16e

[9] Adam, W.; Stegmann, V. R. *J. Am. Chem. Soc.* **2002**, *124*, 3600.

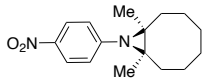
[10] Kobayashi, S.; Pitet, L. M.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2011**, *133*, 5794.

Aziridine 4.16e. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 200 μL of commercially available *cis*-4-octene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16e** as a yellow solid (0.050 g, 80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 2.24 – 2.23 (m, 2H), 1.67 – 1.55 (m, 8H), 1.07 – 1.04 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (C), 142.4 (C), 125.2 (CH), 120.2 (CH), 45.4 (CH), 30.4 (CH_2), 21.5 (CH_2), 14.2 (CH_3).



4.16f

Aziridine 4.16f. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 203 μL of 1-Ethylcyclooctene (1.25 mmol).[11] 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16f** as a yellow solid (0.050 g, 73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.5 Hz, 2H), 2.28 – 2.17 (m, 3H), 1.98 (sextet, *J* = 7.5 Hz, 1H), 1.71 – 1.65 (m, 1H), 1.60 – 1.47 (m, 5H), 1.46 – 1.39 (m, 2H), 1.30 – 1.15 (m, 3H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7 (C), 141.4 (C), 125.1 (CH), 120.0 (CH), 49.8 (C), 48.1 (CH), 28.0 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 9.6 (CH_3).



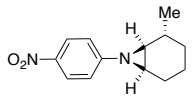
4.16g

Aziridine 4.16g. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 0.173g of 1,2-dimethylcyclooctene (1.25 mmol),[12] 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16g** as a yellow solid (0.066 g, 95%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J*

[11] Einaru, S.; Shitamichi, K.; Nagano, T.; Matsumoto, A.; Asano, K.; Matsubara, S. *Angew. Chemie - Int. Ed.* **2018**, *57*, 13863.

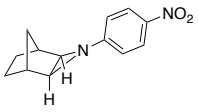
[12] De Orbe, M. E.; Amenós, L.; Kirillova, M. S.; Wang, Y.; López-Carrillo, V.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2017**, *139*, 10302.

= 9.0 Hz, 2H), 2.06 – 2.03 (m, 2H), 1.58 (bs, 4H), 1.51 – 1.39 (m, 6H), 1,24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0 (C), 140.8 (C), 125.2 (CH), 119.5 (CH), 48.2 (C), 33.9 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 17.0 (CH_3).



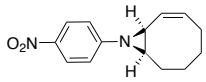
4.16h

Aziridine 4.16h. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 151 μL of commercially available 3-Methylcyclohexene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16h** as a yellow solid (0.022 g, 38%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 2.45 – 2.44 (m, 1H), 2.15 – 2.08 (m, 3H), 1.80 – 1.74 (m, 1H), 1.69 – 1.65 (m, 1H), 1.49 – 1.45 (m, 1H), 1.43 – 1.36 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.93 – 0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (C), 142.2 (C), 125.2 (CH), 120.3 (CH), 45.2 (CH), 40.3 (CH), 29.9 (CH_2), 29.4 (CH), 24.6 (CH_2), 20.5 (CH_3), 18.0 (CH_2).



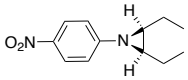
4.16i

Aziridine 4.16i. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 0.118 g of commercially available Norbornene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16i** as a yellow solid (0.039 g, 68%) (*exo* diastereomer). The spectral data of **4.16b** matched that reported by Hill and Zalkow. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 2.59 (s, 2H), 2.41 (s, 2H), 1.53 – 1.51 (m, 3H), 1.25 – 1.23 (m, 2H), 0.90 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6 (C), 141.7 (C), 125.2 (CH), 120.5 (CH), 42.0 (CH), 36.3 (CH), 29.0 (CH_2), 26.1 (CH_2).



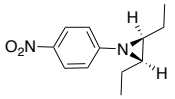
4.16j

Aziridine 4.16j. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 0.118 g of commercially available 1,3-Cyclooctadiene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16j** as a yellow solid (0.044 g, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 5.87 – 5.82 (m, 1H), 5.70 (d, *J* = 11.0 Hz, 1H), 2.86 (d, *J* = 6.5 Hz, 1H), 2.46 – 2.42 (m, 1H), 2.37 – 2.32 (m, 1H), 2.30 – 2.24 (m, 1H), 2.08 – 2.02 (m, 1H), 1.86 – 1.75 (m, 2H), 1.69 – 1.62 (m, 1H), 1.57 – 1.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 ©, 142.6 ©, 135.3 (CH), 125.2 (CH), 122.8 (CH), 120.4 (CH), 47.4 (CH), 42.5 (CH), 28.9 (CH_2), 27.9 (CH_2), 27.1 (CH_2), 25.9 (CH_2).



4.16k

Aziridine 4.16k. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 0.105 g of commercially available *cis*-3-Hexene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by MPLC on neutral Al_2O_3 (20:1 – 10:1 hexanes:EtOAc) to afford the aziridine **4.16k** as a yellow solid (0.040 g, 73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 2.21 – 2.17 (m, 2H), 1.69 – 1.58 (m, 4H), 1.19 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 ©, 142.4 ©, 125.2 (CH), 120.2 (CH), 47.1 (CH), 21.4 (CH_2), 12.3 (CH_3).



4.16l

Aziridine 4.16l. The optimized procedure was followed using 0.0345 g of commercially available *p*-Nitro aniline (0.25 mmol), 0.105 g of commercially available *trans*-3-Hexene (1.25 mmol), 0.0095 g of $Rh_2(esp)_2$ (5 mol %), 0.087 g of 4 Å MS (150 wt %) and 0.161 g of PhIO (0.50 mmol) in 2.50 mL of HFIP / CH_2Cl_2. Purification by preparative TLC on neutral Al_2O_3 (10:1 hexanes:EtOAc) afforded the aziridine **4.16l** as a dark brown oil (0.039 g, 70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* =

8.5 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 2.16 (t, J = 5.5 Hz, 2H), 1.77 – 1.72 (m, 2H), 1.17 (septet, J = 7.0 Hz, 2H), 1.07 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8 (C), 142.2 (C), 125.1 (CH), 120.4 (CH), 47.2 (CH), 24.4 (CH_2), 11.7 (CH_3).

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Chapter 5. Synthesis of bioactive *N*-heterocyclic chemical probes (NAMPT inhibitors for the treatment of pulmonary arterial hypertension and NAMPT activators)

Part A: NAMPT Inhibitors

Pulmonary arterial hypertension (PAH) is a devastating disease that is caused by the changes in the function and structure of pulmonary arteries which leads to increased pulmonary arterial pressure leading to right ventricular (RV) failure and death.[1] Due to vascular remodeling of the pulmonary arterial cells, it leads to increase in pulmonary vascular resistance and pulmonary arterial pressure.[1] The ratio of PAH is 2:1 in females: males and most of the affected females range between the age of 30 and 60. Approximately 500 to 1000 new cases of PAH are diagnosed each year in the United States. Symptoms include shortness of breath, tiredness, chest pain, swelling of the legs, fast heartbeat, pulmonary artery smooth muscle cell (PASMC) and pulmonary artery endothelial cell (PAEC) proliferation and apoptosis resistance.[2,3] There is no current cure for PAH, and once diagnosed, the median survival is three years. Although there has been a lot of important progress in recent years, the precise underlying cause of pulmonary vascular remodeling still continues to evolve, and thus the discovery of potential therapeutic targets that attenuate pulmonary vascular remodeling is of considerable interest.

The current treatment of PAH is vasodilators such as with prostacyclin and thromboxane A_2 metabolites, endothelin-1 receptor antagonists (ambrisentan), nitric oxide, phosphodiesterase-5 inhibitors (e.g., tadalafil, sildenafil citrate, and bosentan), prostaglandin I_2 agonists (e.g., epoprostenol sodium and treprostinil sodium), guanylate cyclase stimulators (e.g., riociguat).[4] However, they address only the side effect of the disease, rather than its underlying cause of vascular remodeling. Further, these molecules can have potential toxicity, solubility and stability issues.[5,6] Thus, there is a significant need to develop medicines which are safe and effective for the treatment of PAH.

Nicotinamide phosphoribosyl transferase (NAMPT), originally identified as pre–B cell colony enhancing factor or visfatin,[7–12] is the rate-limiting enzyme that catalyzes the first step in the biosynthesis of NAD^+ from nicotinamide (Fig. 5.01).[13,13]

[13] Fig. 5.01 has been drawn inspired from Reference # 13.

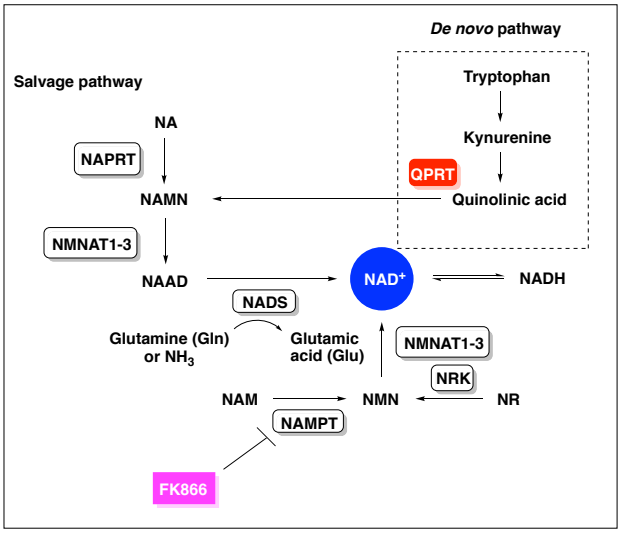


Fig.5.01 NAD+ salvage pathway

Recent studies have shown that NAD+ synthesis mediated by NAMPT in cancer cells plays a very important role in several physiological processes such as metabolism, survival, generation of energy, cell death, repair of DNA and inflammation.[12,8,14] In several forms of cancer like breast, colorectal, gastric, lung, prostate, NAMPT is overexpressed. Not only that, its expression also appears to be related with tumor progression.[15–17] At the pathological level, NAMPT fosters inflammatory responses by increasing inflammatory cell survival and increasing proinflammatory production of cytokine.[10,1] NAMPT also helps in endothelial cell survival and angiogenic activity, as well as smooth muscle cell survival.[18–20] Thus, it was believed that NAMPT may play an important role in promoting pulmonary vascular remodeling during pulmonary hypertension (PH) development and that inhibition of NAMPT could attenuate experimental PH.

For example, FK866 (APO866) and CHS-828 (Fig. 5.02), shown below are small molecule inhibitors of NAMPT[21,22] that were found to both reverse and prevent vascular remodeling caused by PAH in rat models. These compounds, however, do not possess characteristics that would allow for entereal or airway administration required for the chronic treatment of PAH. Further, these compounds are associated with thrombocytopenia[22] , retinopathy, degeneration and loss of the photoreceptor in outer nuclear layers of the retina in the rat.[5]The authors found that among tissues that were examined (retina, liver, brain, bone marrow, testes, heart, jejunum and spleen), mRNA expression was highest for NAPRT1, intermediate for NAMPT, and least for NMNATs. In the retina, however, NAMPT expression was higher than NAPRT1, as a result of which FK866 binds to the tissues in retina causing severe toxicity. Thus, the development of safe and effective therapeutics that inhibit NAMPT would be desirable in the treatment of PAH.

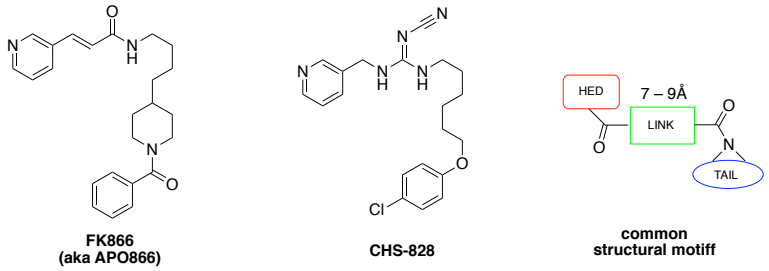


Fig.5.02 Small molecule NAMPT inhibitors

CAMD was performed to determine the general attributes of NAMPT inhibitors. The important interactions were as follows:[23] pyridine moiety of FK866 lies between the Phe193 from one chain of NAMPT and Tyr18' from the other, showing π-stacking interactions. A hydrogen bond was mediated by crystallographic water between the amide nitrogen of FK866 and Asp219, Ser241 and Val242 of NAMPT. FK866 also forms a hydrogen bond between Ser275 and the amide oxygen. In the hydrophobic area, FK866 shows interactions with Arg349. CAMD of NAMPT inhibitors reveal that their structure mostly consists of a 3-pyridyl HED and a *N*-heterocyclic TAIL connected by a LINKER of 7 – 9 Å (Fig. 5.02).[14] CAMD investigations were thus validated by the synthesis of RARI049 (Fig. 3).

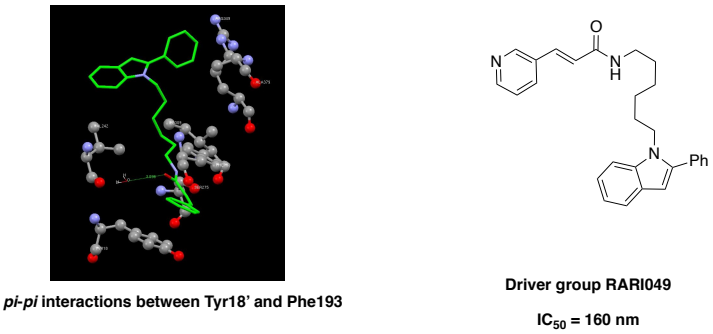


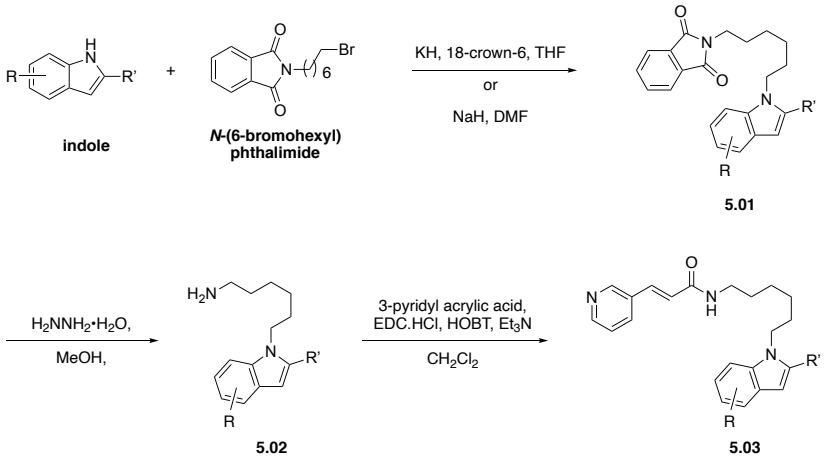
Fig. 5.03 CAMD of NAMPT inhibitors

Based on the initial results, we developed a strategy to synthesize a series (focused library) of analogs to improve inhibition of NAMPT, potential toxicity and water solubility. The synthetic route has been shown below.

Method A (Scheme 5.04). In this method, the indole (which is either commercially available or made by known existing literature methods) were alkylated with KH and crown ether, or alternatively NaH, to form a desired *N*-(6-indolehexyl)-

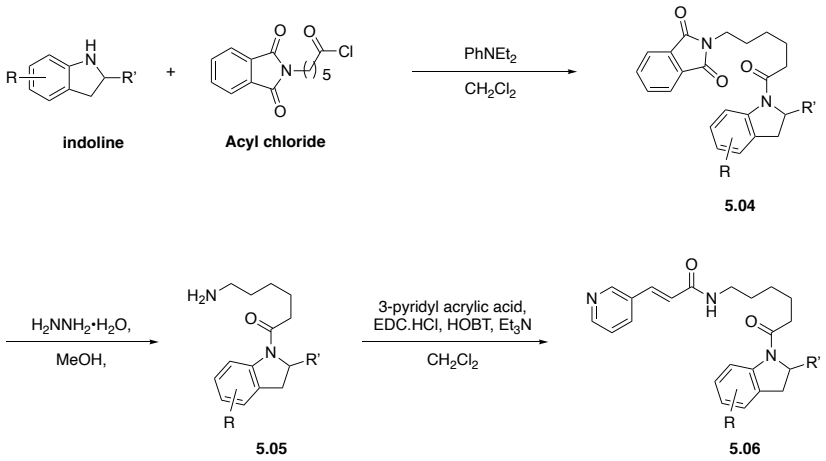
[14] CAMD was performed by Emma Mendonca (Petukhov group) at UIC college of pharmacy

phthalimide. The phthalimide group was then deprotected to form the intermediate with a free amine group. The amine then can be reacted with (*E*)-(pyridine-3-yl) acrylic acid to form the RARI analogues.



Scheme 5.04. General procedure of synthesizing RARI analogues

Method B (Scheme 5.05). In this method, the indoline (which is either commercially available or made by known existing literature methods) were acylated with an organic base to form a desired *N*-(6-indolinoylhexyl)-phthalimide. The phthalimide group was then deprotected to form the intermediate with a free amine group. The amine then can be reacted with (*E*)-(pyridine-3-yl) acrylic acid to form the RARI analogues.



Scheme 5.05. General procedure of synthesizing RARI analogues

Once the RARI analogues were synthesized, their activity towards NAMPT inhibition were also studied (Fig. 5.06).[15]

[15] These studies were done by Dr. Kiiara Ratia (UIC college of pharmacy)

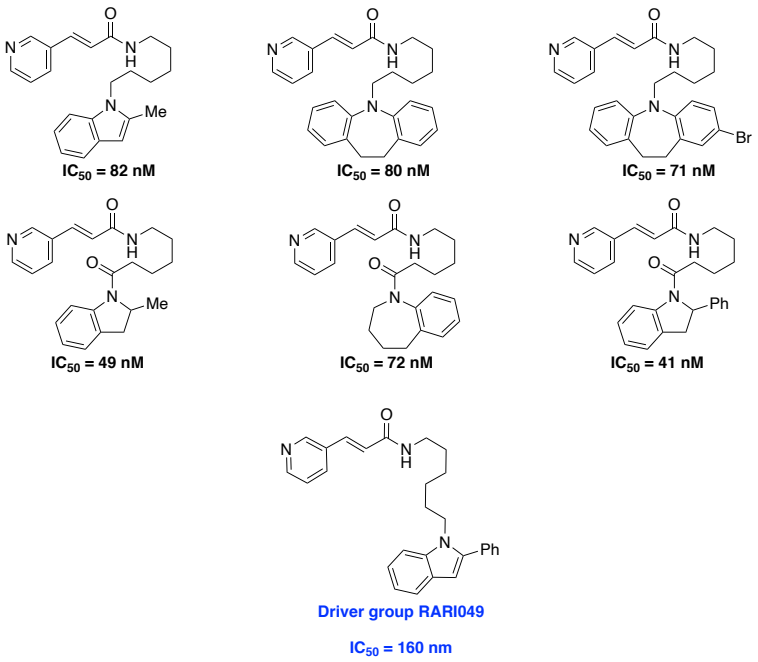


Fig. 5.06. Activity towards NAMPT inhibition

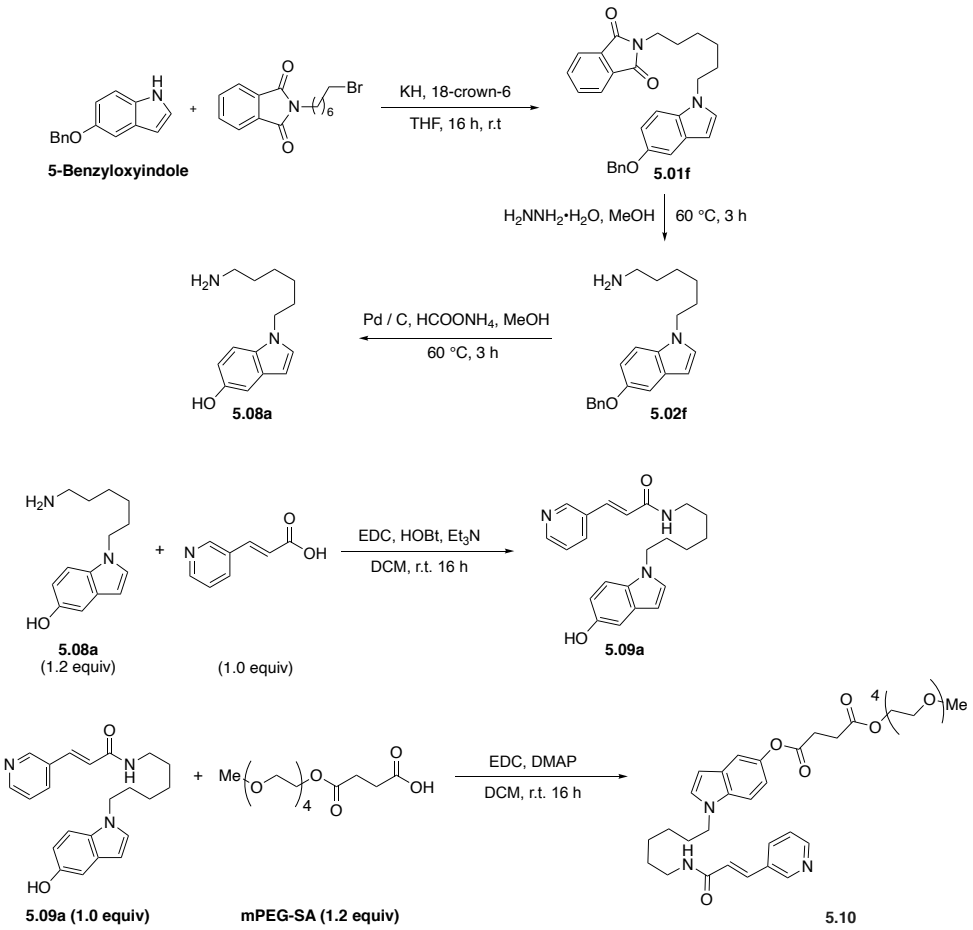
It was found that most of these analogues were much potent than the lead compounds. There was although one problem with the lead compound (RARI049). It had poor water solubility which limits its incorporation as an effective drug. Thus, the solubility issues were solved by two common techniques used in pharmaceutical industries: a) salt formation, b) PEGylation.

Poly(ethylene glycol), PEG, is a polymer which has repeating ethylene oxide units.[24] Since, it is nontoxic, non-immunogenic, non-antigenic, and amphiphilic, FDA has approved PEG for human oral, intravenous and dermal pharmaceutical applications.[25] Because of these properties, PEGylated drugs play an important role in drug delivery, a strategy known as PEGylation.

Most of the commercially available PEGylated pharmaceuticals contains methoxy poly(ethylene glycol) or mPEG units. To date, ten PEGylated proteins, antibody fragments, and oligonucleotides have been approved by FDA which are available on the market.[26] This strategy has thus been extended to small molecules, especially the antitumor agents, which often suffer with problems such as low solubility, high toxicity, fast excretion or untargeted biodistribution.[27–29]

Consequently, I developed a PEGylation strategy to one of our RARI analogue to determine if the resulting compounds would exhibit improved water solubility and maintain NAMPT inhibition (Fig. 5.08). Towards this end, mPEG was reacted with an appropriate anhydride to form the corresponding mPEG-acid. Parallelly, RARI analogue with a free -OH group was synthesized. Then, mPEG-acid and the analogue were subjected to standard esterification reaction conditions to form the PEGylated RARI analogue (Scheme 5.07). The synthesis began with commercially available 5-Benzyloxyindole which reacted with phthalimide protected haloamine to form **5.01f.** The phthalimide group was then removed by hydrazine to form **5.02f**. Then the benzyl group was removed by hydrogenation to form **5.08a**. **5.08a** was then coupled with 3-Pyridine acrylic acid to

form RARI analogue **5.09a** with a free 5-OH group. Then this analogue was treated with **mPEG-SA** to form the PEGylated RARI analogue **5.10.** After it was synthesized, both the RARI analogue and the PEGylated RARI analogue were then tested for activity towards NAMPT inhibition (Fig. 5.09). The results show that the PEGylated RARI analogue has much better solubility as compared to the RARI analogue.



Scheme 5.07. Synthesis of the PEGylated RARI analogue

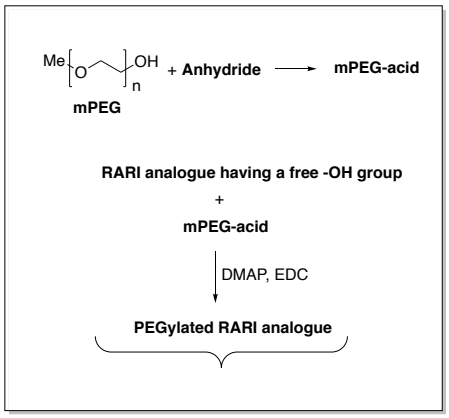


Fig. 5.08. PEGylation strategy

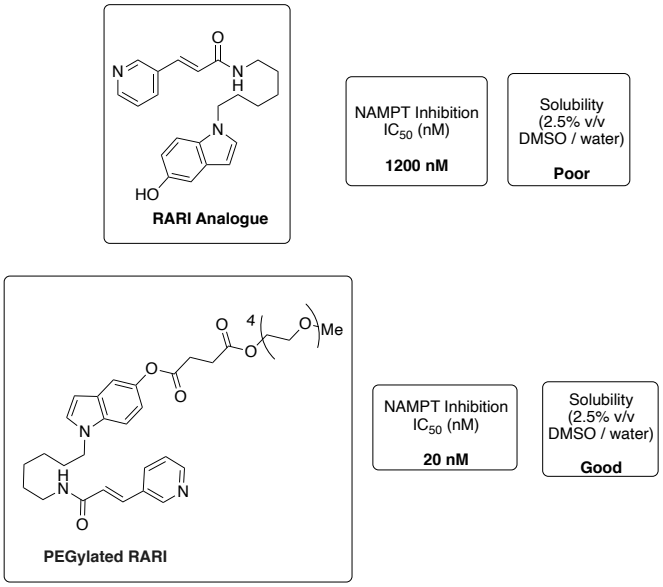


Fig. 5.09. Comparison between the RARI and the PEGylated RARI analogue

Thus, in conclusion, we were not only successful in synthesizing a large number of inhibitors which showed potency towards NAMPT inhibition, but also successful in solving the usual problems like low solubility. The future direction of the project is to reduce the toxicity whose studies are still ongoing at present.

B. NAMPT Activators[30,31]

Regulation of the concentration of NAD+ is critical across a diverse array of cellular processes that concern human health and disease. [18] Seminal discoveries showing NAD+ as a co-substrate for sirtuins and poly-ADP-ribose polymerases[32,33] have diminished the long-standing focus on NAD^+ as a redox enzyme co-factor. These results show that concentration of NAD+ in addition to cellular processes like cell signaling, DNA repair, cell division, and epigenetics is also important in other roles. One such study has shown that increased levels of NAD+ were linked to healthy aging processes.[34] Thus, there is keen interest in pharmacological and nutraceutical strategies to increase intracellular NAD+ levels.[35,36]

Intracellular NAD+ is decreased due to activity of enzymes catalyzed by sirtuins and PARPs. Therefore, a cellular biosynthetic pathway to preserve the levels of NAD+ is crucial.[37] In mammalian cells, the most important contributor to NAD+ synthesis is the nicotinamide (NAM) salvage pathway which involves sequential actions of nicotinamide phosphoribosyl transferase (NAMPT) and NMN adenylyltransferases (NMNAT1-3).[38]

NAMPT plays an important role in the debilitating effects of stroke.[31] Stroke is the second most common cause of death[31,39] and the third most common cause of disability-adjusted life years (DALYs) worldwide,[39] and the leading cause of death in China,[40,41] with characteristics of high morbidity, high mortality, high disability rate, high recurrence rate and high medical expenses.[42] Of all the cases, ischemic stroke constitutes 78% of the cases and the rest are hemorrhagic stroke.[31] There is only one drug that has been approved by Food and Drug Administration which is tissue plasminogen activator (tPA). It can only treat ischemic stroke and not for hemorrhagic stroke. Although tPA has been approved, due to a narrow treatment window, contraindications and complications, only 3% - 5% stroke patients meeting certain criteria could only be treated.[31,43]

Since stroke has a complex pathophysiology, after it's onset. It may lead to a series of injury reactions eventually leading to cell death.[31,44] Though it has many implications, stroke can also mobilize the defense system of our body by improving cell survival, neurogenesis and functional recovery.[31,40] Many studies have shown the stroke injury mechanisms of excitotoxicity, oxidative and nitrosative stress, and inflammation to develop neuroprotective agents against stroke.[31,45] However, these therapeutic strategies are still in preclinical-to-clinical transition. Targeting the endogenous defense mechanisms against stroke has received recent attention and thus considered as a novel target in treating stroke.[31]

The NAMPT-NAD cycle play a very important role in strong defense system against various stresses.[31,46] Experimental and clinical studies have shown that the levels of NAMPT is regulated in people suffering with stroke and other brain injuries. NAMPT is upregulated in the in-vitro cultured neurons of oxygen-glucose deprivation (OGD) model[47] as well as the in-vivo animal stroke models.[47–49] Moreover, the blood NAMPT levels in patients with ischemic stroke,[50–53] hemorrhagic stroke,[54,55] and traumatic brain injury[56,57] are significantly increased. Thus, there is an urgent need for developing new and effective

therapies for the treatment of strokes.

A high-throughput screen of a curated 10K compound ChemDiv library identified two compounds 6.01t and 6.01t' to be potent NAMPT activators (5.10). The structure of these two hits is distinct from the two commercially available activators, P7C3 and P7C3-OMe, and offer the opportunity to investigate how these compounds function to protect NAMPT. Preliminary data reveals that making structural changes to the aryl rings changes the activity of the activators in both enzyme and cellular assays. The modular synthesis of activators 6.01t and 6.01t' (*vide infra*) make them particularly suited to modification to build on the preliminary structure activity relations, to optimize their performance, as well as to attach functional groups to enable biochemical experiments, such as bioconjugation, fluorescence and radio-labeling.

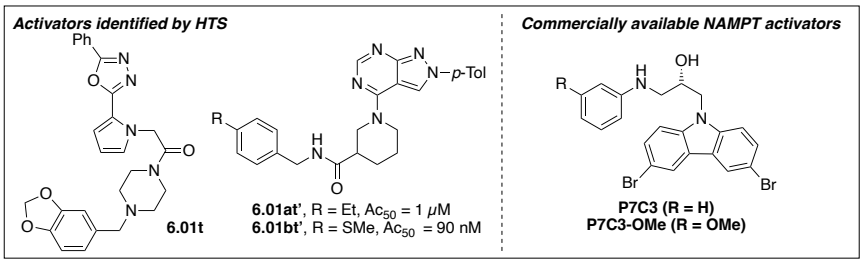


Fig 5.10. Activators identified by HTS and commercially available NAMPT activators

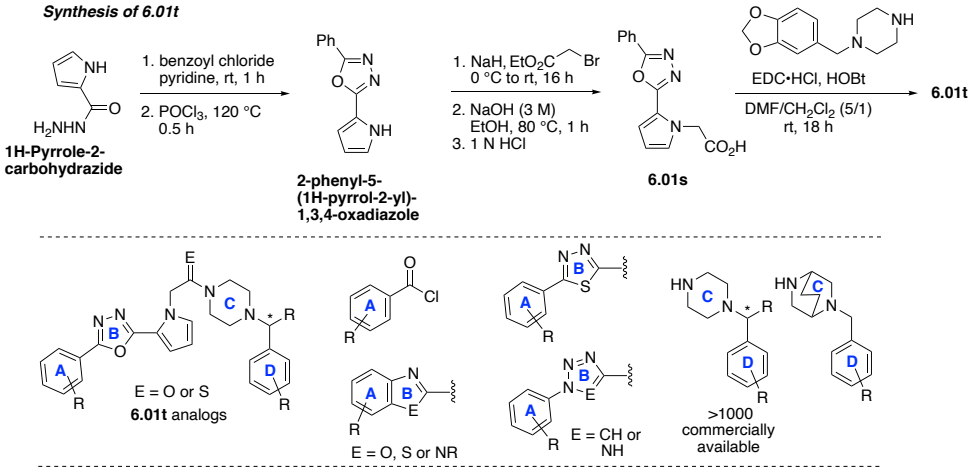


Fig 5.11. SAR investigation of NAMPT activators

Using the chemical synthesis outlined in Figure 5.11, I independently synthesized 0.0060 mmol of the activator **6.01t**. Oxazole was constructed from 2-substituted pyrrole by exposure to benzoyl chloride followed by $POCl_3$-mediated cyclization. Attachment of the piperazine fragment was accomplished by *N*-alkylation of the pyrrole with ethyl bromoacetate and hydrolysis to afford **6.01s**. An EDC-mediated amide formation with piperazine provided the activator **6.01t**.

The modular synthesis of **6.01t** provides the opportunity to modify four regions **A** – **D**. The aryl **A** ring can be modified by changing the identity of the benzoyl chloride used in the first step. The oxadiazole moiety can be readily changed to a thiadiazole by exposing the hydrazide intermediate to either P_4S_{10} or Lawesson's reagent.[16] Alternatively, triazoles or tetrazoles can synthesized from a 2-acetylene or 2-cyano substituted pyrrole;[17] the **A**- and **B**-rings can be conformationally constrained to benzoxazole or benzothiazole by reaction of pyrrole-2-carbaldehyde with 2-aminophenol or 2-aminothiophenol. The large number (>1000) of piperazine fragments (both chiral and achiral) enables systematic variation of the identity of the **D**-ring. The volume of the piperazine piece can be further modified by constraining it as a [2.2.2] bicycle. Thus, with this strategy in hand, I synthesized analogues and created a small library of NAMPT activators. (Figure 5.12).

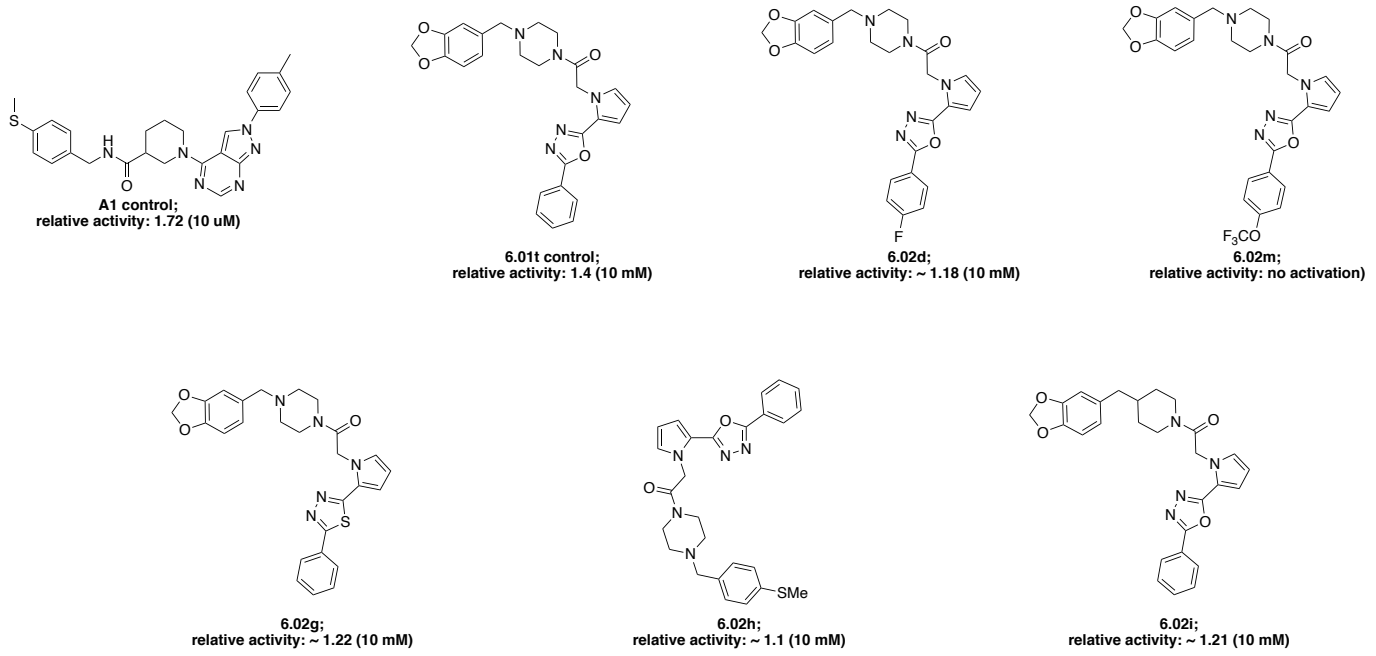


Figure 5.12. Library of NAMPT activators

These compounds were tested for the activation of NAMPT by Dr. Kiira Ratia. The activity of NAMPT was reported at 10mM concentration of the analogs in DMSO. The data shows that **6.01t** showed an activity of 1.4. **6.02d** (*p*-Fluoro) also showed activation of approximately 1.18, however the *p*-OCF_3 didn't show any activation. The thiadiazole analog (**6.02g**) also showed activation as well as **6.02h** and **6.02i**. With these results in hand, it opens the future area for the development of new NAMPT

[16] Lancelot, J. C.; Maume, D.; Robba, M. *J. Heterocycl. Chem.* **1980**, *17*, 625-629.

[17] (a) Sessler, J. L.; Cai, J.; Gong, H.-Y.; Yang, X.; Arambula, J. F.; Hay, B. P. A *J. Am. Chem. Soc.* **2010**, *132*, 14058.

(b) Avula, V. K. R.; Vallela, S.; Anireddy, J. S.; Chamarthi, N. R. *J. Heterocycl. Chem.* **2017**, *54*, 3071.

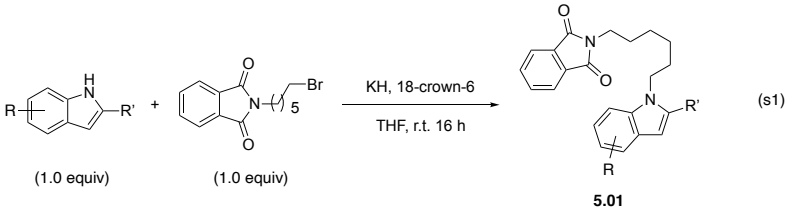
activators. Preliminary data reveals that making structural changes to the aryl rings or to the substituents on the aryl rings changes the activity of the activators in both enzyme and cellular assays. The modular synthesis of activators **A1** and **6.01t** (*vide infra*) make them particularly suited to modification to build on the preliminary structure activity relations. Thus, future studies would be directed to optimize their performance, as well as to attach functional groups to enable biochemical experiments, such as bioconjugation, fluorescence and radio-labeling.

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the d scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed using pumps to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware that was oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, methanol, toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[18] Metal salts were stored in a nitrogen atmosphere dry box.

I. Synthesis of NAMPT inhibitors.

A. Synthesis of *N*-(6-indolehexyl)-phthalimide. (Route A)

1. a) General procedure A.

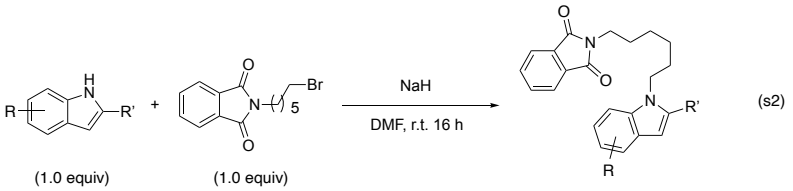


To a stirred 0.5 M solution of 18-crown-6 (1.5 equiv) and KH (1.5 equiv, 30% w/w suspension in mineral oil) in dry THF was added a 0.5 M solution of indole (1.0 equiv) in dry THF dropwise over 10 min under N_2 atmosphere. After stirring at room temperature for 30 min, a 0.5 M solution of *N*-(6-bromohexyl) phthalimide (1.2 equiv) in dry THF was added to the reaction mixture dropwise over 10 min. The reaction mixture was allowed to stir at room temperature overnight. The reactives were

[18] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

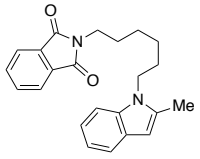
then quenched by the addition of 20 mL of water. The resulting mixture was extracted by 3 × 15 mL of EtOAc. The combined organic extracts were washed with 2 × 20 mL of water and 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the product.

2. b) General procedure B.



In a three-necked flask, equipped with a magnetic stir bar, was charged with indole (1.0 equiv). Dry DMF (3 ml/1 mmol of indole) was added under Ar atmosphere and the reaction mixture cooled to 0 °C. NaH (2.0 equiv, 60 % w/w in mineral oil) was added in a single portion and the reaction mixture stirred at 0 °C. After 10 minutes, the reaction was warmed to room temperature. After 1 h, the reaction mixture was cooled to 0 °C and *N*-(6-bromohexyl) phthalimide (2.0 equiv) dissolved in 2 mL of dry DMF was added dropwise over 10 min. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reactives were then quenched by addition of 20 mL of water. The resulting mixture was extracted with 3 × 15 mL of EtOAc. The combined organic extracts were washed with 2 × 20 mL of water and 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the product.

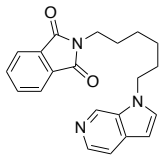
B. Characterization data for *N*-(6-indolehexyl)-phthalimides 5.01.



5.01a

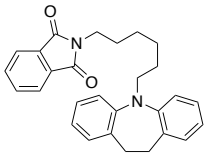
***N*-(6-Indolehexyl)-phthalimide 5.01a.** The general procedure was followed using 131.2 mg of 2-2ethylindole (1.0 mmol), 620.4 mg of *N*-(6-bromohexyl) phthalimide (2.0 mmol), 80 mg of 60 % w/w NaH in mineral oil (2.0 mmol) in total 5 mL of DMF. Purification by MPLC chromatography (10:1 hexanes:EtOAc) afforded **5.01a** as a yellow oil (54 mg, 15% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, 2H), 7.72 – 7.69 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.11 (dt, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.05 – 7.02 (m, 1H), 6.22 (s, 1H), 4.04 (t, *J* = 7.5 Hz, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.75 (quin, *J* = 7.0 Hz, 2H), 1.67 (quin, *J* = 7.0 Hz, 2H), 1.44 – 1.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (C), 136.6 (C), 136.3 (C), 133.9 (CH), 132.1 (C), 128.0 (C), 123.2 (CH), 120.3 (CH), 119.6 (CH), 119.1 (CH), 109.0 (CH), 99.9 (CH), 43.1 (CH_2), 37.8 (CH_2), 30.1 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 26.6 (CH_2), 12.8 (CH_3). ATR-FTIR (thin film): 3054, 2935, 2858,

1771, 1707, 1614, 1550, 1465, 1395, 1357, 1055, 718 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{25}N_2O_2$ $[M + H]^+$: 361.1916, found: 361.1911.



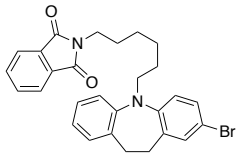
5.01b

***N*-(6-Indolehexyl)-phthalimide 5.01b.** The general procedure was followed using 118.1 mg of 6-azaindole (1.0 mmol), 620.4 mg of *N*-(6-bromohexyl) phthalimide (2.0 mmol), 80 mg of 60 % w/w NaH in mineral oil (2.0 mmol) in total 5 mL of DMF. Purification by MPLC chromatography (5:1 – 1:1 hexanes:EtOAc – 100 % EtOAc) afforded **5.01b** as a yellow oil (70 mg, 20% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.17 (d, *J* = 5.5 Hz, 1H), 7.78 – 7.75 (m, 2H), 7.66 – 7.63 (m, 2H), 7.44 (dd, *J* = 5.5 Hz, 1.0 Hz, 1H), 7.16 (d, *J* = 3.0 Hz, 1H), 6.41 (d, *J* = 3.0 Hz, 1H), 4.13 (t, *J* = 7.5 Hz, 2H), 3.60 (t, *J* = 7.0 Hz, 2H), 1.82 (quin, *J* = 3.5 Hz, 2H), 1.63 – 1.57 (m, 2H), 1.33 – 1.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (C), 138.4 (CH), 133.9 (CH), 133.2 (C), 133.0 (C), 132.8 (CH), 132.0 (C), 131.3 (CH), 123.1 (CH), 115.3 (CH), 100.5 (CH), 46.6 (CH_2), 37.7 (CH_2), 30.3 (CH_2), 28.4 (CH_2), 26.4 (CH_2), 26.4 (CH_2). ATR-FTIR (thin film): 3044, 2934, 2858, 1771, 1707, 1668, 1395, 1090, 818, 719 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_2$ $[M + H]^+$ 348.1712, found: 348.1708.



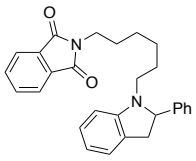
5.01c

***N*-(6-Indolehexyl)-phthalimide 5.01c.** The general procedure was followed using 195.3 mg of iminodibenzyl (1.0 mmol), 372.2 mg of *N*-(6-bromohexyl) phthalimide (1.2 mmol), 60.2 mg of 30 % w/w KH suspension in mineral oil (1.5 mmol) and 396.2 mg of 18-crown-6 (1.5 mmol) in total 6 mL of THF. Purification by MPLC chromatography (10:1 hexanes:EtOAc) afforded **5.01c** as a yellow oil (198 mg, 47% yield) as a mixture of inseparable impurities, which was taken to the next step without any further purification or characterization.



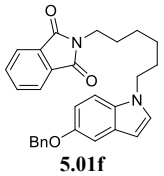
5.01d

***N*-(6-Indolehexyl)-phthalimide 5.01d.** The general procedure was followed using 274.2 mg of 2-bromo-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (1.0 mmol), 372.2 mg of *N*-(6-bromohexyl) phthalimide (1.2 mmol), 60.2 mg of 30 % w/w KH suspension in mineral oil (1.5 mmol) and 396.2 mg of 18-crown-6 (1.5 mmol) in total 6 mL of THF. Purification by MPLC chromatography (10:1 hexanes:EtOAc) afforded **5.01d** as a yellow oil (259 mg, 51% yield) as a mixture of inseparable impurities, which was taken to the next step without any further purification or characterization.



5.01e

***N*-(6-Indolehexyl)-phthalimide 5.01e.** The general procedure was followed using 195.2 mg of 2-phenylindoline (1.0 mmol), 372.2 mg of *N*-(6-bromohexyl) phthalimide (1.2 mmol), 60.2 mg of 30 % w/w KH suspension in mineral oil (1.5 mmol) and 396.2 mg of 18-crown-6 (1.5 mmol) in total 6 mL of THF. Purification by MPLC chromatography (10:1 hexanes:EtOAc) afforded **5.01e** as a yellow oil (260 mg, 61 % yield) as a mixture of inseparable impurities, which was taken to the next step without any additional purification or characterization.



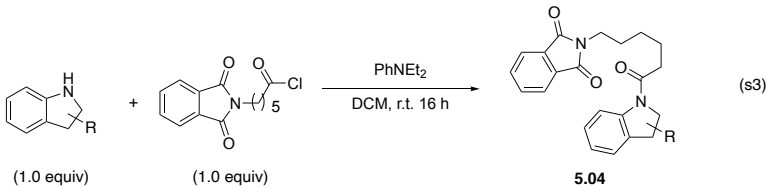
5.01f

***N*-(6-Indolehexyl)-phthalimide 5.01f.** The general procedure was followed using 447 mg of indole (2.00 mmol), 620 mg of *N*-(6-bromohexyl) phthalimide (3.00 mmol), 120 mg of 30 % w/w KH in mineral oil (3.00 mmol), 792 mg of 18-crown-6 in a total of 12 mL of THF. Purification by MPLC chromatography (1:5 EtOAc:hexanes) afforded **5.01f** as a yellow oil (842 mg, 93% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.53 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.97 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 5.07 (s, 2H), 3.95 (t, *J* = 6.8 Hz, 2H), 3.62 (t, *J* = 7.1 Hz, 2H), 1.71 (dd, *J* = 21.2, 15.0 Hz, 2H), 1.66 – 1.50 (m, 2H), 1.28 (d, *J* = 12.8 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2 (C), 153.2 (C), 138.0 (C), 133.8 (C), 132.1 (CH), 131.6 (C), 129.0 (C), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 123.0 (CH), 112.4 (CH), 110.2 (CH),

104.2 (CH), 100.7 (CH), 70.7 (CH_2), 60.3 (CH_2), 46.3 (CH_2), 37.8 (CH_2), 30.2 (CH_2), 28.5 (CH_2), 26.5 (CH_2). ATR-FTIR (thin film): 2933, 2858, 1770, 1705, 1486, 1395, 1233, 1151, 1056, 717cm^{-1}. HRMS (ESI) m/z calcd for $C_{29}H_{29}N_2O_3$ $[M + H]^+$: 453.2178, found: 453.2175.

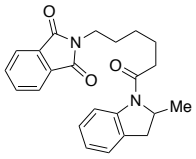
B. Synthesis of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimide. (Route B).

1. General procedure.



The synthesis of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimide **5.04** was performed following the report of Krasnov and co-workers:[19] To a stirred solution of aniline (1.0 equiv) and *N,N*-diethylaniline (1.0 equiv) in 0.2 M dry CH_2Cl_2 was added a 0.2 M solution of acid chloride (1.0 equiv) in dry CH_2Cl_2 dropwise over 10 min. After stirring at room temperature for 16 h, a 1.0 N aq soln of HCl was added to the reaction mixture. After 30 min, the reactives were diluted with 20 mL of EtOAc and washed with 2 × 20 mL of water and 20 mL of a 5% aq soln of $NaHCO_3$. The resulting organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by MPLC to afford the product.

2. **Characterization data of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimides 5.04**.

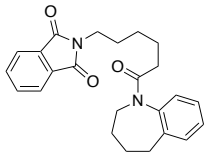


5.04a

2-(6-(Indolin-1-yl)-6-oxohexyl)phthalimide 5.04a. The general procedure was followed using 133.2 mg of 2-methylindoline (1.0 mmol), 149.2 mg of *N,N*-diethylaniline (1.0 mmol) and 279.7 mg of acid chloride (1.0 mmol) in a total 4 mL of CH_2Cl_2. Purification by MPLC chromatography (5:1 – 2:1 hexanes:EtOAc) afforded **5.04a** as a yellow oil (320 mg, 85% yield): ^1H

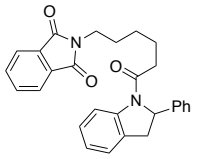
[19] Krasnov, V. P.; Gruzdev, D. A.; Chulakov, E. N.; Vigorov, A. Y.; Musiyak, V. V.; Matveeva, T. V.; Tumashov, A. A.; Levit, G. L.; Charushin, V. N. *Mendeleev Commun.* **2015**, *25*, 412.

NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.76 – 7.74 (m, 2H), 7.64 – 7.62 (m, 2H), 7.11 (t, *J* = 7.0 Hz, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 4.44 (s, 1H), 3.64 (t, *J* = 7.5 Hz, 2H), 3.36 – 3.31 (m, 1H), 2.60 – 2.35 (m, 3H), 1.77 (q, *J* = 8.0 Hz, 2H), 1.69 (quin, *J* = 7.5 Hz, 2H), 1.41 (quin, *J* = 8.0 Hz, 2H), 1.22 – 1.17 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C), 168.3 (C), 141.7 (C), 133.9 (CH), 132.1 (C), 130.2 (C), 127.4 (CH), 124.9 (CH), 123.7 (CH), 123.1 (CH), 117.9 (CH), 55.4 (CH), 37.8 (CH_2), 36.4 (CH_2), 34.7 (CH_2), 28.5 (CH_2), 26.7 (CH_2), 24.7 (CH_2), 21.9 (CH_3). ATR-FTIR (thin film): 3317, 2972, 2928, 2879, 1774, 1717, 1636, 1482, 1378, 1087, 1046, 880, 721 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$: 377.1865, found: 377.1863.



5.04b

2-(6-(Indolin-1-yl)-6-oxohexyl)phthalimide 5.04b. The general procedure was followed using 147.2 mg of 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (1.0 mmol), 149.2 mg of *N,N*-diethylaniline (1.0 mmol) and 279.7 mg of acid chloride (1.0 mmol) in a total 4 mL of CH_2Cl_2. Purification by MPLC chromatography (5:1 – 2:1 hexanes:EtOAc) afforded **5.04b** as a yellow oil (218 mg, 56% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.73 (m, 2H), 7.64 – 7.62 (m, 2H), 7.16 – 7.13 (m, 3H), 7.03 (q, *J* = 4.5 Hz, 1H), 4.63 (td, *J* = 7.0 Hz, 3.5 Hz, 1H), 3.55 (t, *J* = 7.5 Hz, 2H), 2.69 – 2.59 (m, 2H), 2.53 – 2.47 (m, 1H), 2.12 (quin, *J* = 7.5 Hz, 1H), 1.92 – 1.79 (m, 3H), 1.70 – 1.67 (m, 1H), 1.54 (sextet, *J* = 7.5 Hz, 4H), 1.34 – 1.25 (m, 1H), 1.22 – 1.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (C), 168.3 (C), 143.2 (C), 140.6 (C), 133.8 (CH), 132.1 (C), 130.1 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 123.1 (CH), 47.0 (CH_2), 37.8 (CH_2), 34.5 (CH_2), 33.9 (CH_2), 29.1 (CH_2), 28.4 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 24.9 (CH_2). ATR-FTIR (thin film): 3054, 2936, 2854, 1772, 1707, 1645, 1492, 1394, 1265, 768, 718 cm^{-1}. HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_3$ $[M + H]^+$: 391.2022, found: 391.2016.



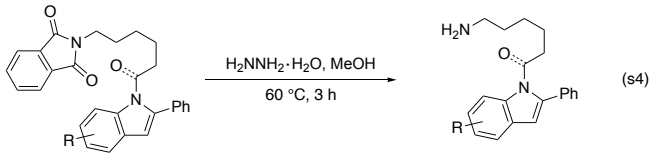
5.04c

2-(6-(Indolin-1-yl)-6-oxohexyl)phthalimide 5.04c. The general procedure was followed using 195.2 mg of 2-phenylindoline (1.0 mmol), 149.2 mg of *N,N*-diethylaniline (1.0 mmol) and 279.7 mg of acid chloride (1.0 mmol) in a total 4 mL of CH_2Cl_2. Purification by MPLC chromatography (5:1 – 2:1 hexanes:EtOAc) afforded **5.04c** as a yellow oil (200 mg, 46% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.81 (m, 2H), 7.71 – 7.69 (m, 2H), 7.28 – 7.19 (m, 4H), 7.15 –

7.11 (m, 3H), 7.03 (t, J = 7.0 Hz, 1H), 5.41 (d, J = 10.0 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.61 (t, J = 7.0 Hz, 2H), 2.96 (d, J = 16.0 Hz, 1H), 2.40 – 2.35 (m, 1H), 2.10 – 2.04 (m, 1H), 1.71 – 1.55 (m, 4H), 1.27 – 1.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9 (C), 168.4 (C), 143.5 (C), 143.3 (C), 133.9 (CH), 132.2 (C), 129.1 (CH), 127.7 (CH), 125.0 (CH), 124.8 (CH), 124.0 (CH), 123.1 (CH), 117.0 (CH), 62.7 (CH), 38.9 (CH_2), 37.8 (CH_2), 35.3 (CH_2), 28.3 (CH_2), 26.4 (CH_2), 24.3 (CH_2); only visible signals. ATR-FTIR (thin film): 3030, 2944, 2862, 1771, 1705, 1656, 1393, 1267, 1046, 734 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{27}N_2O_3$ $[M + H]^+$:439.2022, found: 439.2011.

C. Synthesis of *N*-(6-indolehexyl)-amine and 6-amino-1-(indolin-1-yl)hexan-1-one.

1. General procedure.

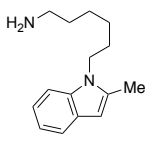


(s4)

5.01 or **5.04** **5.02** or **5.05**

To a solution of *N*-(6-indolehexyl)-phthalimide **5.01** (1.0 equiv) *or* 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimide **5.04** (1.0 equiv) in 0.1 M MeOH was added a solution of hydrazine hydrate (N_2H_4•H_2O, 5.0 equiv). The resulting reaction mixture was heated to reflux at 60 °C for 4 h with monitoring the reaction progress by thin layer chromatography (TLC). After complete consumption of the starting materials, the reaction was cooled to room temperature and 20 mL of a 1 N aq soln of NaOH was added. The resulting mixture was then diluted and extracted by 3× 20 mL of DCM. After additional washes with 2 × 20 mL of a 1 N aq soln of NaOH and 2× 20 mL of water, the organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The amine product was used in the subsequent coupling reaction without additional characterization or purification.

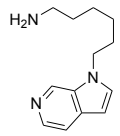
2. Characterization data of 2-(6-(indolin-1-yl)-6-oxohexyl)phthalimides 5.02 or 5.05.



5.02a

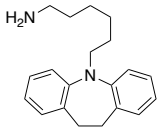
***N*-(6-Indolehexyl)-amine 5.02a.** The general procedure was followed using 36.0 mg of **5.01a** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.02a** was afforded as a yellow gel (23 mg, quant. yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.15 – 7.11 (m, 1H), 7.05 (t, J = 7.5 Hz, 1H),

6.23 (s, 1H), 4.05 (t, *J* = 7.5 Hz, 2H), 2.88 (s, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.75 (quin, *J* = 7.0 Hz, 2H), 1.48 (quin, *J* = 7.0 Hz, 2H), 1.39 – 1.35 (m, 4H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



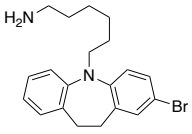
5.02b

***N*-(6-Indolehexyl)-amine 5.02b.** The general procedure was followed using 34.7 mg of **5.01b** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.02b** was afforded as a yellow gel (21 mg, quant. yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.19 (d, *J* = 5.5 Hz, 1H), 7.47 (dd, *J* = 5.5 Hz, 1.0 Hz, 1H), 7.18 (d, *J* = 3.0 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 4.16 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 1.84 (quin, *J* = 7.0 Hz, 2H), 1.45 – 1.23 (m, 8H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



5.02c

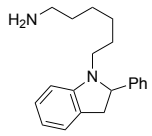
***N*-(6-Indolehexyl)-amine 5.02c.** The general procedure was followed using 42.5 mg of **5.01c** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.02c** was afforded as a yellow gel (29 mg, quant. yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 6H), 6.92 (dt, *J* = 7.0 Hz, 1.5 Hz, 2H), 3.73 (t, *J* = 7.0 Hz, 2H), 3.18 (s, 4H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 2H), 1.58 (quin, *J* = 7.5 Hz, 2H), 1.42 (quin, *J* = 7.5 Hz, 2H), 1.38 – 1.24 (m, 4H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



5.02d

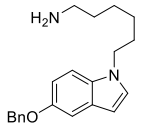
***N*-(6-Indolehexyl)-amine 5.02d.** The general procedure was followed using 50.0 mg of **5.01d** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.02d** was afforded as a yellow gel (37 mg, quant. yield) as a mixture of rotamers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.20 (m, 1.83H), 7.15 – 7.05 (m, 3.22H), 6.95 – 6.90 (m, 2H), 3.73 (t, J = 7.0 Hz, 0.25H), 3.68 (t, J = 7.0 Hz, 1.59H), 3.63 (t, J = 7.0 Hz, 0.17H), 3.17 – 3.09 (m, 3.92H), 2.63 (t, J = 7.0 Hz,

1.95H), 1.59 – 1.51 (m, 2H), 1.41 – 1.23 (m, 6.22H), 1.12 (s, 1.95H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



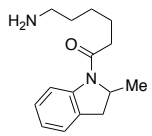
5.02e

***N*-(6-Indolehexyl)-amine 5.02e.** The general procedure was followed using 42.4 mg of **5.01e** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.02e** was afforded as a yellow gel (29 mg, quant. yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.37 – 7.34 (m, 2H), 7.32 – 7.29 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 7.5 Hz, 1H), 4.64 (t, *J* = 10.0 Hz, 1H), 3.37 (dd, *J* = 16.0 Hz, 9.5 Hz, 1H), 3.11 – 3.05 (m, 1H), 2.96 – 2.87 (m, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 1.47 (quin, *J* = 7.0 Hz, 2H), 1.39 – 1.34 (m, 2H), 1.27 – 1.20 (m, 4H), 1.13 (s, 2H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



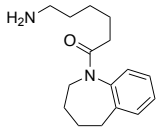
5.02f

***N*-(6-Indolehexyl)-amine 5.02f.** The general procedure was followed using 167 mg of **5.01f** (0.37 mmol), 93.0 mg of hydrazine hydrate (1.85 mmol) in 4.0 mL of MeOH. Purification by MPLC chromatography (1:5 MeOH:DCM) afforded **5.02f** as a yellow gel (78 mg, 65 % yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 11.0 Hz, 2H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.47 (d, *J* = 1.9 Hz, 1H), 5.13 (s, 2H), 4.03 (t, *J* = 6.9 Hz, 2H), 2.65 (t, *J* = 6.5 Hz, 2H), 1.91 – 1.72 (m, 2H), 1.40 (d, *J* = 6.3 Hz, 2H), 1.37 – 1.25 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2 (C), 138.0 (C), 131.6 (C), 129.0 (C), 128.6 (C), 128.5 (CH), 127.8 (CH), 127.6 (CH), 112.5 (CH), 110.2 (CH), 104.2 (CH), 100.6 (CH), 70.89 (CH_2), 46.5 (CH_2), 42.2 (CH_2), 33.7 (CH_2), 30.4 (CH_2), 26.9 (CH_2), 26.6 (CH_2). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



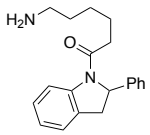
5.05a

6-Amino-1-(indolin-1-yl)hexan-1-one 5.05a. The general procedure was followed using 42.0 mg of **5.04a** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.05a** was afforded as a yellow gel (29 mg, quant. yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 4.47 (t, *J* = 7.0 Hz, 1H), 3.99 – 3.24 (m, 1H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.65 – 2.58 (m, 1H), 2.54 – 2.39 (m, 2H), 1.76 (quin, *J* = 7.5 Hz, 2H), 1.60 – 1.38 (m, 6H), 1.27 – 1.19 (m, 3H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.



5.05b

6-Amino-1-(indolin-1-yl)hexan-1-one 5.05b. The general procedure was followed using 39.0 mg of **5.04b** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.05b** was afforded as a yellow gel (26 mg, quant. yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 3H), 7.03 (t, *J* = 4.5 Hz, 1H), 4.65 – 4.61 (m, 1H), 2.64 (quin, *J* = 8.0 Hz, 2H), 2.55 (t, *J* = 8.0 Hz, 2H), 2.48 (d, *J* = 13.0 Hz, 1H), 2.11 (quin, *J* = 7.5 Hz, 1H), 2.14 – 1.79 (m, 5H), 1.71 – 1.67 (m, 1H), 1.52 – 1.45 (m, 2H), 1.31 – 1.26 (m, 3H), 1.19 – 1.12 (m, 2H). The amine product was used in the subsequent coupling reaction without additional purification or characterization.

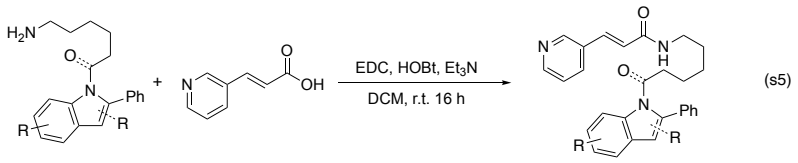


5.05c

6-Amino-1-(indolin-1-yl)hexan-1-one 5.05c. The general procedure was followed using 43.8 mg of **5.04c** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.05c** was afforded as a yellow gel (30 mg, quant. yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.23 (m, 4H), 7.15 – 7.10 (m, 3H), 7.04 – 7.01 (m, 1H), 5.40 (d, *J* = 10.0 Hz, 1H), 3.78 – 3.73 (m, 1H), 2.95 (d, *J* = 16.0 Hz, 1H), 2.60 (s, 2H), 2.41 – 2.35 (m, 1H), 2.11 – 2.04 (m, 1H), 1.65 – 1.50 (m, 2H), 1.32 – 1.20 (m, 6H) .The amine product was used in the subsequent coupling reaction without additional purification or characterization.

D. Synthesis of acrylamide analogues.

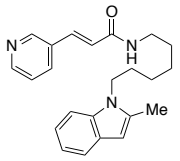
1. General procedure.



5.02 or **5.05** (1.2 equiv) (1.0 equiv) **5.03** or **5.06**

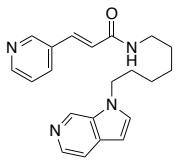
To a solution of *trans*-3-(3-pyridyl) acrylic acid (1.0 equiv) in 0.1 M dry CH_2Cl_2 was added *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC, 2.0 equiv), 1-hydroxybenzotriazole hydrate (HOBt, 1.5 equiv), and triethylamine (1.5 equiv) sequentially. After stirring at room temperature for 5 min, a solution of amine **5.02** (1.2 equiv) or **5.05** (1.2 equiv) in DCM was added slowly to the reaction mixture. The reaction was allowed to stir at room temperature for overnight. After complete consumption of the starting materials indicated by thin layer chromatography (TLC), the reactives were quenched by the addition of 10 mL of a saturated $NaHCO_3$ aqueous solution. The reaction mixture was then washed with 2 × 20 mL water and extracted with 2 × 20 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by MPLC.

2. Characterization data.



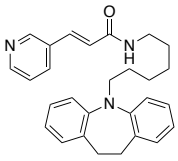
5.03a

(*E*)-*N*-(6-(1*H*-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.03a. The general procedure was followed using 46.1 mg of **5.02a** (0.20 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.170 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of CH_2Cl_2. Purification by MPLC chromatography (2:98 MeOH:CH_2Cl_2) afforded **5.03a** as a yellow gel (40 mg, 65%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.0 Hz, 1H), 8.55 (d, *J* = 5.0 Hz, 1H), 7.75 (td, *J* = 4.0 Hz, 2.0 Hz, 1H), 7.58 (d, *J* = 15.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 15.5 Hz, 1H), 6.23 (s, 1H), 5.84 (t, *J* = 6.0 Hz, 1H), 4.04 (t, *J* = 7.5 Hz, 2H), 3.33 (quin, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.74 (quin, *J* = 7.5 Hz, 2H), 1.52 (quin, *J* = 7.0 Hz, 2H), 1.40 – 1.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (C), 150.3 (CH), 149.1 (CH), 137.2 (CH), 136.6 (C), 136.4 (C), 134.4 (CH), 130.7 (C), 128.1 (C), 123.7 (CH), 122.9 (CH), 120.3 (CH), 119.7 (CH), 119.2 (CH), 109.0 (CH), 99.9 (CH), 43.1 (CH_2), 39.7 (CH_2), 30.1 (CH_2), 29.5 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 12.9 (CH_3). ATR-FTIR (thin film): 3417, 3000, 2915, 1660, 1436, 1385, 1016, 952 701 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{28}N_3O$ $[M + H]^+$: 362.2232, found: 362.2231.



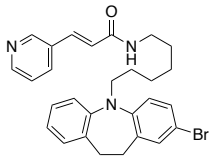
5.03b

(*E*)-*N*-(6-(1*H*-indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.03b. The general procedure was followed using 43.5 mg of **5.02a** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of CH_2Cl_2. Purification by MPLC chromatography (2:98 MeOH:CH_2Cl_2) afforded **5.03b** as a yellow gel (44 mg, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.67 (s, 1H), 8.50 (d, *J* = 5.0 Hz, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 15.5 Hz, 1H), 7.49 (d, *J* = 5.5 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.64 (t, *J* = 5.5 Hz, 1H), 6.49 (d, *J* = 15.5 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 4.16 (t, *J* = 7.0 Hz, 2H), 3.33 (q, *J* = 7.0 Hz, 2H), 1.82 (quin, *J* = 7.5 Hz, 2H), 1.51 (quin, *J* = 7.0 Hz, 2H), 1.37 – 1.25 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (C), 150.2 (CH), 149.1 (CH), 138.2 (CH), 136.9 (CH), 134.3 (CH), 133.3 (C), 133.1 (C), 132.6 (CH), 131.6 (CH), 130.8 (C), 123.7 (CH), 123.1 (CH), 115.5 (CH), 100.6 (CH), 46.7 (CH_2), 39.6 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 26.5 (CH_2), 26.5 (CH_2); ATR-FTIR (thin film): 3418, 3000, 2914, 1651, 1436, 1407, 1313, 1017, 952, 701 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{25}N_4O$ $[M + H]^+$: 349.2028, found: 349.2020.



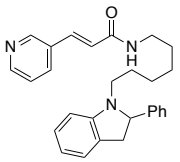
5.03c

(*E*)-*N*-(6-(1*H*-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.03c. The general procedure was followed using 58.9 mg of **5.02a** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of CH_2Cl_2. Purification by MPLC chromatography (2:98 MeOH:CH_2Cl_2) afforded **5.03c** as a yellow gel (46 mg, 63%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 7.71 (td, *J* = 4.0 Hz, 2.0 Hz, 1H), 7.57 (d, *J* = 16.0 Hz, 1H), 7.23 (dd, *J* = 8.0 Hz, 5.0 Hz, 1H), 7.13 – 7.04 (m, 6H), 6.90 (dt, *J* = 7.0 Hz, 1.0 Hz, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.41 (t, *J* = 6.0 Hz, 1H), 3.69 (t, *J* = 7.0 Hz, 2H), 3.31 (q, *J* = 7.0 Hz, 2H), 3.13 (s, 4H), 1.57 – 1.47 (m, 4H), 1.36 – 1.24 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2 (C), 150.1 (CH), 148.9 (CH), 148.4 (C), 136.9 (CH), 134.5 (CH), 134.2 (C), 130.9 (C), 129.8 (CH), 126.3 (CH), 123.7 (CH), 123.3 (CH), 122.3 (CH), 120.0 (CH), 50.6 (CH_2), 39.8 (CH_2), 32.3 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 26.7 (CH_2). ATR-FTIR (thin film): 3280, 3060, 2923, 2853, 1659, 1621, 1552, 1486, 1472, 1229, 978, 764, 751, 741 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{32}N_3O$ $[M + H]^+$: 426.2545, found: 426.2546.



5.03d

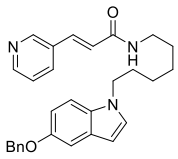
(*E*)-*N*-(6-(1*H*-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.03d. The general procedure was followed using 74.6 mg of **5.02a** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of CH_2Cl_2. Purification by MPLC chromatography (2:98 MeOH:CH_2Cl_2) afforded **5.03d** as a yellow gel (50 mg, 58%) as a 3:1 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 0.99H), 8.55 (d, *J* = 5.0 Hz, 0.98H), 7.74 (d, *J* = 8.0 Hz, 1.03H), 7.59 (d, *J* = 15.5 Hz, 1H), 7.29 – 7.26 (m, 1.23H), 7.22 – 7.19 (m, 2.21H), 7.14 – 7.08 (m, 1.84H), 7.03 (d, *J* = 8.0 Hz, 0.82H), 6.94 – 6.88 (m, 1.97H), 6.44 (d, *J* = 15.5 Hz, 1.01H), 5.89 (s, 0.97H), 3.66 (t, J = 7.0 Hz, 1.43H), 3.61 (t, J = 7.0 Hz, 0.46H), 3.32 (q, *J* = 7.0 Hz, 2.10H), 3.14 – 3.07 (m, 3.87H), 1.56 – 1.47 (m, 4.22H), 1.36 – 1.25 (m, 4.70H) (only visible signals); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (C), 150.3 (C), 149.1 (C), 148.1 (CH), 147.3 (C), 147.0 (C), 137.2 (C), 136.1 (C), 136.1 (C), 134.4 (CH), 134.2 (C), 132.5 (CH), 132.4 (CH), 130.7 (C), 129.7 (CH), 129.3 (CH), 129.1 (CH), 126.5 (CH), 123.7 (CH), 122.9 (CH), 122.8 (CH), 121.8 (CH), 121.7 (CH), 120.2 (CH), 115.3 (C), 114.7 (C), 50.8 (CH_2), 50.6 (CH_2), 39.7 (CH_2), 32.2 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 26.7 (CH_2), 26.7 (CH_2), 26.6 (CH_2) (only visible signals). ATR-FTIR (thin film): 3425, 2997, 2914, 1651, 1482, 1436, 1407, 1312, 1013, 951, 735 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{31}N_3OBr$ $[M + H]^+$: 504.1651, found: 504.1652.



5.03e

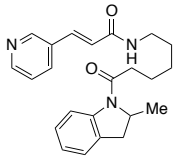
(*E*)-*N*-(6-(1*H*-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.03e. The general procedure was followed using 58.9 mg of **5.02e** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC.HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of DCM. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.03e** as a yellow gel (38 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.5 Hz, 1H), 8.56 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.76 (td, *J* = 4.0 Hz, 2.0 Hz, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.41 – 7.39 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.28 (m, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.82 (t, *J* = 6.0 Hz, 1H), 4.62 (t, *J* = 9.5 Hz, 1H), 3.36 – 3.31 (m, 3H), 3.07 (quin, *J* = 7.5 Hz, 1H), 2.95 – 2.86 (m, 2H), 1.52 – 1.42 (m, 4H), 1.30 – 1.20 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (C), 152.3 (C), 150.3 (CH), 149.1

(CH), 143.1 (C), 137.3 (CH), 134.4 (CH), 130.7 (C), 128.5 (CH), 128.2 (C), 127.6 (CH), 127.6 (CH), 127.4 (CH), 124.1 (CH), 123.7 (CH), 122.9 (CH), 117.2 (CH), 106.3 (CH), 69.0 (CH), 46.5 (CH_2), 39.8 (CH_2), 39.6 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 26.1 (CH_2); ATR-FTIR (thin film): 3265, 3054, 2992, 2928, 2856, 1667, 1625, 1548, 1023, 767 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{30}N_3O$ $[M + H]^+$: 424.2389, found: 424.2388.



5.03f

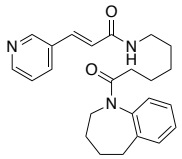
***(E)*-N-(6-(1H-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.03f.** The general procedure was followed using 32.1 mg of **5.02f** (0.100 mmol), 12.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.080 mmol), 30.7 mg of EDC•HCl (0.160 mmol), 16.2 mg of HOBt (0.120 mmol), and 12.1 mg of Et_3N (0.120 mmol) in 1.6 mL of DCM. Purification by MPLC chromatography (5% MeOH in DCM) afforded **5.03f** as a yellow gel (14.9 mg, 33% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 1.1 Hz, 1H), 8.53 (d, *J* = 3.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 15.7 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 1H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.42 (d, *J* = 15.7 Hz, 1H), 6.39 (d, *J* = 3.0 Hz, 1H), 6.07 (t, *J* = 5.5 Hz, 1H), 5.09 (s, 2H), 4.04 (t, *J* = 7.0 Hz, 2H), 3.30 (dd, *J* = 13.2, 6.8 Hz, 2H), 1.95 – 1.65 (m, 2H), 1.53 – 1.44 (m, 2H), 1.34 – 1.27 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$)δ 165.2 (C), 153.1 (C), 150.2 (CH), 149.0 (CH), 137.7 (C), 137.1 (CH), 134.4 (CH), 131.5 (C), 130.8 (C), 128.9 (C), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 123.7 (CH), 123.1 (CH), 112.5 (CH), 110.1 (CH), 104.2 (CH), 100.5 (CH), 71.0 (CH2), 46.5 (CH_2), 39.7 (CH_2), 30.2 (CH_2), 29.5 (CH_2), 26.7 (CH_2), 26.6 (CH_2); IR (thin film): 3404, 3002, 2919, 1659, 1436, 1406, 1314, 1015, 951, 702, 671 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{29}H_{34}N_3O_2$ $(M+H)^+$: 456.2651, found: 456.2645.



5.06a

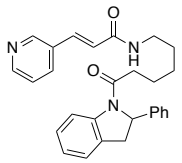
(*E*)-*N*-(6-(1*H*-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.06a. The general procedure was followed using 49.3 mg of **5.05a** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of CH_2Cl_2. Purification by MPLC chromatography (2:98 MeOH:CH_2Cl_2) afforded **5.06a** as a yellow gel (49 mg, 75%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (d, J = 8.5 Hz, 1H), 8.52 (t, J = 6.0 Hz, 1H), 8.16 (dd, J = 11.0 Hz, 5.5 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.73 – 6.69 (m, 1H), 4.60 (d, J = 10.0 Hz, 1H), 3.35

– 3.17 (m, 1H), 3.18 (q, J = 6.5 Hz, 2H), 2.61 – 2.37 (m, 3H), 1.61 (q, J = 7.5 Hz, 2H), 1.49 (q, J = 7.5 Hz, 2H), 1.35 (quin, J = 7.5 Hz, 2H), 1.16 – 1.13 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9 (C), 164.8 (C), 150.5 (CH), 149.5 (CH), 142.0 (C), 135.5 (CH), 134.3 (CH), 131.2 (C), 127.4 (CH), 125.6 (CH), 124.8 (CH), 124.4 (CH), 123.8 (CH), 117.4 (CH), 55.3 (CH), 39.1 (CH_2), 36.3 (CH_2), 34.4 (CH_2), 29.6 (CH_2), 26.7 (CH_2), 24.8 (CH_2), 22.0 (CH_2), 14.5 (CH_3); ATR-FTIR (thin film): 3416, 3001, 2882, 1672, 1629, 1421, 1313, 1016, 952, 702 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{28}N_3O_2$ [M + H]$^+$: 378.2182, found: 378.2176.



5.06b

***(E)*-N-(6-(1H-indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.06b.** The general procedure was followed using 52.1 mg of **5.05b** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC.HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of DCM. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.06b** as a yellow gel (36 mg, 54% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.55 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 15.5 Hz, 1H), 7.30 – 7.20 (m, 4H), 7.10 – 7.08 (m, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.47 (t, *J* = 6.0 Hz, 1H), 4.73 – 4.69 (m, 1H), 3.49 – 3.32 (m, 2H), 2.74 – 2.66 (m, 2H), 2.62 – 2.57 (m, 2H), 2.25 – 2.19 (m, 1H), 1.98 – 1.86 (m, 3H), 1.78 – 1.74 (m, 1H), 1.61 – 1.49 (m, 3H), 1.44 – 1.35 (m, 1H), 1.30 (quin, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0 (C), 165.3 (C), 150.0 (CH), 149.0 (CH), 143.0 (C), 140.5 (C), 136.5 (CH), 134.3 (CH), 131.0 (C), 130.2 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 123.7 (CH), 123.6 (CH), 47.2 (CH_2), 39.2 (CH_2), 34.5 (CH_2), 33.9 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 24.3 (CH_2). ATR-FTIR (thin film): 3434, 3289, 3049, 2929, 2855, 1645, 1633, 1492, 1402, 1025, 952, 730 cm^{-1}. HRMS (ESI) m/z calcd for $C_{24}H_{30}N_3O_2$ [M + H]$^+$: 392.2338, found: 392.2337.



5.06c

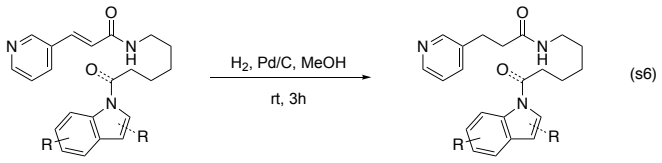
***(E)*-N-(6-(1H-indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.06c.** The general procedure was followed using 61.7 mg of **5.05c** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC•HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of DCM. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.06c** as a yellow gel (45 mg, 60% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 2.5 Hz, 1H), 8.53 (d, *J* = 5.0 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.29 – 7.22 (m, 4H), 7.14 – 7.11

(m, 3H), 7.04 (t, J = 7.5 Hz, 1H), 6.63 (t, J = 5.5 Hz, 1H), 6.55 (d, J = 16.0 Hz, 1H), 5.40 (d, J = 10.0 Hz, 1H), 3.80 – 3.75 (m, 1H), 3.39 – 3.31 (m, 2H), 2.96 (d, J = 16.0 Hz, 1H), 2.44 – 2.38 (m, 1H), 2.16 – 2.05 (m, 1H), 1.64 – 1.44 (5H), 1.30 – 1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (C), 165.2 (C), 150.2 (CH), 149.2 (CH), 143.4 (C), 143.1 (C), 136.7 (CH), 134.2 (CH), 132.0 (C), 130.9 (C), 129.2 (CH), 127.8 (CH), 127.7 (CH), 125.0 (CH), 124.9 (CH), 124.3 (CH), 123.7 (CH), 123.4 (CH), 116.9 (CH), 62.7 (CH), 39.0 (CH_2), 38.9 (CH_2), 35.1 (CH_2), 28.7 (CH_2), 26.1 (CH_2), 23.5 (CH_2); ATR-FTIR (thin film): 3277, 3049, 1727, 1661, 1628, 1402, 1267, 1024, 730 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{30}N_3O_2$ $[M + H]^+$: 440.2338, found: 440.2335.

E. Expanding RARI analogue compound library.

1. Hydrogenation.

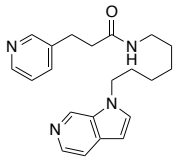
1. General Procedure.



(s6)

A solution of the RARI analogue (1.0 equiv) and 10 wt % Pd/C (0.20 g/mmol) in MeOH was stirred under 1.0 atm of H_2 gas. After stirring at room temperature for 3 h, the reaction mixture was filtered through Celite and dried over Na_2SO_4. The filtrate was concentrated in vacuo. Purification via MPLC afforded the product.

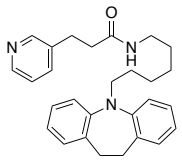
2. Characterization data.



5.07a

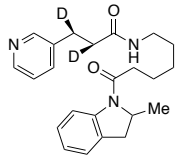
5.07a. The general procedure was followed using 15.0 mg (0.043 mmol) of **5.03b**, 8.6 mg of Pd/C in 1.0 mL of MeOH under H_2 atmosphere. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.07a** as a yellow gel (12.2 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.40 – 8.37 (m, 2H), 8.18 (d, J = 5.5 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.20 (d, J = 3.0 Hz, 1H), 7.15 – 7.12 (m, 1H), 6.46 (d, J = 3.5 Hz, 1H), 6.06 (t, J = 6.0 Hz, 1H), 4.16 (t, J = 7.0 Hz, 2H), 3.15 (q, J = 6.5 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.42 (t, J = 7.5 Hz, 2H), 1.81 (quin, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 2H), 1.28 – 1.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C), 149.7 (CH), 147.6 (CH), 138.1 (CH), 136.4 (C), 136.1 (CH), 133.3 (C), 133.1 (C), 132.6 (CH), 131.6 (CH), 123.4 (CH), 115.4 (CH), 100.6 (CH), 46.7 (CH_2), 39.3 (CH_2), 37.8 (CH_2), 30.3 (CH_2),

29.4 (CH_2), 28.8 (CH_2), 26.5 (CH_2), 26.4 (CH_2). ATR-FTIR (thin film): 3271, 3043, 2926, 2855, 1645, 1552, 1500, 1320, 1028, 817, 775, 730 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{27}N_4O$ $[M + H]^+$: 351.2185, found: 351.2186.



5.07b

5.07b. The general procedure was followed using 15.0 mg (0.035 mmol) of **5.03c**, 7.0 mg of Pd/C in 0.8 mL of MeOH under H_2 atmosphere. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.07b** as a yellow gel (12.0 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 – 8.41 (m, 2H), 7.51 (td, *J* = 4.0 Hz, 2.0 Hz, 1H), 7.16 (dd, *J* = 8.0 Hz, 5.0 Hz, 1H), 7.13 – 7.05 (m, 6H), 6.92 – 6.89 (m, 2H), 5.41 (s, 1H), 3.70 (t, *J* = 7.0 Hz, 2H), 3.17 – 3.13 (m, 6H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.53 (quin, *J* = 7.0 Hz, 2H), 1.39 – 1.24 (m, 4H), 1.20 – 1.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C), 149.8 (CH), 148.4 (C), 147.7 (CH), 136.3 (C), 136.1 (CH), 134.2 (C), 129.8 (CH), 126.3 (CH), 123.4 (CH), 122.3 (CH), 120.0 (CH), 50.5 (CH_2), 39.4 (CH_2), 37.9 (CH_2), 32.2 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 26.5 (CH_2). ATR-FTIR (thin film): 3501, 2995, 2912, 1661, 1487, 1436, 1407, 1309, 1042, 952, 930, 697 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{34}N_3O$ $[M + H]^+$: 428.2702, found: 428.2696.



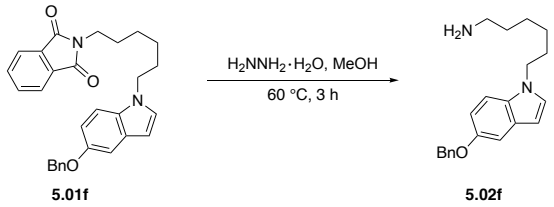
5.07c

5.07c. The general procedure was followed using 10.0 mg (0.026 mmol) of **5.06a**, 5.2 mg of Pd/C in 0.6 mL of MeOD under D_2 atmosphere. Purification by MPLC chromatography (2% MeOH in DCM) afforded **5.07c** as a yellow gel (8.5 mg, 86% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.5 Hz, 2H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.17 – 7.13 (m, 3H), 7.00 (t, *J* = 7.0 Hz, 1H), 6.31 (s, 1H), 4.47 (t, *J* = 7.5 Hz, 1H), 3.40 – 3.33 (m, 1H), 3.23 (q, *J* = 6.5 Hz, 2H), 2.94 – 2.91 (m, 1H), 2.65 – 2.58 (m, 1H), 2.53 – 2.46 (m, 1H), 2.44 – 2.37 (m, 2H), 1.74 – 1.67 (m, 2H), 1.50 – 1.44 (m, 2H), 1.37 – 1.21 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C), 170.9 (C), 149.7 (CH), 147.5 (CH), 141.6 (C), 136.5 (C), 136.1 (CH), 130.3 (C), 127.4 (CH), 125.0 (CH), 123.9 (CH), 123.4 (CH), 117.9 (CH), 55.5 (CH), 39.0 (CH_2), 37.51 (q, *J* = 19.1 Hz, CHD), 36.4 (CH_2), 34.6 (CH_2), 29.0 (CH_2), 28.54 (q, *J* = 19.8 Hz, CHD), 26.4 (CH2), 24.1 (CH_2), 21.8 (CH_3). ATR-FTIR (thin film): 3487, 2996, 2912, 1668, 1557, 1436, 1386, 1310, 1018, 952, 931, 698 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{28}D_2N_3O_2$ $[M + H]^+$: 382.2464, found: 382.2463.

2. PEGylation.

Synthesis of DGMS-RAR-mPEG3.

Step 1:

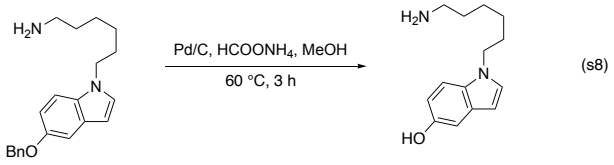


(s7)

5.01f **5.02f**

***N*-(6-Indolehexyl)-amine 5.02f.** The general procedure was followed using 45.3 mg of **5.01f** (0.10 mmol), 25.0 mg of hydrazine hydrate (0.5 mmol) in 1.0 mL of MeOH. The crude product **5.02f** was afforded as a yellow gel (33 mg, quant. yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.18 (s, 1H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 6.40 (d, *J* = 3.0 Hz, 1H), 5.11 (s, 2H), 4.08 (t, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 7.0 Hz, 2H), 1.84 (q, *J* = 7.0 Hz, 2H), 1.44 – 1.28 (m, 8H). The amine product was used in the subsequent reaction without additional purification or characterization.

Step 2:

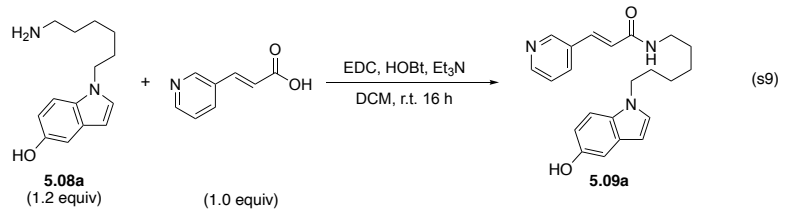


(s8)

5.02f **5.08a**

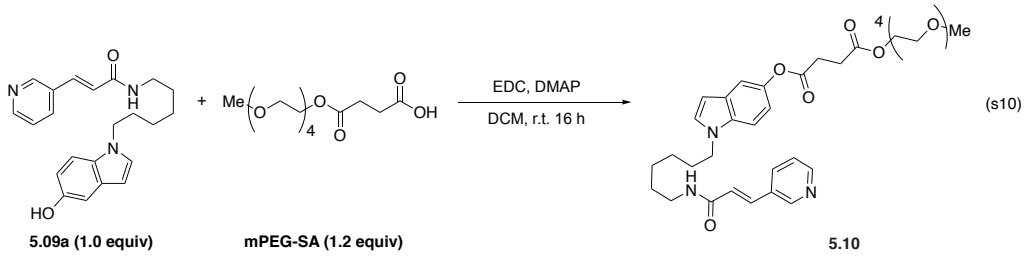
***N*-(6-Indolehexyl)-amine 5.08a.** Benzyl group deprotection was done using general procedure. 32.3 mg of **5.02f (**0.10 mmol), 60 mg of 10 wt % Pd/C (60 mg/0.1 mmol of SM) and 32 mg of $HCOONH_4$ (0.5 mmol, 5.0 equiv) was refluxed in 2.0 mL of MeOH for 3h. When the reaction was complete (as monitored by TLC), the reaction mixture was cooled to room temperature. The reaction mixture was filtered through a small Celite pad. The pad was washed further with 2 X 5 mL MeOH. The solvent was then evaporated under reduced pressure to give the crude product **5.08a** as a yellow gel (23 mg, quant. yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 7.02 – 7.00 (m, 2H), 6.77 – 6.74 (m, 1H), 6.32 – 6.29 (m, 1H), 4.03 (t, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 7.0 Hz, 2H), 1.83 – 1.77 (m, 3H), 1.43 (quin, *J* = 7.0 Hz, 2H), 1.34 – 1.26 (m, 6H). The deprotected product was used in the subsequent reaction without additional purification or characterization.

Step 3:



(*E*)-*N*-(6-(1*H*-Indol-1-yl)hexyl)-3-(pyridin-3-yl)acrylamide 5.09a. The general procedure was followed using 46.5 mg of **5.08a** (0.2 mmol), 25.0 mg of *trans*-3-(3-pyridyl) acrylic acid (0.17 mmol), 65.1 mg of EDC.HCl (0.34 mmol), 35.1 mg of HOBt (0.26 mmol), and 26.3 mg of Et_3N (0.26 mmol) in 4 mL of CH_2Cl_2. Purification by MPLC chromatography (2% MeOH in CH_2Cl_2) afforded **5.09a** as a yellow gel (57 mg, 78% yield). ^{1}H NMR (500 MHz, DMSO) δ 8.73 (d, J = 5.5 Hz, 1H), 8.65 – 8.63 (m, 1H), 8.51 (q, J = 4.5 Hz, 1H), 8.11 (q, J = 6.5 Hz, 1H), 7.93 (t, J = 8.0 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.21 – 7.18 (m, 2H), 6.85 – 6.84 (m, 1H), 6.71 (d, J = 15.5 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.20 – 6.17 (m, 1H), 4.05 – 4.00 (m, 2H), 3.14 (t, J = 6.5 Hz, 2H), 1.68 (q, J = 7.5 Hz, 2H), 1.40 (t, J = 7.5 Hz, 2H), 1.31 – 1.19 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.8 (C), 151.1 (C), 150.5 (CH), 149.5 (CH), 135.5 (CH), 134.3 (CH), 131.2 (C), 130.8 (C), 129.3 (C), 129.2 (CH), 124.8 (CH), 124.4 (CH), 111.6 (CH), 110.5 (CH), 104.7 (CH), 99.7 (CH), 45.9 (CH_2), 39.1 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 26.5 (CH_2), 26.5 (CH_2); ATR-FTIR (thin film): 2844, 1750, 1686, 1473, 1425, 1384, 1198, 909 cm^{-1}. HRMS (ESI) m/z calcd for $C_{22}H_{26}N_3O_2$ $[M + H]^+$: 364.2025, found: 364.2022.

Step 4:

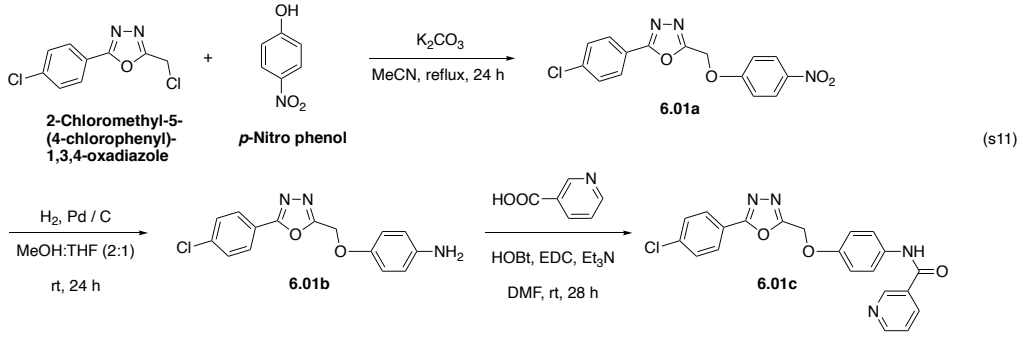


5.10. 36.5 mg of **5.09a** (0.1 mmol), 37.0 mg of **mPEG-SA**[20] (0.12 mmol), 2.44 mg of DMAP (0.02 mmol)and 38.3 mg of EDC.HCl (0.2 mmol) were weighed in a 10 mL flask equipped with a magnetic stir bar. To the reaction mixture 2 mL of CH_2Cl_2 was added and the mixture stirred at room temperature for 16 h. After that the reaction mixture was diluted with 5 mL of CH_2Cl_2 and washed with 3 mL of 2N HCl followed by washing with 3 mL of saturated solution of $NaHCO_3$. The organic

[20]. Godeau, G.; Navailles, L.; Nallet, F.; Lin, X.; McIntosh, T. J.; Grinstaff, M. W. *Macromolecules*, *45*, **2012**, 2509.

layer was then washed with 1 × 5 mL water followed by washing with 1 X 5 mL brine. The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by MPLC (2% MeOH in CH_2Cl_2) to afford **5.10** as a clear oil (13 mg, 21% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 2.5 Hz, 1H), 8.55 – 8.53 (m, 1H), 7.77 – 7.74 (m, 1H), 7.57 (d, *J* = 15.5 Hz, 1H), 7.29 – 7.25 (m, 3H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.89 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.44 (d, *J* = 15.5 Hz, 1H), 6.41 (d, *J* = 3.5 Hz, 1H), 5.99 (t, *J* = 6.0 Hz, 1H), 4.26 (t, *J* = 5.0 Hz, 2H), 4.08 (t, *J* = 6.6 Hz, 2H), 3.70 – 3.68 (m, 2H), 3.66 – 3.60 (m, 10H), 3.53 – 3.51 (m, 2H), 3.35 (s, 3H), 3.28 (q, *J* = 6.5 Hz, 2H), 2.89 (t, *J* = 6.5 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 1.79 (q, *J* = 6.5 Hz, 2H), 1.47 (q, *J* = 7.0 Hz, 2H), 1.31 – 1.24 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (C), 171.8 (C), 165.2 (C), 150.3 (CH), 149.2 (CH), 144.0 (C), 137.0 (CH), 134.3 (CH), 133.9 (C), 130.8 (C), 129.1 (CH), 128.7 (C), 123.7 (CH), 123.0 (CH), 115.4 (CH), 112.8 (CH), 109.7 (CH), 101.2 (CH), 71.9 (CH_2), 70.6 (CH_2), 70.6 (CH_2), 70.5 (CH_2), 69.1 (CH_2), 64.0 (CH_2), 59.0 (CH_3), 46.6 (CH_2), 39.6 (CH_2), 30.0 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.6 (CH_2), 26.5 (CH_2) only peaks visible; ATR-FTIR (thin film): 2878, 1737, 1668, 1626, 1450, 1265, 1219, 1146, 896, 730 cm^{-1}. HRMS (ESI) m/z calcd for $C_{35}H_{48}N_3O_9$ $[M + H]^+$: 654.3391, found: 654.3393.

II. Synthesis of NAMPT activators.



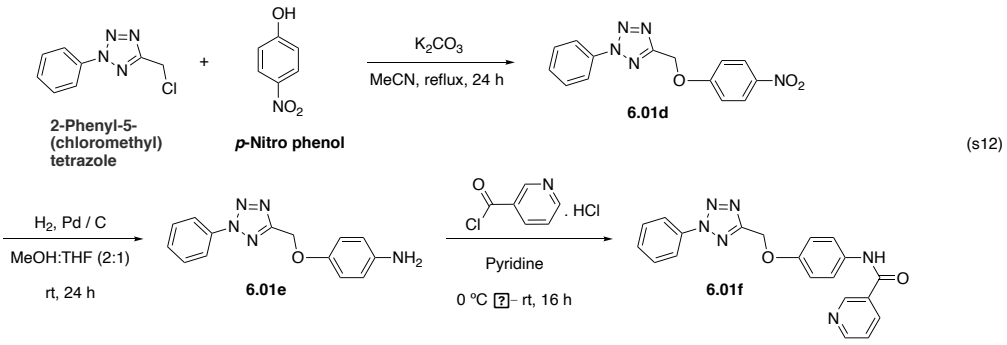
6.01a. The compound was prepared using the general procedure followed by Chang-Hyun and co-workers.[21] To a solution of 0.199 g commercially available oxadiazole (0.87 mmol) and 0.145 g commercially available *p*-nitrophenol (1.04 mmol) in dry acetonitrile (100 mL / mmol of oxadiazole), 0.361 g of anhydrous K_2CO_3 (2.61 mmol) was added and the mixture was refluxed for 24 h. The reaction mixture was the cooled to rt and solvent was evaporated under reduced pressure till dryness, and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine and then dried over anhydrous sodium sulfate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give crude **6.01a**,

[21] Gamal El-Din, M. M.; El-Gamal, M. I.; Abdel-Maksoud, M. S.; Yoo, K. H.; Oh, C. H. *Eur. J. Med. Chem.* **2015**, *90*, 45.

as a brownish white solid (0.131 g, 45%) which was pure enough to be taken to the next step without any additional purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.0 Hz, 2H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 5.43 (s, 2H).

6.01b. To a solution of the 0.100 g of **6.01a** (0.30 mmol) in a mixture of methanol and THF (2:1 v/v, 10 mL), 0.130 g of Pd / C (10% by weight) was added. The mixture was stirred in hydrogen atmosphere at rt for 24 h. The catalyst was cautiously filtered through a pad of celite, and the solvent was removed under reduced pressure to give crude **6.01b** as a brown solid (0.091 g, quant) which was taken to the next step without any additional characterization.

6.01c. To a solution of 0.091 g of **6.01b** (0.30 mmol), 0.031 g of commercially available nicotinic acid (0.25 mmol), 0.079 g of HOBt (0.51 mmol) and 0.053 g of EDC (0.39 mmol) in anhydrous DMF (10 mL / mmol of nicotinic acid), 55µL of Et_3N (0.39 mmol) was added. The reaction mixture was stirred at rt for 28 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (2:1 – 1:1 hexanes:EtOAc followed by 10:1 EtOAc:MeOH) to give **6.01c**, as a cream powder (0.037 g, 36%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.37 (s, 1H), 9.08 (s, 1H), 8.73 (d, *J* = 4.0 Hz, 1H), 8.27 – 8.25 (m, 1H), 8.01 – 7.99 (m, 2H), 7.71 (d, *J* = 9.0 Hz, 2H), 7.64 – 7.58 m (m, 2H), 7.54 (dd, *J* = 7.5 Hz, 4.5 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 2H), 5.47 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 165.2 (C), 164.2 (C), 163.2 (C), 154.2 (C), 152.5 (CH), 149.1 (CH), 135.8 (CH), 133.6 (C), 132.8 (CH), 131.1 (C), 130.0 (CH), 127.2 (CH), 124.0 (CH), 123.5 (C), 122.4 (CH), 115.6 (CH), 60.5 (CH_2).



(s12)

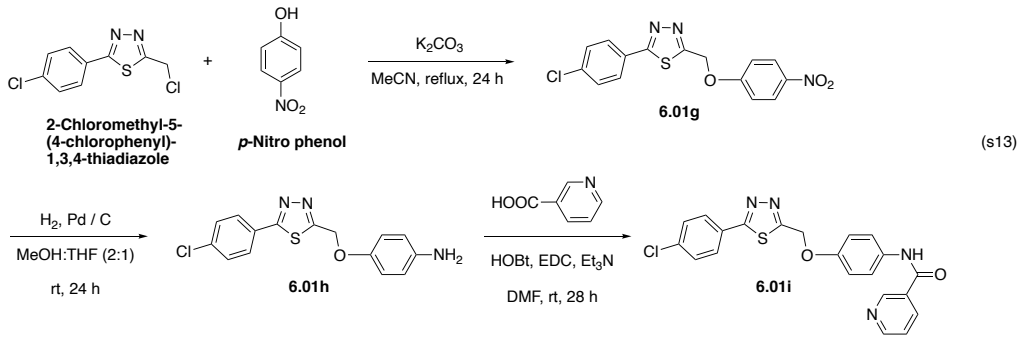
6.01d. The compound was prepared using the general procedure as followed to synthesize **6.01a**. To a solution of 0.065 g tetrazole[22] (0.33 mmol) and 0.056 g commercially available *p*-nitrophenol (0.40 mmol) in dry acetonitrile (100 mL / mmol of

[22] Lippmann, E.; Könnecke, A.; Beyer, G. *Monatshefte für Chemie* **1975**, *106*, 443.

oxadiazole), 0.138 g of anhydrous K_2CO_3 (1.00 mmol) was added and the mixture was refluxed for 24 h. The reaction mixture was the cooled to rt and solvent was evaporated under reduced pressure till dryness, and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine and then dried over anhydrous sodium sulfate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give crude **6.01d**, as a yellow solid (0.091 g, 92%) which was pure enough to be taken to the next step without any additional purification; ^{1}H NMR (500 MHz, Acetone-*d6*) δ 8.28 – 8.25 (m, 2H), 8.16 – 8.12 (m, 2H), 7.70 – 7.67 (m, 2H), 7.64 – 7.61 (m, 1H), 7.37 – 7.34 (m, 2H), 5.71 (s, 2H).

6.01e. To a solution of the 0.091 g of **6.01d** (0.30 mmol) in a mixture of methanol and THF (2:1 v/v, 10 mL), 0.042 g of Pd / C (10% by weight) was added. The mixture was stirred in hydrogen atmosphere at rt for 24 h. The catalyst was cautiously filtered through a pad of celite, and the solvent was removed under reduced pressure to give crude **6.01e** as a brown solid (0.071 g, 86%) which was taken to the next step without any additional characterization.

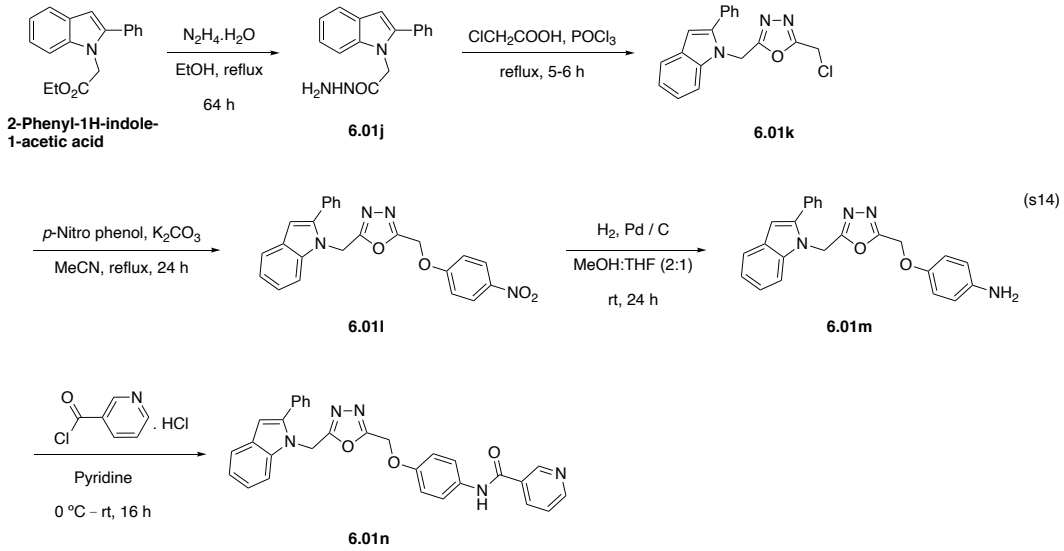
6.01f. To 0.024 g of **6.01e** (0.091 mmol) and 0.016 g of commercially available nicotinoyl chloride (0.091 mmol), pyridine (2 mL / mmol of 6.01e) was added at 0 °C. The reaction mixture was warmed to rt for a period of 2 h and was then stirred at rt for additional 14h. The mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (2:1 hexanes:EtOAc followed by EtOAc) to give **6.01f**, as a brown powder (0.013 g, 37%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.35 (s, 1H), 9.08 (d, J = 2.0 Hz, 1H), 8.73 (dd, J = 4.5 Hz, 1.5 Hz, 1H), 8.26 (dt, J = 4.0 Hz, 2.0 Hz, 1H), 8.10 – 8.08 (m, 2H), 7.70 – 7.65 (m, 4H), 7.62 – 7.59 (m, 1H), 7.56 – 7.53 (m, 1H), 7.12 – 7.09 (m, 2H), 5.49 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 164.2 (C), 163.3 (C), 154.5 (C), 152.5 (CH), 149.1 (CH), 136.5 (C), 135.8 (CH), 133.2 (C), 131.1 (C), 130.9 (CH), 130.7 (CH), 124.0 (CH), 122.4 (CH), 120.5 (CH), 115.4 (CH), 61.0 (CH_2).



6.01g. The compound was prepared using the general procedure as followed to synthesize **6.01a**. To a solution of 0.096 g commercially available thiadiazole (0.40 mmol) and 0.067 g commercially available *p*-nitrophenol (0.48 mmol) in dry acetonitrile (100 mL / mmol of oxadiazole), 0.166 g of anhydrous K_2CO_3 (1.20 mmol) was added and the mixture was refluxed for 24 h. The reaction mixture was the cooled to rt and solvent was evaporated under reduced pressure till dryness, and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine and then dried over anhydrous sodium sulfate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give crude **6.01g**, as a brown solid (0.133 g, 95%) which was pure enough to be taken to the next step without any additional purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 – 8.20 (m, 2H), 7.90 – 7.87 (m, 2H), 7.47 – 7.45 (m, 2H), 7.13 – 7.10 (m, 2H), 5.62 (s, 2H).

6.01h. To a solution of the 0.133 g of **6.01g** (0.40 mmol) in a mixture of methanol and THF (2:1 v/v, 10 mL), 0.055 g of Pd / C (10% by weight) was added. The mixture was stirred in hydrogen atmosphere at rt for 24 h. The catalyst was cautiously filtered through a pad of celite, and the solvent was removed under reduced pressure to give crude **6.01h** as a brown solid (0.114 g, 89%) which was taken to the next step without any additional characterization.

6.01i. To a solution of 0.114 g of **6.01h** (0.36 mmol), 0.102 g of commercially available nicotinic acid (0.30 mmol), 0.064 g of HOBt (0.47 mmol) and 0.095 g of EDC (0.61 mmol) in anhydrous DMF (10 mL / mmol of nicotinic acid), 66 µL of Et_3N (0.47 mmol) was added. The reaction mixture was stirred at rt for 28 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (2:1 – 1:1 hexanes:EtOAc followed by 10:1 EtOAc:MeOH) to give **6.01i**, as a cream powder (0.013 g, 10%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.36 (s, 1H), 9.07 (s, 1H), 8.73 (d, J = 5.0 Hz, 1H), 8.27 – 8.25 (m, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.54 (dd, J = 7.5 Hz, 4.5 Hz, 1H), 7.10 (d, J = 9.0 Hz, 2H), 5.62 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 168.4 (C), 167.7 (C), 164.2 (C), 154.1 (C), 152.5 (CH), 149.1 (CH), 136.6 (C), 135.9 (CH), 133.5 (C), 131.1 (C), 130.0 (CH), 129.9 (CH), 128.7 (C), 124.0 (CH), 122.5 (CH), 115.6 (CH), 64.9 (CH_2).



6.01j. The compound was prepared according to a general procedure followed by Khan and Dhar.[23] To a solution of 0.485 g of commercially available 2-phenyl-indole acetic acid (1.73 mmol) in EtOH (3.5 mL / 1 mmol of indole acetic acid), 0.21 mL of $N_2H_4.H_2O$ (4.33 mmol) was added and the mixture was refluxed for 48 h. Another 0.21 mL of $N_2H_4.H_2O$ (4.33 mmol) was added and the reaction mixture was refluxed for additional 16 h. After that the solution was cooled to rt, solvent was removed in vacuo to give the crude **6.01j** as a white solid (0.329 g, 72%) which was taken to the next step without any additional purification; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.42 (s, 1H), 7.61 – 7.60 (m, 2H), 7.57 – 7.55 (m, 1H), 7.49 – 7.46 (m, 2H), 7.43 – 7.41 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.16 – 7.13 (m, 1H), 7.08 – 7.05 (m, 1H), 6.55 (s, 1H), 4.67 (s, 2H), 4.32 (d, *J* = 2.5 Hz, 2H).

6.01k. The compound was prepared according to a general procedure followed by Padmavathi and co-workers.[24] A mixture of 0.171 g of **6.01j** (1.00 mmol), 0.095 g of chloroacetic acid (1.00 mmol) and $POCl_3$ (0.70 ml / 1 mmol of 6.01j) was heated under reflux for 5-6 h. The excess $POCl_3$ was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution and then with water, dried and recrystallized from ethanol to obtain **6.01k**, as a white solid (0.200 g, 86%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.61 – 7.59 (m, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 9.0 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.66 (s, 1H), 5.48 (2H), 4.60 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1 (C), 163.2 (C), 141.5 (C), 137.8 (C), 131.8 (C),

[23] Dhar, N.; Husain, A.; Khan, M. *Pharmacophore* **2012**, *3* , 55.

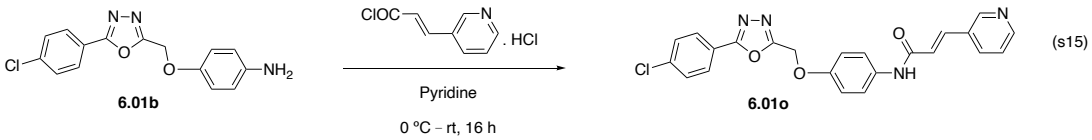
[24] Padmavathi, V.; Dinneswara Reddy, G.; Nagi Reddy, S.; Mahesh, K. *Eur. J. Med. Chem.* **2011**, *46*, 1367.

129.7 (CH), 128.9 (CH), 128.7 (CH), 128.5 (C), 122.7 (CH), 121.1 (CH), 120.9 (CH), 109.9 (CH), 103.8 (CH), 39.1 (CH_2), 32.8 (CH_2).

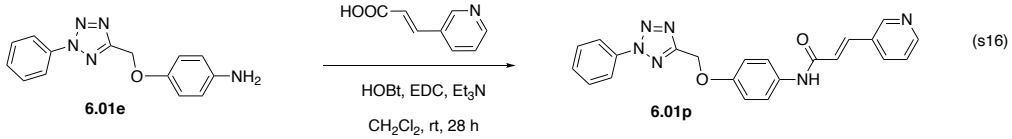
6.01l. The compound was prepared using the general procedure as followed to synthesize **6.01a**. To a solution of 0.105 g of **6.01k** (0.32 mmol) and 0.053 g commercially available *p*-nitrophenol (0.38 mmol) in dry acetonitrile (100 mL / mmol of 6.01k), 0.133 g of anhydrous K_2CO_3 (1.20 mmol) was added and the mixture was refluxed for 24 h. The reaction mixture was the cooled to rt and solvent was evaporated under reduced pressure till dryness, and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine and then dried over anhydrous sodium sulfate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give crude **6.01l**, as a brown solid (0.127 g, 93%) which was taken to the next step without any additional characterization.

6.01m. To a solution of the 0.127 g of **6.01l** (0.30 mmol) in a mixture of methanol and THF (2:1 v/v, 10 mL), 0.046 g of Pd / C (10% by weight) was added. The mixture was stirred in hydrogen atmosphere at rt for 24 h. The catalyst was cautiously filtered through a pad of celite, and the solvent was removed under reduced pressure to give crude **6.01m** as a brown solid (0.106 g, 89%) which was taken to the next step without any additional characterization.

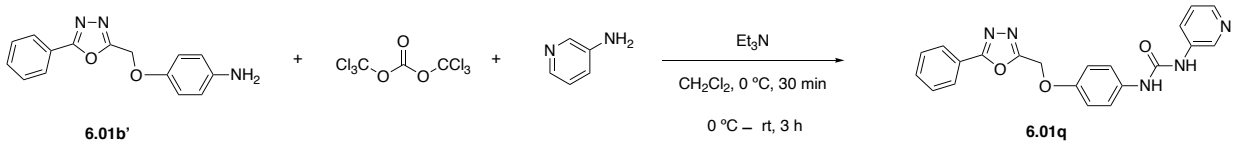
6.01n. To 0.106 g of **6.01m** (0.27 mmol) and 0.048 g of commercially available nicotinoyl chloride (0.27 mmol), pyridine (2 mL / mmol of 6.01m) was added at 0 °C. The reaction mixture was warmed to rt for a period of 2 h and was then stirred at rt for additional 14h. The mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (2:1 hexanes:EtOAc followed by EtOAc) to give **6.01n**, as a brown powder (0.035 g, 26%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.37 (s, 1H), 9.10 (s, 1H), 8.75 – 8.74 (m, 1H), 8.28 – 8.26 (m, 1H), 7.68 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.56 – 7.53 (m, 4H), 7.50 – 7.41 (3H), 7.22 – 7.17 (m, 1H), 7.13 – 7.10 (m, 1H), 7.01 – 6.98 (m, 2H), 6.63 (s, 1H), 5.69 (s, 2H), 5.31 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 164.3 (C), 164.2 (C), 163.6 (C), 154.1 (C), 152.5 (CH), 149.1 (CH), 141.4 (C), 138.2 (C), 135.9 (CH), 133.6 (C), 131.9 (C), 131.1 (C), 129.6 (CH), 129.3 (CH), 128.9 (CH), 128.4 (C), 124.0 (CH), 122.6 (CH), 122.3 (CH), 121.0 (CH), 120.9 (CH), 115.6 (CH), 111.0 (CH), 103.6 (CH), 60.3 (CH_2), 39.3 (CH_2).



6.01o. To 0.051 g of **6.01b** (0.17 mmol) and 0.035 g of (2E)-3-(pyridine-3-yl)prop-2-enoyl chloride hydrochloride (0.17 mmol), pyridine (2 mL / mmol of 6.01b) was added at 0 °C. The reaction mixture was warmed to rt for a period of 2 h and was then stirred at rt for additional 14h. The mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (2:1 hexanes:EtOAc followed by EtOAc) to give **6.01o**, as a brown powder (0.017 g, 23%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.24 (s, 1H), 8.79 (s, 1H), 8.56 – 8.55 (m, 1H), 8.01 – 7.99 (m, 3H), 7.67 – 7.57 (m, 6H), 7.09 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 10.5 Hz, 1H), 5.45 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 165.2 (C), 163.2 (C), 153.9 (C), 150.8 (CH), 149.7 (CH), 137.0 (CH), 134.6 (CH), 134.0 (C), 132.8 (CH), 131.1 (C), 130.0 (CH), 127.2 (CH), 124.8 (CH), 124.5 (C), 123.5 (C), 121.2 (CH), 115.8 (CH), 102.6 (C), 60.5 (CH_2).



6.01p. To a solution of 0.067 g of **6.01e** (0.25 mmol), 0.031 g of commercially available *trans*-3-(3-Pyridyl)acrylic acid (0.21 mmol), 0.045 g of HOBt (0.33 mmol) and 0.067 g of EDC (0.43 mmol) in anhydrous CH_2Cl_2 (10 mL / mmol of nicotinic acid), 70 µL of Et_3N (0.50 mmol) was added. The reaction mixture was stirred at rt for 28 h. The mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (2:1 – 1:1 hexanes:EtOAc followed by 10:1 EtOAc:MeOH) to give **6.01p**, as a white powder (0.026 g, 26%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.2 (s, 1H), 8.79 (s, 1H), 8.56 (d, *J* = 4.5 Hz, 1H), 8.09 – 8.08 (m, 2H), 8.01 – 8.00 (m, 1H), 7.67 – 7.64 (m, 4H), 7.61 – 7.57 (2H), 7.45 (t, *J* = 5.5 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 6.90 (d, *J* = 11.0 Hz, 1H), 5.47 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 163.3 (C), 163.2 (C), 154.2 (C), 150.8 (CH), 149.7 (CH), 136.9 (CH), 136.5 (C), 134.5 (CH), 133.7 (C), 131.1 (C), 130.9 (CH), 130.7 (CH), 124.8 (CH), 124.5 (CH), 121.2 (CH), 120.5 (CH), 115.6 (CH), 61.0 (CH_2).

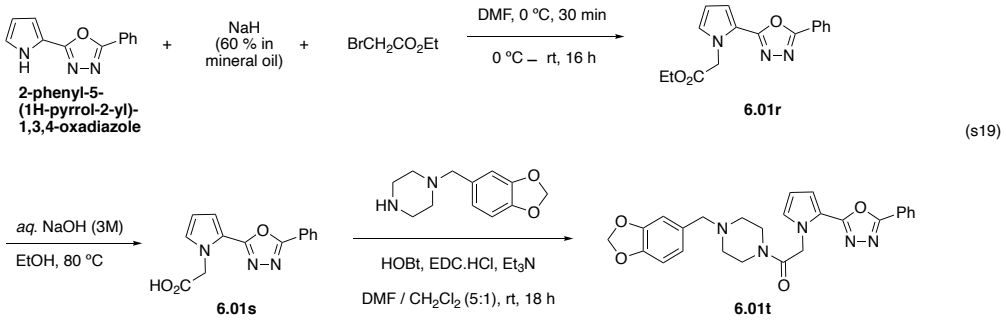


6.01b'

6.01q

(s18)

6.01q. To a solution of 0.088 g of **6.01b'** (0.30 mmol) in CH_2Cl_2 (20 mL / 1 mmol) at 0 °C was added 0.187 g of triphosgene (0.63 mmol) and Et_3N (7.50 mL / 1 mmol). The mixture was stirred at 0 °C for 30 mins. 0.059 g of 3-amino pyridine (0.63 mmol) was added to the reaction mixture and stirred for another 3 h at rt. Solvent was concentrated *in vacuo* and purified using MPLC (EtOAc followed by 19:1 EtOAc:MeOH) to give **6.01q**, as a white solid (0.046 g, 36%). ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.80 (s, 1H), 8.69 (s, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 8.16 – 8.15 (m, 1H), 8.01 – 7.99 (m, 2H), 7.92 – 7.90 (m, 1H), 7.65 – 7.58 (m, 3H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.27 (dd, *J* = 8.5 Hz, 5.0 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 5.43 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 165.2 (C), 163.3 (C), 153.2 (C), 153.1 (C), 143.2 (CH), 140.5 (CH), 137.0 (C), 134.2 (C), 132.8 (CH), 130.0 (CH), 127.1 (CH), 125.5 (CH), 124.1 (CH), 123.5 (C), 120.6 (CH), 115.9 (CH), 60.6 (CH_2).



(s19)

6.01r. The compound was prepared by modifying the general procedure followed by Xie and co-workers.[25] To a solution of 0.121 g of 2-phenyl-5-(1H-pyrrol-2-yl)-1,3,4-oxadiazole (0.60 mmol)[26] in anhydrous DMF (5 mL / 1 mmol of SM) at 0 °C was added 0.035 g of sodium hydride (0.90 mmol, 60% dispersion in mineral oil). The suspension was stirred at the same temperature for 1 h. It was then treated with 110 μL of ethyl bromoacetate (0.90 mmol) in 2 mL of DMF. The reaction was stirred at 0 °C and warmed to rt and stirred for an additional 16 h. The residue was then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine and then dried over anhydrous sodium sulfate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give crude product which was purified using MPLC (5:1 hexanes:EtOAc – 2:1 hexanes:EtOAc) to give **6.01r**, as a yellow oil (0.117 g, 66%).^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.02

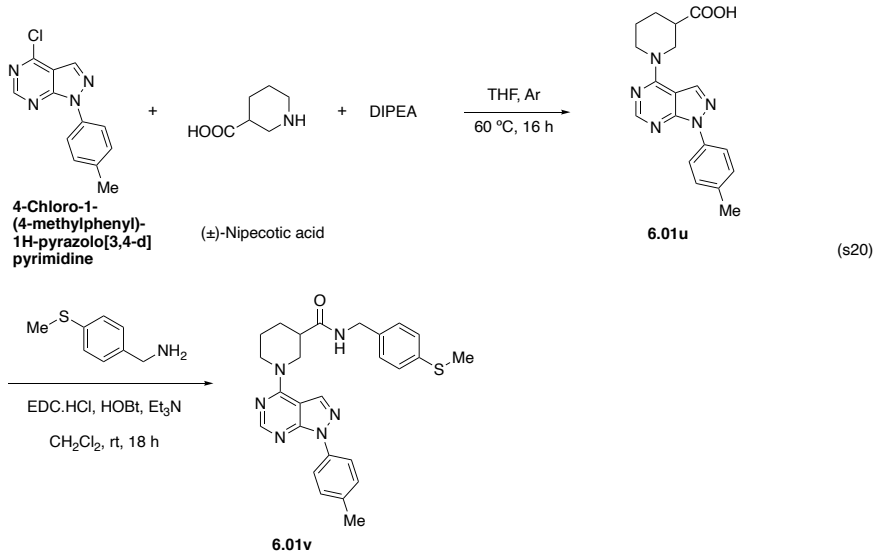
[25] Ding, H. S.; Yang, C. H.; Xie, Y. Y. *Synth. Commun.* **2005**, *35*, 2625.

[26] Compound prepared according to the reference provided on footnote 4.

(d, J = 6.5 Hz, 2H), 7.60 (d, J = 6.5 Hz, 3H), 7.22 (s, 1H), 7.04 – 7.03 (m, 1H), 6.29 (s, 1H), 5.30 (s, 2H), 4.13 (quartet, J = 7.0 Hz, 2H), 1.17 (t, J = 7.0 Hz, 3H) ; ^{13}C NMR (125 MHz, DMSO-*d6*) δ 169.2 (C), 162.5 (C), 159.1 (C), 132.4 (CH), 130.1 (CH), 129.9 (CH), 126.9 (CH), 123.7 (C), 117.3 (C), 115.0 (CH), 109.7 (CH), 61.2 (CH_2), 50.6 (CH_2), 14.5 (CH_3).

6.01s. The compound was prepared by a general procedure followed by Xie and co-workers. 0.117 g of **6.01r** (0.40 mmol) was dissolved in EtOH (7 mL / 1 mmol of 6.01r). 0.70 mL of 3M NaOH solution (2.00 mmol) was added and the mixture was stirred at 80 °C. The reaction was monitored by TLC. Once all the SM was consumed (1h), the reaction mixture was cooled to rt. 10 ml of water was added and the mixture was washed with CH_2Cl_2 (2 X 10 mL). Then, the water phase was acidified with dilute hydrochloride solution. Crude **6.01s** (0.097 g, 91%) was obtained after filtration and drying as a white solid which was taken to the next step without any additional characterization.

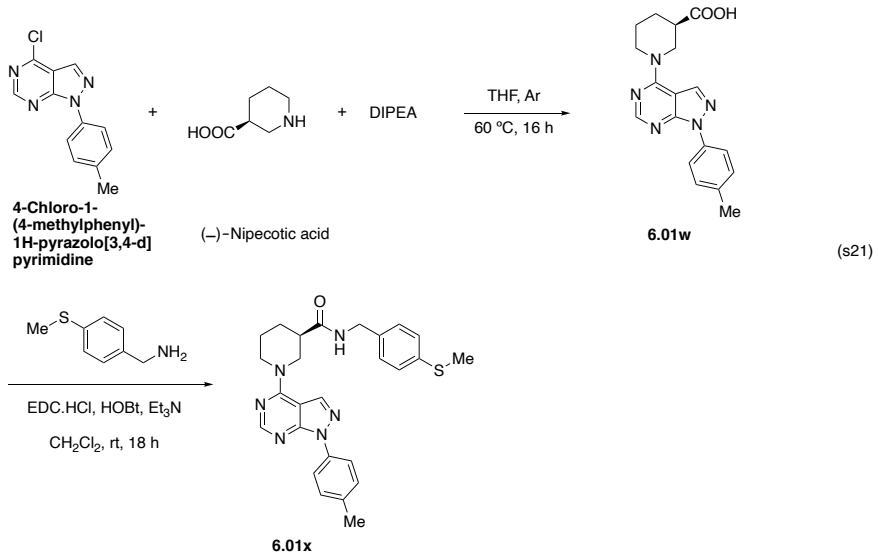
6.01t. To a solution of 0.043 g of **6.01s** (0.16 mmol), 0.029 g of commercially available 1-(4-Piperonyl)piperazine (0.13 mmol), 0.029 g of HOBt (0.21 mmol) and 0.052 g of EDC.HCl (0.27 mmol) in 5:1 anhydrous DMF : CH_2Cl_2 (10 mL / mmol of 6.01s), 35 µL of Et_3N (0.47 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.01t**, as a white solid (0.028 g, 37%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.03 – 8.01 (m, 2H), 7.64 – 7.57 (m, 3H), 7.11 (s, 1H), 6.98 (t, J = 2.0 Hz, 1H), 6.88 – 6.84 (m, 2H), 6.76 (d, J = 7.5 Hz, 1H), 6.24 – 6.24 (m, 1H), 5.98 (s, 2H), 5.38 (s, 2H), 3.54 – 3.53 (m, 2H), 3.43 – 3.40 (m, 4H), 2.48 – 2.46 (m, 4H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 166.2 (C), 162.3 (C), 159.4 (C), 147.7 (C), 146.7 (C), 132.3 (CH), 132.0 (C), 130.2 (CH), 129.9 (CH), 126.9 (CH), 123.7 (C), 122.6 (CH), 117.5 (C), 114.6 (CH), 109.6 (CH), 109.3 (CH), 108.4 (CH), 101.3 (CH_2), 62.0 (CH_2), 52.8 (CH_2), 52.4 (CH_2), 50.8 (CH_2).



6.01u. The compound was prepared by modifying a general procedure followed by Riguera and co-workers.[27] Under an inert atmosphere of Argon , 0.050 g of commercially available 4-Chloro-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (0.20 mmol) and 0.026 g of commercially available *rac*-Nipecotic acid (0.20 mmol) in THF (10 mL / 1 mmol of SM) was added 34 μL of DIPEA (0.20 mmol). The reaction mixture was refluxed for 16 h. After the reaction mixture was cooled to rt, the solvent was concentrated *in vacuo* and purified using MPLC (EtOAc followed by 15:1 EtOAc:MeOH) to give **6.01u**, as a white powder (0.023 g, 33%); ^{1}H NMR (500 MHz, CD_3OD) δ 8.31 (s, 1H), 8.26 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.87 (s, 2H), 4.36 – 4.33 (m, 1H), 3.62 – 3.53 (m, 2H), 2.67 – 2.62 (m, 1H), 2.40 (s, 3H), 2.16 – 2.11 (m, 1H), 1.93 – 1.86 (m, 2H), 1.68 – 1.61 (m, 1H) ; ^{13}C NMR (125 MHz, CD_3OD) δ 175.1 (C), 156.9 (C), 155.1 (CH), 153.6 (C), 136.9 (C), 136.1 (C), 134.1 (CH), 129.2 (CH), 122.3 (CH), 101.2 (C), 40.8 (CH), 26.8 (CH_2), 23.9 (CH_2), 19.7 (CH_3) (only visible peaks).

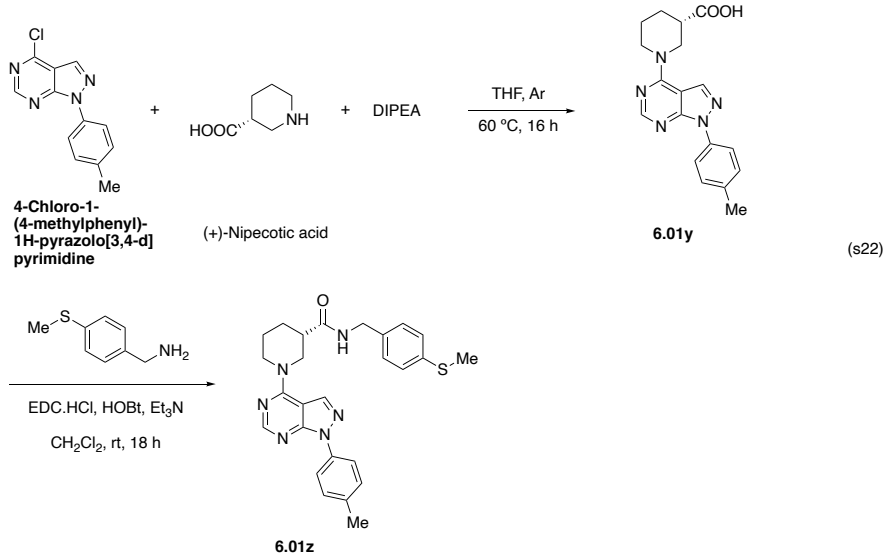
6.01v. To a solution of 0.023 g of **6.01u** (0.07 mmol), 0.012 g of commercially available 4-(Methylthio)benzyl amine (0.08 mmol), 0.015 g of HOBt (0.11 mmol) and 0.027 g of EDC.HCl (0.14 mmol) in CH_2Cl_2 (10 mL / mmol of 6.01u), 20 μL of Et_3N (0.11 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.01v**, as a white powder (0.019 g, 59%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.51 (s, 1H), 8.47 (t, *J* = 5.5 Hz, 1H), 8.37 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.20 (m, 4H), 4.25 (d, *J* = 4.0 Hz, 2H), 3.41 – 3.33 (m, 5H), 2.45 (s, 3H), 2.37 (s, 3H), 1.99 – 1.95 (m, 1H), 1.90 – 1.82 (m, 2H), 1.59 – 1.50 (m, 1H) ; ^{13}C NMR (125 MHz, DMSO-*d6*) δ 172.8 (C), 156.7 (C), 155.8 (CH), 154.2 (C), 136.8 (C), 136.7 (C), 136.2 (C), 135.2 (CH), 129.9 (CH), 128.3 (CH), 126.6 (CH), 121.6 (CH), 110.0 (C), 101.4 (C), 42.4 (CH), 42.0 (CH_2), 28.0 (CH_2), 24.6 (CH_3), 24.5 (CH_3), 21.0 (CH_2), 15.4 (CH_2) (only visible peaks).

[27] Quintela, M.; Peinador, C.; Gonza, L.; Devesa, I.; Alcaraz, J.; Riguera, R.; Ferra, M. L. *Bioorg. Med. Chem.* **2003**, *11*, 863.



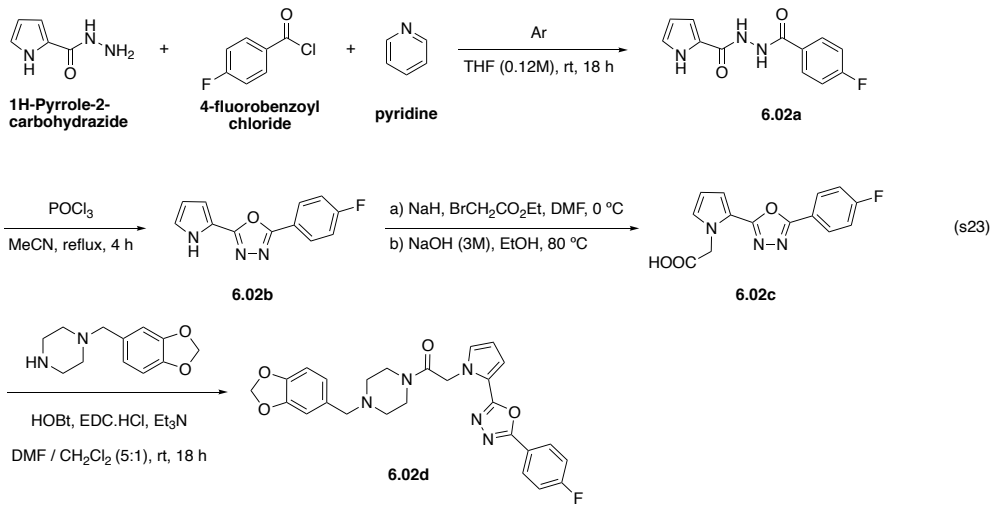
6.01w. The compound was prepared by same procedure as followed to synthesize **6.01u** using 0.050 g of commercially available 4-Chloro-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (0.20 mmol), 0.026 g of commercially available (–)-Nipecotic acid (0.20 mmol) and 34 μL of DIPEA (0.20 mmol). The crude product was purified using MPLC (EtOAc followed by 15:1 EtOAc:MeOH) to give **6.01w**, as a white powder (0.047 g, 70%); The NMR of **6.01w** matched that of **6.01u**.

6.01x. To a solution of 0.044 g of **6.01w** (0.13 mmol), 0.025 g of commercially available 4-(Methylthio)benzyl amine (0.16 mmol), 0.030 g of HOBt (0.22 mmol) and 0.052 g of EDC.HCl (0.27 mmol) in CH_2Cl_2 (10 mL / mmol of 6.01w), 32 μL of Et_3N (0.22 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.01x**, as a white powder (0.036 g, 58%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.51 (s, 1H), 8.47 (t, *J* = 5.5 Hz, 1H), 8.37 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.24 – 7.20 (m, 4H), 4.25 (d, *J* = 4.5 Hz, 2H), 3.40 – 3.36 (m, 5H), 2.45 (s, 3H), 2.37 (s, 3H), 1.99 – 1.95 (m, 1H), 1.89 – 1.82 (m, 2H), 1.58 – 1.51 (m, 1H) ; ^{13}C NMR (125 MHz, DMSO-*d6*) δ 172.8 (C), 156.7 (C), 155.8 (CH), 154.2 (C), 136.8 (C), 136.7 (C), 136.2 (C), 135.2 (CH), 129.9 (CH), 128.3 (CH), 126.6 (CH), 121.6 (CH), 110.0 (C), 101.4 (C), 42.4 (CH), 42.0 (CH_2), 28.0 (CH_2), 24.6 (CH_3), 24.5 (CH_3), 21.0 (CH_2), 15.4 (CH_2) (only visible peaks).



6.01y. The compound was prepared by same procedure as followed to synthesize **6.01u** using 0.050 g of commercially available 4-Chloro-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (0.20 mmol), 0.026 g of commercially available (+)-Nipecotic acid (0.20 mmol) and 34 µL of DIPEA (0.20 mmol). The crude product was purified using MPLC (EtOAc followed by 15:1 EtOAc:MeOH) to give **6.01y**, as a white powder (0.052 g, 77%); The NMR of **6.01y** matched that of **6.01u**.

6.01z. To a solution of 0.050 g of **6.01y** (0.15 mmol), 0.028 g of commercially available 4-(Methylthio)benzyl amine (0.18 mmol), 0.032 g of HOBt (0.24 mmol) and 0.060 g of EDC.HCl (0.32 mmol) in CH_2Cl_2 (10 mL / mmol of 6.01y), 36 µL of Et_3N (0.24 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.01z**, as a white powder (0.042 g, 59%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.50 (s, 1H), 8.47 (t, J = 5.5 Hz, 1H), 8.36 (s, 1H), 8.03 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.23 – 7.21 (m, 4H), 4.25 (d, J = 3.5 Hz, 2H), 3.39 – 3.35 (m, 5H), 2.45 (s, 3H), 2.37 (s, 3H), 1.98 – 1.94 (m, 1H), 1.89 – 1.81 (m, 2H), 1.59 – 1.49 (m, 1H) ; ^{13}C NMR (125 MHz, DMSO-*d6*) δ 172.9 (C), 156.7 (C), 155.8 (CH), 154.2 (C), 136.8 (C), 136.7 (C), 136.1 (C), 135.2 (CH), 129.9 (CH), 128.3 (CH), 126.6 (CH), 121.6 (CH), 110.0 (C), 101.4 (C), 42.4 (CH), 42.0 (CH_2), 28.0 (CH_2), 24.6 (CH_3), 24.5 (CH_3), 21.0 (CH_2), 15.4 (CH_2) (only visible peaks).



(s23)

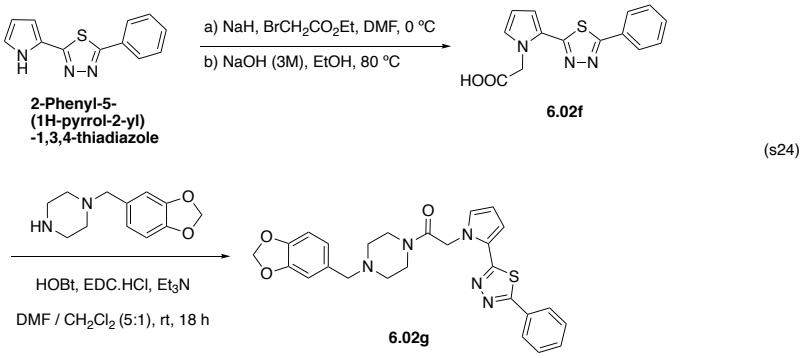
6.02a. The compound was prepared using a general procedure followed by Robba and co-workers.[28] To 0.350 g of 1H-pyrrole-2-carbohydrazide (2.80 mmol) in tetrahydrofuran (6 mL / 1 mmol of hydrazide) was added 0.33 mL of 4-fluorobenzoyl chloride (2.80 mmol) and 0.46 ml pyridine (5.60 mmol) at room temperature under Argon. After 18 h of stirring at room temperature, the desired product precipitated. The precipitate was filtered, washed with minimum dichloromethane and methanol and dried to afford **6.02a** as a white solid (0.544 g, 79%).^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.40 (s, 1H), 10.03 (s, 1H), 8.01 – 7.99 (m, 2H), 7.38 – 7.35 (m, 2H), 6.94 (s, 2H), 6.15 (s, 1H) ; ^{13}C NMR (125 MHz, DMSO-*d6*) δ 165.6 (C), 165.5 (d, J_{C-F} = 216.8 Hz, C), 160.8 (C), 130.6 (d, J_{C-F} = 9.0 Hz, CH), 129.6 (C), 124.6 (C), 122.7 (CH), 116.0 (d, J_{C-F} = 21.5 Hz, CH), 111.5 (CH), 109.3 (CH).

6.02b. The compound was prepared using a general procedure followed by Robba and co-workers. To 0.156 g of **6.02a** (0.63 mmol) was added 25 μL phosphoryl trichloride (0.26 mmol). The reaction was stirred for 25 minutes at 120 °C. The reaction was cooled to 0 °C and ice was added. The resulting solid was filtered, and washed with water, NH_4OH, CH_2Cl_2 and EtOAc to give crude **6.02b**, as a yellow solid (0.046 g, 32%), which was taken to the next step without any additional purification. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.18 – 8.15 (m, 2H), 7.37 – 7.34 (m, 2H), 7.11 – 7.10 (m, 1H), 7.02 – 7.01 (m, 1H), 6.36 (t, *J* = 3.0 Hz, 1H).

6.02c. The compound was prepared by same procedure as followed to synthesize **6.01r** and **6.01s,** using 0.046 g of 6.02b (0.20 mmol), 0.015 g of sodium hydride (0.30 mmol, 60% dispersion in mineral oil), 32 μL of ethyl bromoacetate (0.30 mmol) in 2 mL of DMF to give crude product which was treated with 0.50 mL of 3M NaOH solution (1.00 mmol) to give crude **6.02c**, as a white solid (0.054 g, 94% over two steps), which was taken to the next step without any additional characterization.

[28] Compound prepared according to the reference provided on footnote 4.

6.02d. To a solution of 0.015 g of **6.02c** (0.05 mmol), 0.010 g of commercially available 1-(4-Piperonyl)piperazine (0.04 mmol), 0.010 g of HOBt (0.068 mmol) and 0.017 g of EDC.HCl (0.088 mmol) in 5:1 anhydrous DMF : CH_2Cl_2 (10 mL / mmol of 6.02c), 10 µL of Et_3N (0.068 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.02d**, as a white powder (0.013 g, 62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.95 (m, 2H), 7.12 – 7.09 (m, 2H), 6.87 – 6.84 (m, 2H), 6.75 (s, 1H), 6.64 (s, 2H), 6.22 – 6.21 (m, 1H), 5.83 (s, 2H), 5.30 (s, 2H), 3.50 (bs, 4H), 3.35 (s, 2H), 2.44 (bs, 2H), 2.31 (bs, 2H).

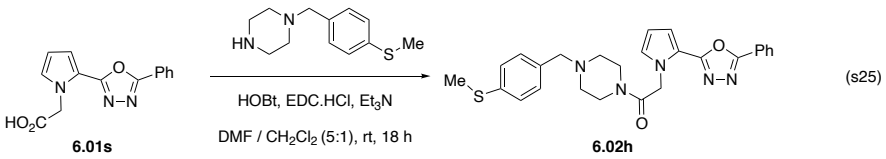


(s24)

6.02f. The compound was prepared by same procedure as followed to synthesize **6.01r** and **6.01s,** using 0.060 g of 2-Phenyl-5-(1H-pyrrol-2-yl)-1,3,4-thiadiazole (0.30 mmol), 0.022 g of sodium hydride (0.45 mmol, 60% dispersion in mineral oil), 60 µL of ethyl bromoacetate (0.45 mmol) in 2 mL of DMF to give crude product which was treated with 0.40 mL of 3M NaOH solution (1.15 mmol) to give crude **6.02f**, as a white solid (0.049 g, 58% over two steps), which was taken to the next step without any additional characterization.

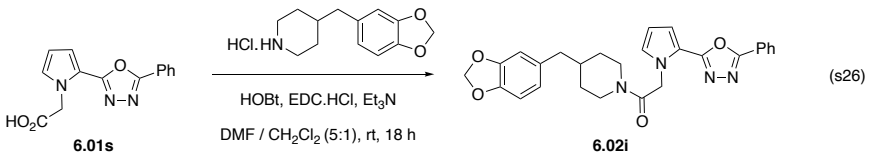
6.02g. To a solution of 0.036 g of **6.02f** (0.13 mmol), 0.024 g of commercially available 1-(4-Piperonyl)piperazine (0.11 mmol), 0.023 g of HOBt (0.17 mmol) and 0.043 g of EDC.HCl (0.22 mmol) in 5:1 anhydrous DMF : CH_2Cl_2 (10 mL / mmol of 6.02f), 30 µL of Et_3N (0.17 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.02g**, as a white powder (0.024 g, 44%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.96 (q, *J* = 3.0 Hz, 2H), 7.58 (t, *J* = 3.0 Hz, 3H), 7.07 (bs, 1H), 6.90 (d, *J* = 0.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.82 – 6.81 (m, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.23 – 6.22 (m, 1H), 6.00 (s, 2H), 5.43 (s, 2H), 3.57 – 3.56 (m, 2H), 3.45 – 3.42 (m, 4H), 2.51 (bs, 2H), 2.31 (bs, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 166.3 (C), 164.9 (C), 160.5 (C), 156.5 (C), 147.7 (C), 146.7 (C),

132.1 (C), 131.6 (CH), 130.0 (CH), 129.9 (CH), 128.0 (CH), 122.5 (CH), 116.5 (CH), 109.6 (CH), 109.5 (CH), 108.3 (CH), 101.3 (C), 62.1 (CH_2), 55.4 (CH_2), 52.8 (CH_2), 52.5 (CH_2), 50.9 (CH_2), 44.8 (CH_2), 42.2 (CH_2).



6.01s 6.02h (s25)

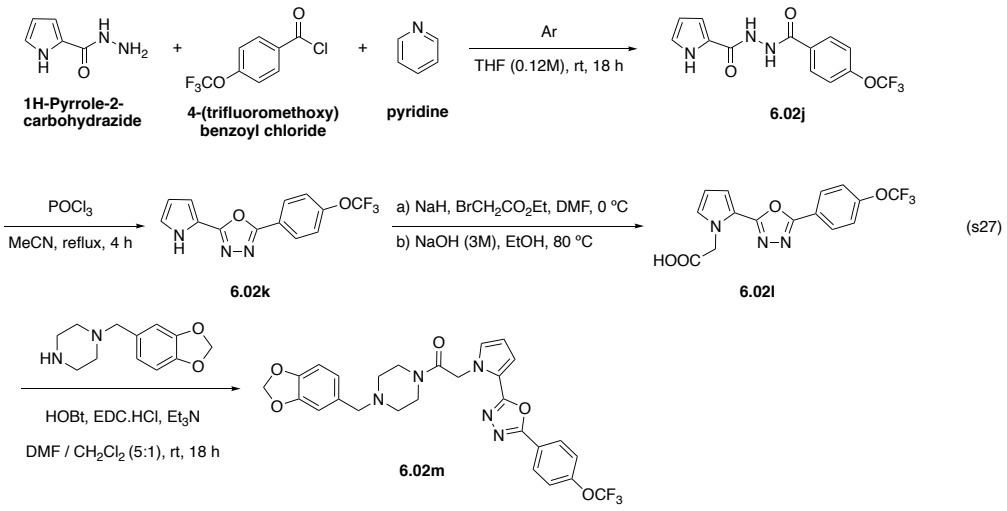
6.02h. To a solution of 0.019 g of **6.01s** (0.071 mmol), 0.013 g of commercially available 1-[(4-Methylthio)benzyl]piperazine (0.059 mmol), 0.012 g of HOBt (0.09 mmol) and 0.024 g of EDC.HCl (0.12 mmol) in 5:1 anhydrous DMF : CH_2Cl_2 (10 mL / mmol of 6.01s), 20 µL of Et_3N (0.09 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.02h**, as a brown powder (0.014 g, 48%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.04 (d, *J* = 7.0 Hz, 2H), 7.66 – 7.59 (m, 3H), 7.29 – 7.24 (m, 4H), 7.14 (bs, 1H), 7.01 – 7.00 (m, 1H), 6.27 – 6.26 (m, 1H), 5.40 (s, 2H), 3.57 (bs, 2H), 3.43 (bs, 2H), 2.51 (bs, 4H), 2.48 (s, 3H), 2.32 (bs, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 166.2 (C) 162.3 (C), 159.4 (C), 137.1 (C), 134.8 (C), 132.3 (C), 130.2 (CH), 130.1 (CH), 129.9 (CH), 126.9 (CH), 126.3 (CH), 123.7 (C), 117.9 (CH), 114.6 (CH), 109.2 (CH), 61.8 (CH_2), 52.9 (CH_2), 52.5 (CH_2), 50.8 (CH_2), 44.7 (CH_2), 42.1 (CH_2), 15.3 (CH_3).



6.01s 6.02i (s26)

6.02i. To a solution of 0.019 g of **6.01s** (0.071 mmol), 0.015 g of commercially available 4-(1,3-Benzodioxol-5-ylmethyl)piperidine (0.059 mmol), 0.012 g of HOBt (0.09 mmol) and 0.024 g of EDC.HCl (0.12 mmol) in 5:1 anhydrous DMF : CH_2Cl_2 (10 mL / mmol of 6.01s), 20 µL of Et_3N (0.09 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.02i**, as a brown powder (0.013 g, 47%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.05 – 8.04 (m, 2H), 7.66 – 7.60 (m, 3H), 7.14 – 7.13 (m, 1H), 7.00 (q, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.79 (bs, 1H), 6.65 – 6.63 (1H), 6.27 – 6.26 (m, 1H), 5.97 (s, 2H), 5.44 – 5.34 (m, 2H), 4.26 – 4.22 (m, 1H), 3.96 – 3.91 (m, 1H), 3.09 – 3.03 (m, 1H), 2.58 – 2.54 (m, 1H), 2.51 – 2.47 (m, 2H), 1.79 – 1.74 (m, 1H), 1.69 – 1.64 (m, 1H), 1.58 – 1.53 (m, 1H), 1.36 – 1.25 (m, 1H), 1.03 – 0.92 (m, 1H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 165.8 (C), 162.3(C),

159.4 (C), 147.6 (C), 145.8 (C), 134.3 (C), 132.3 (CH), 130.2 (CH), 129.9 (CH), 126.8 (CH), 123.8 (C), 122.3 (CH), 117.5 (C), 114.6 (CH), 109.8 (CH), 109.2 (CH), 108.4 (CH), 101.1 (CH_2), 50.9 (CH_2), 44.8 (CH_2), 42.3 (CH_2), 42.2 (CH_2), 37.8 (CH), 32.3 (CH_2), 31.7 (CH_2).



6.02j. The compound was prepared using a general procedure followed by Robba and co-workers.[29] To 0.350 g of 1H-pyrrole-2-carbohydrazide (2.80 mmol) in tetrahydrofuran (6 mL / 1 mmol of hydrazide) was added 0.44 mL of 4-(trifluoromethoxy)benzoyl chloride (2.80 mmol) and 0.46 ml pyridine (5.60 mmol) at room temperature under Argon. After 18 h of stirring at room temperature, the desired product precipitated. The precipitate was filtered, washed with minimum dichloromethane and methanol and dried to afford crude **6.02j** as a white solid (0.544 g, 79%).^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.51 (s, 1H), 10.08 (s, 1H), 8.90 (d, *J* = 5.0 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 2H), 6.15 – 6.14 (m, 1H);

6.02k. The compound was prepared using a general procedure followed by Robba and co-workers. To 0.626 g of **6.02j** (2.00 mmol) was added 0.37 mL phosphoryl trichloride (3.92 mmol). The reaction was stirred for 25 minutes at 120 °C. The reaction was cooled to 0 °C and ice was added. The resulting solid was filtered, and washed with water, NH_4OH, CH_2Cl_2 and EtOAc and purified by MPLC (7:1 hexanes:EtOAc) to give crude **6.02k**, as a yellow solid (0.294 g, 50%). ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.20 (d, *J* = 9.0 Hz, 7.63 (d, *J* = 8.5 Hz, 2H), 7.16 – 7.15 (m, 1H), 6.96 – 6.95 (m, 1H), 6.33 – 6.31 (m, 1H).

[29] Compound prepared according to the reference provided on footnote 4.

6.02l. The compound was prepared by same procedure as followed to synthesize **6.01r** and **6.01s,** using 0.100 g of 6.02k (0.34 mmol), 0.025 g of sodium hydride (0.51 mmol, 60% dispersion in mineral oil), 55 μL of ethyl bromoacetate (0.51 mmol) in 2 mL of DMF to give crude product which was treated with 0.60 mL of 3M NaOH solution (1.70 mmol) to give crude **6.02l**, as a white solid (0.120 g, 100% over two steps), which was taken to the next step without any additional characterization.

6.02m. To a solution of 0.120 g of **6.02l** (0.34 mmol), 0.062 g of commercially available 1-(4-Piperonyl)piperazine (0.28 mmol), 0.060 g of HOBt (0.44 mmol) and 0.111 g of EDC.HCl (0.58 mmol) in 5:1 anhydrous DMF : CH_2Cl_2 (10 mL / mmol of 6.02c), 70 μL of Et_3N (0.44 mmol) was added. The reaction mixture was stirred at rt for 18 h. The mixture was diluted with 20 mL of H_2O and extracted with EtOAc (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and purified using MPLC (EtOAc) to give **6.02m**, as a white powder (0.070 g, 45%); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.15 (s, 1H), 7.01 – 7.00 (m, 1H), 6.89 (bs, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.26 (d, *J* = 2.5 Hz, 1H), 6.00 (s, 2H), 5.40 (s, 2H), 3.56 (bs, 2H), 3.43 (bs, 4H), 2.48 (bs, 2H), 2.30 (bs, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 166.1 (C), 161.3 (C), 159.6 (C), 150.9 (C), 147.7 (C), 146.7 (C), 132.0 (C), 130.4 (CH), 129.2 (CH), 122.9 (C), 122.5 (CH), 122.3 (CH), 120.4 (q, J_{C-F} = 255.5 Hz, C), 117.3 (C), 114.8 (CH), 109.6 (CH), 109.3 (CH), 108.3 (CH), 101.3 (CH_2), 62.0 (CH_2), 52.9 (CH_2), 52.5 (CH_2), 50.8 (CH_2), 44.7 (CH_2), 42.1 (CH_2).

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APPENDIX

VITA

Wrickban Mazumdar
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845 W Taylor Street, Room 4500, Chicago, IL 60607. Phone: 312-282-9463, Email: wmazum2@uic.edu

Summary

- Six years research experience in organic chemistry involving strategic planning for compound design, synthesis, reaction mechanism studies, and medicinal chemistry
- Strong academic background in organic chemistry, biochemistry, organometallics, and analytical chemistry
- Solid hands-on experiences on HPLC, UPLC, GC/LC-MS, LC-MS/MS, Prep-LC, NMR, FTIR, UV/Vis spectroscopy, handling air-sensitive chemicals with air-free techniques
- Experience in literature mining, writing/publishing scientific articles, and presentations at research symposiums demonstrating strong written and oral communication skills

Research Experiences

Graduate Research Assistant, Organic Chemistry, University of Illinois at Chicago, Chicago, IL **Fall 2014-May 2020**
Research Advisor: Prof. Tom Driver

- Synthesized, isolated, characterized, purified > 500 organic compounds resulting in 2 peer reviewed publications
- Organic method development and reaction optimization of 3+ new transition metal-mediated reactions to synthesize *N*-heterocycles
- Designed and synthesized > 50 NAMPT-targeted small molecule therapeutics to treat pulmonary arterial hypertension
- Collaborated with colleagues and cross-functional experts to propose 2+ new ideas to identify a drug target resulting in 1 patent
- Data interpretation using NMR, HPLC, GC/LC-MS, and X-ray crystallography
- Contributed in lab management and mentored 2 undergraduate and 1 graduate students

Senior Executive in Analytical Research and Development, Dr. Reddy's Laboratories, Hyderabad, India **2010-2011**

- Assisted in developing analytical methods for complex formulations and transferring methods to other analytical release functions to support the timely release of API batches
- Partnered with other analytical functions to evolve, integrate and optimize analytical support.
- Carry out assay, identification of unknown impurities of a formulation, dissolution profile of a drug using dissolution apparatus, HPLC and GC.

Research Intern, Chemistry, Indian Institute of Technology, Mumbai, India **Spring 2013**
Research Advisor: Prof. Rodney Fernandes

- Assisted graduate students in developing methodologies for tandem oxidative dihydroxylation of vinyl and alkenyl benzyl alcohols
- Learned common separation techniques and analytical techniques to characterize the molecules synthesized

Publications and Patents (* Advisor)

1. Tianning Deng, **Wrickban Mazumdar,** Russel Ford, Navendu Jana, Ragda Izar, Donald J. Wink, Tom Driver*, "Oxidation of Non-Activated Anilines to Generate *N*-Aryl Nitrenoids." *J. Am. Chem. Soc*. **2020**, *142*, 4456.
2. **Wrickban Mazumdar,** Navendu Jana, Bryant T. Thurman, Donald J. Wink, Tom Driver*. "Rh_2(II)-Catalyzed Ring Expansion of Cyclobutanol-Substituted Aryl Azides To Access Medium-Sized N-Heterocycles." *J. Am. Chem. Soc*. **2017**, *139*, 5031.
3. Tom Driver*, **Wrickban Mazumdar,** Xinyu Guan, Naijing Su, Angelia Denise Lockett, Roberto F. Machado, Kiira Ratia, Jason Ralph Hickok. "Nicotinamide phosphoribosyltransferase inhibitors and methods for use of the same." International Patent Application No. PCT/US19/16684 filed 2-16-2019.
4. Tom Driver*, **Wrickban Mazumdar,** Xinyu Guan, Naijing Su, Angelia Denise Lockett, Roberto F. Machado, Kiira Ratia, Jason Ralph Hickok. "Novel Nicotinamide Phosphoribosyltransferase Inhibitors as Potential Treatment for Pulmonary Arterial Hypertension." UIC Invention Disclosure 2018-090.

Presentations

1. MIKI Conference, College of Pharmacy, University of Illinois at Chicago **2018**
   "Synthesis of NAMPT-Targeted Small Molecule Therapeutics for Pulmonary Arterial Hypertension"
   Wrickban Mazumdar, Xinyu Guan, Naijing Su, Tom Driver*, Roberto F. Machado, Kiira Ratia, Jason Ralph Hickok

2. Chemistry Graduate Student Association Research Colloquium, University of Illinois at Chicago **2016**
   "Rh_2(II)-Catalyzed Ring Expansion of Cyclobutanol-Substituted Aryl Azides To Access Medium-Sized N-Heterocycles"
   Wrickban Mazumdar, Navendu Jana, Bryant T. Thurman, Donald J. Wink, Tom Driver*

3. Chicago Organic Symposium, University of Illinois at Chicago **2015**
   "Rh_2(II)-Catalyzed Ring Expansion of Cyclobutanol-Substituted Aryl Azides To Access Medium-Sized N-Heterocycles"
   Wrickban Mazumdar, Navendu Jana, Bryant T. Thurman, Donald J. Wink, Tom Driver*

Technical/Language Skills/Hobbies

- Chemistry lab techniques (e.g. HPLC, UPLC, GC/LCMS, LC-MS/MS, Prep-LC, NMR, FTIR, UV/Vis, etc.)
- ChemDraw, Microsoft Office (Excel, PowerPoint, Word), Scifinder, Reaxys
- Fluent in English, Bengali, Hindi
- Passionate cook, Tennis player, Music lover

Education Background

Graduate Research Assistant, Organic Chemistry, University of Illinois at Chicago, IL	**Fall 2014-May 2020**
Master of Science, Vellore Institute of Technology, Vellore, India	**2011-2013**
Bachelor of Science, Osmania University, Hyderabad, India	**2007-2010**

Teaching Experiences

- Teaching Assistant, Department of Chemistry, University of Illinois at Chicago
- Organic Chemistry I, Organic Chemistry II and Organic Chemistry Lab
- General Chemistry I, General Chemistry II and General Chemistry Lab

Achievements and Awards

- University gold medalist, Vellore Institute of Technology, Vellore, India
- Best poster award for the research work entitled "Investigations on synthesis and medicinal properties of Novel Organometallic Complexes- A Neglected Area of Research" organized by the International Consortium on Affordable Medical Technologies-CAMTech, Vellore, India

References

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