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Arene Dearomatization via Radical Hydrofunctionalization

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Arene Dearomatization via Radical Hydrofunctionalization

By

Kelly A. McDaniel

B.S., University of Mary Washington, 2017

Advisor: Nathan T. Jui, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
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Abstract

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Dearomative functionalization methods are highly sought-after for their ability to efficiently transform simple, planar aromatics to more complex, three-dimensional structures. We envisioned the extension of previously developed olefin hydroarylation systems to the hydroarylation of arenes. We initially found success in the photoredox-catalyzed hydroarylation of indoles, where an organic cyanoarene catalyst and trialkylamine reductant proved key to selective product formation. Mechanistically, radical termination occurred primarily via stepwise reduction/protonation, with a small contribution from concerted hydrogen atom transfer. This mechanistic understanding prompted the extension of this reactivity to benzenoid dearomatization, where aryl radical cyclization onto unactivated arenes yielded spirocyclic 1,4-diene products. In this case, selectivity is dictated by regioselective protonation of the Birch-like dienyl anion. This broadly applicable method allowed for the rapid synthesis of an NPY Y5 receptor antagonist. Finally, the dearomative cyclization of α-acyl radicals to form spirocyclic lactam products was demonstrated. In exploring this reactivity, we discovered that the rate of reductive radical formation must be slower than the rate of reductive radical-polar crossover. Otherwise, a buildup of the cyclized radical intermediate occurs, leading to dimerization via radical-radical coupling. This method was effective across a broad range of (hetero)arenes. Derivatization of the resulting spirocyclic lactam/cyclohexadiene products was shown, including the synthesis of the anticonvulsant Gabapentin. The transformations described herein demonstrate the rapid formation of drug-like, three-dimensional products from simple aromatic precursors.

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Jeff, I am so grateful to have chosen the desk next to you when joining the Jui lab. I am also grateful for colorful silica plugs, needle caps, and the sulfamide for bringing us closer together. Your friendship and love have helped me through some of my toughest times. I am so lucky to be starting the next phase of my life with you by my side. To our sweet girls, Maddie and Lizzie, thank you for filling every night and weekend with incessant purring, extreme cuteness, and unlimited cuddles.

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List of Abbreviations

3DPA2FBN	2,4,6-tris(diphenylamino)-3,5-difluorobenzonitrile
3DPAFIPN	2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile
4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
5CzBN	pentabenzyl 6-cyanobenzene-1,2,3,4,5-pentacarboxylate
AcOH	acetic acid
AIBN	azobisisobutyronitrile
APCI	atmospheric-pressure chemical ionization
ASE	aromatic stabilization energy
CDI	1,1'-carbonyldiimidazole
CySH	cyclohexanethiol
CV	cyclic voltammetry
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFT	density functional theory
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
DMF	dimethylformamide
EI	electron ionization
ESI	electrospray ionization
Et_2O	diethyl ether
EtOAc	ethyl acetate

FTIR	Fourier-transform infrared spectroscopy
GCMS	gas chromatography mass spectrometry
HAT	hydrogen atom transfer
HBTU	*N,N,N′,N′*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HDH	hydrodehalogenation
HEH	Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
LCMS	liquid chromatography mass spectrometry
LRMS	high-resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
***m*CPBA**	*meta*-chloroperoxybenzoic acid
MeCN	acetonitrile
MeOH	methanol
NBO	natural bond orbital
N-POX(Ph$_2$)$_2$	3,7-di([1,1'-biphenyl]-4-yl)-10-(naphthalen-1-yl)-10*H*-phenoxazine
NMR	nuclear magnetic resonance
PC	photocatalyst
PCET	proton-coupled electron transfer
PDI	*N*,*N*-bis(2,6-diisopropylphenyl)perylene3,4,9,10-bis(dicarboximide)
PhSH	thiophenol

PTFE	polytetrafluoroethylene
SCE	saturated calomel electrode
SET	single electron transfer
SI	supporting information
T3P	propanephosphonic acid cyclic anhydride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography

Chapter 1

Introduction to Radical Dearomatization

1.1 Dearomatization

Aromatic petroleum resources (i.e., benzene, toluene, xylenes) serve as crucial elementary synthetic precursors, and the manipulation of petrochemical derivatives, such as aryl halides in cross-coupling reactions, is essential to the production of agrichemicals and pharmaceuticals.[1] Given the three-dimensional nature of enzymatic architecture, methods that deliver stereochemically dense scaffolds from readily available arenes are highly attractive (Figure 1.1),[2] but overcoming thermodynamic aromatic stabilization energy (ASE; 36 kcal/mol for benzene)[3] remains a critical challenge.

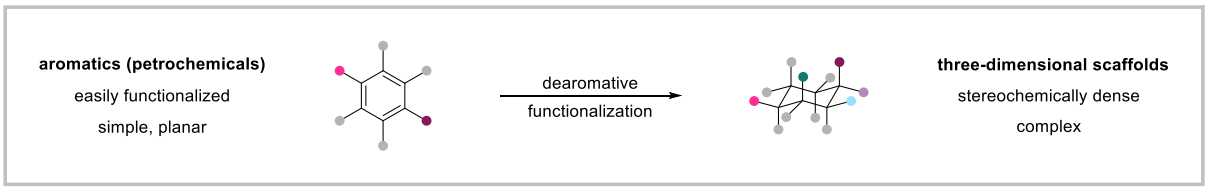

Figure 1.1: Attributes of dearomative functionalization

There are a number of existing approaches to dearomatization, including simple reductive methods (net addition of H_2) and dearomative functionalization methods, which add additional complexity to the ring system.

---

[1] (a) Magano, J.; Dunetz, J. R. Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals. *Chem. Rev.* **2011**, *111*, 2177−2250. (b) Watson, W. Transition Metal-Catalyzed Couplings in Process Chemistry: Case Studies from the Pharmaceutical Industry. *Org. Process Res. Dev.* **2014**, *18*, 277. (c) Devendar, P.; Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F. Palladium-Catalyzed Cross-Coupling Reactions: A Powerful Tool for the Synthesis of Agrochemicals. *J. Agric. Food Chem.* **2018**, *66*, 8914− 8934. (d) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium- Catalyzed C-N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564 −12649.

[2] (a) Kingwell, K. Exploring the Third Dimension. *Nat. Rev. Drug Discovery* **2009**, *8*, 931. (b) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.

[3] (a) Schleyer, P. V. R.; Puhlhofer, F. Recommendations for the Evaluation of Aromatic Stabilization Energies. *Org. Lett.* **2002**, *4*, 2873−2876. (b) Wertjes, W. C.; Southgate, E. H.; Sarlah, D. Recent Advances in Chemical Dearomatization of Nonactivated Arenes. *Chem. Soc. Rev.* **2018**, *47*, 7996−8017.

1.1.1 Established dearomatization methods

Simple dearomatization

One of the earliest approaches to dearomatization is the Birch reduction, which converts a benzene derivative to a 1,4-cyclohexadiene (Scheme 1.1A).[4] This reaction utilizes an alkali metal and ammonia to form a solvated electron, which reduces the aromatic ring. Alkenes are typically unreactive under these conditions, so the system is not reduced past the 1,4-diene product. In contrast, high-pressure hydrogenation methods fully reduce benzenoids to cyclohexane products (Scheme 1.1B).[5] These methods typically rely on a transition-metal catalyst, which, in the presence of a chiral ligand, can facilitate stereoselective reduction. Complete reduction occurs since the initial benzene hydrogenation has a high kinetic barrier due to ASE, while the barrier to subsequent alkene hydrogenation is significantly lower.

Dearomative functionalization

Arene dioxygenase enzymes enact benzenoid *cis*-dihydroxylation in a highly stereoselective manner (Scheme 1.1C).[6] These enzymes utilize an NADH-dependent flavoprotein reductase, iron-sulfur clusters, and an Fe^{II} center to add O_2 to an arene. Phenol oxidation is another oxidative dearomatization method (Scheme 1.1D).[7] A common approach to this transformation is the use of hypervalent iodine reagents, which activate phenol for nucleophilic addition at the 2- or 4-position, resulting in the formation of substituted dienone products. A number of dearomative

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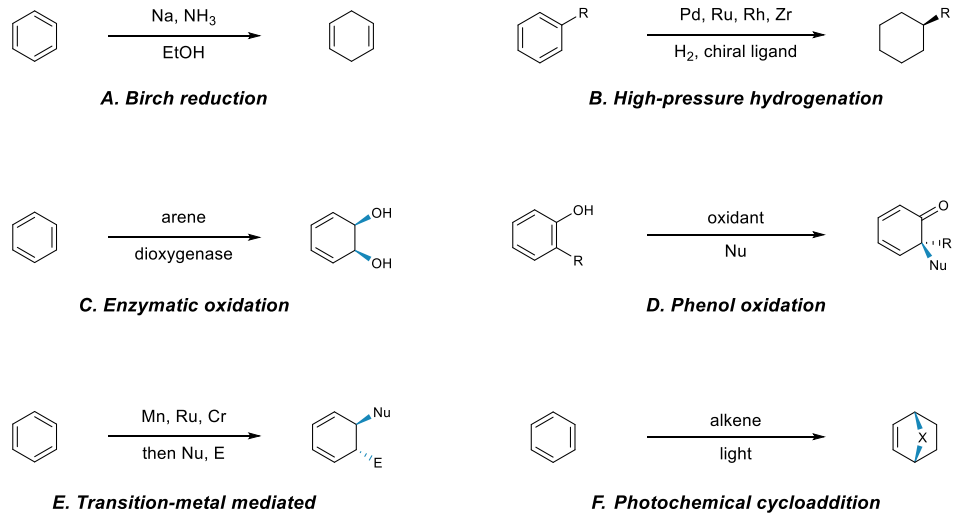
[4] Rabideau, P. W. The Birch Reduction of Aromatic Compounds. *Org. React.* **1992**, *42*, 1−334.
[5] (a) Stanislaus, A.; Cooper, B. H. Aromatic Hydrogenation Catalysis: A Review. *Catal. Rev.: Sci. Eng.* **1994**, *36*, 75−123. (b) Wiesenfeldt, M. P.; Nairoukh, Z.; Dalton, T.; Glorius, F. Selective Arene Hydrogenation for Direct Access to Saturated Carbo- and Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 10460−10476.
[6] (a) Hudlicky, T.; Olivo, H. F.; McKibben, B. Microbial Oxidation of Aromatics in Enantiocontrolled Synthesis. 3. 1 Design of Amino Cyclitols (Exo-Nitrogenous) and Total Synthesis of (+)-Lycoricidine via Acylnitrosyl Cycloaddition to Polarized 1-Halo-1, 3-Cyclohexadienes. *J. Am. Chem. Soc.* **1994**, *116*, 5108−5115. (b) Boyd, D. R.; Bugg, T. D. H. Arene Cis-Dihydrodiol Formation: From Biology to Application. *Org. Biomol. Chem.* **2006**, *4*, 181−192.
[7] Pouységu, L.; Deffieux, D.; Quideau, S. Hypervalent Iodine-Mediated Phenol Dearomatization in Natural Product Synthesis. *Tetrahedron* **2010**, *66*, 2235−2261.

functionalization reactions are transition-metal mediated (Scheme 1.1E).[8] In these cases, a transition-metal catalyst coordinates to an arene (η^6 or η^2), activating it for the stepwise addition of a nucleophile then electrophile. Stereoselectivity can be imparted through the use of a chiral auxiliary, ligand, or nucleophile. Dearomative photochemical cycloaddition reactions demonstrate the unique reactivity that is possible under photochemical conditions.[9] The photoexcitation of a benzene derivative is followed by cycloaddition with an alkene (Scheme 1.1F); this reactivity is inaccessible in the arene ground state. A recent example of this reactivity is the visible-light mediated cycloaddition between arenophiles (e.g. *N*-methyl-1,2,4-triazoline-3,5-dione) and simple arenes demonstrated by the Sarlah lab.[10] *In situ* functionalization of the cycloadducts allows for the synthesis of complex cyclohexene products.

Scheme 1.1: Established dearomatization methods

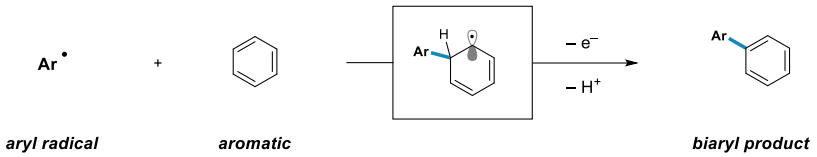


[8] Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. Transition-Metal-Mediated Dearomatization Reactions. *Chem. Rev.* **2000**, *100 (8)*, 2917−2940.
[9] Cornelisse, J. The Meta Photocycloaddition of Arenes to Alkenes. *Chem. Rev.* **1993**, *93*, 615−669.
[10] Wertjes, W. C.; Southgate, E. H.; Sarlah, D. Recent Advances in Chemical Dearomatization of Nonactivated Arenes. *Chem. Soc. Rev.* **2018**, *47*, 7996−8017.

1.1.2 Hypothesis: Dearomatization with high-energy aryl radicals

We aimed to develop a dearomatization method complementary to those already well-established, envisioning the hydroarylation of arenes via photochemically-generated aryl radical intermediates. Radicals are high energy species that can overcome ASE, as is demonstrated by the Minisci reaction.[11] Mechanistically, radical addition breaks aromaticity but is followed by single electron oxidation and protonation, yielding the functionalized aromatic product (Scheme 1.2). A successful method for the reductive hydroarylation of arenes would evade this undesired oxidative pathway.

Scheme 1.2: Undesired Minisci reactivity



1.2 Aryl radicals

1.2.1 Traditional methods for aryl radical generation

Highly-reactive aryl radicals can be generated in a number of ways. Arenediazonium salts, which are formed from the corresponding anilines, are converted to aryl radicals via single-electron reduction and N_2 extrusion. This reactivity can be accessed under electrochemical, stoichiometric metal mediated, and photocatalytic conditions.[12] However, arenediazonium salts are unstable, highly reactive, and difficult to access from heteroaromatic anilines.

---

[11] Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic character of alkyl radicals—VI : A new convenient selective alkylation of heteroaromatic bases. *Tetrahedron* **1971**, *27*, 3575–3579.

[12] (a) Kindt, S.; Heinrich, M. R., Recent Advances in Meerwein Arylation Chemistry. *Synthesis* **2016,** *48*, 1597-1606. (b) Galli, C., Radical reactions of arenediazonium ions: An easy entry into the chemistry of the aryl radical. *Chem. Rev.* **1988,** *88*, 765-792.

Aryl radicals can also be generated from aryl halides, which are commercially available and more stable than their arenediazonium salt counterparts. The generation of aryl radicals from aryl halides traditionally occurs under atom transfer [e.g. Bu_3SnH or $(Me_3Si)_3SiH$] or reductive conditions (e.g. SmI_2).[13] However, many of these harsh, toxic methods demonstrate limited scopes.

1.2.2 Aryl radical generation via photoredox catalysis

Recently, photoredox catalysis has emerged as an efficient approach to the mild, selective generation of radicals.[14] Through this approach, highly-selective radical reactivity is possible

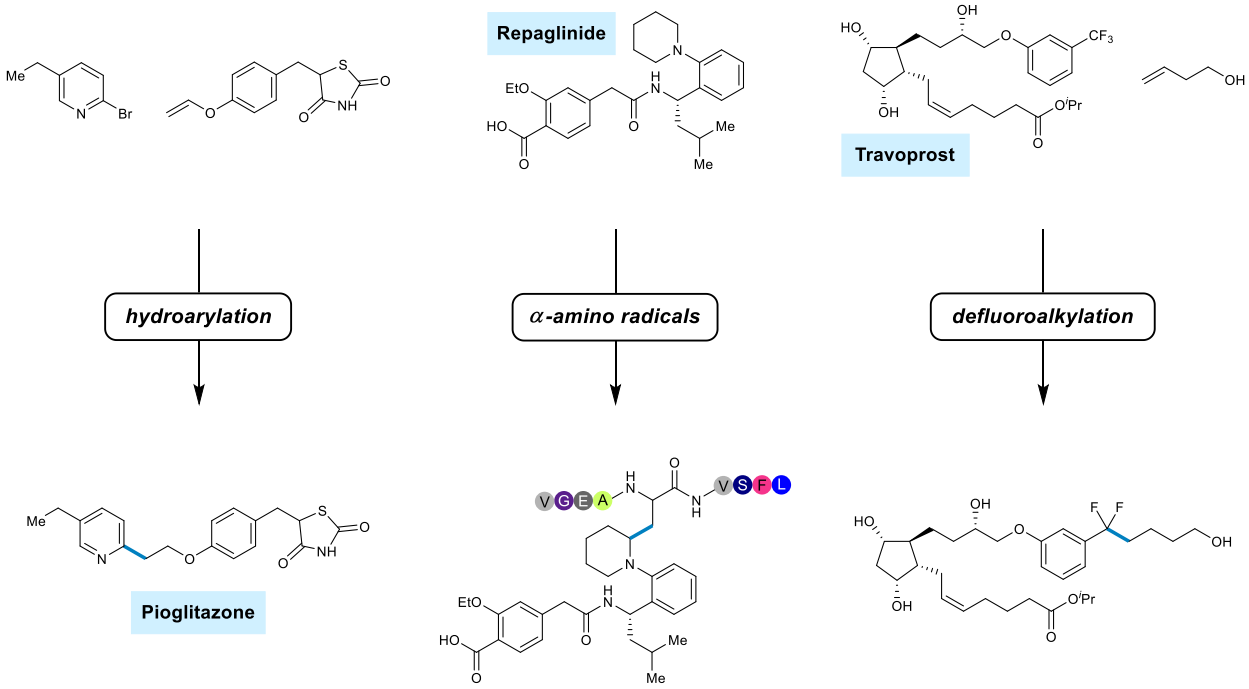


Figure 1.2: Highly-selective photoredox-catalyzed radical reactions in the Jui lab

[13] (a) Curran, D. P.; Jasperse, C. P.; Totleben, M. J., Approximate absolute rate constants for the reactions of tributyltin radicals with aryl and vinyl halides. *J. Org. Chem.* **1991,** *56*, 7169-7172. (b) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B., Tris(trimethylsilyl)silane as a radical-based reducing agent in synthesis. *J. Org. Chem.* **1991,** *56*, 678-683. (c) Krief, A.; Laval, A.-M., Coupling of Organic Halides with Carbonyl Compounds Promoted by SmI2, the Kagan Reagent. *Chem. Rev.* **1999,** *99*, 745-778.

[14] (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W., Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev.* **2013,** *113*, 5322-5363. (b) Romero, N. A.; Nicewicz, D. A., Organic Photoredox Catalysis. *Chem. Rev.* **2016,** *116*, 10075-10166.

under conditions with high functional group tolerance. This is demonstrated by previous methods developed in the Jui lab (Figure 1.2), where selective radical generation and olefin addition occurs in the presence of a plethora of functional groups.[15]

Classical examples of photochemical reactions utilize high energy UV light with the ability to excite most organic molecules, making selectivity challenging.[16] In contrast, photoredox catalysis is powered by lower energy visible light, allowing for the selective excitation of photocatalysts, which in turn transfer energy to the reactants. This process is described in Figure 1.3. A photocatalyst (PC) is excited by visible light, resulting in the singlet excited state S_1. Intersystem crossing yields the long-lived triplet state T_1, which can act as either an oxidant or reductant. Under an oxidative quenching mechanism, the triplet state is oxidized to give $PC^{\bullet+}$, a powerful oxidant that returns to its ground state after performing a single-electron oxidation (Figure 1.3, top pathway). Conversely, under a reductive quenching mechanism, the triplet state is reduced to give $PC^{\bullet-}$, a powerful reductant that returns to its ground state after performing a single-electron reduction (Figure 1.3, bottom pathway).[17]

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[15] (a) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T., Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018,** *140*, 15525-15534. (b) Aycock, R. A.; Pratt, C. J.; Jui, N. T., Aminoalkyl Radicals as Powerful Intermediates for the Synthesis of Unnatural Amino Acids and Peptides. *ACS Catal.* **2018,** *8*, 9115-9119. (c) Vogt, D. B.; Seath, C. P.; Wang, H.; Jui, N. T., Selective C–F Functionalization of Unactivated Trifluoromethylarenes. *J. Am. Chem. Soc.* **2019,** *141*, 13203-13211.

[16] John D. Robert and Marjorie C. Caserio, **1977**, *Basic Principles of Organic Chemistry, Second Edition.* W. A. Benjamin, Inc.

[17] (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W., Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev.* **2013,** *113*, 5322-5363. (b) Romero, N. A.; Nicewicz, D. A., Organic Photoredox Catalysis. *Chem. Rev.* **2016,** *116*, 10075-10166.

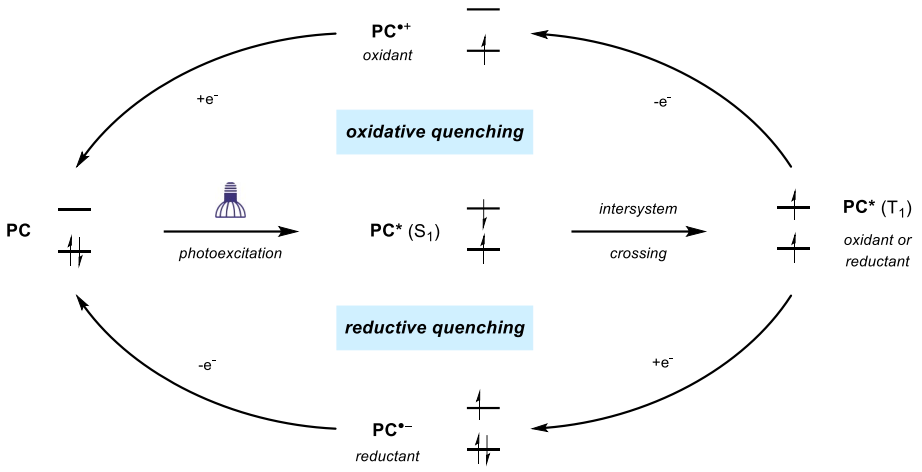
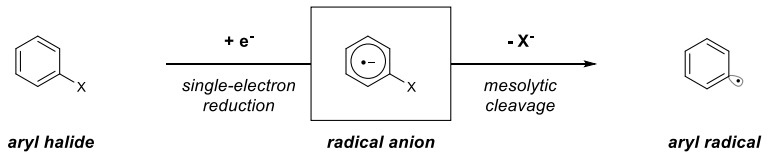


Figure 1.3: Photocatalytic quenching cycles

Under the principles of photoredox catalysis, aryl radical formation occurs through the single-electron reduction of an aryl halide by PC* (oxidative quenching pathway) or $PC^{\bullet-}$ (reductive quenching pathway). The resulting radical anion undergoes mesolytic cleavage, expelling the halide anion and resulting in regioselective aryl radical formation (Scheme 1.3).

Scheme 1.3: Aryl radical formation via single-electron reduction of an aryl halide



Initial reports

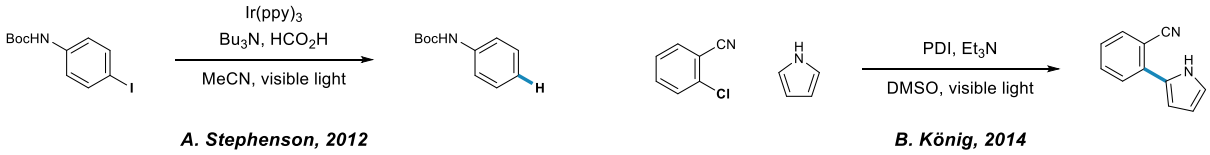
Aryl radical formation via visible-light-mediated photoredox catalysis was first reported in by the Stephenson lab in 2012.[18] Through the use of highly-reducing iridium photocatalyst *fac*-

[18] Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. Engaging unactivated alkyl, alkenyl and aryl iodides in visible-light-mediated free radical reactions. *Nat. Chem.* **2012**, *4*, 854–859.

$Ir(ppy)_3$ [$E_{1/2}°(Ir^{IV}/Ir^{III}*)$ = – 1.73 V vs SCE] powered by visible light and a tributylamine reductant, a range of aryl iodides were reduced to give hydrodehalogenation (HDH) products (Scheme 1.4A). This reduction is also demonstrated on alkyl and alkenyl iodides.

In 2014, the König lab described a more highly-reducing organic photocatalyst, *N*,*N*-bis(2,6-diisopropylphenyl)perylene3,4,9,10-bis(dicarboximide) (PDI). This catalyst undergoes a consecutive photoinduced electron transfer (conPET) mechanism in which $PDI^{\bullet-}$ absorbs visible light, undergoing a second excitation to form $PDI^{\bullet-}*$, the active reductant. With a triethylamine reductant, a range of aryl iodides, bromides, and chlorides are reduced to give hydrodehalogenation products. Additionally, the coupling of these aryl radicals with pyrrole was demonstrated, with 25-50 equivalents of the trapping agent required (Scheme 1.4B). [19]

Scheme 1.4: Seminal reports of photoredox-catalyzed aryl radical formation



A. Stephenson, 2012 ***B. König, 2014***

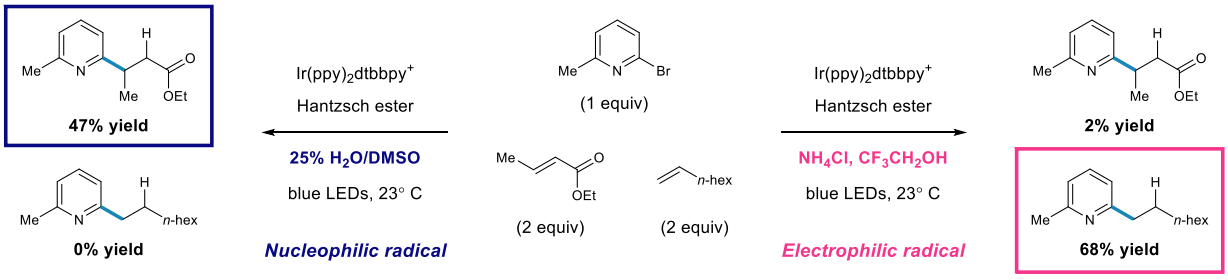
Aryl radicals in the Jui lab: Olefin hydroarylation

Because hydrogen atom transfer to aryl radicals is rapid, coupling reactions with aryl radicals are challenging and often require a large excess of the coupling partner to overcome the propensity towards hydrodehalogenation.[20] In surmounting this challenge, our group has made significant strides in the area of photoredox-catalyzed olefin hydroarylation. We initially tackled

[19] Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B. Reduction of aryl halides by consecutive visible light-induced electron transfer processes. *Science* **2014**, *346*, 725-728.
[20] Ghosh, et al. *Science* **2014**, *346*, 725-728.

the Giese-type coupling of pyridyl radicals with conjugate acceptors.[21] An iridium photocatalyst in concert with Hantzsch ester (HEH; stoichiometric reductant and H-atom source) in H_2O/DMSO reduces halopyridines in the presence of blue light. Conjugate addition of the resulting nucleophilic pyridyl radical leads to hydroarylation products (Scheme 1.5, left). Soon after, a similar protocol was developed for the hydroarylation of simple olefins.[22] In this case, a change in solvent to 2,2,2-trifluoroethanol along with an acid additive results in an electrophilic pyridyl radical that undergoes addition to unactivated alkenes (Scheme 1.5, right). Importantly, selectivity between these systems is high, as shown in Scheme 1.5. Upon subjecting a mixture of 2-bromo-6-methylpyridine, ethyl crotonate, and 1-octene to the H_2O/DMSO conditions, exclusive coupling with the electron-poor alkene is seen. When the conditions are modified to acidic CF_3CH_2OH solvent, high selectivity is seen for addition to the neutral alkene (68%) with a small amount of conjugate addition observed (2%). This experiment demonstrates the high levels of selectivity that can be achieved by radicals formed under mild conditions.

Scheme 1.5: Divergent reactivity of pyridyl radicals in different solvents



[21] Aycock, R. A.; Wang, H.; Jui, N. T. A Mild Catalytic System for Radical Conjugate Addition of Nitrogen Heterocycles. *Chem. Sci.* **2017**, *8*, 3121−3125.
[22] Boyington, A. J.; Riu, M. L. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 6582−6585.

The conditions for the hydroarylation of simple alkenes were later extended to the hydroarylation of functionalized olefins.[23] In this case, polarity reversal catalyst cyclohexanethiol (CySH) is a necessary additive. Mechanistically, the iridium photocatalyst is excited by blue light and undergoes reductive quenching from HEH•, yielding an Ir^{II} species and Hantzsch pyridine (HP). Single electron transfer (SET) from Ir^{II} to the bromopyridine is followed by mesolytic cleavage to yield a pyridyl radical. This radical, which is electrophilic in acidic CF_3CH_2OH, adds to the electron-rich olefin, yielding an α-oxy radical. This nucleophilic radical is efficiently trapped via hydrogen atom transfer (HAT) from CySH, yielding the desired hydroarylation product. The resulting electrophilic thiyl radical abstracts a hydrogen atom from nucleophilic HEH, regenerating CySH. In the absence of CySH, polymerization of the α-oxy radical is observed.

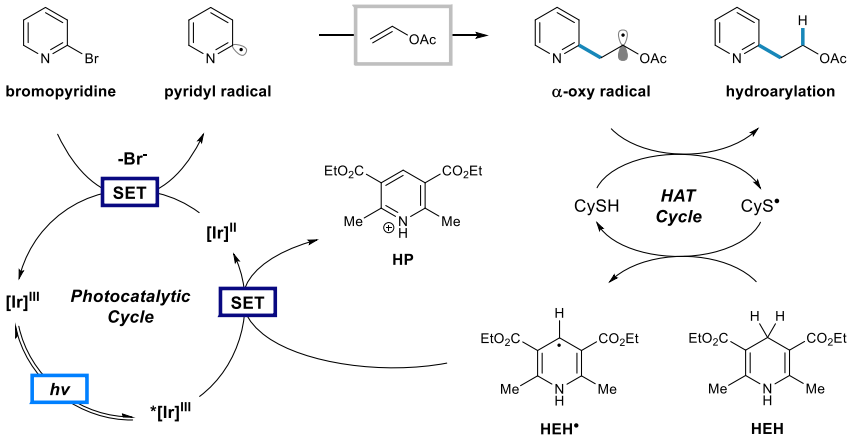


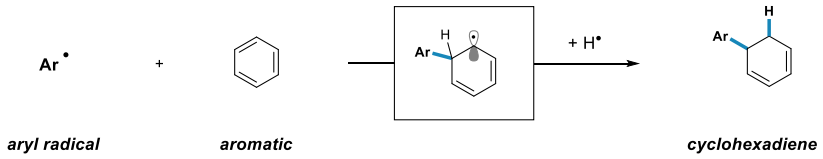
Figure 1.4: Mechanism for radical hydroarylation of functionalized olefins

[23] Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525−15534.

1.3 Dearomatization via photocatalytically-generated radicals

As previously discussed, aryl radicals are high-energy species that are known to add to aromatic systems; however, radical addition is typically followed by an oxidation/deprotonation sequence, leading to the restoration of aromaticity and formation of biaryl products.[24] We sought to overcome this challenge by applying mechanistic principles of olefin hydroarylation (Figure 1.4) to arene hydroarylation.[25] Under this net-reductive mechanism, aryl radical addition to an aromatic system would be followed by HAT, yielding cyclohexadiene products with the potential for further functionalization (Scheme 1.6).

Scheme 1.6: Desired hydroarylation mechanism



In this dissertation, we detail the development of a program for dearomative hydrofunctionalization reactions inspired by the olefin hydroarylation systems developed in the Jui lab. Systems for the intramolecular hydroarylation of indoles,[26] hydroarylation of unactivated

[24] (a) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic character of alkyl radicals—VI : A new convenient selective alkylation of heteroaromatic bases. *Tetrahedron* **1971**, *27*, 3575–3579. (b) Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B. Reduction of aryl halides by consecutive visible light-induced electron transfer processes. *Science* **2014**, *346*, 725-728.

[25] (a) Aycock, R. A.; Wang, H.; Jui, N. T. A Mild Catalytic System for Radical Conjugate Addition of Nitrogen Heterocycles. *Chem. Sci.* **2017**, *8*, 3121−3125. (b) Boyington, A. J.; Riu, M. L. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 6582−6585. (c) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525−15534. (d) Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z.; Jui, N. T. Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 4147−4153.

[26] McDaniel, K. A.; Jui, N. T. Dearomatization through Photoredox Hydroarylation: Discovery of a Radical-Polar Crossover Strategy. *Org. Lett.* **2021**, *23*, 5576–5580.

arenes,[27] and hydroalkylaton of (hetero)arenes[28] have been discovered for the synthesis of three-dimensional arylindoline and spirocyclic 1,4-diene products (Figure 1.5). Key to these systems is the unanticipated radical-polar crossover mechanism, where the cyclized radical intermediate is trapped via single-electron reduction, mitigating pathways leading towards the restoration of aromaticity. We detail additional mechanistic insights, along with the efficient synthesis of known drug molecules.

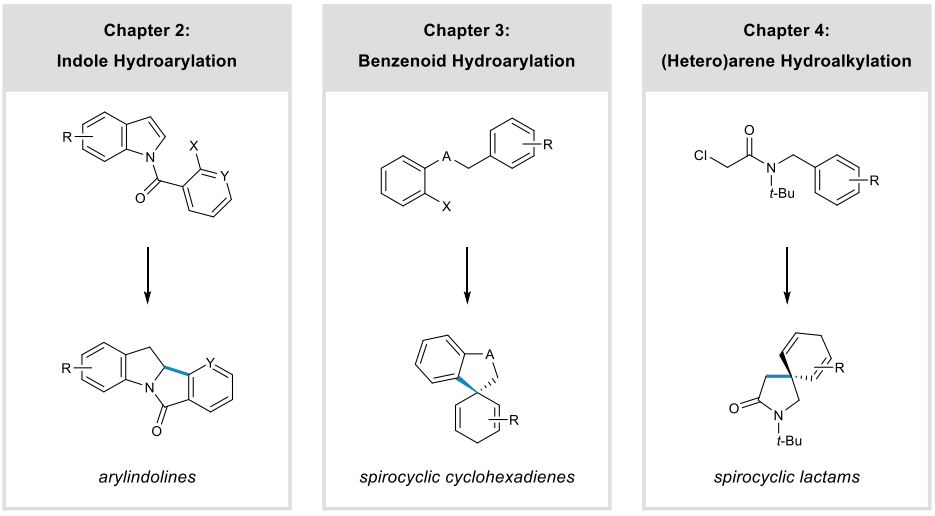


Figure 1.5: Summary of radical dearomatization reactions discussed in this dissertation

[27] Flynn, A. R.; McDaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020**, *142*, 9163–9168.
[28] McDaniel, K. A.; Blood, A. R.; Smith, G. C.; Jui, N. T. Dearomatization of Unactivated Arenes via Catalytic Hydroalkylation. *ACS Catal.* **2021**, *11*, 4968-4972.

Chapter 2

Dearomatization Through Photoredox Hydroarylation: Discovery of a Radical-Polar Crossover Strategy

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McDaniel, K. A.; Jui, N. T. *Org. Lett.* **2021**, *23*, 5576–5580.

https://doi.org/10.1021/acs.orglett.1c02006

Abstract: The dearomatization of indoles has been achieved via radical hydroarylation. Through the use of an organic photoredox catalyst powered by visible light and a trialkylamine reductant, a range of indole derivatives readily undergo hydroarylation to form 2-arylindoline products. Mechanistically, reductive aryl radical formation is followed by rapid 5-exo cyclization. The resulting radical intermediate is trapped through reductive radical-polar crossover. This work prompted our understanding of how reductive radical-polar crossover can drive highly-selective dearomatization pathways.

2.1 Introduction

Inspired by previous methods developed in the Jui lab for photoredox-catalyzed olefin hydroarylation (see section 1.2.2),[29] we imagined the hydroarylation of aromatic substrates under the same mechanistic paradigm (Figure 2.1A). We anticipated two major challenges to realizing this reactivity. The first was overcoming aromatic stabilization energy (ASE),[30] which would make radical addition to arenes more difficult than radical addition to olefins. The second challenge was the reductive trapping of the key radical intermediate (Figure 2.1A). In many processes that involve radical addition to arenes, such as the Minisci reaction,[31] the radical intermediate is rapidly oxidized then deprotonated, leading to the restoration of aromaticity. In order to avoid this

[29] (a) Aycock, R. A.; Wang, H.; Jui, N. T. A Mild Catalytic System for Radical Conjugate Addition of Nitrogen Heterocycles. *Chem. Sci.* **2017**, *8*, 3121−3125. (b) Boyington, A. J.; Riu, M. L. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 6582−6585. (c) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525−15534. (d) Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z.; Jui, N. T. Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 4147−4153.

[30] Schleyer, P. V. R.; Puhlhofer, F. Recommendations for the Evaluation of Aromatic Stabilization Energies. *Org. Lett.* **2002**, *4*, 2873−2876.

[31] Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic character of alkyl radicals—VI : A new convenient selective alkylation of heteroaromatic bases. *Tetrahedron* **1971**, *27*, 3575–3579.

undesired pathway, reductive trapping of this intermediate is crucial, and we imagined doing so through hydrogen atom transfer (HAT). We anticipated this process giving rise to cyclohexadiene products that could be further functionalized, giving rise to complex, three-dimensional structures.

Here, we detail the first system we developed for dearomatization, where radical indole dearomatization is terminated via unanticipated reductive radical-polar crossover (Figure 2.1B).

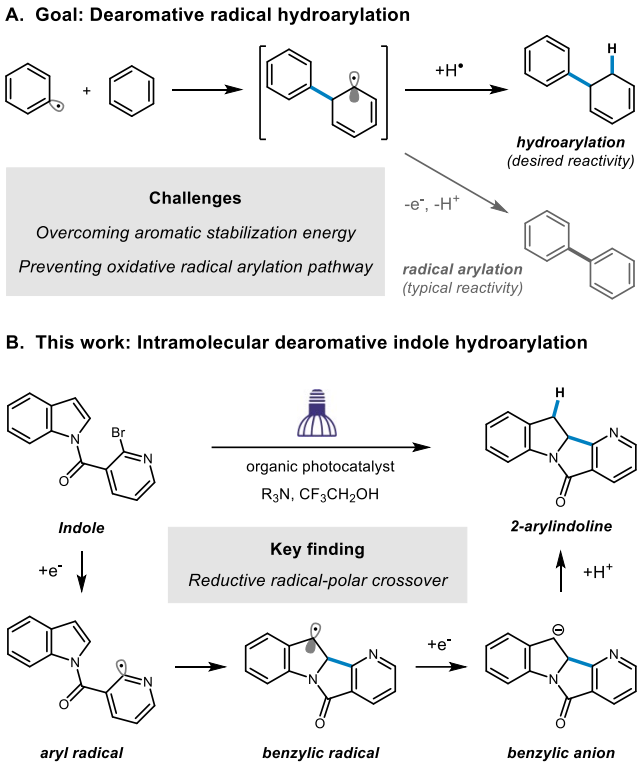

Figure 2.1: Hypothesis for photoredox-catalyzed dearomative hydroarylation

2.2 Results and Discussion

Under olefin hydroarylation conditions developed in our lab,[32] intermolecular dearomatization, such as that shown in Figure 2.1A, proved unsuccessful. As previously reported, the use of benzene as the acceptor arene resulted in biaryl products.[33] This finding led us to consider downstream parts of the catalytic cycle as key to unlocking the desired reactivity. We chose to interrogate the intramolecular dearomatization of indole substrate **1**, where intramolecular

[32] Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525−15534.
[33] (a) Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B., Reduction of aryl halides by consecutive visible light-induced electron transfer processes. *Science* **2014**, *346 (6210)*, 725-728. (b) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. Direct C−H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids. *J. Am. Chem. Soc.* **2010**, *132 (38)*, 13194-13196. (c) Boyington, A. J.; Riu, M. L. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 6582−6585.

cyclization of the pyridyl radical would allow us to focus on trapping the cyclized radical intermediate. It is notable that a substantial amount of work has been done by Jia,[34] Lautens,[35] and others[36] on the synthesis of this type of scaffold through reductive Heck reactions and Heck/anionic capture sequences. However, these methods operate with the requirement of the formation of a quaternary center at C2; without alkyl substitution at C2, β-hydride elimination occurs and the arylated indole product is formed. Radical approaches to this scaffold have been shown to form the arylindoline product without the need for C2 substitution; however, the scope of early methods is limited due to the use of harsh conditions [Bu_3SnH or $(Me_3Si)_3SiH$, AIBN, heat].[37] Recent work by Yu demonstrated a photoredox-catalyzed arylcarboxylation reaction,

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[34] (a) Shen, C.; Liu, R. R.; Fan, R. J.; Li, Y. L.; Xu, T. F.; Gao, J. R.; Jia, Y. X. Enantioselective Arylative Dearomatization of Indoles via Pd-Catalyzed Intramolecular Reductive Heck Reactions. *J Am Chem Soc* **2015,** *137 (15)*, 4936-4939. (b) Liu, R. R.; Wang, Y. G.; Li, Y. L.; Huang, B. B.; Liang, R. X.; Jia, Y. X. Enantioselective Dearomative Difunctionalization of Indoles by Palladium-Catalyzed Heck/Sonogashira Sequence. *Angew. Chem. Int. Ed. Engl.* **2017,** *56 (26)*, 7475-7478. (c) Liu, R. R.; Xu, T. F.; Wang, Y. G.; Xiang, B.; Gao, J. R.; Jia, Y. X. Palladium-catalyzed dearomative arylalkynylation of indoles. *Chem. Commun.* **2016,** *52 (94)*, 13664-13667. (d) Liang, R.-X.; Wang, K.; Wu, Q.; Sheng, W.-J.; Jia, Y. X. Palladium-Catalyzed Dearomative Arylvinylation Reaction of Indoles with N-Arylsulfonylhydrazones. *Organometallics* **2019,** *38 (20)*, 3927-3930. (e) Li, X.; Zhou, B.; Yang, R. Z.; Yang, F. M.; Liang, R. X.; Liu, R. R.; Jia, Y. X. Palladium-Catalyzed Enantioselective Intramolecular Dearomative Heck Reaction. *J. Am. Chem. Soc.* **2018,** *140 (42)*, 13945-13951. (f) Liang, R. X.; Xu, D. Y.; Yang, F. M.; Jia, Y. X. A Pd-catalyzed domino Larock annulation/dearomative Heck reaction. *Chem. Commun.* **2019,** *55 (53)*, 7711-7714. (g) Liang, R.-X.; Wang, K.; Song, L.-J.; Sheng, W.-J.; Jia, Y.X. Synthesis of tetracyclic indolin-3-ones through Pd-catalyzed intramolecular deacetylative dearomatization of 3-acetoxy-indoles. *RSC Advances* **2019,** *9 (25)*, 13959-13967.

[35] (a) Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. Dearomative Indole Bisfunctionalization via a Diastereoselective Palladium-Catalyzed Arylcyanation. *Org. Lett.* **2015,** *17 (19)*, 4838-4841. (b) Marchese, A. D.; Lind, F.; Mahon, A. E.; Yoon, H.; Lautens, M. Forming Benzylic Iodides via a Nickel Catalyzed Diastereoselective Dearomative Carboiodination Reaction of Indoles. *Angew. Chem. Int. Ed. Engl.* **2019,** *58 (15)*, 5095-5099. (c) Zeidan, N.; Beisel, T.; Ross, R.; Lautens, M. Palladium-Catalyzed Arylation/Heteroarylation of Indoles: Access to 2,3-Functionalized Indolines. *Org. Lett.* **2018,** *20 (22)*, 7332-7335. (d) Petrone, D. A.; Kondo, M.; Zeidan, N.; Lautens, M. Pd(0)-Catalyzed Dearomative Diarylation of Indoles. *Chem. Eur. J.* **2016,** *22 (16)*, 5684-5691.

[36] (a) Douki, K.; Ono, H.; Taniguchi, T.; Shimokawa, J.; Kitamura, M.; Fukuyama, T. Enantioselective Total Synthesis of (+)-Hinckdentine A via a Catalytic Dearomatization Approach. *J. Am. Chem. Soc.* **2016,** *138 (44)*, 14578-14581. (b) Zhao, L.; Li, Z.; Chang, L.; Xu, J.; Yao, H.; Wu, X. Efficient Construction of Fused Indolines with a 2-Quaternary Center via an Intramolecular Heck Reaction with a Low Catalyst Loading. *Org. Lett.* **2012,** *14 (8)*, 2066-2069. (c) Chen, S.; Wu, X. X.; Wang, J.; Hao, X. H.; Xia, Y.; Shen, Y.; Jing, H.; Liang, Y. M. Palladium-Catalyzed Intramolecular Dearomatization of Indoles via Decarboxylative Alkynyl Termination. *Org. Lett.* **2016,** *18 (16)*, 4016-4019. (d) Qin, X.; Lee, M. W. Y.; Zhou, J. S. Nickel-Catalyzed Asymmetric Reductive Heck Cyclization of Aryl Halides to Afford Indolines. *Angew. Chem. Int. Ed.* **2017,** *56 (41)*, 12723-12726. (e) Wang, H.; Wu, X. F. Palladium-Catalyzed Carbonylative Dearomatization of Indoles. *Org. Lett.* **2019,** *21 (13)*, 5264-5268.

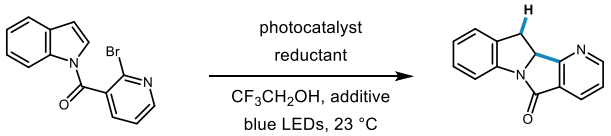
[37] (a) Zhang, W.; Pugh, G. Free radical reactions for heterocycle synthesis. Part 6: 2-Bromobenzoic acids as building blocks in the construction of nitrogen heterocycles. *Tetrahedron* **2003,** *59 (17)*, 3009-3018. (b) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. Radical cyclisation reactions with indoles. *Tetrahedron Lett.* **2003,** *44*, 1795-1798. (c)

where aryl radical cyclization is followed by reduction and nucleophilic addition to CO_2.[38] In a similar manner, our approach enables access to this scaffold without the need for C2 substitution.

2.2.1 Optimization of reaction conditions for indole hydroarylation

Upon subjecting **1** to conditions previously developed in our lab for the hydroarylation of functionalized olefins,[39] we obtained dearomatized product **2** in 40% yield. Modification of the conditions to increase the Hantzsch ester loading, increase the acidity, and decrease the concentration (see Supporting Information (SI) for details), led to the formation of cyclized product **2** in 77% yield (Table 2.1, entry 1). These conditions, however, were not ideal. Besides being extremely dilute (0.02 M) and using a precious metal photocatalyst, the Hantzsch ester byproduct, Hantzsch pyridine, made purification difficult. Consequently, we explored trialkylamine reductants, finding tributylamine as a suitable replacement with a yield of 59% (Table 2.1, entries 2-4). Increasing the reaction concentration and removing the thiol additive improved the yield to 84% (Table 2.1, entry

Table 2.1: Optimization of conditions for dearomative indole hydroarylation[a]



aryl radical precursor 1 — arylindoline product 2

entry	reductant	additive	photocatalyst	yield of **2**[d] (%)
1	HEH	AcOH, PhSH	$Ir(ppy)_2dtbbpy^+$	77
2	Et_3N	PhSH	$Ir(ppy)_2dtbbpy^+$	24
3	*i*-Pr_2NEt	PhSH	$Ir(ppy)_2dtbbpy^+$	43
4	Bu_3N	PhSH	$Ir(ppy)_2dtbbpy^+$	59
5[b]	Bu_3N	—	$Ir(ppy)_2dtbbpy^+$	84
6[b,c]	Bu_3N	—	4CzIPN	80
7[b,c]	Bu_3N	—	3DPAFIPN	83

[a] Conditions: aryl radical precursor (1 equiv), $[Ir(ppy)_2dtbbpy]PF_6$ (1 mol %), AcOH (20 equiv), reductant (3 equiv), PhSH (5 mol %), 2,2,2-trifluoroethanol (0.02 M), blue LEDs, 23 °C, 16h. [b]0.2 M. [c]5 mol % photocatalyst. [d]Yields determined by GC.

Zhang, W.; Pugh, G. Free radical reactions for heterocycle synthesis: formation of tri- and tetracyclic isoindolinones. *Tetrahedron Lett.* **1999,** *40*, 7591-7594.

[38] Zhou, W. J.; Wang, Z. H.; Liao, L. L.; Jiang, Y. X.; Cao, K. G.; Ju, T.; Li, Y.; Cao, G. M.; Yu, D. G. Reductive dearomative arylcarboxylation of indoles with CO_2 via visible-light photoredox catalysis. *Nat. Commun.* **2020,** *11 (1)*, 3263.

[39] Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525−15534.

5). This finding was surprising because our lab has previously seen thiol play a key role in hydrogen atom transfer processes.[40] Finally, we found that $Ir(ppy)_2dtbbpy^+$ can be replaced with the organic donor-acceptor cyanoarene catalysts 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) and 3DPAFIPN (2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile) to give **2** in comparable yield (Table 2.1, entries 6-7).[41]

At this point, an assortment of substrates underwent facile hydroarylation on a small scale; however, in many cases, these yields were inconsistent on a larger scale. While scalability can be challenging for photochemical reactions due to limited light penetration, the use of a light source with a higher photon flux did not solve this issue. Rather, we noticed that the solubility of both the photocatalyst and substrates was low and postulated that improving the solubility through the addition of a cosolvent would mitigate issues with light penetration. Indeed, the addition of toluene improved the solubility of the reaction components, and product yields became consistent across a range of scales (0.1 to 0.5 mmol). Therefore, the optimized conditions were modified to include a 25% (v/v) toluene cosolvent.

---

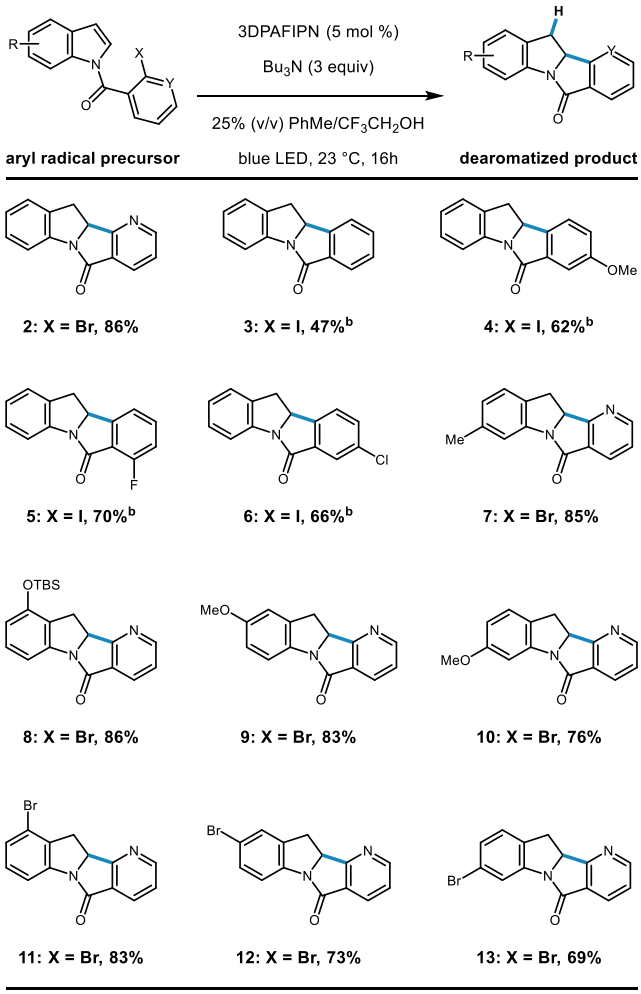
[40] (a) Wang, H.; Jui, N. T. Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, *140 (1)*, 163-166. (b) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525−15534. (c) Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z.; Jui, N. T. Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 4147−4153.

[41] (a) Uoyama, H.; Goushi, K.; Shizu, K.; Nomura, H.; Adachi, C. Highly Efficient Organic Light-Emitting Diodes from Delayed Fluorescence. *Nature* **2012**, *492*, 234−238. (b) Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353−15365.

2.2.2 Scope of dearomative hydroarylation

Under these conditions, hydroarylation of a variety of indole substrates was efficacious (Table 2.2). Both bromopyridines and aryl iodides effectively reduced and cyclized under these conditions (**2-3**, 47-86%). These aryl radical precursors were tolerant of electron-donating groups and further halogenation (**4-6**, 62-70%). Indole substitution is also well-tolerated. Electron-rich indoles containing methyl, silyl ether, and methoxy substituents undergo hydroarylation in great yields (**7-10**, 76-86%). Bromination at the 4, 5, and 6 position of indole is also tolerated and yields the desired dearomatized products in good yields (**11-13**, 69-83%), demonstrating the regioselective reduction of the most electron-poor ring in the system. These aryl bromides, which would not typically survive Pd-catalyzed arylation conditions, serve as handles for further reactivity.[42] A limitation of this method was seen with substrates

Table 2.2: Scope of dearomative indole hydroarylation[a]



[a]Conditions: aryl radical precursor (1.0 equiv), 3DPAFIPN (5 mol%), tributylamine (3.0 equiv), 25% (v/v) toluene/2,2,2-trifluoroethanol (0.1 M), blue LEDs, 23 °C, 16 h, isolated yields. [b]Conditions: aryl radical precursor (1.0 equiv), 4CzIPN (5 mol%), tributylamine (3.0 equiv), 2,2,2-trifluoroethanol (0.1 M), blue LEDs, 40 °C, 16 h, isolated yields.

[42] (a) Liu, R. R.; Wang, Y. G.; Li, Y. L.; Huang, B. B.; Liang, R. X.; Jia, Y. X., Enantioselective Dearomative Difunctionalization of Indoles by Palladium-Catalyzed Heck/Sonogashira Sequence. *Angew. Chem. Int. Ed.* **2017**, *56*,

containing electron-poor indoles. In these cases, we observed amide solvolysis instead of the desired arylindoline product.

2.2.3 Mechanism of indole hydroarylation reaction and analysis of termination event

Our initially proposed mechanism for indole hydroarylation based on our understanding of olefin hydroarylation systems is shown in Figure 2.2A. Reductive quenching of the excited state of the photocatalyst by tributylamine gives $PC^{\bullet-}$ ($3DPAFIPN^{\bullet-}$, $E_{1/2}° = -1.59$ V vs. SCE).[43] Single electron (SET) transfer to aryl radical precursor **1** delivers pyridyl radical **14** upon mesolytic cleavage. Intramolecular 5-*exo*-trig cyclization gives benzylic radical **15**. We anticipated the trapping of this dearomatized intermediate to occur through HAT from the oxidized amine, giving hydroarylation product **2**. To probe this mechanistic hypothesis, we replaced tributylamine with triethyl-d_{15}-amine, where HAT from the oxidized amine would result in deuterium incorporation in the product **2**. However, under these conditions, we saw only 5% deuterium incorporation at the benzylic position of **2**.

Subsequently, we interrogated the alternative mechanistic possibility: reductive radical-polar crossover. In this scenario, reduction of benzylic radial **15** to anion **16** ($E_{1/2}° = -1.24$ V vs SCE; see SI for details) followed by protonation yields dearomatized product **2**. By replacing TFE with 2,2,2-trifluoroethanol-OD under standard reaction conditions, we saw 86% deuterium incorporation at the benzylic position of **2**. This suggests that the operative mechanism in this system is reductive radical-polar crossover.

7475-7478. (b) Zeidan, N.; Beisel, T.; Ross, R.; Lautens, M., Palladium-Catalyzed Arylation/Heteroarylation of Indoles: Access to 2,3-Functionalized Indolines. *Org. Lett.* **2018**, *20*, 7332-7335. (c) Wang, H.; Wu, X. F., Palladium-Catalyzed Carbonylative Dearomatization of Indoles. *Org. Lett.* **2019**, *21*, 5264-5268.

[43] Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353−15365.

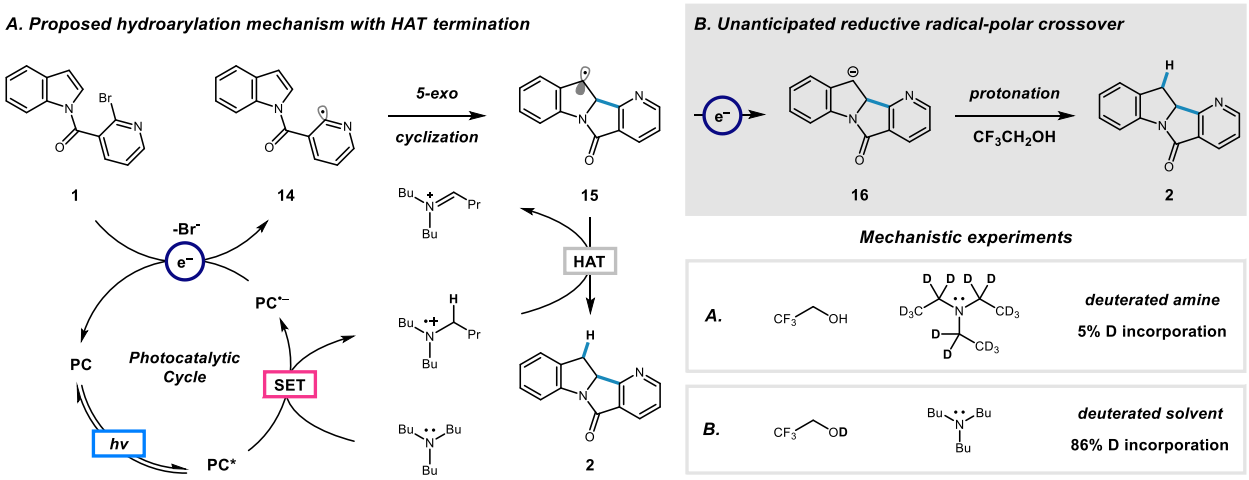


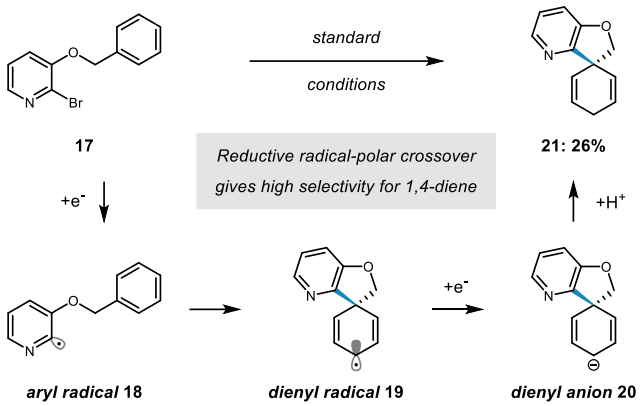
Figure 2.2: Mechanistic hypothesis for indole hydroarylation and deuterium labeling experiments to determine the termination event

2.2.4 Extension of reactivity to the hydroarylation of unactivated arenes

We then imagined the application of this reductive radical-polar crossover mechanism to the dearomatization of benzene derivatives (Scheme 2.1). We anticipated a mechanism in which pyridyl radical **18**, formed through reduction of bromopyridine **17**, would undergo 5-*exo*-trig cyclization, forming a quaternary center that would prevent aromatization of the acceptor arene. Reductive-radical polar crossover of the resulting dienyl radical **19** would yield dienyl anion **20**. This Birch-like intermediate would be selectively protonated to form spirocyclic 1,4-cyclohexadiene **21**.[44] Gratifyingly, upon subjecting **17** to our standard reaction conditions, we saw the formation of **21** in 26% yield (Scheme 2.1). Deuterium-labeling studies demonstrated >95% D incorporation from solvent, supporting the predicted reductive radical-polar crossover mechanism. The further development of this system for radical benzene dearomatization is discussed in Chapter 3.

[44] Birch, A. J. Reduction by Dissolving Metals. Part I. *J. Chem. Soc.* **1944**, 430. (b) Rabideau, P. W. The Birch Reduction of Aromatic Compounds. *Org. React.* **1992**, *42*, 1−334.

Scheme 2.1: Extension of dearomative hydroarylation to benzene derivatives



2.3 Conclusions

In conclusion, we have developed a system for the intramolecular dearomatization of indoles based on the olefin hydroarylation methods previously developed by our lab. This system functions under mild conditions powered by light and an organic photocatalyst. This protocol is tolerant of halogenation and electron-donating groups and acts without the requirement of C2 substitution. Deuterium-labelling experiments support a mechanism that terminates through reductive radical-polar crossover. We used this mechanistic information to expand this reactivity to the dearomatization of benzene derivatives, forming spirocyclic 1,4-cyclohexadienes.

2.4 Supporting Information

2.4.1 General

General Reagent Information:

Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Astatech, and TCI America and used as received, unless stated otherwise. Photoredox catalysts $[Ir(ppy)_2dtbbpy]PF_6$, 4CzIPN, 3DPAFIPN were prepared according to literature procedure.[45,46] Organic solutions were concentrated under reduced pressure on a rotary evaporator using a water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on 230–400 mesh silica gel. Thin-layer chromatography (TLC) was performed on 250 μm SiliCycle silica gel F-254 plates. Visualization of the developed plates was performed by fluorescence quenching or staining using $KMnO_4$. All reactions were conducted under nitrogen atmosphere while subjected to irradiation from blue LEDs (HydroFarm powerPAR LED Grow Light Blue 15 Watt/440 nm, available at www.1000bulbs.com). Reaction solvent was prepared by degassing under weak vacuum while subjected to sonication.

General Analytical Information:

Unless otherwise noted, all yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. New compounds were characterized by NMR, IR, and HRMS. ^{1}H and ^{13}C NMR spectra were obtained from the Emory University NMR facility and recorded on an INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), or VNMR 400 (400 MHz), and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as

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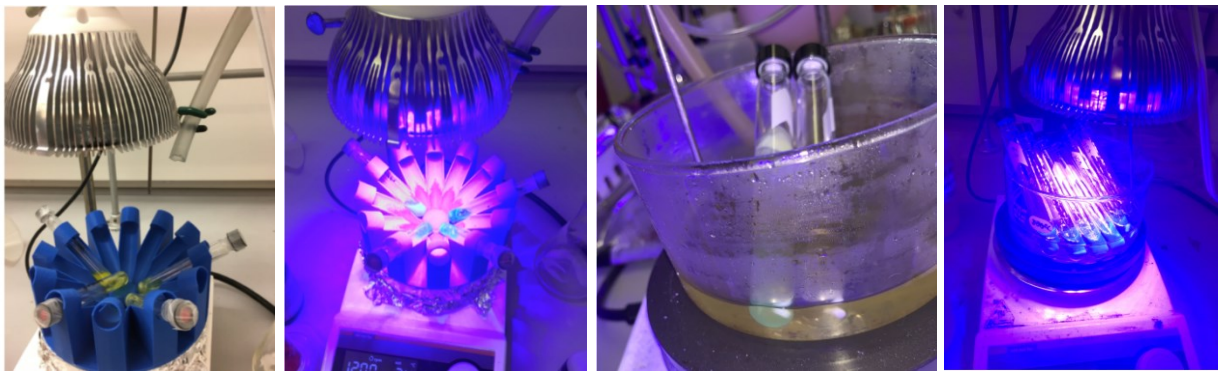
[45] Slinker, J. D.; Gorodetsky, A. A.; Lowry, M. S.; Wang, J.; Parker, S.; Rohl, R.; Bernhard, S.; Malliaras, G. G. Efficient Yellow Electroluminescence from a Single Layer of a Cyclometalated Iridium Complex. *J. Am. Chem. Soc.* **2004**, *126*, 2763-2767.

[46] Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353−15365.

follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, dtd= doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), and integration. Data for decoupled ^{13}C NMR are reported in terms of chemical shift and multiplicity when applicable. IR spectra were recorded on a Thermo Fisher DiamondATR and reported in terms of frequency of absorption (cm^{-1}). High Resolution mass spectra were obtained from the Emory University Mass Spectral facility.

General Photoredox Reaction Setup:

To run multiple reactions, an appropriately sized 3D printed carousel was used, which exposed the reactions to the blue light evenly. A 15 W LED array lamp was used as a blue light source. These lamps were routinely used for up to 12 reactions at a time. The reactions were cooled with a line of compressed air. The blue LEDs were positioned approximately 6 cm above the reaction vials to get good light coverage without overheating the reactions. Reactions run at elevated temperatures were irradiated in a shallow oil bath.



2.4.2 Optimization Details

Optimization Procedure A

A screw-top test tube equipped with a stir bar was charged with the photocatalyst (1 mol%), (2-bromopyridin-3-yl)(1H-indol-1-yl)methanone (**1**) (30.1 mg, 0.1 mmol, 1 equiv), and Hantzsch ester and sealed with a PTFE/silicon septum. The atmosphere was exchanged three times by applying vacuum and backfilling with N_2. Under N_2 atmosphere, thiophenol (5 mol%) and acetic acid were added via microsyringe. Degassed 2,2,2-trifluoroethanol was added via syringe and the resulting mixture was stirred for 16 hours under irradiation with blue LEDs. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. The combined organic extracts were filtered through a silica plug which was washed with ethyl acetate. An internal standard of dodecane (10 μL, 0.044 mmol) was added. A sample was analyzed by GC-FID, and the integral values were used to calculate the data given in Table 2.3.

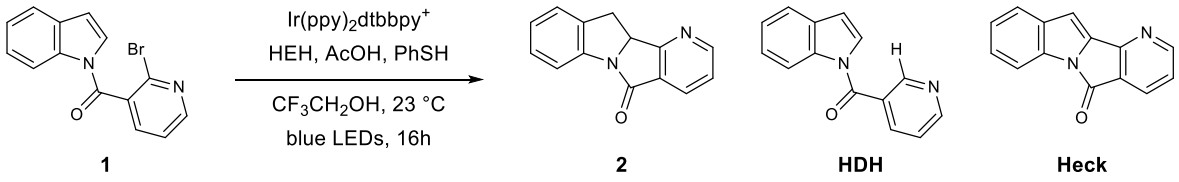
Optimization Procedure B

A screw-top test tube equipped with a stir bar was charged with the photocatalyst and (2-bromopyridin-3-yl)(1H-indol-1-yl)methanone (**1**) (30.1 mg, 0.1 mmol, 1 equiv). The atmosphere was exchanged three times by applying vacuum and backfilling with N_2. Under N_2 atmosphere, thiophenol (0.5 μL, 5 mol%) and amine (3 equiv) were added via microsyringe. Degassed 2,2,2-trifluoroethanol was added via syringe and the resulting mixture was stirred for 16 hours under irradiation with blue LEDs. The reaction was diluted with ethyl acetate and filtered through a silica plug which was washed with ethyl acetate. An internal standard of dodecane (10 μL, 0.044 mmol) was added. A sample was analyzed by GC-FID, and the integral values were used to calculate the data given in Table 2.4

Gas Chromatography Method Conditions:

The gas chromatography system hardware are reported in section 2.4.1, General Analytical Information. The injection volume for each trial is 0.5 μL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. With no hold time, the temperature ramp rate is adjusted to 25 °C/min until reaching the maximum temperature of 325 °C. Maximum temperature is held for one minute before concluding the run. Using this method, the retention times were 11.04 min for (2-bromopyridin-3-yl)(1H-indol-1-yl)methanone (**1**), 10.46 min for 11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (**2**), 10.09 min for (1H-indol-1-yl)(pyridin-3-yl)methanone (**HDH**), and 10.56 min for 5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (**Heck**). The retention time for the dodecane standard was 4.93 min.

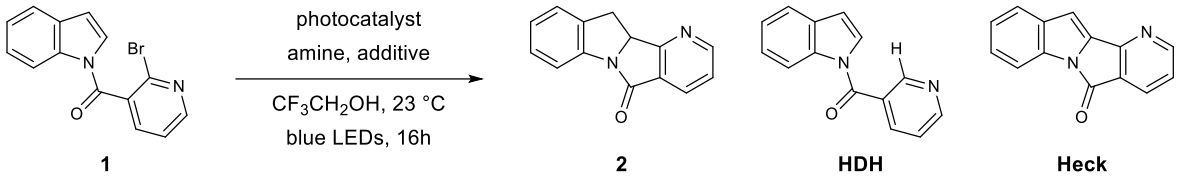
Table 2.3: Optimization Table A[a]



Entry	HEH equiv	Conc. (M)	AcOH equiv	1[b]	2[b]	HDH[b]	Heck[b]
1	1.3	0.1	2.0	31	40	12	10
2	2.0	0.1	2.0	25	59	14	5
3	3.0	0.1	2.0	4	62	25	3
4	5.0	0.1	2.0	1	57	45	4
5	3.0	0.02	2.0	5	72	6	13
6	3.0	0.02	20	0	77	7	7

[a]Conditions: **1** (0.1 mmol), [Ir(ppy)$_2$dtbbpy]PF$_6$ (1.0 mol%), thiophenol (5 mol %), acetic acid, 2,2,2-trifluoroethanol, blue LEDs, 23 °C, 16h. [b]Percent yields determined by GC.

Table 2.4: Optimization Table B[a]



Entry	Amine	Conc. (M)	Additive	Photocatalyst	1[c]	2[c]	HDH[c]	Heck[c]
1	Et_3N	0.02	PhSH	$Ir(ppy)_2dtbbpy^+$	29	24	1	17
2	*i*-Pr_2NEt	0.02	PhSH	$Ir(ppy)_2dtbbpy^+$	4	43	0	25
3	Bu_3N	0.02	PhSH	$Ir(ppy)_2dtbbpy^+$	2	59	0	23
4	Bu_3N	0.1	PhSH	$Ir(ppy)_2dtbbpy^+$	1	71	2	13
5	Bu_3N	0.2	PhSH	$Ir(ppy)_2dtbbpy^+$	0	77	3	9
6	Bu_3N	0.2	—	$Ir(ppy)_2dtbbpy^+$	0	84	2	6
7[b]	Bu_3N	0.2	—	4CzIPN	0	80	2	8
8[b]	Bu_3N	0.2	—	3DPAFIPN	0	83	0	2

[a]Conditions: aryl radical precursor (1 equiv), $[Ir(ppy)_2dtbbpy]PF_6$ (1 mol %), thiophenol (5 mol %), 2,2,2-trifluoroethanol (0.02 M), blue LEDs, 23 °C, 16h. [b]5 mol % photocatalyst. [c]Percent yields determined by GC.

2.4.3 General Procedures

Acylation Procedure A

Adapted from a literature procedure by Umehara, *et al.*[47] To an oven-dried round-bottomed flask was added the nicotinic acid derivative (1 equiv), indole (1 or 2.5 equiv), and DMAP (20 mol%). The atmosphere was exchanged three times by applying vacuum and backfilling with N_2.

[47] Umehara, A.; Ueda, H.; Tokuyama, H. Condensation of Carboxylic Acids with Non-Nucleophilic *N*-Heterocycles and Anilides Using Boc_2O. *J. Org. Chem.* **2016**, *81*, 11444-11453.

Acetonitrile (0.5 M) and 2,6-lutidine (30 mol%) were then added via syringe. Di-*tert*-butyl dicarbonate (2.5 or 1.5 equiv) was added portionwise, and the reaction was heated to 30 °C for 16-24 hours. The reaction was then concentrated *in vacuo* and purified by column chromatography.

Acylation Procedure B

Adapted from a literature procedure by Heller, *et al.*[48] To an oven-dried round-bottomed flask was added the acyl imidazole (1.1 equiv). The atmosphere was exchanged three times by applying vacuum and backfilling with N_2. Acetonitrile (0.33 M), indole (1 equiv), and DBU (20 mol%) were added, and the mixture was stirred for 16 hours. The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with ethyl acetate. The combined organic layers were washed two times with brine, filtered through a plug of silica, and concentrated *in vacuo*. The crude residue was purified by column chromatography, if necessary.

General Hydroarylation Procedure A

A 20 mL screw-top test tube equipped with a stir bar was charged with 3DPAFIPN (16 mg, 5 mol %) and the aryl radical precursor (0.5 mmol, 1 equiv) and sealed with a PTFE/silicon septum. The atmosphere was exchanged three times by applying vacuum and backfilling with N_2. Under N_2 atmosphere, tributylamine (0.36 mL, 1.5 mmol, 3 equiv) and degassed 25% (v/v) toluene/2,2,2-trifluoroethanol (5 mL, 0.1 M) were added via syringe. The resulting mixture was stirred for 16 hours under irradiation with blue LEDs. The reaction was concentrated *in vacuo*. The crude residue was purified by column chromatography.

[48] Heller, S. T.; Schultz, E. E.; Sarpong, R. Chemoselective N-Acylation of Indoles and Oxazolidinones with Carbonylazoles. *Angew. Chem. Int. Ed.* **2012**, *51*, 8304-8308.

General Hydroarylation Procedure B

A 20 mL screw-top test tube equipped with a stir bar was charged with 4CzIPN (20 mg, 5 mol %) and the aryl radical precursor (1 equiv) and sealed with a PTFE/silicon septum. The atmosphere was exchanged three times by applying vacuum and backfilling with N_2. Under N_2 atmosphere, tributylamine (3 equiv) and degassed 2,2,2-trifluoroethanol (0.1 M) were added via syringe. The resulting mixture was stirred for 16 hours at 40 °C under irradiation with blue LEDs. The reaction was concentrated *in vacuo*. The crude residue was purified by column chromatography.

2.4.4 Computational Details

All DFT calculations were carried out using the Gaussian 9 software package[49] at the (U)B3LYP[50] or R(B3LYP)[5] level of theory with the 6-311+G(d,p)[51] basis set. The CPCM formalism for the Self Consistent Reaction Field (SCRF) model of solvation was employed in calculations to account for solvation in MeCN, and the default parameters as implemented in Gaussian were used.

Reduction potentials were calculated using a modified procedure as described by Nicewicz and coworkers.[52] Geometry optimizations were carried out for the reduced and neutral forms of

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[49]M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

[50](a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B,* **1988**, *37* (2), 785–789. (b) Becke, A. D. *J. Chem. Phys*. **1993**, *98* (7), 5648–5652.

[51] McLean, A. D.; Chandler, G. S. Contracted Gaussian Basis Sets for Molecular Calculations. I. Second Row Atoms, Z=11–18. *J. Chem. Phys*. **1980**, *72*, 5639– 5648.

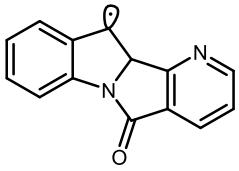
[7] Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single Electron Redox Chemistry. *Synlett* **2016**, *27* (05), 714–723.

each molecule, and frequency calculations were performed on the minimized structures to ensure no imaginary frequencies existed. Gibbs free energies (G_{298}) were obtained from the calculation and employed in the following equation:

$$E_{1/2}^{0,calc} = -\frac{(G_{298}[reduced] - G_{298}[oxidized])}{n_e\mathcal{F}} - E_{1/2}^{0,SHE} + E_{1/2}^{0,SCE}$$

Where n_e is the number of electrons transferred (n_e= 1 for all calculations here), $\mathcal{F}$ is the Faraday constant (value 23.061 kcal mol^{-1} V^{-1}), $E_{1/2}^{0,SHE}$ is the absolute value for the standard hydrogen electrode (SHE, value = 4.281 V) and $E_{1/2}^{0,SCE}$ is the potential of the saturated calomel electrode (SCE) relative to the SHE in MeCN (value = –0.141V)[53], and G_{298}[oxidized] and G_{298}[reduced] are the Gibbs free energies in MeCN obtained from DFT calculations.

Molecular coordinates of optimized structures:



Charge: 0

Multiplicity: 2

Number of imaginary frequencies: 0

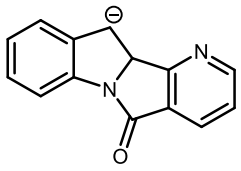
Solvation: MeCN

G_{298} = -723.646901 Hartree

C	6.01047210	3.84282338	-3.36995921
C	6.82220823	2.97977439	-2.67728796
C	8.08541859	3.36146323	-2.23789742

[8] Isse, A. A.; Gennaro, A. Absolute Potential of the Standard Hydrogen Electrode and the Problem of Interconversion of Potentials in Different Solvents. *J. Phys. Chem. B* **2010**, *114* (23), 7894–7899.
[9] Roy Dennington TK and JM. GaussView, Version 5, Semichem Inc, Shawnee Mission KS, **2009**.

C	8.46426425	4.70849038	-2.42902512
C	7.56603969	5.62933981	-3.03540245
C	6.30993608	5.19277183	-3.50785493
H	8.74260047	2.66243554	-1.76421792
H	9.43069851	5.03945544	-2.11064337
H	7.84513866	6.65732090	-3.13668740
H	5.61942585	5.87238365	-3.96197320
C	4.79669352	3.04643061	-3.81808263
H	4.22666066	3.14278913	-4.71845898
C	4.64957221	2.00719387	-2.72813051
H	4.09720654	2.40388300	-1.90203736
N	6.09953308	1.69242210	-2.46169951
C	6.38454962	0.63151814	-3.44197989
C	4.05499899	0.68589768	-3.25273266
C	5.04433241	-0.05579219	-3.74722429
O	7.50777597	0.33921303	-3.92828314
N	2.65646019	0.24545277	-3.26903460
C	4.76342039	-1.35965441	-4.48138328
H	5.54789933	-1.93732227	-4.92386790
C	3.46456714	-1.75383803	-4.53990342
H	3.20084730	-2.66041368	-5.04336388
C	2.35938328	-0.88224011	-3.86685510
H	1.34119034	-1.20990225	-3.89550214



Charge: -1

Multiplicity: 1

Number of imaginary frequencies: 0

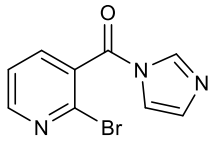
Solvation: MeCN

G_{298} = -723.763927 Hartree

C	6.01047210	3.84282338	-3.36995921
C	6.82220823	2.97977439	-2.67728796
C	8.08541859	3.36146323	-2.23789742
C	8.46426425	4.70849038	-2.42902512
C	7.56603969	5.62933981	-3.03540245
C	6.30993608	5.19277183	-3.50785493
H	8.74260047	2.66243554	-1.76421792
H	9.43069851	5.03945544	-2.11064337
H	7.84513866	6.65732090	-3.13668740
H	5.61942585	5.87238365	-3.96197320
C	4.79669352	3.04643061	-3.81808263
H	4.22666066	3.14278913	-4.71845898
C	4.64957221	2.00719387	-2.72813051
H	4.09720654	2.40388300	-1.90203736
N	6.09953308	1.69242210	-2.46169951
C	6.38454962	0.63151814	-3.44197989

C	4.05499899	0.68589768	-3.25273266
C	5.04433241	-0.05579219	-3.74722429
O	7.50777597	0.33921303	-3.92828314
N	2.65646019	0.24545277	-3.26903460
C	4.76342039	-1.35965441	-4.48138328
H	5.54789933	-1.93732227	-4.92386790
C	3.46456714	-1.75383803	-4.53990342
H	3.20084730	-2.66041368	-5.04336388
C	2.35938328	-0.88224011	-3.86685510
H	1.34119034	-1.20990225	-3.89550214

2.4.5 Preparation of Starting Materials

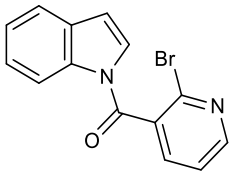


(2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (S1): CDI (8.92 g, 55 mmol) was added to a stirred solution of 2-bromonicotinic acid (10.1 g, 50 mmol) in THF (100 mL). After 15 hours, the solvent was removed *in vacuo*. The resulting residue was dissolved in DCM, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the title compound (9.6 g, 76%) as a yellow, viscous oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (ddd, *J* = 4.8, 2.0, 0.6 Hz, 1H), 7.69 (ddd, *J* = 7.6, 2.0, 0.6 Hz, 1H), 7.67 (s, 1H), 7.32 (ddd, *J* = 7.6, 4.8, 0.6 Hz, 1H), 7.20 (t, *J* = 1.6 Hz, 1H), 6.88 (dd, *J* = 1.8, 0.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 152.5, 138.2, 137.8, 137.5, 131.7, 122.8, 116.8 ppm.

FTIR (neat) ν_{max}: 3126, 3050, 2989, 1718, 1575, 1555, 1470, 1395, 1374, 1306, 1290, 1241, 1216, 1183, 1093, 1079, 1050, 1012, 893, 811, 747, 718, 643, 594 cm^{-1}.



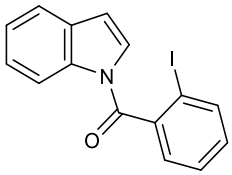
(2-bromopyridin-3-yl)(1H-indol-1-yl)methanone (1): Following the general acylation procedure A, the reaction of 2-bromonicotinic acid (2.02 g, 10 mmol, 1 equiv), indole (2.93 g, 25 mmol, 2.5 equiv), DMAP (0.244 g, 2.0 mmol, 20 mol%), 2,6-lutidine (0.35 mL, 3.0 mmol, 30 mol%), and Di-*tert*-butyl dicarbonate (5.46 g, 25 mmol, 2.5 equiv) provided the title compound (2.12 g, 71%) as a white amorphous solid after purification by silica gel chromatography (20-60% EtOAc/Hex).

^{1}H NMR (600 MHz, $CDCl_3$, 59 °C) δ 8.56 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.37 (s, 1H), 7.78 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 7.4, 4.7 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1H), 6.95 (s, 1H), 6.64 (d, *J* = 3.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.9, 151.8, 138.9, 137.4, 135.6, 134.4, 131.2, 126.2, 125.8, 124.9, 122.9, 121.3, 116.7, 110.8 ppm.

FTIR (neat) ν_{max}: 3116, 3034, 1680, 1605, 1554, 1543, 1449, 1395, 1381, 1350, 1204, 1187, 1100, 1083, 1049, 1015, 885, 871, 808, 768, 744, 725, 655, 625, 613 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{10}ON_2Br$, 300.99710; found, 300.99723.



(1H-indol-1-yl)(2-iodophenyl)methanone (S2): CDI (1.78 g, 11 mmol) was added to a stirred solution of 2-iodobenzoic acid (2.48 g, 10 mmol) in THF (20 mL). After 16 hours, the solvent was

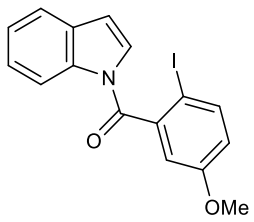
removed *in vacuo*. The resulting residue was dissolved in DCM, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain crude (1H-imidazol-1-yl)(2-iodophenyl)methanone (2.39 g, 80%) as a yellow oil. Following the general acylation procedure B, the reaction of (1H-imidazol-1-yl)(2-iodophenyl)methanone (1.97 g, 6.6 mmol, 1.1 equiv), indole (0.70 g, 6.0 mmol, 1 equiv), and DBU (0.18 mL, 1.0 mmol, 20 mol%) provided the title compound (2.04 g, 98%) as a white amorphous solid after purification by silica gel chromatography (10-30% EtOAc/Hex).

^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 8.42 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.98 (s, 1H), 6.62 (d, *J* = 3.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 141.0, 139.5, 135.5, 131.6, 131.1, 128.3, 128.3, 126.8, 125. 3, 124.4, 121.1, 116.5, 109.8, 92.5 ppm.

FTIR (neat) ν_{max}: 3151, 3116, 3053, 3034, 1679, 1541, 1447, 1431, 1379, 1346, 1203, 1187, 1150, 1075, 1015, 886, 856, 774, 744, 725, 717, 690, 647, 626 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{11}ONI$, 347.98798; found, 347.98802.



(1H-indol-1-yl)(2-iodo-5-methoxyphenyl)methanone (S3): CDI (268 mg, 1.65 mmol) was added to a stirred solution of 2-iodo-5-methoxybenzoic acid (417 mg, 1.5 mmol) in THF (5 mL). After 1 hour, the solvent was removed *in vacuo*. The resulting residue was dissolved in DCM, washed with brine, filtered through a plug of silica, and concentrated *in vacuo* to obtain crude (1H-imidazol-1-yl)(2-iodo-5-methoxyphenyl)methanone (431 mg, 88%) as a white amorphous solid.

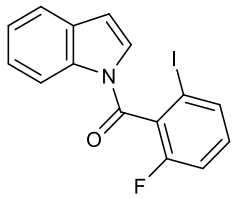
Following the general acylation procedure B, the reaction of (1H-imidazol-1-yl)(2-iodo-5-methoxyphenyl)methanone (427 mg, 1.3 mmol, 1.1 equiv), indole (141mg, 1.2 mmol, 1.0 equiv), and DBU (36 μL, 0.24 mmol, 20 mol%) provided the title compound (346 mg, 76%) as a white amorphous solid after purification by silica gel chromatography (30-50% EtOAc/Hex).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 8.37 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.59 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.33 (td, *J* = 7.5, 1.1 Hz, 1H), 7.00 (m, 2H), 6.82 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.62 (d, *J* = 3.7 Hz, 1H), 3.82 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 160.0, 142.0, 140.4, 135.6, 131.3, 126.9, 125.4, 124.5, 121.1, 118.4, 116.7, 114.2, 110.0, 80.8, 55.8 ppm.

FTIR (neat) ν_{max}: 3151, 3107, 3872, 2942, 2847, 1685, 1583, 1535, 1467, 1448, 1391, 1377, 1342, 1301, 1227, 1204, 1174, 1073, 1030, 1006, 907, 859, 818, 751, 724, 632, 580 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}O_2NI$, 377.99855; found, 377.99830.



(2-fluoro-6-iodophenyl)(1H-indol-1-yl)methanone (S4): CDI (0.892 g, 5.5 mmol) was added to a stirred solution of 2-fluoro-6-iodobenzoic acid (1.33 g, 5 mmol) in THF (10 mL). After 1 hour, the solvent was removed *in vacuo*. The resulting residue was dissolved in DCM, washed with brine, filtered through a plug of silica, and concentrated *in vacuo* to obtain crude (2-fluoro-6-iodophenyl)(1H-imidazol-1-yl)methanone (0.899 g, 57%) as a light yellow amorphous solid. Following the general acylation procedure B, the reaction of (2-fluoro-6-iodophenyl)(1H-imidazol-1-yl)methanone (695 mg, 2.2 mmol, 1.1 equiv), indole (234 mg, 2.0 mmol, 1 equiv), and

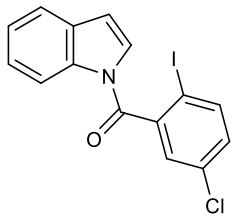
DBU (60 μL, 0.4 mmol, 20 mol%) provided the title compound (489 mg, 67%) as a white amorphous solid after purification by silica gel chromatography (5-10% EtOAc/Hex).

^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 8.64 (d, J = 8.2 Hz, 1H), 7.74 (t, J = 4.5 Hz, 1H), 7.59 (dd, J = 7.9, 1.1 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.28 – 7.20 (m, 2H), 6.86 (s, 1H), 6.63 (s, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 158.8 (d, $^1J_{C\text{-}F}$ = 254.1 Hz), 135.6, 135.3, 135.2, 133.0 (d, $^2J_{C\text{-}F}$ = 8.2 Hz), 131.3, 126.1, 125.7, 124.9, 121.2, 117.1, 116.1 (d, $^2J_{C\text{-}F}$ = 20.8 Hz), 110.6, 93.2 (d, $^3J_{C\text{-}F}$ = 2.4 Hz) ppm.

FTIR (neat) ν_{max}: 3147, 3122, 3070, 3052, 3034, 1686, 1596, 1562, 1541, 1447, 1379, 1346, 1244, 1236, 1203, 1149, 1124, 1072, 885, 872, 851, 788, 767, 741, 718, 688, 637 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}ONFI$, 365.97856; found, 365.97856.



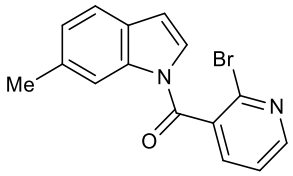
(5-chloro-2-iodophenyl)(1H-indol-1-yl)methanone (S5): CDI (0.892 g, 5.5 mmol) was added to a stirred solution of 5-chloro-2-iodobenzoic acid (1.41 g, 5 mmol) in THF (10 mL). After 1 hour, the solvent was removed *in vacuo*. The resulting residue was dissolved in DCM, washed with brine, filtered through a plug of silica, and concentrated *in vacuo* to obtain crude (5-chloro-2-iodophenyl)(1H-imidazol-1-yl)methanone (1.35 g, 81%) as a yellow amorphous solid. Following the general acylation procedure B, the reaction of (5-chloro-2-iodophenyl)(1H-imidazol-1-yl)methanone (732 mg, 2.2 mmol, 1.1 equiv), indole (234 mg, 2.0 mmol, 1 equiv), and DBU (60 μL, 0.4 mmol, 20 mol%) provided the title compound (719 mg, 94%) as a white amorphous solid.

^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 8.36 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.23 (dt, *J* = 8.5, 2.3 Hz, 1H), 6.94 (s, 1H), 6.64 (d, *J* = 3.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 142.7, 140.9, 135.5, 135.2, 132.0, 131.2, 128.6, 126.5, 125.7, 124.8, 121.3, 116.7, 110.5, 89.8 ppm.

FTIR (neat) ν_{max}: 3153, 3128, 3110, 3073, 3052, 1689, 1541, 1450, 1384, 1343, 1232, 1206, 1185, 1149, 1096, 1074, 1012, 907, 882, 809, 779, 767, 754, 746, 723, 632, 617 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}ONClI$, 381.94901; found, 381.94937.



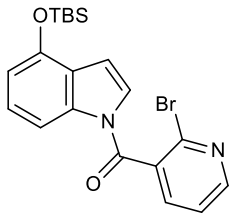
(2-bromopyridin-3-yl)(6-methyl-1H-indol-1-yl)methanone (S6): Following the general acylation procedure B, the reaction of (2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (**S1** (555 mg, 2.2 mmol, 1.1 equiv), 6-methylindole (262 mg, 2.0 mmol, 1 equiv), and DBU (60 μL, 0.4 mmol, 20 mol%) provided the title compound (532 mg, 84%) as a white amorphous solid after purification by silica gel chromatography (20% EtOAc/Hex).

^{1}H NMR (400 MHz, $CDCl_3$, 59 °C) δ 8.57 (dd, *J* = 4.9, 2.0 Hz, 1H), 8.36 (s, 1H), 7.79 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.19 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.82 (s, 1H), 6.60 (dd, *J* = 3.8, 0.8 Hz, 1H), 2.52 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 151.5, 138.6, 137.2, 135.8, 134.2, 128.7, 126.2, 125.5, 122.8, 120.7, 116.9, 110.6, 22.0 ppm.

FTIR (neat) ν_{max}: 3132, 3110, 3066, 3034, 2914, 2854, 1687, 1574, 1528, 1426, 1384, 1346, 1200, 1173, 1122, 1084, 1041, 884, 812, 757, 711, 648, 619, 596 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{12}ON_2Br$, 315.01275; found, 315.01251.



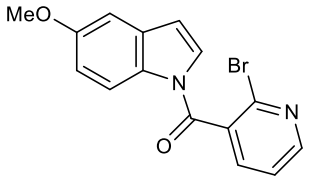
(2-bromopyridin-3-yl)(4-((tert-butyldimethylsilyl)oxy)-1H-indol-1-yl)methanone (S7): Following the general acylation procedure B, the reaction of (2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (**S1** (832 mg, 3.3 mmol, 1.1 equiv), 4-hydroxyindole (399 mg, 3.0 mmol, 1 equiv), and DBU (90 μL, 0.6 mmol, 20 mol%) provided crude (2-bromopyridin-3-yl)(4-hydroxy-1H-indol-1-yl)methanone (879 mg). The crude solid was then dissolved in MeCN (10 mL) with imidazole (408 mg, 6.0 mmol). TBSCl (452 mg, 3.0 mmol) was added and the resulting solution was stirred for 20 hours. The reaction was diluted with EtOAc, washed with brine (3x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The title compound was obtained as a white amorphous solid after purification by silica gel chromatography (10-20% EtOAc/Hex).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 8.57 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.97 (s, 1H), 7.78 (ddd, *J* = 7.6, 2.0, 0.9 Hz, 1H), 7.45 (ddd, *J* = 7.6, 5.0, 0.9 Hz, 1H), 7.25 (t, *J* = 8.2 Hz, 1H), 6.84 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.71 (dt, *J* = 3.9, 0.9 Hz, 1H), 1.05 (s, 9H), 0.26 (s, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 151.7, 149.0, 138.8, 137.3, 137.1, 134.4, 126.6, 124.7, 124. 2, 122.9, 114.4, 110.0, 108.1, 25.9, 18.4, -4.2 ppm.

FTIR (neat) ν_{max}: 2955, 2929, 2856, 1678, 1594, 1578, 1481, 1431, 1389, 1350, 1284, 1255, 1227, 1151, 1090, 1015, 868, 834, 814, 779, 748, 722, 684, 643 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{24}O_2N_2BrSi$, 431.07849; found, 431.07832.



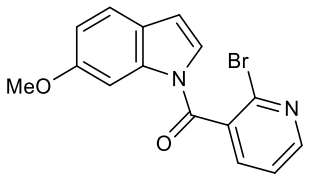
(2-bromopyridin-3-yl)(5-methoxy-1H-indol-1-yl)methanone (S8): Following the general acylation procedure B, the reaction of (2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (555 mg, 2.2 mmol, 1.1 equiv), 5-methoxyindole (294 mg, 2.0 mmol, 1 equiv), and DBU (60 µL, 0.4 mmol, 20 mol%) provided the title compound (655 mg, 99%) as a light brown amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$, 59 °C) δ 8.53 (dd, *J* = 4.7, 1.8 Hz, 1H), 8.31 (s, 1H), 7.77 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.42 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 1H), 6.99 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.88 (s, 1H), 6.56 (d, *J* = 3.8 Hz, 1H), 3.86 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 157.4, 151.7, 138.8, 137.3, 134.3, 132.2, 130.1, 126.9, 122.8, 117.4, 113.8, 110.6, 104.2, 55.8 ppm.

FTIR (neat) ν_{max}: 3160, 3107, 3053, 3005, 2964, 2841, 1691, 1471, 1444, 1399, 1370, 1342, 1333, 1274, 1257, 1194, 1182, 1149, 1095, 1051, 1042, 1022, 881, 823, 814, 794, 749, 736, 717, 650, 632, 582 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{12}O_2N_2Br$, 331.00767; found, 331.00828.



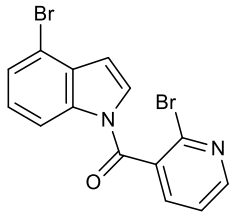
(2-bromopyridin-3-yl)(6-methoxy-1H-indol-1-yl)methanone (S9): Following the general acylation procedure B, the reaction of (2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (**S1** (555 mg, 2.2 mmol, 1.1 equiv), 6-methoxyindole (294 mg, 2.0 mmol, 1 equiv), and DBU (60 µL, 0.4 mmol, 20 mol%) provided the title compound (549 mg, 83%) as a white amorphous solid after purification by silica gel chromatography (10-30% EtOAc/Hex).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 8.57 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1H), 8.07 (s, 1H), 7.79 (ddd, *J* = 7.4, 2.0, 0.7 Hz, 1H), 7.50 – 7.42 (m, 2H), 6.98 (ddd, *J* = 8.6, 2.4, 0.8 Hz, 1H), 6.79 (s, 1H), 6.57 (d, *J* = 3.7 Hz, 1H), 3.91 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 158.7, 151.6, 138.7, 137.2, 136.5, 134.2, 124.9, 124.6, 122.8, 121.6, 113.9, 110.5, 100.9, 55.8 ppm.

FTIR (neat) ν_{max}: 3101, 3060, 2946, 2898, 2838, 1682, 1574, 1540, 1479, 1434, 1384, 1352, 1276, 1221, 1172, 1083, 1041, 1026, 884, 866, 801, 750, 708, 649, 616 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{12}O_2N_2Br$, 331.00767; found, 331.00813.



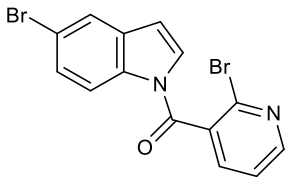
(4-bromo-1H-indol-1-yl)(2-bromopyridin-3-yl)methanone (S10): Following the general acylation procedure B, the reaction of (2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (**S1** (555 mg, 2.2 mmol, 1.1 equiv), 4-bromoindole (392 mg, 2.0 mmol, 1 equiv), and DBU (60 μL, 0.4 mmol, 20 mol%) provided the title compound (647 mg, 85%) as a white amorphous solid after purification by silica gel chromatography (10-20% EtOAc/Hex).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 8.59 (dd, *J* = 4.9, 2.0 Hz, 1H), 8.39 (s, 1H), 7.80 (ddd, *J* = 7.6, 2.0, 0.6 Hz, 1H), 7.52 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.48 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H), 7.00 (s, 1H), 6.74 (d, *J* = 3.9 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 152.0, 138.7, 137.4, 135.8, 133.9, 131.8, 127.8, 126.8, 126.8, 122.9, 115.7, 115.0, 110.4 ppm.

FTIR (neat) ν_{max}: 3139, 3110, 3053, 1698, 1687, 1578, 1533, 1418, 1340, 1175, 1043, 882, 765, 747, 560 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_9ON_2Br_2$, 378.90761; found, 378.90751.



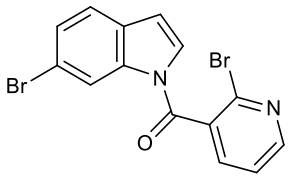
(5-bromo-1H-indol-1-yl)(2-bromopyridin-3-yl)methanone (S11): Following the general acylation procedure B, the reaction of (2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (**S1** (832 mg, 3.3 mmol, 1.1 equiv), 5-bromoindole (588 mg, 3.0 mmol, 1 equiv), and DBU (90 μL, 0.6 mmol, 20 mol%) provided the title compound (1.01 g, 88%) as a white amorphous solid after purification by silica gel chromatography (20-30% EtOAc/Hex).

^{1}H NMR (600 MHz, $CDCl_3$, 59 °C) δ 8.59 (dt, *J* = 4.9, 2.1 Hz, 1H), 8.36 (s, 1H), 7.81 (ddd, *J* = 7.5, 2.5, 1.9 Hz, 1H), 7.74 (t, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.51 – 7.46 (m, 1H), 6.94 (s, 1H), 6.60 (dd, *J* = 3.7, 1.7 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 151.9, 138.6, 137.4, 134.1, 133.8, 132.8, 128.4, 127.3, 123.9, 122.9, 118.1, 117.9, 109.8 ppm.

FTIR (neat) ν_{max}: 3155, 3132, 3082, 3044, 1689, 1575, 1446, 1374, 1195, 1182, 1051, 876, 803, 751, 728, 717, 627 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_9ON_2Br_2$, 378.90761; found, 378.90825.



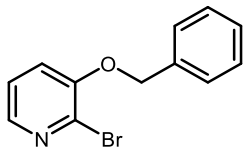
(6-bromo-1H-indol-1-yl)(2-bromopyridin-3-yl)methanone (S12): Following the general acylation procedure B, the reaction of (2-bromopyridin-3-yl)(1H-imidazol-1-yl)methanone (**S1** (832 mg, 3.3 mmol, 1.1 equiv), 6-bromoindole (588 mg, 3.0 mmol, 1 equiv), and DBU (90 μL, 0.6 mmol, 20 mol%) provided the title compound (997 mg, 87%) as an off-white amorphous solid.

^{1}H NMR (600 MHz, $CDCl_3$, 59 °C) δ 8.73 (s, 1H), 8.59 (dd, *J* = 4.9, 2.0 Hz, 1H), 7.81 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.51 – 7.43 (m, 3H), 6.88 (s, 1H), 6.62 (dd, *J* = 3.8, 0.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 152.0, 138.8, 137.4, 136.2, 133.9, 130.0, 128.2, 126.7, 123.0, 122.3, 120.0, 119.5, 110.4 ppm.

FTIR (neat) ν_{max}: 3110, 3041, 2930, 1683, 1572, 1530, 1378, 1343, 1200, 1095, 1051, 1041, 1025, 1005, 883, 807, 750, 725, 665, 636, 618, 579 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_9ON_2Br_2$, 378.90761; found, 378.90823.



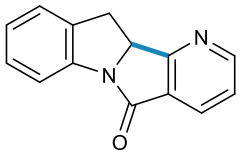
3-(benzyloxy)-2-bromopyridine (17): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (5.0 g, 29 mmol, 1.0 equiv) and K_2CO_3 (8.0 g, 58 mmol, 2.0 equiv). DMF was added, followed by benzyl bromide (3.7 mL, 31 mmol, 1.1 equiv). The reaction was heated to 80 °C and stirred for 16 h. The reaction was cooled to room temperature and then partitioned between EtOAc and water. The organic layer was washed with brine 3x, dried with $MgSO_4$ and purified on silica gel (20–50% EtOAc/hexanes eluent) to afford the title compound as a white solid (7.5 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 3.8, 2.4 Hz, 1H), 7.47 – 7.27 (m, 5H), 7.18 – 7.09 (m, 2H), 5.15 (s, 2H) ppm.

^{1}H NMR spectrum is consistent with reported values.[54]

[54] Flynn, A. R.; McDaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020**, *142*, 9163–9168.

2.4.6 Characterization Data



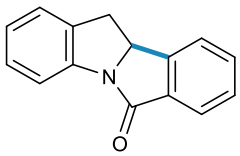
11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (2): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (2-bromopyridin-3-yl)(1H-indol-1-yl)methanone (**1**) (151 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (95.9 mg, 86%) as an off-white amorphous solid after purification by silica gel chromatography (50-70% EtOAc/Hex + 1% AcOH).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.17 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 7.7, 5.0 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.11 (td, *J* = 7.5, 1.1 Hz, 1H), 5.64 (dd, *J* = 10.4, 8.8 Hz, 1H), 3.56 (dd, *J* = 15.5, 9.0 Hz, 1H), 3.18 (dd, *J* = 15.5, 10.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 165.9, 153.5, 140.5, 135.9, 133.1, 128.4, 128.3, 125.8, 125.1, 123.9, 117.0, 66.8, 32.6 ppm.

FTIR (neat) ν_{max}: 3045, 2963, 2921, 2857, 1696, 1597, 1578, 1478, 1459, 1371, 1346, 1311, 1293, 1245, 1216, 1109, 1071, 819, 776, 756, 731, 720, 711, 697, 653, 607, 588, 558, 537, 529 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{11}ON_2$, 223.08659; found, 223.08656.



10b,11-dihydro-6H-isoindolo[2,1-a]indol-6-one (3): Following the general hydroarylation procedure B, the reaction of 4CzIPN (20 mg, 5 mol %), (1H-indol-1-yl)(2-iodophenyl)methanone (**S2**) (104 mg, 0.3 mmol, 1 equiv), and Bu_3N (0.21 mL, 0.9 mmol, 3 equiv) in 2,2,2-trifluoroethanol

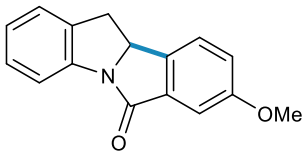
(3 mL, 0.1 M) at 40 °C provided the title compound (31.1 mg, 47%) as a yellow amorphous solid after purification by silica gel chromatography (5-20% EtOAc/Hex) and washing with 1M HCl (aq).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.08 (td, *J* = 7.5, 1.1 Hz, 1H), 5.67 – 5.58 (m, 1H), 3.47 (dd, *J* = 15.3, 8.5 Hz, 1H), 3.06 (dd, *J* = 15.2, 10.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 146.2, 140.8, 136.1, 134.4, 132.7, 128.9, 128.1, 125.5, 125.0, 124.6, 123.0, 116.6, 65.6, 34.0 ppm.

FTIR (neat) ν_{max}: 2957, 2927, 2871, 2858, 1696, 1478, 1461, 1372, 1302, 1160, 1139, 1100, 752, 729, 688, 527 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{12}ON$, 222.09134; found, 222.09133.



8-methoxy-10b,11-dihydro-6H-isoindolo[2,1-a]indol-6-one (4): Following the general hydroarylation procedure B, the reaction of 4-CzIPN (20 mg, 5 mol %), (1H-indol-1-yl)(2-iodo-5-methoxyphenyl)methanone (**S3**) (37.7 mg, 0.1 mmol, 1 equiv), and Bu_3N (71 µL, 0.3 mmol, 3 equiv) in 2,2,2-trifluoroethanol (1 mL, 0.1 M) at 40 °C provided the title compound (15.6 mg, 62%) as a light yellow amorphous solid after purification by silica gel chromatography (10% EtOAc/Hex + 1% AcOH).

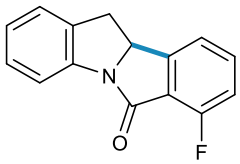
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.16 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.07 (td, *J*

= 7.5, 1.1 Hz, 1H), 5.57 (dd, *J* = 10.1, 8.6 Hz, 1H), 3.88 (s, 3H), 3.42 (dd, *J* = 15.2, 8.6 Hz, 1H), 3.02 (dd, *J* = 15.1, 10.2 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 160.6, 140.9, 138.6, 136.3, 135.8, 128.1, 125.5, 124.6, 123.8, 121.0, 116.6, 107.6, 65.2, 55.9, 34.2 ppm.

FTIR (neat) ν_{max}: 3069, 3043, 2919, 2860, 1688, 1680, 1600, 1469, 1451, 1432, 1357, 1277, 1225, 1277, 1225, 1158, 1134, 1058, 1022, 851, 828, 773, 750, 734, 599, 582 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{14}O_2N$, 252.10191; found, 252.10155.



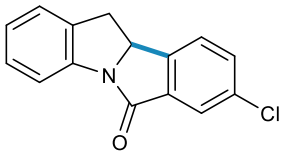
7-fluoro-10b,11-dihydro-6H-isoindolo[2,1-a]indol-6-one (5): Following the general hydroarylation procedure B, the reaction of 4-CzIPN (20 mg, 5 mol %), (2-fluoro-6-iodophenyl)(1H-imidazol-1-yl)methanone (**S4**) (110 mg, 0.3 mmol, 1 equiv), and Bu_3N (0.21 mL, 0.9 mmol, 3 equiv) in 2,2,2-trifluoroethanol (3 mL, 0.1 M) at 40 °C provided the title compound (50.2 mg, 70%) as a yellow amorphous solid after purification by silica gel chromatography (10-25% EtOAc/Hex) and washing with 1M HCl (aq).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.58 (td, *J* = 7.9, 4.6 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 9.1 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 5.60 (dd, *J* = 9.9, 9.1 Hz, 1H), 3.46 (dd, *J* = 15.1, 8.8 Hz, 1H), 3.08 (dd, *J* = 15.2, 10.4 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.29 (d, $^{1}J_{C\text{-}F}$ = 1.6 Hz), 159.52 (d, $^{1}J_{C\text{-}F}$ = 262.1 Hz), 148.78 (d, $^{3}J_{C\text{-}F}$ = 2.8 Hz), 140.59, 135.68, 134.83 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz), 128.15, 125.44, 124.74, 121.40 (d, $^{2}J_{C\text{-}F}$ = 13.5 Hz), 119.01 (d, $^{4}J_{C\text{-}F}$ = 4.1 Hz), 116.74, 116.17 (d, $^{2}J_{C\text{-}F}$ = 19.3 Hz), 65.16 (d, $^{4}J_{C\text{-}F}$ = 1.4 Hz), 33.95 ppm.

FTIR (neat) ν_{max}: 3055, 3024, 2908, 2853, 1692, 1626, 1590, 1476, 1461, 1369, 1308, 1293, 1251, 1208, 1160, 1139, 1081, 1053, 933, 796, 742, 724, 705, 691, 662, 635, 598 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{11}ONF$, 240.08192; found, 240.08195.



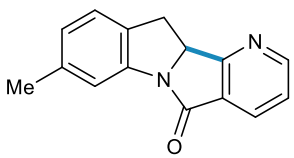
8-chloro-10b,11-dihydro-6H-isoindolo[2,1-a]indol-6-one (6): Following the general hydroarylation procedure B, the reaction of 4-CzIPN (20 mg, 5 mol %), (5-chloro-2-iodophenyl)(1H-indol-1-yl)methanone (**S5**) (38.2 mg, 0.1 mmol, 1 equiv), and Bu_3N (71 µL, 0.3 mmol, 3 equiv) in 2,2,2-trifluoroethanol (1 mL, 0.1 M) at 40 °C provided the title compound (17.0 mg, 66%) as a yellow amorphous solid after purification by silica gel chromatography (5-15% EtOAc/Hex) and washing with 1M HCl (aq).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.9 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.57 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.45 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 0H), 7.09 (t, *J* = 7.5 Hz, 1H), 5.59 (dd, *J* = 10.4, 8.6 Hz, 1H), 3.46 (dd, *J* = 15.1, 8.6 Hz, 1H), 3.05 (dd, *J* = 15.0, 10.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 144.2, 140.5, 136.2, 135.9, 135.2, 132.8, 128.2, 125.6, 125.0, 124.9, 124.2, 116.6, 65.3, 33.9 ppm.

FTIR (neat) ν_{max}: 3079, 3037, 2963, 2908, 2847, 1697, 1603, 1477, 1460, 1417, 1365, 1308, 1290, 1259, 1207, 1194, 1175, 1134, 1116, 1078, 1050, 889, 830, 775, 749, 719, 690, 667, 594 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{11}ONCl$, 256.05237; found, 256.05241.



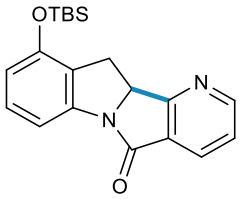
8-methyl-11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (7): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (2-bromopyridin-3-yl)(6-methyl-1H-indol-1-yl)methanone (**S6**) (158 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (100 mg, 85%) as an off-white amorphous solid after purification by silica gel chromatography (50% EtOAc/Hex + 1% AcOH).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.17 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.52 (s, 1H), 7.44 (ddd, *J* = 7.7, 4.9, 0.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.62 (dd, *J* = 10.2, 9.0 Hz, 1H), 3.51 (dd, *J* = 15.3, 8.9 Hz, 1H), 3.13 (dd, *J* = 15.8, 10.5 Hz, 1H), 2.41 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 165.8, 153.3, 140.4, 138.2, 132.9, 132.8, 128.3, 125.6, 125.2, 123.7, 117.5, 67.0, 32.1, 21.5 ppm.

FTIR (neat) ν_{max}: 2955, 2923, 2854, 1693, 1602, 1580, 1493, 1418, 1361, 1303, 1193, 1090, 862, 810, 782, 760, 727, 697, 657, 592, 555, 543 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{13}ON_2$, 237.10224; found, 237.10196.



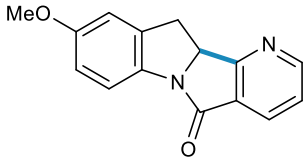
10-((tert-butyldimethylsilyl)oxy)-11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (8): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (2-bromopyridin-3-yl)(4-((tert-butyldimethylsilyl)oxy)-1H-indol-1-yl)methanone (**S7**) (216 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (151 mg, 86%) as an off-white amorphous solid after purification by silica gel chromatography (20-30% EtOAc/Hex + 1% AcOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.16 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.7, 5.0 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 5.62 (t, *J* = 9.6 Hz, 1H), 3.57 (dd, *J* = 15.6, 9.1 Hz, 1H), 3.03 (dd, *J* = 15.4, 10.0 Hz, 1H), 0.99 (s, 9H), 0.24 (s, 3H), 0.17 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 153.4, 152.6, 141.9, 133.1, 129.3, 128.4, 125.8, 123.9, 116.1, 110.2, 66.9, 29.9, 25.8, 18.3, -4.0, -4.1 ppm.

FTIR (neat) ν_{max}: 2949, 2928, 2901, 2858, 1691, 1591, 1472, 1453, 1371, 1307, 1286, 1248, 1205, 1141, 1108, 1001, 862, 837, 823, 811, 797, 772, 707, 667, 603, 571 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{25}O_2N_2Si$, 353.16798; found, 353.16733.



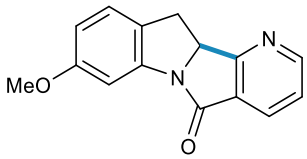
9-methoxy-11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (9): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (2-bromopyridin-3-yl)(5-methoxy-1H-indol-1-yl)methanone (**S8**) (166 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (105 mg, 83%) as a light yellow amorphous solid after purification by silica gel chromatography (50-70% EtOAc/Hex + 1% AcOH).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 5.0, 1.4 Hz, 1H), 8.15 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.44 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.85 (s, 1H), 6.82 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.65 – 5.58 (m, 1H), 3.80 (s, 3H), 3.52 (dd, *J* = 15.5, 8.8 Hz, 1H), 3.15 (dd, *J* = 15.5, 10.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 165.8, 157.5, 153.2, 137.5, 134.0, 132.9, 128.4, 123.8, 117.3, 112.7, 112.3, 67.1, 55.9, 32.8 ppm.

FTIR (neat) ν_{max}: 3069, 2961, 2929, 2837, 1692, 1581, 1488, 1476, 1440, 1381, 1315, 1239, 1230, 1139, 1094, 1072, 1021, 859, 807, 773, 773, 749, 728, 717, 549, 530 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{13}O_2N_2$, 253.09715; found, 253.09717.



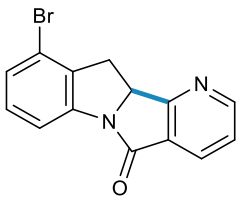
8-methoxy-11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (10): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (2-bromopyridin-3-yl)(6-methoxy-1H-indol-1-yl)methanone (**S9**) (166 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (96.3 mg, 76%) as a light yellow amorphous solid after purification by silica gel chromatography (40-60% EtOAc/Hex + 1% AcOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.17 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.8, 5.0, 0.6 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.65 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.70 – 5.61 (m, 1H), 3.87 (s, 3H), 3.49 (dd, *J* = 15.0, 9.0 Hz, 1H), 3.11 (dd, *J* = 15.3, 10.4 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 166.0, 160.1, 153.5, 141.5, 133.1, 128.3, 127.4, 126.0, 123.9, 111.0, 103.1, 67.5, 55.9, 31.8 ppm.

FTIR (neat) ν_{max}: 3079, 2996, 2917, 2832, 1694, 1581, 1491, 1452, 1438, 1366, 1310, 1282, 1213, 1166, 1143, 1093, 1027, 851, 795, 780, 756, 727, 696, 655, 619, 578, 555, 533 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{13}O_2N_2$, 253.09715; found, 253.09705.



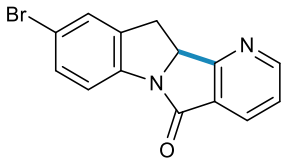
10-bromo-11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (11): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (4-bromo-1H-indol-1-yl)(2-bromopyridin-3-yl)methanone (**S10**) (190 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (125 mg, 83%) as an off-white amorphous solid after purification by silica gel chromatography (30-50% EtOAc/Hex + 1% AcOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.17 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.62 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.47 (ddd, *J* = 7.7, 4.9, 0.6 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.23 – 7.14 (m, 1H), 5.66 (t, *J* = 9.6 Hz, 1H), 3.63 (dd, *J* = 16.2, 9.2 Hz, 1H), 3.18 (dd, *J* = 16.6, 10.2 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 165.8, 153.8, 141.6, 136.4, 133.2, 129.8, 128.0, 127.8, 124.0, 119.8, 115.6, 65.7, 33.9 ppm.

FTIR (neat) ν_{max}: 2961, 2927, 2860, 1712, 1596, 1449, 1417, 1356, 1301, 1267, 1230, 1157, 1100, 1071, 891, 870, 827, 811, 773, 736, 694, 678, 600, 571, 542 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{10}ON_2Br$, 300.99710; found, 300.99692.



9-bromo-11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (12): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (5-bromo-1H-indol-1-yl)(2-bromopyridin-3-yl)methanone (**S11**) (190 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (110 mg, 73%) as an off-white amorphous solid after purification by silica gel chromatography (30% EtOAc/Hex + 1% AcOH).

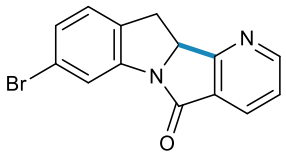
^{1}H NMR (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.79 (ddd, *J* = 4.9, 1.6, 0.6 Hz, 1H), 8.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.46 (ddt, *J* = 7.7, 4.9, 0.7 Hz,

1H), 7.44 – 7.41 (m, 2H), 5.66 – 5.62 (m, 1H), 3.55 (dd, *J* = 15.7, 9.0 Hz, 1H), 3.18 (dd, *J* = 15.8, 10.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 165.6, 153.7, 139.6, 138.0, 133.2, 131.1, 128.8, 127.9, 124.0, 118.0, 117.8, 66.6, 32.4 ppm.

FTIR (neat) ν_{max}: 2956, 2927, 2870, 2797, 1694, 1599, 1582, 1467, 1364, 1300, 1177, 826, 771, 734, 710, 533 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. For $C_{14}H_{10}ON_2Br$, 300.99710; found, 300.99738.



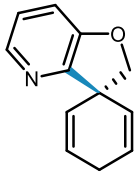
8-bromo-11,11a-dihydro-5H-pyrido[2',3':3,4]pyrrolo[1,2-a]indol-5-one (13): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), (6-bromo-1H-indol-1-yl)(2-bromopyridin-3-yl)methanone (**S12**) (190 mg, 0.5 mmol, 1 equiv), and Bu_3N (0.36 mL, 1.5 mmol, 3 equiv) provided the title compound (105 mg, 69%) as an off-white amorphous solid after purification by silica gel chromatography (30-50% EtOAc/Hex + 1% AcOH).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.18 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.84 (d, *J* = 1.9 Hz, 1H), 7.46 (ddd, *J* = 7.7, 5.0, 0.6 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.13 (dt, *J* = 8.0, 1.1 Hz, 1H), 5.68 – 5.62 (m, 1H), 3.52 (dd, *J* = 15.6, 9.0 Hz, 1H), 3.12 (ddd, *J* = 15.7, 10.3, 1.4 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 165.7, 153.7, 141.7, 134.8, 133.2, 127.9, 127.8, 126.8, 124.0, 121.4, 120.0, 66.9, 32.2 ppm.

FTIR (neat) ν_{max}: 2956, 2927, 2876, 2806, 1695, 1593, 1581, 1473, 1417, 1358, 1298, 1115, 1070, 860, 806, 774, 736, 708, 646, 584, 550 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{10}ON_2Br$, 300.99710; found, 300.99732.



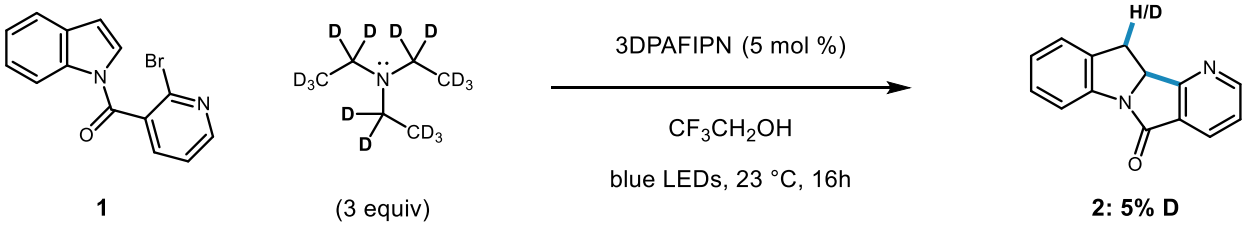
2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (21): Following the general hydroarylation procedure A, the reaction of 3DPAFIPN (16 mg, 5 mol %), 3-(benzyloxy)-2-bromopyridine (**17**) (132 mg, 0.5 mmol, 1 equiv) and Bu_3N (0.28 mL, 1.5 mmol, 3 equiv) provided the title compound (24.5 mg, 26%) as an off-white amorphous solid after purification by silica gel chromatography (20-60% EtOAc/Hex + 1% AcOH).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.05 (dd, *J* = 8.1, 4.7 Hz, 1H), 6.02 (dt, *J* = 10.2, 3.4 Hz, 2H), 5.75 (dt, *J* = 10.3, 2.0 Hz, 2H), 4.46 (s, 2H), 2.93 (dtt, *J* = 23.3, 3.3, 2.1 Hz, 1H), 2.74 (dtt, *J* = 23.4, 3.5, 2.1 Hz, 1H) ppm.

^{1}H NMR spectrum is consistent with reported values.[55]

2.4.7 Deuterium Labeling Study

A. Deuterated amine



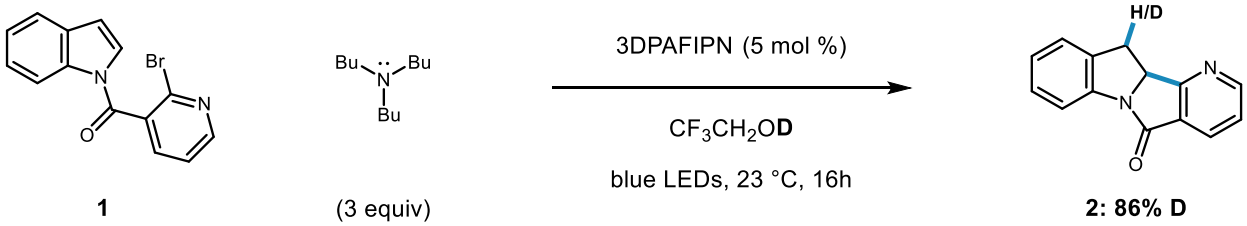
1 (3 equiv) **2: 5% D**

An oven-dried screw-top test tube equipped with a stir bar was charged with 3DPAFIPN (3.2 mg, 5 mol %) and (2-bromopyridin-3-yl)(1H-indol-1-yl)methanone (**1**) (30.1 mg, 0.1 mmol, 1 equiv). The atmosphere was exchanged three times by applying vacuum and backfilling with N_2. Under

[55] Flynn, A. R.; McDaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020**, *142*, 9163–9168.

N_2 atmosphere, triethyl-d_{15}-amine (42 µL, 0.3 mmol, 3 equiv) was added via microsyringe. Degassed 2,2,2-trifluoroethanol (1 mL, 0.1 M) was added via syringe and the resulting mixture was stirred for 16 hours under irradiation with blue LEDs. The reaction was concentrated *in vacuo*, and the crude mixture was analyzed by ^{1}H NMR before purification. The crude residue was purified by silica gel chromatography (30-50% EtOAc/Hex) to provide the desired product. ^{1}H NMR analysis (d1 = 10 sec) showed 5% deuterium incorporation.

B. Deuterated solvent



1 (3 equiv) **2: 86% D**

An oven-dried screw-top test tube equipped with a stir bar was charged with 3DPAFIPN (3.2 mg, 5 mol %) and (2-bromopyridin-3-yl)(1H-indol-1-yl)methanone (**1**) (30.1 mg, 0.1 mmol, 1 equiv). The atmosphere was exchanged three times by applying vacuum and backfilling with N_2. Under N_2 atmosphere, tributylamine (71 µL, 0.3 mmol, 3 equiv) was added via microsyringe. Degassed CF_3CH_2OD (1 mL, 0.1 M) were added via syringe and the resulting mixture was stirred for 16 hours under irradiation with blue LEDs. The reaction was concentrated *in vacuo*, and the crude mixture was analyzed by ^{1}H NMR before purification. The crude residue was purified by silica gel chromatography (30-50% EtOAc/Hex) to provide the desired product. ^{1}H NMR analysis (d1 = 10 sec) showed 86% deuterium incorporation.

Chapter 3:

Hydroarylation of Arenes via Reductive Radical-Polar Crossover

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Flynn, A. R.;‡ McDaniel, K. A.;‡ Hughes, M. E.; Vogt, D. B.; Jui, N. T. *J. Am. Chem. Soc.* **2020**, *142*, 9163–9168.

https://pubs.acs.org/doi/abs/10.1021/jacs.0c03926

A. R. Flynn synthesized the NPY Y5 receptor antagonist and contributed to reaction optimization, initial scope exploration, and the isolation of dearomatized products. M. E. Hughes contributed to the isolation of dearomatized products. D. B. Vogt conducted DFT calculations.

Abstract: A system for the dearomative hydroarylation of benzene derivatives has been developed. Under the mild conditions of an organic photoredox catalyst powered by light and a stoichiometric amine reductant, a range of spirocyclic 1,4-cyclohexadiene products have been constructed from simple aryl halide—arene precursors. The regioselectivity of this process results from reductive radical-polar crossover of the radical intermediate. The utility of this method is demonstrated through the efficient synthesis of an NPY Y5 receptor antagonist.

3.1 Introduction

In pursuing the goal of radical dearomatization, we previously described a system for the intramolecular hydroarylation of indoles (Figure 3.1; Chapter 2).[56] This method is enabled mechanistically by reductive radical-polar crossover, where the cyclized benzylic radical is reduced to the anion and protonated by solvent. Preliminary results showed that, under the same set of conditions, the hydroarylation of a benzene derivative was possible (in low yield), forming a spirocyclic 1,4-diene product. This type of spirocyclic scaffold is

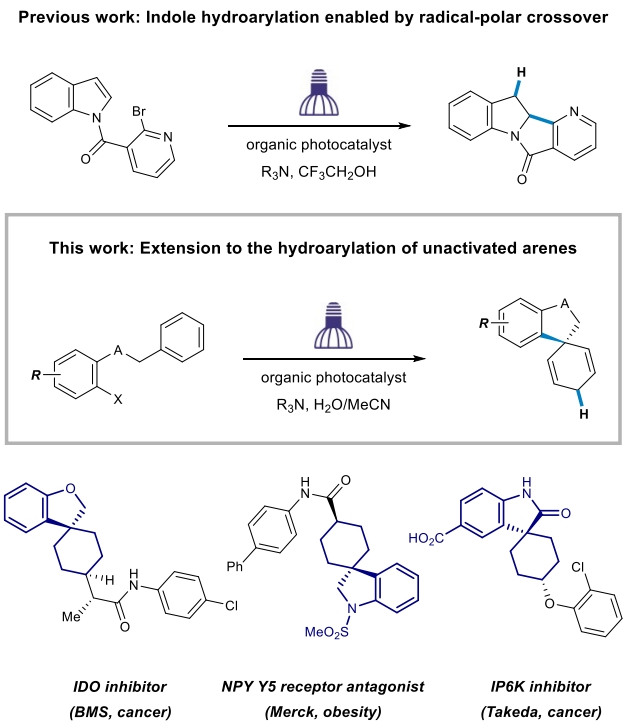


Figure 3.1: Hydroarylation of unactivated arenes for the synthesis of biologically-relevant spirocycles.

[56] McDaniel, K. A.; Jui, N. T. Dearomatization through Photoredox Hydroarylation: Discovery of a Radical-Polar Crossover Strategy. *Org. Lett.* **2021**, *23*, 5576–5580.

particularly interesting because it is prevalent in a number of biologically active small molecules (Figure 3.1).[57] Previous methods developed by Crich and Tanaka have demonstrated dearomatization with aryl radical intermediates; however, these methods rely on the use of toxic reagents (Bu_3SnH/RSeOH or SmI_2/HMPA) and demonstrate unpredictable reaction outcomes.[58] Herein, we describe the development of a system for the hydroarylation of unactivated arenes that functions under mild conditions and on a broad range of substrates, yielding 1,4-diene products with high regioselectivity.

3.2 Results and Discussion

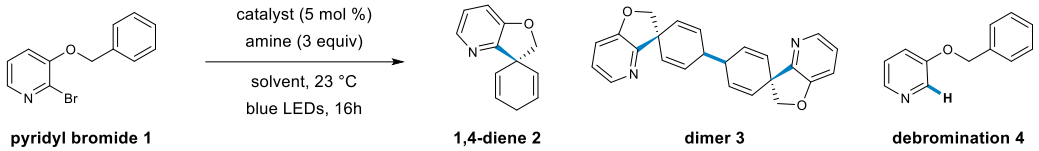
3.2.1 Optimization of system for the dearomative hydroarylation of unactivated arenes

Under the previously developed conditions for indole hydroarylation (Chapter 2), the cyclization of pyridyl bromide **1** to form spirocyclic 1,4-diene **2** occurred in 26% yield.[59] The major byproducts seen under these conditions were the dimer of the cyclized radical **3** and debromination product **4**. In optimizing the conditions for benzene hydroarylation, we found that

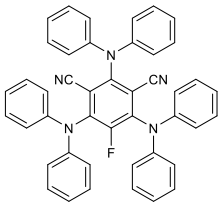
[57] (a) Terao, Y.; Takahashi, M.; Hara, R.; Hidaka, K.; Furukawa, H.; Yamasaki, T.; Kasai, S. Takeda Pharmaceutical Company Limited. IP6K Inhibitors. International Publication No. WO 2018/182051 A1, Oct 4, 2018. (b) Sakamoto, T.; Moriya, M.; Haga, Y.; Takahashi, T.; Shibata, T.; Okamoto, O.; Nonoshita, K.; Kitazawa, H.; Hidaka, M.; Gomori, A.; Iwaasa, H.; Ishihara, A.; Kanatani, A.; Fukami, T.; Gao, Y. D.; MacNeil, D. J.; Yang, L. Identification of Novel and Orally Active Spiroindoline NPY Y5 Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2009**, *19 (6)*, 1564−1568.
[58] (a) Crich, D.; Hwang, J.-T. Stannane-Mediated Radical Addition to Arenes. Generation of Cyclohexadienyl Radicals and Increased Propagation Efficiency in the Presence of Catalytic Benzeneselenol. *J. Org. Chem.* **1998**, *63*, 2765−2770. (b) Crich, D.; Sannigrahi, M. Rapid Assembly of Tetrahydrodibenzofurans and Tetrahydrocarbazoles from Benzene and *o*-Iodophenols and *o*-Iodoanilines: Reductive Radical Arylation of Benzene in Action. *Tetrahedron* **2002**, *58*, 3319−3322. (c) Crich, D.; Hao, X.; Lucas, M. A. Inhibition of Stannane-Mediated Radical Rearrangements by a Recoverable, Minimally Fluorous Selenol. *Org. Lett.* **1999**, *1*, 269− 271. (d) Ohno, H.; Iwasaki, H.; Eguchi, T.; Tanaka, T. The First Samarium(II)-Mediated Aryl Radical Cyclisation Onto an Aromatic Ring. *Chem. Commun.* **2004**, 2228−2229. (e) Iwasaki, H.; Eguchi, T.; Tsutsui, N.; Ohno, H.; Tanaka, T. Samarium(II)-Mediated Spirocyclization by Intramolecular Aryl Radical Addition onto an Aromatic Ring. *J. Org. Chem.* **2008**, *73*, 7145−7152.
[59] McDaniel, K. A.; Jui, N. T. Dearomatization through Photoredox Hydroarylation: Discovery of a Radical-Polar Crossover Strategy. *Org. Lett.* **2021**, *23*, 5576–5580.

the same donor-acceptor cycanoarene catalyst, 3DPAFIPN,[60] was most effective; however, modification of the other reaction components resulted in a higher yield of **2** (Table 3.1; see the Supporting Information (SI) for more details). Notably, by changing the solvent from 2,2,2-trifluoroethanol to acetonitrile, we saw suppression of the dimer byproduct **3**. We were able to lower the yield of the debromination byproduct **4** by decreasing the reaction concentration from 0.1 M to 0.033 M. Additional boosts in the yield of **2** were seen when diisopropylethylamine, or Hünig's base, was used as the amine reductant and when water was used as a cosolvent. Under this optimized set of conditions, the isolated yield of **2** increased to 72%.

Table 3.1: Conditions for the dearomative hydroarylation of benzene derivatives



conditions	*indole hydroarylation*	*benzene hydroarylation*
catalyst	3DPAFIPN	3DPAFIPN
amine reductant	tributylamine	Hünig's base
solvent	PhMe/CF_3CH_2OH	H_2O/MeCN
concentration	0.1 M	0.033 M
yield of **2**	26%	72%



3DPAFIPN

3.2.2 Mechanism of benzene hydroarylation reaction

This dearomative hydroarylation reaction follows the mechanistic blueprint outlined in Figure 3.2A. Single-electron reduction of aryl iodide **5** followed by mesolytic cleavage yields aryl radical **6**. Cyclization via the 5-*exo*-trig mode yields radical intermediate **7**, which is trapped via reductive radical-polar crossover, yielding anionic intermediate **8**. Protonation from solvent results

[60] Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353−15365.

in the spirocyclic 1,4-diene **9**. Reducing electrons come from the radical anion of the photocatalyst, 3DPAFIPN$^{\bullet-}$ ($E_{1/2}°$ = -1.59 V vs SCE),[61] which is formed via photoexcitation of 3DPAFIPN, intersystem crossing, and reductive quenching from Hünig's base (Figure 3.2B). The regioselectivity of the product formed is dictated by the formation of dienyl anion **8**. The density functional theory (DFT) calculated natural bond orbital (NBO) of this Birch-like intermediate shows that the anion primarily resides at the diallyl position (Fiugre 3.2C; see SI for details).[62] Deuterium labeling studies further confirm the presence of this intermediate; the replacement of H_2O with D_2O results in deuterium incorporation at the diallyl position in >95%.

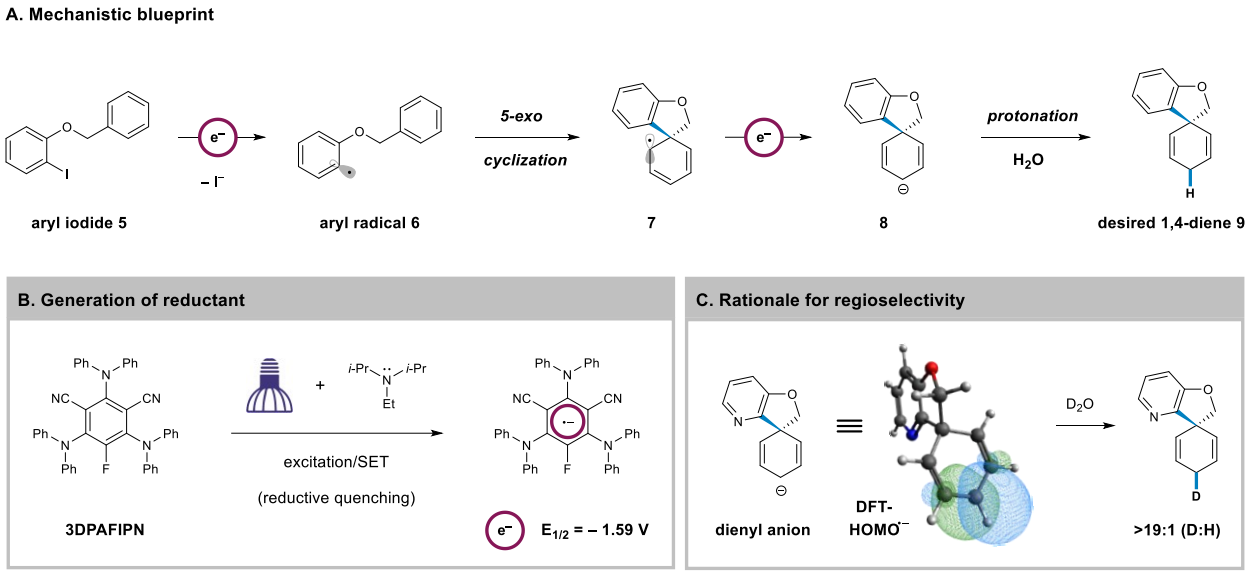


Figure 3.2: Design of a system for dearomative spirocyclization.
(A) Proposed arene hydroarylation mechanism via reductive radical-polar crossover. (B) Generation of a catalytic reductant via reductive quenching of 3DPAFIPN* with Hünig's base ($E_{1/2}$ vs SCE). (C) Rationale for selectivity for 1,4-diene based on computed anion orbital.

[61] Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353−15365.
[62] Zimmerman, H. E.; Wang, P. A. The Regioselectivity of the Birch Reduction. *J. Am. Chem. Soc.* **1993**, *115*, 2205−2216.

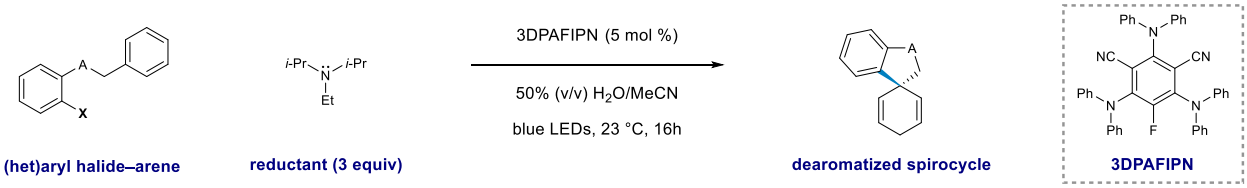
3.2.3 Scope of the dearomative hydroarylation of benzene derivatives

This dearomative spirocyclization method is broadly applicable across a range of substrates (Table 3.2). The linker between the aryl radical precursor to the acceptor arene can be varied to give spirocyclic indoline (**10-11**; 65-79%), oxindole (**12**; 55%), and dihydro-benzofuran (**2**; 72%) products. The ether-containing linker is tolerant of substitution (**13**; 50%) and can be extended to form a six-membered ring (**14**; 46%). The aryl radical precursor is tolerant of electron-donating groups (**15-16**; 71-84%) and electron-withdrawing groups (**17-18**; 54-64%). Additionally, this reactivity functions from a variety of bromopyridine regioisomers (**19-20**; 77-89%).

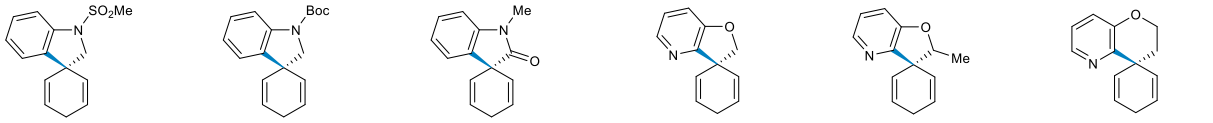
The acceptor arene component can also be widely varied. Electron-donating groups, such as methyl and methoxy are tolerated at the *ortho* (**21**; 87%), *meta* (**22-23, 25**; 68-84%), and *para* (**24**; 62%) positions. Through the cyclization of a quinoline-containing substrate, we are able to demonstrate the selective dearomatization of the more stable aromatic ring in the system (**26**, 94%; ASE = 36 kcal/mol for benzene, 27 kcal/mol for pyridine).[63] The acceptor arene is also tolerant of fluorination and chlorination at the *ortho* (**27, 30, 32**; 64-83%) and *meta* (**25, 28, 31**; 57-83%) positions, resulting in the formation of a series of vinylic halides. Cyclization into a *para*-chlorobenzene derivative results in the hydroxylated product, which presumably results from solvolysis of the diallylic chloride product (**29**, 85%).

[63] Wertjes, W. C.; Southgate, E. H.; Sarlah, D. Recent Advances in Chemical Dearomatization of Nonactivated Arenes. *Chem. Soc. Rev.* **2018**, *47*, 7996−8017.

Table 3.2: Photocatalytic Radical Hydroarylation of Aromatics: Scope of Spirocyclic Products[a]

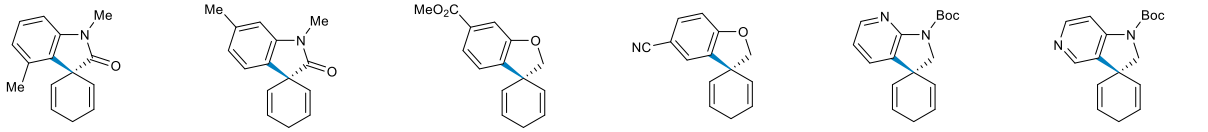


linker



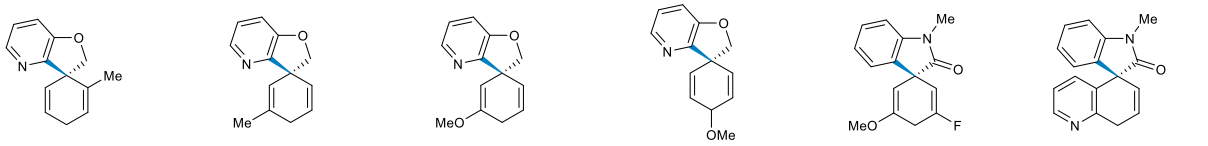
10: X = I, 65% | 11: X = Br, 79% | 12: X = I, 55% | 2: X = Br, 72% | 13: X = Br, 50%[b] | 14: X = Br, 46%

aryl radical precursor

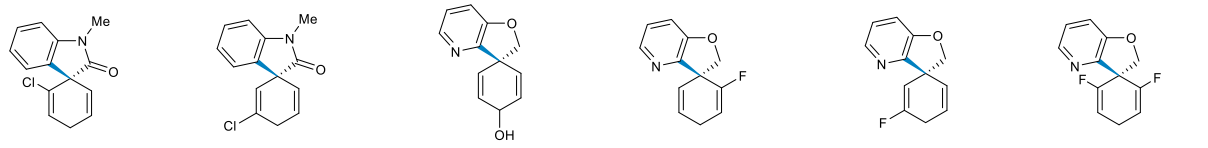


15: X = Br, 84% | 16: X = Br, 71% | 17: X = I, 64% | 18: X = Cl, 54%[b] | 19: X = Br, 77% | 20: X = Br, 89%

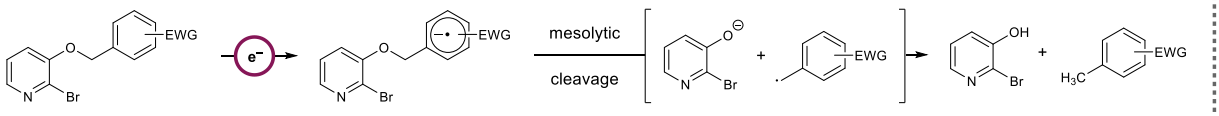
acceptor arene



21: X = Br, 87% | 22: X = Br, 72% | 23: X = Br, 84% | 24: X = Br, 62%[b,c] | 25: X = I, 68% | 26: X = I, 94%



27: X = I, 70% | 28: X = I, 57% | 29: X = Br, 85%[d] | 30: X = Br, 83% | 31: X = Br, 83% | 32: X = Br, 64%



[a]Reaction conditions: (het)arylhalide–arene (1 equiv), 3DPAFIPN (5 mol %), *i*-Pr_2NEt (3 equiv), $MeCN/H_2O$ (1:1 v/v, 15 mL/mmol), blue LEDs, 23 °C, 16 h. Isolated yields shown. [b]Reaction conducted with 10 equiv of i-Pr_2NEt. [c]4:1 d.r., isolated yield of major diastereomer shown. [d]1.8:1 d.r., isolated yield of combined diastereomers shown; *para*-chlorobenzene dearomatization was followed by chloride solvolysis.

A limitation in of this system was seen when dearomative cyclization into electron-poor arenes was attempted. In these cases, we would see fragmentation to the phenol and toluene components of the starting material instead of aryl radical formation and cyclization. This results from the pathway shown in the bottom box of Table 3.2, where preferential reduction of the electron-deficient acceptor arene is followed by mesolytic cleavage to the phenoxy anion and toluyl radical. Protonation of the anion and hydrogen atom transfer (HAT) to the radical yield the observed products. This limitation could not be overcome, as the use of a linker that would not fragment (amide) resulted in no conversion of the starting material.

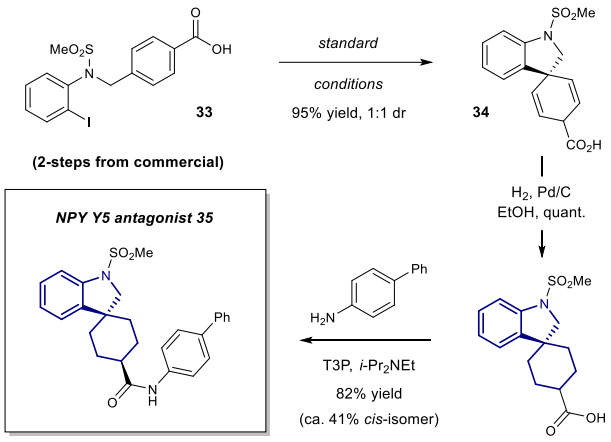
3.2.4 Efficient synthesis of NPY Y5 receptor antagonist

To further demonstrate the utility of this method, we undertook the synthesis of NPY Y5 receptor antagonist **35** developed by Merck (Scheme 3.1).[64] We imagined construction of the spirocyclic core via our dearomative spirocyclization methodology. Prior to cyclization, **33** was synthesized from commercial starting materials (62% over two steps). Under our standard reaction conditions, the cyclization of **33** resulted in the formation of **34** in 95% yield with a 1:1 dr. This is notable because this reaction typically is not tolerant of electron-withdrawing groups on the acceptor arene, and **33** contains a carboxylic acid. However, under our basic reaction conditions, this moiety exists as the carboxylate, allowing us to overcome this limitation. Hydrogenation of diene **34** followed by amidation with 4-aminobiphenyl yields NPY Y5 antagonist **35** in 82% yield (ca. 41% of the more active *cis*-isomer).

---

[64] (a) Sakamoto, T.; Moriya, M.; Haga, Y.; Takahashi, T.; Shibata, T.; Okamoto, O.; Nonoshita, K.; Kitazawa, H.; Hidaka, M.; Gomori, A.; Iwaasa, H.; Ishihara, A.; Kanatani, A.; Fukami, T.; Gao, Y. D.; MacNeil, D. J.; Yang, L. Identification of Novel and Orally Active Spiroindoline NPY Y5 Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2009**, *19 (6)*, 1564−1568. (b) Gao, Y. D.; Macneil, D. J.; Morin, N. R.; Fukami, T.; Kanatani, A.; Fukuroda, T.; Ishii, Y.; Morin, M. Merck & Co., Inc. Spiroindolines as Y5 Receptor Antagonists. International Publication No. WO 00/27845, May 18, 2000.

Scheme 3.1: Direct dearomative approach to spiroindoline **35**



3.3 Conclusions

In conclusion, we successfully extended our method for dearomative indole hydroarylation to the hydroarylation of unactivated arenes. Optimization of this system demonstrated that the organic photocatalyst 3DPAFIPN and an amine reductant are crucial components of this dearomatization manifold. Mechanistically, reductive radical formation is followed by 5-*exo* cyclization, forming the spirocyclic center. Reductive radical-polar crossover and protonation selectively yields the 1,4-diene product. The scope of this reactivity is broad, with the major limitation being competitive reduction of electron-poor acceptor arenes. Finally, we further exhibited the utility of this method through the synthesis of a spirocyclic NPY Y5 antagonist.

3.4 Supporting Information

3.4.1 General Information

General Reagent Information

Solvents used in anhydrous reactions were purified by passing over activated alumina and storing under argon. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Astatech, and TCI America and used as received, unless stated otherwise. n-Butyllithium (n-BuLi) was used as a 1.6 M or 2.5 M solution in hexanes (Aldrich), and stored at 4 °C and titrated prior to use. Organic solutions were concentrated under reduced pressure on a rotary evaporator using a water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on 230–400 mesh silica gel. Preparative HPLC was carried out using an Agilent Technologies 1260 Infinity HPLC with a 21.2 x 250 mm, 7µm pore size, ZORBAX Eclipse XDB-C18 Column. Eluents used were unmodified unless otherwise stated. Preparative thin-layer chromatography (PTLC) separations were carried out on 1000 µm SiliCycle silica gel F-254 plates. Thin-layer chromatography (TLC) was performed on 250 µm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or staining using $KMnO_4$, p-anisaldehyde, or ninhydrin stains. All photoredox reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs, unless stated otherwise (LED wholesalers PAR38 Indoor Outdoor 16-Watt LED Flood Light Bulb, Blue; or Hydrofarm® PPB1002 PowerPAR LED Bulb-

Blue 15W/E27 (available from Amazon. Photoredox catalysts 3DPAFIPN, 3DPA2FBN, 4CzIPN, 5CzBN, N-POX(Ph_2)$_2$ were all prepared according to literature procedures.[65,66]

General Analytical Information.

Unless otherwise noted, all yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. New compounds were characterized by NMR, IR, HRMS, and melting point (when solid). ^{1}H and ^{13}C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), VNMR 400 (400 MHz), or Mercury 300 (300 MHz), and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, dtd= doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), integration, and assignment, when applicable. Data for decoupled ^{13}C NMR are reported in terms of chemical shift and multiplicity when applicable. IR spectra were recorded on a Thermo Fisher DiamondATR and reported in terms of frequency of absorption (cm $^{-1}$). High Resolution mass spectra were obtained from the Emory University Mass Spectral facility. Gas Chromatography Mass Spectrometry (GC-MS) was performed on an Agilent 5977A mass spectrometer with an Agilent 7890A gas chromatography inlet. Liquid Chromatography Mass Spectrometry (LC-MS) was performed on an Agilent 6120 mass spectrometer with an Agilent 1220 Infinity liquid chromatography inlet. Preparative High Pressure Liquid chromatography

[65] Pearson, R. M.; Lim, C.-H.; McCarthy, B. G.; Musgrave, C. B.; Miyake, G. M. Organocatalyzed Atom Transfer Radical Polymerization Using N-Aryl Phenoxazines as Photoredox Catalysts. *J. Am. Chem. Soc.* **2016**, *138* (35), 11399–11407.

[66] Speckmeier, E.; Fischer, T.; Zeitler, K. A Toolbox Approach to Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140* (45), 15354–15365.

(Prep-HPLC) was performed on an Agilent 1200 Infinity Series chromatograph using an Agilent Prep-C18 30 x 250 mm 10 µm column, or an Agilent Prep-C18 21.2 x 100 mm, 5 µm column.

3.4.2 General Procedures

General Procedure A

A 20 mL screw-top test tube was charged with photocatalyst (0.015 mmol, 5 mol%), and substrate (0.5 mmol, 1.0 equiv). The tube was equipped with a stir bar was sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, separated degased solvent was added via syringe (7.5 mL of each MeCN and H_2O to give a 0.03 M solution), followed by DIPEA (3.0 equiv).The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with ethyl acetate (3 x), dried with $MgSO_4$, and concentrated. The residue was purified on silica using the indicated solvent mixture as eluent to afford the title compound.

General Procedure B

A 20 mL screw-top test tube was charged with photocatalyst (0.015 mmol, 5 mol%), and substrate (0.5 mmol, 1.0 equiv). The tube was equipped with a stir bar was sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, separated degased solvent was added via syringe (7.5 mL of each MeCN and H_2O to give a 0.03 M solution), followed by DIPEA (10.0 equiv). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with ethyl acetate (3 x), dried with $MgSO_4$, and concentrated. The residue was purified on silica using the indicated solvent mixture as eluent to afford the title compound.

Optimization Procedure

An 8 mL screw-top test tube was charged with photocatalyst (0.005 mmol, 5 mol%) and 3-(benzyloxy)-2-bromopyridine (**1**). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, separately degased solvent was added via syringe, followed by reductant. The resulting mixture was stirred at 800 RPM for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with ethyl acetate (3 x), dried with $MgSO_4$, and concentrated. Deutro-chloroform with an internal standard of dibromomethane (7 µL, 0.1 mmol) was added. The sample was analyzed by ^1H NMR (d = 5 s), and the integral values were used to calculate the data given in the optimization table.

Reaction Setup

To run multiple reactions, (for either optimization or product preparation) an appropriately sized 3D printed carousel was used, which exposed the reactions to the blue light evenly. A 15 W LED array lamp was used as a blue light source. These lamps were routinely used for up to 12 reactions at a time. The reactions were cooled with a line of compressed air. The blue LED was positioned approximately 6 cm above the reaction vials, to get good light coverage but without overheating the reactions.

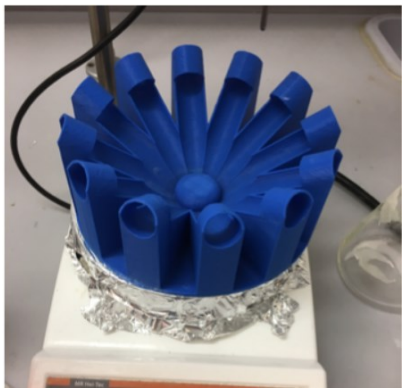
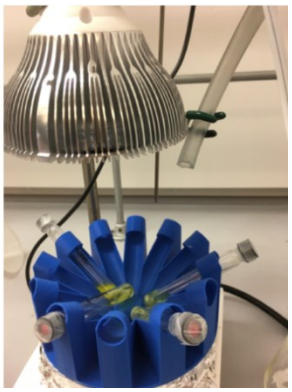
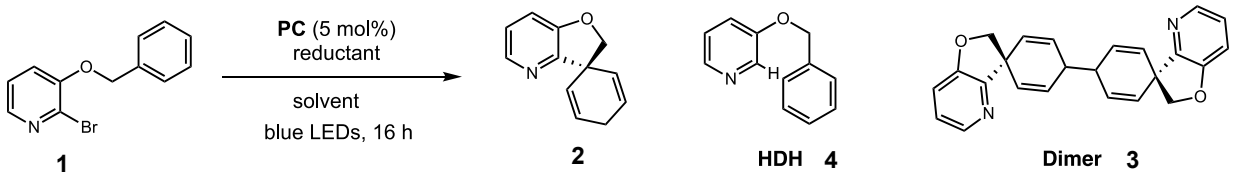
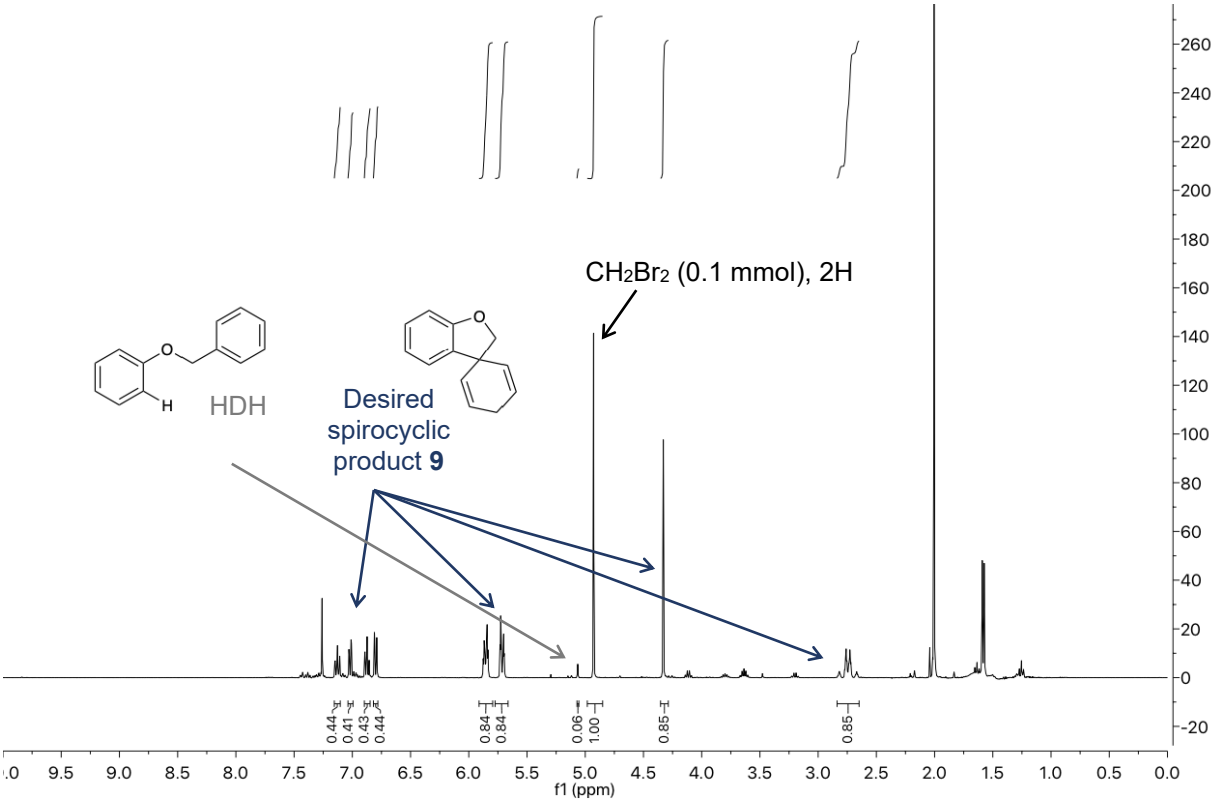




Table 3.3: Optimization of arene dearomatization via radical hydroarylation



entry	PC	reductant (equiv)	% water	cosolvent (rxn conc)	1	2	HDH	dimer
1	3DPAFIPN	tributylamine (3)	10	DMF (0.1 M)	19	29	27	0
2	3DPAFIPN	tributylamine (3)	10	EtOH (0.1 M)	2	51	20	0
3	3DPAFIPN	tributylamine (3)	10	TFE (0.1 M)	0	57	7	15
4	3DPAFIPN	tributylamine (3)	10	DMSO (0.1 M)	11	43	7	0
5	3DPAFIPN	tributylamine (3)	10	MeCN (0.1 M)	0	60	19	0
6	3DPAFIPN	tributylamine (3)	50	MeCN (0.1 M)	0	71	14	0
7	3DPAFIPN	tributylamine (3)	80	MeCN (0.1M)	0	39	66	0
8	3DPAFIPN	DIPEA (3)	50	MeCN (0.1 M)	0	81	21	0
9	3DPAFIPN	DIPEA (0.5)	50	MeCN (0.1 M)	80	13	7	0
10	3DPAFIPN	DIPEA (2)	50	MeCN (0.1 M)	16	66	26	0
11	3DPAFIPN	DIPEA (10)	50	MeCN (0.1 M)	0	65	48	0
12	**3DPAFIPN**	**DIPEA (3)**	**50**	**MeCN (0.03M)**	**5**	**86**	**6**	**0**
13	4CzIPN	DIPEA (3)	50	MeCN (0.03 M)	46	49	5	0
14	5CzBN	DIPEA (3)	50	MeCN (0.03 M)	36	46	20	0
15	3DPA2FBN	DIPEA (3)	50	MeCN (0.03 M)	0	66	5	9
16	$Ir(ppy)_2(dtbbpy)\ PF_6$	DIPEA (3)	50	MeCN (0.03 M)	14	66	15	0
17	$Ir(ppy)_3$	DIPEA (3)	50	MeCN (0.03 M)	17	31	8	14
18	$N\text{-}POX(Ph_2)_2$	HCOONa (3)	50	MeCN (0.03 M)	94	trace	trace	0
19	3DPAFIPN	DIPEA (3)	0	MeCN (0.03 M)	6	68	13	8
20[a]	3DPAFIPN	DIPEA (3)	50	MeCN (0.03 M)	49	44	5	0
21	3DPAFIPN	triethylamine (3)	50	MeCN (0.03 M)	41	65	5	0
22	3DPAFIPN	none	50	MeCN (0.03 M)	100	0	0	0
23	none	DIPEA (3)	50	MeCN (0.03 M)	100	0	0	0
24[b]	3DPAFIPN	DIPEA (3)	50	MeCN (0.03 M)	100	0	0	0

3.4.3 Example of Selectivity



1-(benzyloxy)-2-iodobenzene (0.1 mmol) was subjected to General Conditions A. The reaction was then extracted with ethyl acetate (3x), dried with $MgSO_4$, and concentrated. $CDCl_3$ with an internal standard of dibromomethane (7 µL, 0.1 mmol) was added. The sample was analyzed by ^1H NMR (d = 5 s), and the integral values are shown in the crude NMR above. NMR was compared to (and was consistent with) reported literature values.[67]

[67] Iwasaki, H.; Eguchi, T.; Tsutsui, N.; Ohno, H.; Tanaka, T. Samarium(II)-Mediated Spirocyclization by Intramolecular Aryl Radical Addition onto an Aromatic Ring. *J. Org. Chem.* **2008**, *73* (18), 7145–7152.

3.4.4 Fluorescence Quenching and Stern-Volmer Plots

All fluorescence measurements were recorded using a Horiba Scientific Dual-FL Fluorometer. Quenching studies were conducted in MeCN at 20 ± 0.5 °C (Peltier temperature controller) with a photocatalyst (3DPAFIPN) concentration of $9.01*10^{-6}$ M. Samples were prepared in Starna quartz cuvettes (3-Q-10-GL14-S) with septum seal caps. Dry N2 was bubbled through the prepared sample for 4 minutes before analysis. Raw fluorescence intensity was measured at l = 542 nm after excitation at l = 380 nm in the quartz cuvettes with a path length of 1 cm and 0.1 second integration. Measurements of the quenchers shown were plotted using Igor Pro 8; data points were fit with a linear trend line.

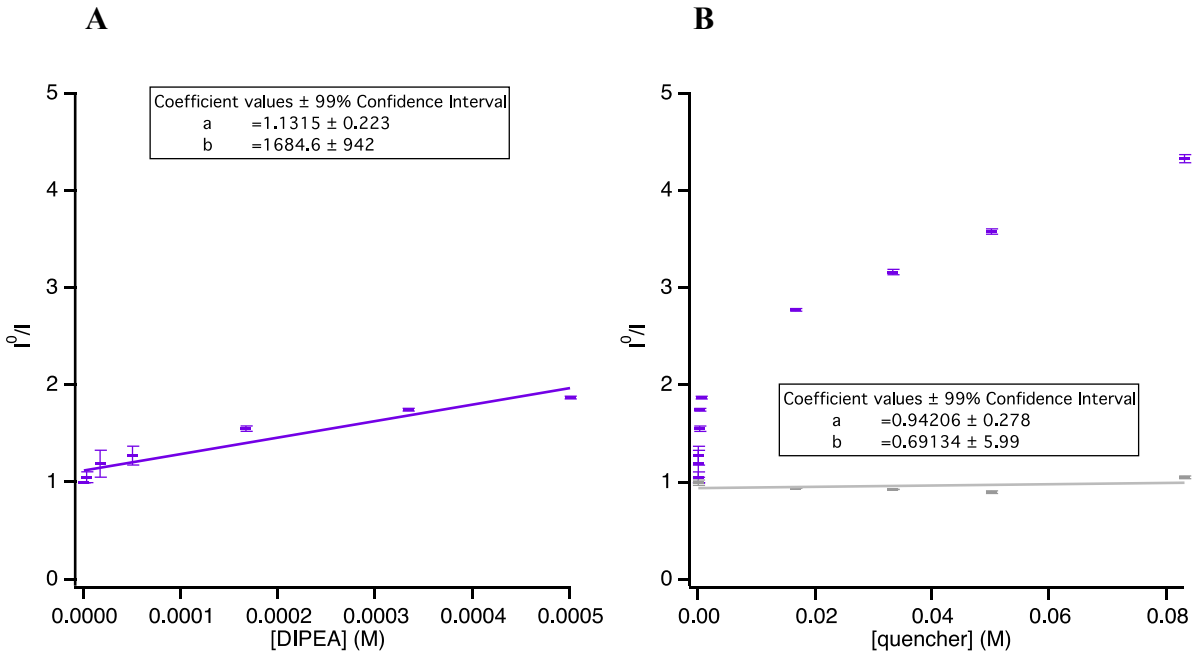


Figure 3.3: Stern-Volmer plots for DIPEA and 3-(benzyloxy)-2-bromopyridine (**1**) with respect to 3DPAFIPN

(A) DIPEA at low concentrations and (B) DIPEA and 3-(benzyloxy)-2-bromopyridine up to ~ 10,000 equivalents

Table 3.4: Fluorescence quenching data

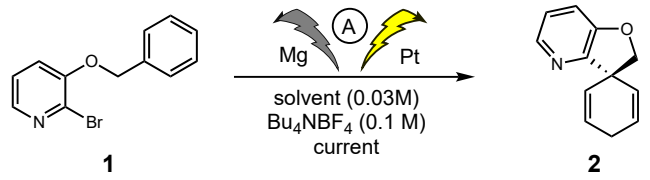
Compound (Quencher)	**[Quencher] (M)**	**I^0/I**	**Equiv *vs* PC**	**Coefficients**
Diisopropylethylamine	0	1	0	y = a + bx
Diisopropylethylamine	$3.3*10^{-6}$	1.06	0.4	a = 1.1 ± 0.2
Diisopropylethylamine	$1.67*10^{-5}$	1.20	1.9	b = 1684 ± 942
Diisopropylethylamine	$5.0*10^{-5}$	1.27	5.6	
Diisopropylethylamine	$1.67*10^{-4}$	1.56	19	± 99% CI
Diisopropylethylamine	$3.33*10^{-4}$	1.76	37	
Diisopropylethylamine	$5.0*10^{-4}$	1.88	55	
Diisopropylethylamine	$1.67*10^{-2}$	2.77	1854	
Diisopropylethylamine	$3.33*10^{-2}$	3.16	3696	
Diisopropylethylamine	$5.0*10^{-2}$	3.59	5549	
Diisopropylethylamine	$8.3*10^{-2}$	4.33	9212	
3-(benzyloxy)-2-bromopyridine	0	1	0	y = a + bx
3-(benzyloxy)-2-bromopyridine	$1.67*10^{-2}$	0.94	1854	a = 0.94 ± 0.28
3-(benzyloxy)-2-bromopyridine	$3.33*10^{-2}$	0.94	3696	b = 0.69 ± 5.99
3-(benzyloxy)-2-bromopyridine	$5.0*10^{-2}$	0.91	5549	
3-(benzyloxy)-2-bromopyridine	$8.3*10^{-2}$	1.06	9212	± 99% CI

3.4.5 Electrochemical Reaction Optimization Procedure

To an ElectraSyn vial charged with stir bar was added 3-(benzyloxy)-2-bromopyridine (**1**) (0.2 mmol, 1 equiv), electrolyte (to make the indicated concentration), and solvent (6 mL) An IKA Mg (anode) and Pt (cathode) plate electrodes were connected to an ElectraSyn vial cap. The ElectraSyn was setup as follows: New exp. > constant current > **X** mA > no ref. electrode > total charge > 0.2 mmol, 3 F/mol > no alternating polarity > start. The reaction was allowed to run with stirring until the ElectraSyn had measured 3 F/mol input. The reaction was then concentrated. Deutro-chloroform with an internal standard of dibromomethane (7 μL, 0.1 mmol) was added. The sample

was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the data given in the following table.

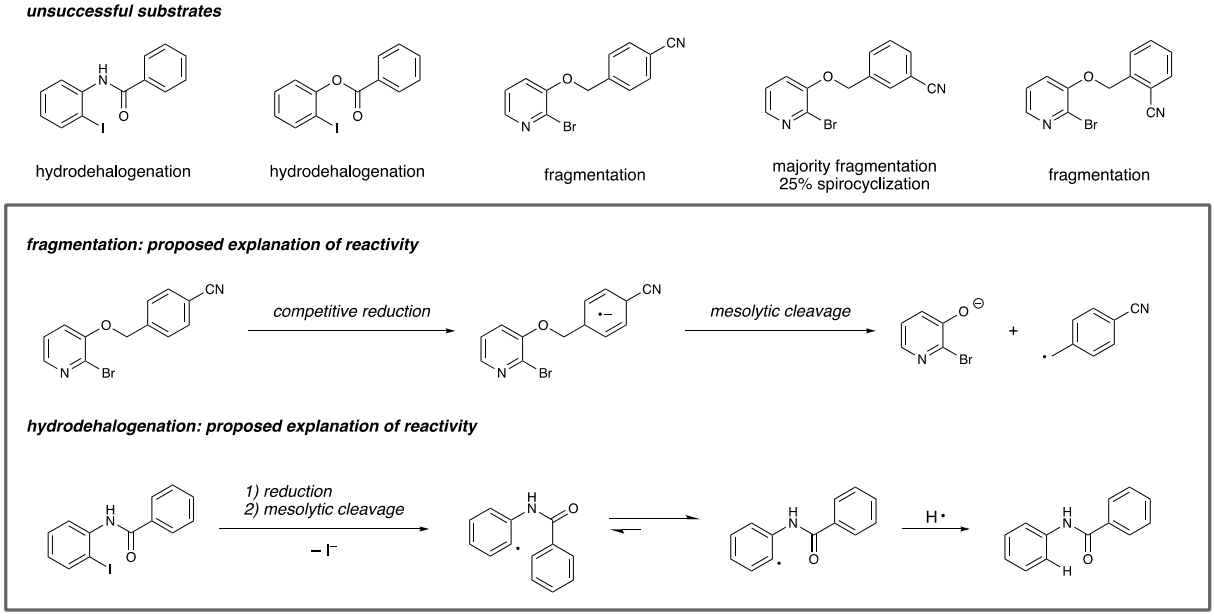
Table 3.5: Preliminary results for electrochemical spirocyclization



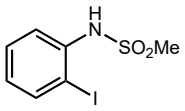
entry	current	1	2	HDH
1	2 mA	100	0	0
2	5 mA	71	0	30
3	10 mA	28	3	60
4	50 mA	29	8	63

3.4.6 Unsuccessful Substrates

Table 3.6: Unsuccessful Substrates



3.4.7 Preparation of Starting Materials



_N_-(2-iodophenyl)methanesulfonamide (S1)

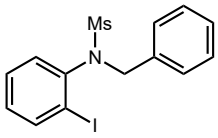
To a solution of 2-iodoaniline (572 mg, 2.6 mmol, 1 equiv) in dichloromethane was added methanesulfonyl chloride (250 µL, 3.2 mmol, 1.2 equiv) dropwise via syringe, followed by pyridine (250 µL, 2.8 mmol, 1.1 equiv). The resulting mixture was stirred at room temperature for 4 h and concentrated. The resulting residue was purified on silica gel (20–50% eluent) to afford the title compound as a white solid (770 mg, >99%).

^{1}H NMR (399 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.0, 1.5 Hz, 1H), 7.61 (dd, J = 8.2, 1.5 Hz, 1H), 7.35 (tdd, J = 8.0, 1.5, 0.5 Hz, 1H), 6.91 (ddd, J = 8.0, 7.4, 1.5 Hz, 1H), 6.67 (bs, 1H), 2.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.6, 129.9, 127.3, 122.6, 92.3, 40.2.

LRMS (APCI) m/z: $[M-H]^-$ calc'd. for $C_7H_7INO_2S$, 295.9; found 295.8.

^{1}H NMR spectrum is consistent with reported values.[68]



_N_-benzyl-_N_-(2-iodophenyl)methanesulfonamide (S2)

A 20 mL screw-top vial was charged with *N*-(2-iodophenyl)methanesulfonamide (**S1**), (459 mg, 1.6 mmol, 1.0 equiv) and K_2CO_3 (365 mg, 2.6 mmol, 1.6 equiv). DMF was added, followed by benzyl bromide (450 µL, 3.7 mmol, 2.3 equiv). The reaction was stirred overnight (ca. 16 h) at room temperature, then heated to 60 °C and heated until starting material was consumed (as

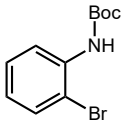
[68] Fernández, A.; Varela, J.; Saá, C. Formation of Indoles, Dihydroisoquinolines, and Dihydroquinolines by Ruthenium-catalyzed Heterocyclizations. *Synthesis,* **2012**, *44*, 3285–3295.

determined by LCMS). The reaction was cooled to room temperature and then partitioned between EtOAc and water. The organic layer was washed with brine 3x, dried with $MgSO_4$ and purified on silica gel (10-50% eluent) to afford the title compound as a colorless oil (394 mg, 66%).

^{1}H NMR (399 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 6H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 5.05 (d, *J* = 14.6 Hz, 1H), 4.54 (d, *J* = 14.6 Hz, 1H), 3.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 140.4, 135.4, 133.1, 130.2, 129.7, 129.0, 128.5, 128.2, 101.0, 54.9, 41.8.

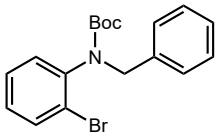
LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{15}INO_2S$, 387.9; found 387.7.



***tert*-butyl (2-bromophenyl)carbamate (S3):** In a round bottom flask, 2-bromoaniline (15 g, 88 mmol, 1.0 equiv) was dissolved in DCM and cooled to 0 °C. Di-tert-butyl decarbonate (43 g, 195 mmol, 2.2 equiv) was added slowly to the reaction over the course of 30 minutes. Dimethylaminopyridine (1.8 g, 15 mmol, 0.2 equiv) was then added slowly to the reaction mixture (caution: on this large scale significant exotherm and evolution of CO_2 is possible.). The resulting mixture was stirred until consumption of the starting material was detected by TLC. The reaction was then poured onto water, washed with $NaHCO_3$, and extracted with EtOAc x3. The combined organic layers were dried with $MgSO_4$. The crude oil was identified as the di-boc product by ^{1}H NMR. One Boc was removed by stirring the crude oil in a dilute solution of TFA in DCM at 0 °C. This reaction was monitored carefully by TLC until the complete removal of one boc was detected. The reaction was then basified, poured onto water and extracted with EtOAc x3. The crude oil was purified on silica (10-30% EtOAc/Hex eluent) to afford the title product as a colorless oil (19 g, 80% over 2 steps).

^{1}H NMR (400 MHz, CDCl3) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.0, 1.7 Hz, 1H), 7.32 – 7.16 (m, 1H), 6.97 (bs, 1H), 6.88 (t, *J* = 7.7 Hz, 1H), 1.52 (s, 9H).

^{1}H NMR spectrum is consistent with reported values.[69]

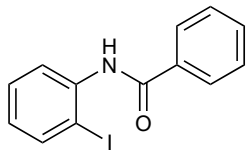


***tert*-butyl benzyl(2-bromophenyl)carbamate (S4):** In a round bottom flask under nitrogen, sodium hydride as a 60% dispersion in mineral oil (180 mg, 4.5 mmol, 1.3 equiv) was suspended in DMF and cooled to 0 °C. **S3** as a solution in DMF (976 mg, 3.6 mmol, 1.0 equiv) was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of benzyl bromide (513 µL, 4.3 mmol, 1.2 equiv). The reaction was removed from the ice bath, and after reacting for 4.5 h was quenched with methanol then water at 0 °C. The resulting mixture was diluted with ethyl acetate and washed with brine 3x. The organic layer was dried with $MgSO_4$, concentrated *in vacuo*, and purified on silica gel (05% EtOAc/Hex eluent) to afford the title compound as a colorless oil (238 mg, >99%).

^{1}H NMR (500 MHz, $CDCl_3$, 60 °C) δ 7.59 (bd, *J* = 7.9 Hz, 1H), 7.26 (bm, 5H), 7.10 (bm, 2H), 6.84 (bs, 1H), 5.21 (s, 1H), 4.23 (d, *J* = 14.9 Hz, 1H), 1.44 (bm, *J* = 61.2 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$, 60 °C) δ 154.4, 141.2, 137.9, 133.1, 130.9, 128.9, 128.4, 128.2, 127.6, 127.3, 123.8, 80.5, 52.7, 28.2.

LRMS (APCI) m/z: $[M-C_4H_9H + H]^+$ calc'd. for $C_{14}H_{12}BrNO_2$, 305.0; found 305.8.



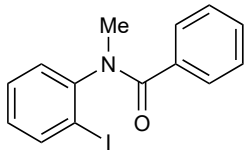
[69] Zhang, Z.; Liu, Y-H.; Zhang.X.; Wang, X-C. $KMnO_4$-Mediated oxidative C-N bond cleavage of tertiary amines: synthesis of amides and sulfonamides. *Tetrahedron*, **2019**, *75*, 2763–2770.

***N*-(2-iodophenyl)benzamide (S5):** To a solution of 2-iodoaniline (641 mg, 2.9 mmol, 1.0 equiv) in dichloromethane was added benzoyl chloride (375 µL, 3.2 mmol, 1.1 equiv) dropwise via syringe, followed by triethylamine (500 µL, 3.6 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 4 h, quenched with methanol, and concentrated. The resulting solid was purified on silica gel (10–20% eluent) to afford the title compound as a white solid. (945 mg, >99 %).

^{1}H NMR (399 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.30 (bs, 1H), 8.01 – 7.88 (m, 2H), 7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.61 – 7.45 (m, 3H), 7.37 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 6.86 (td, *J* = 7.7, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 138.8, 138.3, 134.5, 132.2, 129.4, 128.9, 127.2, 126.1, 121.9, 90.4.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{11}INO$, 323.1; found 323.7.



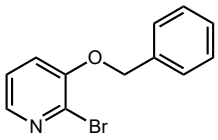
***N*-(2-iodophenyl)-*N*-methylbenzamide (S6):** In a vial under nitrogen, sodium hydride as a 60% dispersion in mineral oil (120 mg, 3.0 mmol, 2.0 equiv) was suspended in DMF and cooled to 0 °C. **S5** as a solution in DMF (476 mg, 1.5 mmol, 1.0 equiv) was added to the sodium hydride suspension and stirred for 30 minutes before the addition of methyl iodide (140 µL, 2.2 mmol, 1.5 equiv). The reaction was removed from the ice bath, and after reacting for 1.5 h was quenched with methanol then water at 0 °C. The resulting mixture was diluted with ethyl acetate and washed with brine 3x. The organic layer was dried with $MgSO_4$, concentrated *in vacuo*, and purified on silica gel (10-25% EtOAc/Hex eluent) to afford the title compound as a white solid (312 mg, 62%).

^{1}H NMR (399 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.43 – 7.27 (m, 2H), 7.20 – 7.01 (m, 5H), 6.85 (td, *J* = 7.6, 1.7 Hz, 1H), 3.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 146.9, 140.1, 135.6, 130.1, 129.8, 129.3, 129.1, 128.3, 127.6, 99.1, 37.5.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{13}INO$, 337.9; found 337.7

^{1}H NMR spectrum is consistent with reported values.[70]

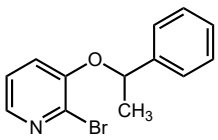


3-(benzyloxy)-2-bromopyridine (1): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (5.0 g, 29 mmol, 1.0 equiv) and K_2CO_3 (8.0 g, 58 mmol, 2.0 equiv). DMF was added, followed by benzyl bromide (3.7 mL, 31 mmol, 1.1 equiv). The reaction was heated to 80 °C and stirred for 16 h. The reaction was cooled to room temperature and then partitioned between EtOAc and water. The organic layer was washed with brine 3x, dried with $MgSO_4$ and purified on silica gel (20–50% EtOAc/hexanes eluent) to afford the title compound as a white solid (7.5 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 3.8, 2.4 Hz, 1H), 7.47 – 7.27 (m, 5H), 7.18 – 7.09 (m, 2H), 5.15 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0, 141.6, 135.5, 133.3, 128.7, 128.3, 127.0, 123.3, 120.5, 70.9.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_{11}BrNO$, 264.0; found 263.8



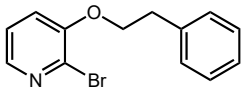
[70] Colobert, F; Valdivia, V.; Choppin, S.; Leroux, F.; Fernández, I.; Álvarez, E.; Khiar, N. Axial chirality control during Suzuki-Miyaura cross-coupling reactions: the tert-butylsulfinyl group as an efficient chiral auxiliary. *Org. Lett.* **2009**, *11(25)*, 5130–5133.

(±) 2-bromo-3-(1-phenylethoxy)pyridine (S7): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by (1-bromoethyl)benzene (0.41 mL, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 18 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a colorless oil (834 mg, >99%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dt, *J* = 4.6, 1.3 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.35 (tt, *J* = 6.5, 1.0 Hz, 2H), 7.31 – 7.24 (m, 1H), 7.01 (ddt, *J* = 8.2, 4.6, 1.2 Hz, 1H), 6.99 – 6.95 (m, 1H), 5.35 (q, *J* = 6.4 Hz, 1H), 1.72 (dd, *J* = 6.4, 1.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.4, 141.5, 141.3, 133.8, 128.9, 128.0, 125.6, 123.2, 121.9, 77.8, 24.4.

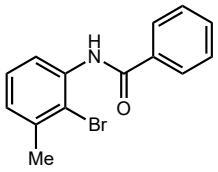
LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{13}BrNO$, 278.0; found 277.8.



2-bromo-3-phenethoxypyridine (S8): A 20mL screw-top vial was charged with 2-bromo-3-hydroxypyridine (452 mg, 2.6 mmol, 1.0 equiv) and K_2CO_3 (716 mg, 5.1 mmol, 2.0 equiv). DMF was added, followed by 2(bromoethyl)benzene (380 µL, 2.9 mmol, 1.1 equiv). The reaction was heated to 80 °C and stirred for 16 h. The reaction was cooled to room temperature and then partitioned between EtOAc and water. The organic layer was washed with brine 3x, dried with $MgSO_4$ and purified on silica gel (20–60% EtOAc/hexanes eluent) to afford the title compound as a white solid (378 mg, 52%).

^{1}H NMR (399 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.34 – 7.31 (m, 4H), 7.27 – 7.22 (m, 1H), 7.14 (dd, *J* = 8.1, 4.6 Hz, 1H), 7.04 (dd, *J* = 8.2, 1.5 Hz, 1H), 4.18 (t, *J* = 6.8 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H).

^{1}H NMR spectrum is consistent with reported values.[71]

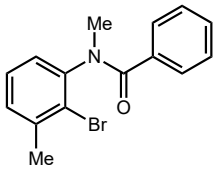


***N*-(2-bromo-3-methylphenyl)benzamide (S9):** To a solution of 2-bromo-3-methylaniline (0.41 mL, 3.3 mmol, 1.1 equiv) in dichloromethane was added benzoyl chloride (0.35 mL, 3.0 mmol, 1.0 equiv) dropwise via syringe, followed by triethylamine (0.46 mL, 3.3 mmol, 1.1 equiv). The resulting mixture was stirred at room temperature for 22 h, washed with 1M HCl (aq), dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a white solid. (732 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.43 – 8.37 (m, 1H), 7.99 – 7.91 (m, 2H), 7.64 – 7.56 (m, 1H), 7.56 – 7.49 (m, 2H), 7.29 (d, J = 7.8 Hz, 1H), 7.05 (ddd, J = 7.5, 1.7, 0.8 Hz, 1H), 2.46 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 165.5, 138.7, 136.1, 135.0, 132.3, 129.1, 127.9, 127.3, 126.4, 119.3, 116.7, 24.0 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{13}BrNO$, 290.0; found 289.7.



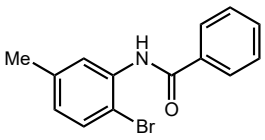
[71] Hu, Q.; Kunde, J.; Hanke, N; Hartmann, R. Identification of 4-(4-nitro-2-phenethoxyphenyl)pyridine as a promising new lead for discovering inhibitors of both human and rat 11ß-hydroxylase. *Eur. J. Med. Chem.* **2015**, *96*, 139–150.

***N*-(2-bromo-3-methylphenyl)-*N*-methylbenzamide (S10):** In a vial under nitrogen, sodium hydride as a 60% dispersion in mineral oil (120 mg, 3.0 mmol, 1.5 equiv) was suspended in DMF and cooled to 0 °C. **S9** as a solution in DMF (580 mg, 2.0 mmol, 1.0 equiv) was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of methyl iodide (0.15 mL, 2.4 mmol, 1.2 equiv). The reaction was removed from the ice bath, and after reacting for 1.5 h was quenched water. The resulting mixture was diluted with ethyl acetate and washed with brine 3x. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a light pink solid (573 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dt, J = 7.0, 1.4 Hz, 2H), 7.26 – 7.17 (m, 1H), 7.14 (tt, J = 6.7, 1.7 Hz, 2H), 7.09 – 7.01 (m, 2H), 6.91 (dd, J = 7.5, 2.1 Hz, 1H), 3.38 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 144.1, 140.4, 136.1, 129.9, 129.8, 128.2, 127.8, 127.7, 125.5, 37.3, 23.9 ppm.

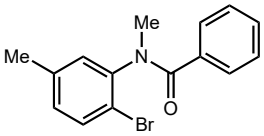
LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{15}BrNO$, 304.0; found 303.7.



***N*-(2-bromo-5-methylphenyl)benzamide (S11):** To a solution of 2-bromo-5-methylaniline (614 mg, 3.3 mmol, 1.1 equiv) in dichloromethane was added benzoyl chloride (0.35 mL, 3.0 mmol, 1.0 equiv) dropwise via syringe, followed by triethylamine (0.46 mL, 3.3 mmol, 1.1 equiv). The resulting mixture was stirred at room temperature for 16 h, quenched with sat. aq. NH_4Cl, and extracted with DCM 3x. The combined organic layers were washed with 1M HCl (aq) and brine, dried over MgSO4, and concentrated *in vacuo* to afford the title compound as an off-white solid (839 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.37 (m, 2H), 7.92 (d, J = 7.0 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.3 Hz, 2H), 7.43 (d, J = 8.2 Hz, 1H), 6.83 (dd, J = 8.2, 2.1 Hz, 1H), 2.35 (s, 3H) ppm.

^{1}H NMR spectrum is consistent with reported values.[72]

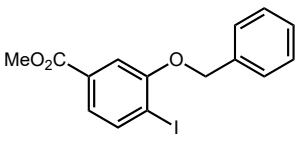


***N*-(2-bromo-5-methylphenyl)-*N*-methylbenzamide (S12):** In a vial under nitrogen, sodium hydride as a 60% dispersion in mineral oil (120 mg, 3.0 mmol, 1.5 equiv) was suspended in DMF and cooled to 0 °C. **S11** as a solution in DMF (580 mg, 2.0 mmol, 1.0 equiv) was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of methyl iodide (0.15 mL, 2.4 mmol, 1.2 equiv). The reaction was removed from the ice bath, and after reacting for 1 h was quenched with water and extracted with EtOAc 3x. The combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a light yellow solid (577 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 4H), 7.27 – 7.18 (m, 1H), 7.15 (t, J = 7.5 Hz, 2H), 6.92 – 6.83 (m, 2H), 3.37 (s, 3H), 2.17 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 143.5, 138.8, 135.9, 133.4, 131.3, 130.0, 129.8, 128.2, 127.7, 119.3, 37.2, 20.8 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{15}BrNO$, 304.0; found 303.7.

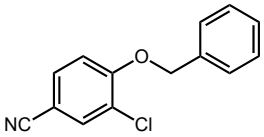


[72] Zheng, N.; Anderson, K.; Huang, X.; Nguyen, H.; Buchwald, S. A palladium-catalyzed regiospecific synthesis of N-aryl benzimidazoles. *Angew. Chem. Int. Ed.* **2007**, *40*, 7509–7512.

Methyl 3-(benzyloxy)-4-iodobenzoate (S13): A round bottom flask was charged with methyl 3-hydroxy-4-iodobenzoate (417 mg, 1.5 mmol, 1.0 equiv) and K_2CO_3 (415 mg, 1.5 mmol, 1.0 equiv). MeCN (10 mL) was added, followed by benzyl bromide (0.18 mL, 3.0 mmol, 2.0 equiv). The reaction was heated to 60 °C and stirred for 18 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a white solid (535 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 1H), 7.56 – 7.50 (m, 3H), 7.44 – 7.37 (m, 3H), 7.34 (t, J = 7.3 Hz, 1H), 5.21 (s, 2H), 3.91 (s, 3H) ppm.

^{1}H NMR spectra are consistent with reported values.[73]



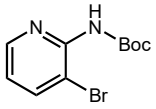
4-(benzyloxy)-3-chlorobenzonitrile (S14): A round bottom flask was charged with 3-chloro-4-hydroxybenzonitrile (461 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by benzyl bromide (0.36 mL, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 16 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and purified on silica gel (5–10% EtOAc/hexanes eluent) to afford the title compound as a white solid (303 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 2.0 Hz, 1H), 7.51 (ddd, J = 8.6, 2.1, 0.3 Hz, 1H), 7.47 – 7.31 (m, 5H), 7.01 (d, J = 8.6 Hz, 1H), 5.23 (s, 2H) ppm.

[73] Palmerinin, C.; Tartacca, F.; Mazzoni, M.; Granieri, L.; Goracci, L.; Scrascia, A.; Lepri, S. Synthesis of new indole-based bisphosphonates and evaluation of their chelating ability in PE/CA-PJ15 cells. *Eur. J. Med. Chem.* **2015**, *102*, 403–442.

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.9, 135.3, 133.9, 132.5, 129.0, 128.7, 127.2, 124.4, 118.1, 113.9, 105.2, 71.2 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{10}ClNO$, 243.1; found 243.1.

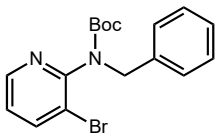


***tert*-butyl (3-bromopyridin-2-yl)carbamate (S15):** To a solution of 2-amino-3-bromopyridine (692 mg, 4.0 mmol, 1.0 equiv) in THF was added triethylamine (1.3 mL, 9.6 mmol, 2.4 equiv), di-*tert*-butyl decarbonate (1.92 g, 8.8 mmol, 2.2 equiv), and DMAP (49 mg, 0.4 mmol, 0.1 equiv). The resulting solution was stirred for 19 h, quenched with sat. aq. NH_4Cl, and extracted with EtOAc 3x. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was dissolved in DCM (40 mL) and cooled to 0 °C. Trifluoroacetic acid was added dropwise, and the resulting solution was stirred for 5.5 h, quenched with sat. aq. $NaHCO_3$, extracted with DCM 3x, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a light yellow solid (997 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 4.8, 1.6 Hz, 2H), 7.82 (dd, J = 7.9, 1.7 Hz, 2H), 7.30 (s, 1H), 6.89 (dd, J = 7.9, 4.7 Hz, 2H), 1.55 (s, 17H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.7, 148.8, 147.5, 141.0, 119.8, 109.4, 81.6, 28.3 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{10}H_{14}BrN_2O_2$, 273.0; found 272.7.



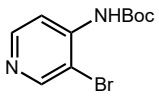
***tert*-butyl benzyl(3-bromopyridin-2-yl)carbamate (S16):** In a round bottom flask under nitrogen, sodium hydride as a 60% dispersion in mineral oil (180 mg, 4.5 mmol, 1.5 equiv) was suspended in DMF and cooled to 0 °C. **S15** as a solution in DMF (819 mg, 3.0 mmol, 1.0 equiv)

was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of benzyl bromide (0.43 mL, 3.6 mmol, 1.2 equiv). The reaction was removed from the ice bath, and after reacting for 1.5 h was quenched with water and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and purified on silica gel (10-20% EtOAc/Hex eluent) to afford the title compound as a white solid (830 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 3.4 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.32 (s, 2H), 7.25 – 7.16 (m, 3H), 7.03 (dd, J = 7.9, 4.7 Hz, 1H), 5.00 (s, 1H), 4.89 (s, 1H), 1.41 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 153.7, 153.6, 147.5, 142.0, 137.9, 128.3, 127.3, 123.2, 120.8, 81.4, 52.4, 28.4 ppm.

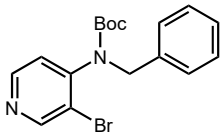
LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{20}BrN_2O_2$, 363.0; found 362.8.



***tert*-butyl (3-bromopyridin-4-yl)carbamate (S17):** To a solution of 3-bromo-4-pyradinamine (692 mg, 4.0 mmol, 1.0 equiv) in THF (20 mL) was added triethylamine (1.3 mL, 9.6 mmol, 2.4 equiv), di-*tert*-butyl decarbonate (1.92 g, 8.8 mmol, 2.2 equiv), and DMAP (49 mg, 0.4 mmol, 0.1 equiv). After stirring for 2.5 h, 1M aq. HCl (20 mL) was added, and the resulting solution was stirred for 17 h. The reaction was neutralized with 1M aq. NaOH (20 mL), extracted with EtOAc 3x, dried over $MgSO_4$, concentrated *in vacuo*, and purified on silica gel (30% EtOAc/Hex eluent) to afford the title compound as a white solid (807 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 0.4 Hz, 1H), 8.37 (dd, J = 5.7, 0.6 Hz, 1H), 8.15 (d, J = 5.7 Hz, 1H), 7.17 (s, 1H), 1.54 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[74]

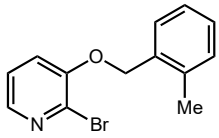


***tert*-butyl benzyl(3-bromopyridin-4-yl)carbamate (S18):** In a round bottom flask under nitrogen, sodium hydride as a 60% dispersion in mineral oil (120 mg, 3.0 mmol, 1.5 equiv) was suspended in DMF and cooled to 0 °C. **S17** as a solution in DMF (546 mg, 2.0 mmol, 1.0 equiv) was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of benzyl bromide (0.29 mL, 2.4 mmol, 1.2 equiv). The reaction was removed from the ice bath, and after reacting for 4 h was quenched water and extracted with EtOAc 3x. The combined organic layers were washed with water and brine, dried with $MgSO_4$, concentrated *in vacuo*, and purified on silica gel (10-20% EtOAc/Hex eluent) to afford the title compound as a yellow oil (488 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.37 (d, J = 5.1 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.21 (dd, J = 7.5, 2.0 Hz, 2H), 6.86 (s, 1H), 5.12 (s, 1H), 4.43 (s, 1H), 1.42 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$, 50 °C) δ 153.5, 153.4, 149.3, 148.8, 137.2, 128.7, 127.9, 125.3, 122.0, 81.7, 65.4, 52.7, 28.3 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{20}BrN_2O_2$, 363.0; found 362.8



2-bromo-3-((2-methylbenzyl)oxy)pyridine (S19): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0

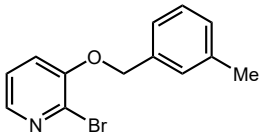
[74] Fan, J.; Yao, Q-J.; Liu, Y-H.; Liao, G.; Zhang, S.; Shi, B-F. Asymmetric total synthesis of TAN-1085 facilitated by Pd-catalyzed atroposelective C-H olefination. *Org. Lett.* **2019**, *21(9)*, 3352–3356.

equiv). MeCN (15 mL) was added, followed by 2-methylbenzyl bromide (0.40 mL, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 16 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and purified on silica gel (20% EtOAc/hexanes eluent) to afford the title compound as a white solid (677 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (t, J = 3.1 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.32 – 7.22 (m, 4H), 7.20 (d, J = 3.1 Hz, 1H), 5.14 (s, 2H), 2.41 (s, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.3, 141.7, 136.7, 133.6, 133.5, 130.7, 128.8, 128.5, 126.3, 123.5, 120.4, 69.8, 19.2 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{13}BrNO$, 278.0; found 277.8.

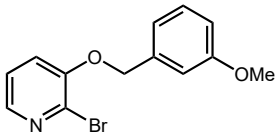


2-bromo-3-((3-methylbenzyl)oxy)pyridine (S20): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by 1-(bromomethyl)-3-methylbenzene (0.41 mL, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 15.5 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a light brown solid (826 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 4.1, 2.1 Hz, 1H), 7.32 – 7.22 (m, 3H), 7.19 – 7.11 (m, 3H), 5.15 (s, 2H), 2.38 (s, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.3, 141.7, 138.7, 135.6, 133.6, 129.3, 128.8, 127.9, 124.3, 123.5, 120.7, 71.2, 21.6 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{13}BrNO$, 278.0; found 277.8.

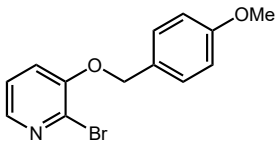


2-bromo-3-((3-methoxybenzyl)oxy)pyridine (S21): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by 3-methoxybenzyl bromide (0.42 mL, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 15 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a white solid (733 mg, 83%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (dd, J = 4.2, 2.0 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.21 – 7.14 (m, 2H), 7.07 – 6.98 (m, 2H), 6.88 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 5.17 (s, 2H), 3.83 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.0, 152.0, 141.6, 137.1, 133.3, 129.8, 123.4, 120.5, 119.1, 113.8, 112.4, 70.7, 55.3.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{13}BrNO_2$, 294.0; found 293.8.



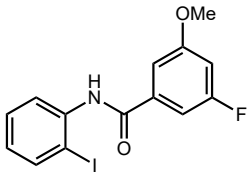
2-bromo-3-((4-methoxybenzyl)oxy)pyridine (S22): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by 4-methoxybenzyl bromide (0.49 mL, 3.6 mmol, 1.2 equiv). The reaction was heated to 60 °C and stirred for 22 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were

washed with brine, dried over $MgSO_4$, and purified on silica gel (10-40% EtOAc/hexanes eluent) to afford the title compound as a white solid (699 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 3.7, 2.5 Hz, 1H), 7.38 (dt, J = 8.8, 0.6 Hz, 2H), 7.19 – 7.14 (m, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.11 (s, 2H), 3.82 (s, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.9, 152.3, 141.7, 133.7, 129.0, 127.7, 123.5, 120.8, 114.3, 71.1, 55.5 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{13}BrNO_2$, 294.0; found 293.8.



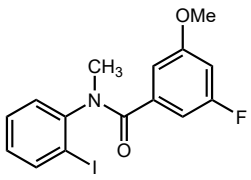
3-fluoro-*N*-(2-iodophenyl)-5-methoxybenzamide (S23): To a solution of 3-fluoro-5-methoxybenzoic acid (510 mg, 3.0 mmol, 1.0 equiv) was added HBTU (1.25 g, 3.3 mmol, 1.1 equiv), 2-iodoaniline (723 mg, 3.3 mmol, 1.1 equiv), and diisopropylethylamine (1.04 mL, 6.0 mmol, 2.0 equiv). After heating at 80 °C for 16.5 h, the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc 3x. The combined organic layers were washed with water, 1M aq HCl, and brine, dried over $MgSO_4$, and purified on silica gel (5% EtOAc/hexanes eluent) to afford the title compound as a light yellow solid (334 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, J = 8.3, 1.6 Hz, 1H), 8.20 (s, 1H), 7.83 (dd, J = 8.0, 1.4 Hz, 1H), 7.46 – 7.37 (m, 1H), 7.30 (t, J = 1.9 Hz, 1H), 7.23 (dt, J = 8.6, 1.9 Hz, 1H), 6.91 (td, J = 7.7, 1.6 Hz, 1H), 6.83 (dt, J = 10.2, 2.3 Hz, 1H), 3.89 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2 (d, $^4J_{C-F}$ = 3.2 Hz), 163.7 (d, $^1J_{C-F}$ = 247.5 Hz), 161.5 (d, $^3J_{C-F}$ = 11.1 Hz), 139.0, 138.1, 137.4 (d, $^3J_{C-F}$ = 8.6 Hz), 129.6, 126.5, 122.0, 109.0 (d, $^4J_{C-F}$ = 2.6 Hz), 106.6 (d, $^2J_{C-F}$ = 23.5 Hz), 105.6 (d, $^2J_{C-F}$ = 25.1 Hz), 90.5, 56.0 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -109.6 (dd, J = 10.0, 8.5 Hz) ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{12}FINO_2$, 372.0; found 371.6.



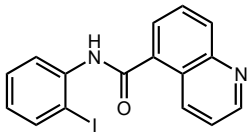
3-fluoro-*N*-(2-iodophenyl)-5-methoxy-*N*-methylbenzamide (S24): In a vial under nitrogen, sodium hydride as a 60% dispersion in mineral oil (48 mg, 1.2 mmol, 1.5 equiv) was suspended in DMF and cooled to 0 °C. **S23** as a solution in DMF (297 mg, 0.80 mmol, 1.0 equiv) was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of methyl iodide (60 µL, 0.96 mmol, 1.5 equiv). The reaction was removed from the ice bath, and after reacting for 1 h was quenched with water and extracted with EtOAc 3x. The combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a yellow solid (287 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.9, 1.4 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.09 (dd, J = 7.9, 1.6 Hz, 1H), 6.94 (td, J = 7.8, 1.6 Hz, 1H), 6.73 – 6.65 (m, 2H), 6.48 (dt, J = 10.4, 2.4 Hz, 1H), 3.66 (s, 3H), 3.36 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2 (d, $^4J_{C-F}$ = 3.3 Hz), 162.6 (d, $^1J_{C-F}$ = 246.0 Hz), 160.1 (d, $^3J_{C-F}$ = 10.9 Hz), 146.6, 140.2, 138.0 (d, $^3J_{C-F}$ = 8.3 Hz), 130.0, 129.5, 129.4, 109.2, 107.9 (d, $^2J_{C-F}$ = 23.8 Hz), 103.8 (d, $^4J_{C-F}$ = 24.5 Hz), 98.9, 55.6, 37.5 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.5 (t, J = 9.6 Hz) ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{14}FINO_2$, 386.0; found 385.6.

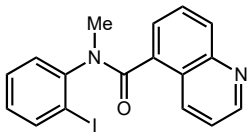


***N*-(2-iodophenyl)quinoline-5-carboxamide (S25):** To a solution of quinoline-5-carboxylic acid (520 mg, 3.0 mmol, 1.0 equiv) was added HBTU (1.25 g, 3.3 mmol, 1.1 equiv), 2-iodoaniline (723 mg, 3.3 mmol, 1.1 equiv), and diisopropylethylamine (1.04 mL, 6.0 mmol, 2.0 equiv). After heating at 80 °C for 20.5 h, the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc 3x. The combined organic layers were washed with water, 1M aq HCl, and brine, dried over $MgSO_4$, and purified on silica gel (30-50% EtOAc/hexanes eluent) to afford the title compound as an off-white solid (385 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (dd, J = 4.3, 1.6 Hz, 1H), 8.95 (d, J = 8.7 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.12 (s, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.86 (dd, J = 8.0, 1.4 Hz, 1H), 7.82 (t, J = 7.8 Hz, 1H), 7.55 (dd, J = 8.7, 4.2 Hz, 1H), 7.46 (dd, J = 8.5, 7.1 Hz, 1H), 6.97 – 6.92 (m, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 151.3, 148.5, 139.2, 138.4, 134.5, 134.0, 133.3, 129.7, 128.6, 126.8, 126.2, 125.9, 122.5, 122.4, 90.7 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{16}H_{12}IN_2O$, 375.0; found 374.6.



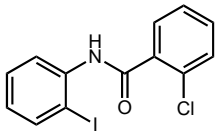
***N*-(2-iodophenyl)-*N*-methylquinoline-5-carboxamide (S26):** In a vial under nitrogen, sodium hydride as a 60% dispersion in mineral oil (48 mg, 1.2 mmol, 1.5 equiv) was suspended in DMF and cooled to 0 °C. **S25** as a solution in DMF (299 mg, 0.80 mmol, 1.0 equiv) was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of methyl iodide (60 μL, 0.96 mmol, 1.5 equiv). The reaction was removed from the ice bath, and after reacting for 1 h was quenched with water and extracted with EtOAc 3x. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and purified on silica gel (30-50%

EtOAc/hexanes eluent) to afford the title compound as a white solid (218 mg, 70%). Appeared as rotameric mixtures in ^{1}H NMR; no coalescence of peaks in $CDCl_3$ up to 60 °C; major observed reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (dd, J = 4.2, 1.7 Hz, 1H), 8.66 – 8.60 (m, 1H), 7.95 (dt, J = 8.2, 1.2 Hz, 1H), 7.74 (dd, J = 7.9, 1.4 Hz, 1H), 7.53 – 7.37 (m, 3H), 7.04 – 6.92 (m, 2H), 6.80 (ddd, J = 7.9, 7.2, 1.8 Hz, 1H), 3.52 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 150.7, 148.1, 146.3, 140.4, 134.5, 133.8, 131.1, 129.5, 129.4, 129.4, 128.0, 126.0, 125.6, 121.7, 98.8, 37.2 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{14}IN_2O$, 389.0; found 388.6.

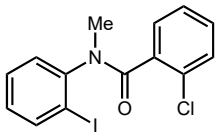


2-chloro-*N*-(2-iodophenyl)benzamide (S27): To a solution of 2-iodoaniline (604 mg, 2.8 mmol, 1.0 equiv) in dichloromethane was added 2-chlorobenzoyl chloride (390 µL, 3.0 mmol, 1.1 equiv) dropwise via syringe, followed by triethylamine (450 µL, 3.2 mmol, 1.1 equiv). The resulting mixture was stirred at room temperature for 4 h, quenched with methanol, and concentrated. The resulting solid was purified on silica gel (10–20% eluent) to afford the title compound as a white solid. (695 mg, 71 %).

^{1}H NMR (399 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.3 Hz, 1H), 8.16 (s, 1H), 7.81 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.76 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.55 – 7.31 (m, 4H), 6.89 (td, *J* = 7.7, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 139.1, 138.2, 134.9, 131.9, 130.9, 130.6, 130.2, 129.3, 127.3, 126.5, 122.4, 90.1.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{10}ClINO$, 357.9; found 357.6.

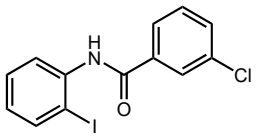


2-chloro-*N*-(2-iodophenyl)-*N*-methylbenzamide (S28): In a vial under nitrogen, sodium hydride as a 60% dispersion in mineral oil (90 mg, 2.2 mmol, 1.8 equiv) was suspended in DMF and cooled to 0 °C. **S27** as a solution in DMF (441 mg, 1.2 mmol, 1.0 equiv) was added to the sodium hydride suspension dropwise and stirred for 30 minutes before the addition of methyl iodide (120 µL, 1.8 mmol, 1.5 equiv). The reaction was removed from the ice bath, and after reacting for 1.5 h was quenched with methanol then water at 0 °C. The resulting mixture was diluted with ethyl acetate and washed with brine 3x. The organic layer was dried with $MgSO_4$, concentrated *in vacuo*, and purified on silica gel (10-25% EtOAc/Hex eluent) to afford the title compound as a white solid (384 mg, 84%). Appeared as rotameric mixtures in ^{1}H NMR; no coalescence of peaks in $CDCl_3$ up to 60 °C; major observed reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.35 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.14 (td, *J* = 7.6, 1.4 Hz, 1H), 7.07 (td, *J* = 7.7, 1.8 Hz, 1H), 7.00 (td, *J* = 7.5, 1.3 Hz, 1H), 6.83 (td, *J* = 7.6, 1.6 Hz, 1H), 3.39 (s, 3H).

^{13}C NMR (100 MHz, $cdcl_3$) δ 167.9, 145.4, 139.9, 136.0, 130.0, 129.6, 129.4, 129.3, 129.0, 127.9, 127.0, 126.20 98.8, 36.4.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{12}ClINO$, 371.9; found 371.6.



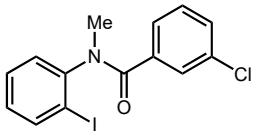
3-chloro-*N*-(2-iodophenyl)benzamide (S29): To a solution of 2-iodoaniline (608 mg, 2.8 mmol, 1.0 equiv) in dichloromethane was added 3-chlorobenzoyl chloride (380 µL, 3.0 mmol, 1.1 equiv) dropwise via syringe, followed by triethylamine (450 µL, 3.2 mmol, 1.1 equiv). The resulting

mixture was stirred at room temperature for 4 h, quenched with methanol, and concentrated. The resulting solid was purified on silica gel (10–20% eluent) to afford the title compound as a white solid. (767 mg, 77 %).

^{1}H NMR (399 MHz, CDCl3) δ 8.39 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.20 (s, 1H), 8.01 – 7.90 (m, 1H), 7.86 – 7.75 (m, 2H), 7.55 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.40 (m, 1H), 6.89 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 138.8, 137.9, 136.3, 135.2, 132.2, 130.2, 129.4, 127.7, 126.4, 125.0, 121.9, 90.4.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{10}ClINO$, 357.9; found 357.6.

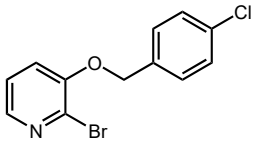


3-chloro-*N*-(2-iodophenyl)-*N*-methylbenzamide (S30): In a vial under nitrogen, sodium hydride as a 60% dispersion in mineral oil (66 mg, 1.7 mmol, 1.9 equiv) was suspended in DMF and cooled to 0 °C. **S29** as a solution in DMF (321 mg, 0.9 mmol, 1.0 equiv) was added dropwise to the sodium hydride suspension and stirred for 30 minutes before the addition of methyl iodide (90 µL, 1.4 mmol, 1.6 equiv). The reaction was removed from the ice bath, and after reacting for 1.5 h was quenched with methanol then water at 0 °C. The resulting mixture was diluted with ethyl acetate and washed with brine 3x. The organic layer was dried with $MgSO_4$, concentrated *in vacuo*, and purified on silica gel (10-25% EtOAc/Hex eluent) to afford the title compound as a white solid (215 mg, 64%).

^{1}H NMR (399 MHz, CDCl3) δ 7.77 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.39 (t, *J* = 1.9 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.16 (dd, *J* = 7.9, 1.9 Hz, 2H), 7.09 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.03 (dd, *J* = 8.4, 7.3 Hz, 1H), 6.90 (td, *J* = 7.7, 1.6 Hz, 1H), 3.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 146.4, 140.2, 137.3, 133.7, 130.0, 129.9, 129.5, 129.4, 128.9, 128.6, 126.3, 98.9, 37.5.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{12}ClINO$, 371.9; found 371.6.

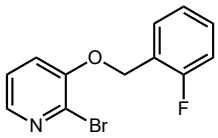


2-bromo-3-((4-chlorobenzyl)oxy)pyridine (S31): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by 4-chlorobenzyl bromide (740 mg, 3.6 mmol, 1.2 equiv). The reaction was heated to 60 °C and stirred for 20 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and purified on silica gel (20% EtOAc/hexanes eluent) to afford the title compound as a white solid (771 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J = 4.6, 1.6 Hz, 1H), 7.44 – 7.34 (m, 4H), 7.19 (dd, J = 8.1, 4.6 Hz, 1H), 7.14 (dd, J = 8.1, 1.6 Hz, 1H), 5.15 (s, 2H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 141.9, 134.3, 134.1, 133.5, 129.0, 128.5, 123.4, 120.5, 70.3 ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_{10}BrClNO$, 298.0; found 297.7



2-bromo-3-((2-fluorobenzyl)oxy)pyridine (S32): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by 2-fluorobenzyl bromide (0.36 mL, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 15 h. The reaction was cooled to room

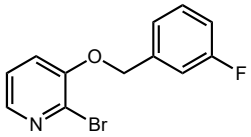
temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and purified on silica gel (10-30% EtOAc/hexanes eluent) to afford the title compound as a white solid (753 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 3.8, 2.4 Hz, 1H), 7.60 (tdd, J = 7.5, 1.9, 0.8 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.24 – 7.17 (m, 3H), 7.10 (ddd, J = 10.3, 8.2, 1.1 Hz, 1H), 5.25 (s, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.3 (d, $^1J_{C-F}$ = 246.6 Hz), 152.0, 142.1, 133.6, 130.2 (d, $^3J_{C-F}$ = 8.3 Hz), 129.5 (d, $^3J_{C-F}$ = 3.8 Hz), 124.8 (d, $^4J_{C-F}$ = 3.7 Hz), 123.6, 123.0 (d, $^2J_{C-F}$ = 13.9 Hz), 120.5, 115.5 (d, $^2J_{C-F}$ = 21.0 Hz), 64.8 (d, $^3J_{C-F}$ = 4.6 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$-d) δ -117.7 – -121.1 (m) ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_{10}BrFNO$, 282.0; found 281.8.



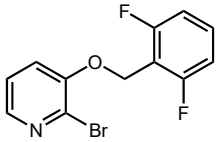
2-bromo-3-((3-fluorobenzyl)oxy)pyridine (S33): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by 3-fluorobenzyl bromide (0.37 mL, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 15 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, dried over $MgSO_4$, and purified on silica gel (10-30% EtOAc/hexanes eluent) to afford the title compound as a white solid (765 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 4.6, 1.7 Hz, 1H), 7.37 (td, J = 7.9, 5.7 Hz, 1H), 7.25 – 7.17 (m, 3H), 7.14 (dd, J = 8.1, 1.7 Hz, 1H), 7.04 (tdd, J = 8.6, 2.7, 0.9 Hz, 1H), 5.17 (s, 2H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{C-F}$ = 247.0 Hz), 152.0, 142.1, 138.3 (d, $^3J_{C-F}$ = 7.4 Hz), 133.6, 130.6 (d, $^3J_{C-F}$ = 8.3 Hz), 123.5, 122.5 (d, $^4J_{C-F}$ = 3.0 Hz), 120.5, 115.4 (d, $^2J_{C-F}$ = 21.2 Hz), 114.1 (d, $^2J_{C-F}$ = 22.6 Hz), 70.3 (d, $^4J_{C-F}$ = 2.1 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.2 (td, J = 9.1, 5.9 Hz) ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_{10}BrFNO$, 282.0; found 281.8.



2-bromo-3-((2,6-difluorobenzyl)oxy)pyridine (S34): A round bottom flask was charged with 2-bromo-3-hydroxypyridine (522 mg, 3.0 mmol, 1.0 equiv) and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). MeCN (15 mL) was added, followed by 2,6-difluorobenzyl bromide (621 mg, 3.0 mmol, 1.0 equiv). The reaction was heated to 60 °C and stirred for 15 h. The reaction was cooled to room temperature, diluted with water, and extracted with EtOAc 3x. The combined organic layers were washed with brine, and dried over $MgSO_4$ to afford the title compound as an off-white solid (868 mg, 96%).

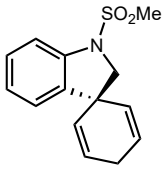
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 1H), 7.41 – 7.31 (m, 2H), 7.25 – 7.21 (m, 1H), 6.96 (dd, J = 8.3, 7.4 Hz, 2H), 5.22 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.1 (dd, $^1J_{C-F}$ = 251.6, $^3J_{C-F}$ = 7.3 Hz), 152.2, 142.4, 134.0, 131.5 (t, $^3J_{C-F}$ = 10.5 Hz), 123.5, 121.4, 111.8 (dd, $^2J_{C-F}$ = 21.0, $^4J_{C-F}$ = 4.8 Hz), 111.7 (t, $^2J_{C-F}$ = 18.8 Hz), 59.6 (t, $^3J_{C-F}$ = 3.7 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.1 (t, J = 6.8 Hz) ppm.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_9BrF_2NO$, 300.0; found 299.8.

3.4.8 Preparation of Dearomatized Spirocycles

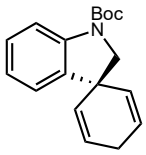


1'-(methylsulfonyl)spiro[cyclohexane-1,3'-indoline]-2,5-diene (10): Prepared according to General Procedure A using *N*-benzyl-*N*-(2 iodophenyl) methanesulfonamide (**S3**) (100 mg, 0.25 mmol, 1.0 equiv), DIPEA (134 µL, 0.75 mmol, 3 equiv) and 3DPAFIPN (8.2 mg, 5 mol%). After 16 h, the reaction was purified on silica (10 – 30% EtOAc/hexanes) to provide the desired product as a colorless oil (35 mg, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.1, 0.7 Hz, 1H), 7.22 (ddd, *J* = 8.0, 5.2, 3.5 Hz, 1H), 7.08 – 7.03 (m, 3H), 5.91 (dtt, *J* = 10.3, 3.4, 1.1 Hz, 3H), 5.69 (app. dp, *J* = 10.4, 2.3 Hz, 2H), 3.81 (s, 2H), 2.92 (s, 3H), 2.85 – 2.70 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3, 138.1, 128.6, 128.6, 125.5, 124.7, 124.1, 113.3, 63.4, 45.2, 34.5, 25.9.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{16}NO_2S$, 262.0824, found 262.0884.

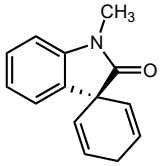


***tert*-butyl spiro[cyclohexane-1,3'-indoline]-2,5-diene-1'-carboxylate (11):** Prepared according to General Procedure A using *tert*-butyl benzyl(2-bromophenyl)carbamate (**S4**) (181 mg, 0.5 mmol, 1 equiv), DIPEA (0.26 mL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16.2 mg, 5 mol%). After 16 h, the reaction was purified by preparative TLC (5% EtOAc/hexanes) to provide the desired product as a light yellow oil (43 mg, 70% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.20 (ddd, *J* = 8.3, 7.4, 1.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.97 (td, *J* = 7.4, 1.1 Hz, 1H), 5.87 (dt, *J* = 10.2, 3.4 Hz, 2H), 5.71 (dt, *J* = 10.3, 2.0 Hz, 2H), 3.87 (s, 2H), 2.81 (dddd, *J* = 23.1, 5.4, 3.3, 2.1 Hz, 1H), 2.74 (dtt, *J* = 23.2, 3.5, 2.0 Hz, 1H), 1.60 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.4, 141.1, 138.1, 130.0, 128.0, 124.8, 123.4, 122.7, 114.7, 80.9, 61.7, 44.5, 28.5, 25.9.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{18}H_{22}NO$, 284.1572; found 284.1657.

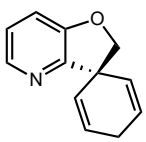


1'-methylspiro[cyclohexane-1,3'-indoline]-2,5-dien-2'-one (12): Prepared according to General Procedure A using *N*-(2-iodophenyl)-*N*-methylbenzamide (**S6**) (128.8 mmol, 0.38 mmol, 1.0 equiv), DIPEA (200 μL, 1.14 mmol, 3 equiv) and 3DPAFIPN (17 mg, 7 mol%). After 16 h, the reaction was purified on spherical silica (10–20% EtOAc/hexanes) to provide the desired product as a white solid (44 mg, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (tt, *J* = 7.7, 1.2 Hz, 1H), 7.14 – 7.11 (m, 1H), 7.06 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.85 (d, *J* = 7.8, 0.8 Hz, 1H), 6.14 (dtd, *J* = 10.3, 3.4, 0.9 Hz, 2H), 5.39 (dtd, *J* = 10.5, 2.0, 0.9 Hz, 2H), 3.23 (s, 3H), 3.02 – 2.94 (m, 1H), 2.90 – 2.81 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 143.0, 134.2, 128.4, 127.3, 124.7, 123.8, 122.9, 108.0, 51.8, 26.6, 25.7.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{24}NO$, 212.0997; found 212.1118.

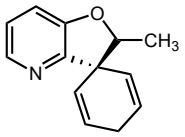


2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (2): Prepared according to General Procedure A using 3-(benzyloxy)-2-bromopyridine (**1**) (128 mg, 0.5 mmol, 1 equiv), DIPEA(270 μL, 1.5 mmol, 3 equiv) and 3DPAFIPN (18 mg, 6 mol %). After 16 h, the reaction was purified on silica (20 – 40% Et_2O/hexanes) to provide the desired product as a colorless oil (65 mg, 72% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.05 (dd, *J* = 8.1, 4.7 Hz, 1H), 6.02 (dt, *J* = 10.2, 3.4 Hz, 2H), 5.75 (dt, *J* = 10.3, 2.0 Hz, 2H), 4.46 (s, 2H), 2.93 (dtt, *J* = 23.3, 3.3, 2.1 Hz, 1H), 2.74 (dtt, *J* = 23.4, 3.5, 2.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.1, 152.6, 142.8, 127.0, 125.8, 122.8, 116.6, 83.0, 47.6, 26.0

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{12}NO$, 186.0840; found 186.1081.

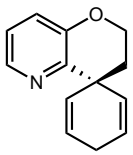


2'-methyl-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (13): Prepared according to General Procedure B using 2-bromo-3-(1-phenylethoxy)pyridine (**S7**) (152 mg, 0.55 mmol, 1 equiv), DIPEA(1.1 mL, 6.2 mmol, 10 equiv) and 3DPAFIPN (17 mg, 4 mol%).. After 16 h, the reaction was purified on silica (15– 20% EtOAc/hexanes) to provide the desired product as a yellow oil (54 mg, 50% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 4.5, 1.7 Hz, 1H), 7.07 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.04 (dd, *J* = 8.1, 4.5 Hz, 1H), 6.15 (dtd, *J* = 10.0, 3.4, 1.6 Hz, 1H), 5.98 (dtd, *J* = 10.1, 3.4, 1.6 Hz, 1H), 5.67 (dq, *J* = 10.0, 2.1 Hz, 1H), 5.59 (dq, *J* = 10.1, 2.1 Hz, 1H), 4.57 (q, *J* = 6.6 Hz, 1H), 2.91 (dtt, *J* = 23.4, 3.7, 2.0 Hz, 1H), 2.76 (dtt, *J* = 23.3, 3.2, 2.2 Hz, 1H), 1.42 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.3, 152.4, 142.7, 127.9, 126.4, 125.9, 124.5, 122.8, 116.4, 88.7, 50.7, 26.3, 15.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{14}NO$, 200.0997; found 200.1184.

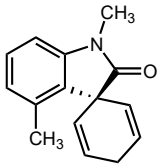


2',3'-dihydrospiro[cyclohexane-1,4'-pyrano[3,2-*b*]pyridine]-2,5-diene (14): Prepared according to General Procedure A using 2-bromo-3-phenethoxypyridine (**S8**) (127 mg, 0.46 mmol, 1 equiv) DIPEA(270 µL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol %). After 16 h, the reaction was purified on silica (40 – 50% Et_2O/hexanes) to provide the desired product as a colorless oil (38 mg, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.05 (dd, *J* = 8.2, 4.5 Hz, 1H), 5.96 (dt, *J* = 10.3, 3.4 Hz, 2H), 5.77 (dt, *J* = 10.4, 2.0 Hz, 2H), 4.35 – 4.19 (m, 2H), 2.92 (dtt, *J* = 23.0, 3.6, 1.8 Hz, 1H), 2.73 (dddd, *J* = 23.0, 5.5, 3.1, 2.4 Hz, 1H), 2.11 – 2.01 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.4, 148.4, 142.4, 131.0, 124.4, 124.4, 122.8, 77.2, 77.0, 76.8, 62.4, 39.3, 37.4, 26.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{14}NO$, 200.0997, found 200.1247.

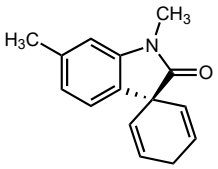


1',4'-dimethylspiro[cyclohexane-1,3'-indoline]-2,5-dien-2'-one (15): Prepared according to General Procedure A using *N*-(2-bromo-3-methylphenyl)-*N*-methylbenzamide (**S10**) (170 mg, 0.56 mmol, 1 equiv), DIPEA(300 µL, 1.7 mmol, 3 equiv) and 3DPAFIPN (15 mg, 4 mol %). After 16 h, the reaction was purified on silica (20 % EtOAc/hexanes) to provide the desired product as a yellow solid (106 mg, 84% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.8 Hz, 1H), 6.85 (dt, *J* = 7.8, 0.8 Hz, 1H), 6.72 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.17 (dt, *J* = 10.3, 3.4 Hz, 2H), 5.36 (dt, *J* = 10.3, 2.0 Hz, 2H), 3.23 (s, 3H), 3.04 (dtt, *J* = 23.3, 3.4, 2.1 Hz, 1H), 2.82 (dtt, *J* = 23.2, 3.4, 2.1 Hz, 1H), 2.22 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.6, 143.1, 136.0, 130.1, 128.3, 127.7, 125.1, 122.7, 105.7, 51.8, 26.7, 25.8, 16.7.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{16}NO$, 226.1154; found 226.1323.



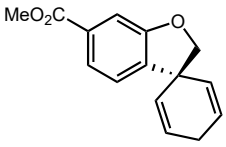
1',6'-dimethylspiro[cyclohexane-1,3'-indoline]-2,5-dien-2'-one (16):

Prepared according to General Procedure A using *N*-(2-bromo-5-methylphenyl)-*N*-methylbenzamide (**S12**) (61 mg,0.2 mmol, 1 equiv), DIPEA (100 µL, 0.6 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol%).After 16 h, purification via preparative HPLC on an Agilent 1200 Infinity Series chromatograph using an Agilent PrepC18 30 x 250 mm 10 µm column, with a linear gradient using water and 0.1% formic acid (FA) (Solvent A) and MeCN and 0.1% FA (Solvent B); t=0 min, 50% B, t = 25 min, 99% B, with a flow rate 40 mL/min, afforded the title compounds desired product as a light yellow solid (28 mg, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 7.5 Hz, 1H), 6.87 (ddd, J = 7.4, 1.5, 0.8 Hz, 1H), 6.67 (dd, J = 1.6, 0.8 Hz, 1H), 6.16 – 6.07 (m, 2H), 5.37 (dt, J = 10.3, 2.0 Hz, 2H), 3.21 (s, 3H), 2.97 (dtt, J = 23.3, 3.3, 2.2 Hz, 1H), 2.84 (dtt, J = 23.2, 3.6, 2.0 Hz, 1H), 2.39 (d, J = 0.7 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 143.2, 138.8, 131.5, 127.2, 124.6, 124.2, 123.5, 109.1, 51.7, 26.7, 25.9, 21.9 ppm.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{16}NO$, 226.1154; found 226.1303.

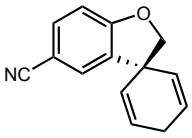


methyl 2*H*-spiro[benzofuran-3,1'-cyclohexane]-2',5'-diene-6-carboxylate (17): Prepared according to General Procedure A using methyl 3-(benzyloxy)-4-iodobenzoate (**S13**) (156 mg, 0.4 mmol, 1 equiv) DIPEA(260 µL, 1.5 mmol, 3 equiv) and 3DPAFIPN (17 mg, 5 mol %). After 16 h, the reaction was purified on silica (10 – 30% EtOAc/hexanes) to provide the desired product as a yellow oil (66 mg, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.44 (d, *J* = 1.5 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 5.90 (dt, *J* = 10.1, 3.4 Hz, 2H), 5.70 (dt, *J* = 10.2, 2.0 Hz, 2H), 4.39 (s, 2H), 3.89 (s, 3H), 2.81 (dddd, *J* = 23.3, 5.4, 3.2, 2.1 Hz, 1H), 2.72 (dtt, *J* = 23.3, 3.5, 2.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.9, 159.0, 139.7, 130.8, 128.3, 124.6, 124.6, 123.1, 110.7, 83.7, 77.2, 77.0, 76.8, 52.1, 47.4, 25.9.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{15}O_3$, 243.0943; found 243.1062.

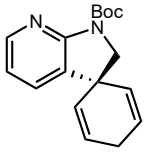


2*H*-spiro[benzofuran-3,1'-cyclohexane]-2',5'-diene-5-carbonitrile (18): Prepared according to General Procedure B using 4-(benzyloxy)-3-chlorobenzonitrile (**S14**) (119 mg, 0.5 mmol, 1 equiv), DIPEA (900 µL, 5.2 mmol, 10 equiv) and 3DPAFIPN (18 mg, 6 mol %). After 16 h, the reaction was purified on silica (5% EtOAc/hexanes) to provide the desired product as a yellow solid (55 mg, 54% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.31 (d, *J* = 1.8 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.94 (dt, *J* = 10.1, 3.4 Hz, 2H), 5.69 (dt, *J* = 10.2, 2.0 Hz, 2H), 4.44 (s, 2H), 2.83 (dddd, *J* = 23.4, 5.4, 3.4, 2.1 Hz, 1H), 2.75 (dtt, *J* = 23.4, 3.7, 2.0 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.4, 136.1, 133.8, 129.3, 127.9, 125.1, 119.4, 110.7, 104.3, 84.3, 47.0, 25.8.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{12}NO$, 210.0841; found 210.0954.



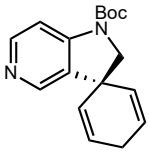
***tert*-butyl spiro[cyclohexane-1,3'-pyrrolo[2,3-*b*]pyridine]-2,5-diene-1'(2'*H*)-carboxylate (19):**

Prepared according to General Procedure A using *tert*-butyl benzyl(3-bromopyridin-2-yl)carbamate (**S16**) (182 mg, 0.5 mmol, 1 equiv), DIPEA (0.26 mL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol%). After 16 h, the reaction was purified on silica (10 – 30% EtOAc/hexanes) to provide the desired product as a yellow oil (109 mg, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (dd, J = 5.1, 1.7 Hz, 1H), 7.27 – 7.23 (m, 1H), 6.84 (dd, J = 7.4, 5.1 Hz, 1H), 5.88 (dt, J = 10.2, 3.4 Hz, 2H), 5.65 (dt, J = 10.3, 2.0 Hz, 2H), 3.85 (s, 2H), 2.78 (dtt, J = 23.3, 3.3, 2.1 Hz, 1H), 2.72 (dtt, J = 23.3, 3.4, 2.1 Hz, 1H), 1.55 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 151.0, 148.1, 133.3, 131.7, 129.2, 124.4, 118.1, 81.6, 60.9, 42.5, 28.5, 26.0 ppm.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{21}N_2O_2$, 285.1525; found 285.1752.



***tert*-butyl spiro[cyclohexane-1,3'-pyrrolo[3,2-*c*]pyridine]-2,5-diene-1'(2'*H*)-carboxylate (20):**

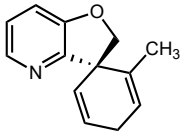
Prepared according to General Procedure A using *tert*-butyl benzyl(3-bromopyridin-4-yl)carbamate (**S18**) (182 mg, 0.5 mmol, 1 equiv), DIPEA (0.26 mL, 1.5 mmol, 3 equiv) and

3DPAFIPN (16 mg, 5 mol%). After 16 h, the reaction was purified on silica (20-30% EtOAc/hexanes) to provide the desired product as a yellow oil (127 mg, 89% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (d, J = 5.5 Hz, 1H), 8.12 (d, J = 0.8 Hz, 1H), 7.67 (s, 1H), 5.88 (dt, J = 10.1, 3.4 Hz, 2H), 5.67 (dt, J = 10.3, 2.0 Hz, 2H), 3.85 (s, 2H), 2.81 (dddd, J = 23.3, 5.4, 3.3, 2.1 Hz, 1H), 2.73 (dtt, J = 23.4, 3.8, 2.1 Hz, 1H), 1.57 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.0, 149.8, 148.1, 146.7, 133.8, 129.2, 124.3, 109.5, 82.3, 62.2, 43.4, 28.5, 25.9 ppm.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{21}N_2O_2$, 285.1525; found 285.1696.

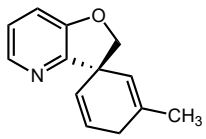


2-methyl-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (21): Prepared according to General Procedure A using 2-bromo-3-((2-methylbenzyl)oxy)pyridine (**S19**) (156 mg, 0.56 mmol, 1 equiv),) DIPEA (260 µL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 4 mol%). After 16 h, the reaction was purified on silica (15 – 30% EtOAc/hexanes) to provide the desired product as a yellow oil (97 mg, 87% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.04 (dd, *J* = 8.1, 4.6 Hz, 1H), 6.00 (dtd, *J* = 9.9, 3.4, 1.5 Hz, 1H), 5.71 – 5.67 (m, 2H), 4.65 (d, *J* = 9.3 Hz, 1H), 4.37 (d, *J* = 9.3 Hz, 1H), 2.91 (dtt, *J* = 23.3, 3.7, 1.9 Hz, 1H), 2.73 (dtt, *J* = 23.3, 3.4, 1.9 Hz, 1H), 1.53 (q, *J* = 1.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 153.3, 142.8, 132.0, 127.7, 125.6, 122.7, 122.2, 116.6, 81.5, 50.6, 27.0, 19.0.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{13}NO$, 200.0997; found 200.1057.

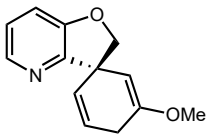


3-methyl-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (22): Prepared according to General Procedure A using 2-bromo-3-((3-methylbenzyl)oxy)pyridine (**S20**) (148 mg, 0.5 mmol, 1 equiv),) DIPEA(300 µL, 1.7 mmol, 3 equiv) and 3DPAFIPN (18 mg, 6 mol %). After 16 h, the reaction was purified on silica (20 – 30% EtOAc/hexanes) to provide the desired product as a llight yellow solid (63 mg, 59% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.07 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.03 (dd, *J* = 8.1, 4.8 Hz, 1H), 5.99 (dt, *J* = 9.9, 3.4 Hz, 1H), 5.72 (dq, *J* = 9.9, 2.1 Hz, 1H), 5.46 (p, *J* = 1.7 Hz, 1H), 4.41 (d, *J* = 1.2 Hz, 2H), 2.82 (d, *J* = 23.2 Hz, 1H), 2.62 (d, *J* = 23.5 Hz, 1H), 1.79 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 152.6, 142.7, 133.4, 126.9, 125.7, 122.7, 121.8, 116.5, 83.1, 48.8, 30.8, 23.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{14}NO$, 200.0997; found 200.1304.



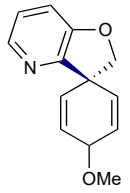
3-methoxy-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (23): Prepared according to General Procedure A using 2-bromo-3-((3-methoxybenzyl)oxy)pyridine (**S21**) (145 mg, 0.5 mmol, 1 equiv),) DIPEA(260 µL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol%). After 16 h, the reaction was purified on silica (20 – 30% EtOAc/hexanes) to provide the desired product as an orange solid (89 mg, 84% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.05 (dd, *J* = 8.1, 4.7 Hz, 1H), 5.91 (dt, *J* = 9.9, 3.5 Hz, 1H), 5.71 (dq, *J* = 9.8, 2.1 Hz, 1H), 4.69 (q, *J*

= 1.3 Hz, 1H), 4.47 (d, *J* = 8.9 Hz, 1H), 4.42 (d, *J* = 9.0 Hz, 1H), 3.57 (s, 3H), 2.97 (d, *J* = 22.0 Hz, 1H), 2.78 (d, *J* = 22.0 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6, 154.7, 152.5, 142.8, 127.4, 124.2, 122.7, 116.6, 95.5, 83.7, 54.0, 49.6, 28.6.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{14}NO_2$, 216.0946; found 216.1049.

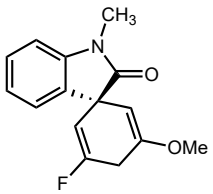


4-methoxy-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (24): Prepared according to General Procedure B using 2-bromo-3-((4-methoxybenzyl)oxy)pyridine (**S22**) (159 mg, 0.5 mmol, 1 equiv),) DIPEA(900 µL, 5.2 mmol, 10 equiv) and 3DPAFIPN (19 mg, 5 mol %). After 16 h, the reaction was purified on silica (20 – 50% EtOAc/hexanes) to isolate a single diastereomer as a light yellow oil (72 mg, 62% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.12 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.13 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.08 (dd, *J* = 8.1, 4.8 Hz, 1H), 6.13 (dd, *J* = 10.2, 3.2 Hz, 2H), 6.02 (dd, *J* = 10.1, 1.6 Hz, 2H), 4.61 (tt, *J* = 3.2, 1.6 Hz, 1H), 4.54 (s, 2H), 3.39 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 153.1, 142.8, 130.7, 126.6, 123.2, 117.0, 80.7, 69.2, 54.4, 48.5.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{14}NO_2$, 216.0946; found 216.1081.



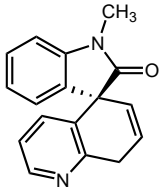
3-fluoro-5-methoxy-1'-methylspiro[cyclohexane-1,3'-indoline]-2,5-dien-2'-one (25): Prepared according to General Procedure A using 3-fluoro-*N*-(2-iodophenyl)-5-methoxy-*N*-methylbenzamide (**S24**) (193 mg, 0.5 mmol, 1 equiv), DIPEA (0.26 mL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol%). After 16 h, the reaction was purified on silica (10-20% EtOAc/hexanes) to provide the desired product as a yellow oil (70 mg, 54% yield).

^{z1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, J = 7.6, 1.5 Hz, 1H), 7.13 (ddd, J = 7.4, 1.5, 0.6 Hz, 1H), 7.07 (td, J = 7.4, 1.0 Hz, 1H), 6.85 (dt, J = 7.8, 0.8 Hz, 1H), 4.98 (dq, J = 14.7, 1.5 Hz, 1H), 4.33 (t, J = 1.6 Hz, 1H), 3.54 (s, 3H), 3.24 (s, 3H), 3.24 (dt, J = 20.8, 1.5 Hz, 1H), 3.09 (dq, J = 21.0, 1.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.2, 158.9 (d, $^1J_{C\text{-}F}$ = 257.2 Hz), 154.5 (d, $^3J_{C\text{-}F}$ = 16.1 Hz), 142.8, 133.9, 128.7, 124.8, 123.2, 101.6 (d, $^2J_{C\text{-}F}$ = 18.4 Hz), 92.9, 54.8, 52.1 (d, $^3J_{C\text{-}F}$ = 9.2 Hz), 29.6 (d, $^2J_{C\text{-}F}$ = 28.2 Hz), 26.76 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -103.4 (d, J = 14.6 Hz) ppm.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{15}FNO$, 260.1009; found 260.1191.

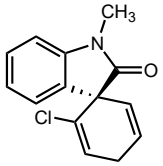


1-methyl-8'*H*-spiro[indoline-3,5'-quinolin]-2-one (26): Prepared according to General Procedure A using *N*-(2-iodophenyl)-*N*-methylquinoline-5-carboxamide (**S26**) (194 mg, 0.5 mmol, 1 equiv), DIPEA (0.26 mL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol%). After 16 h, the reaction was purified on silica (30-75% EtOAc/hexanes) to provide the desired product as a yellow solid (126 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, J = 4.7, 1.7 Hz, 1H), 7.35 (td, J = 7.7, 1.4 Hz, 1H), 7.07 (td, J = 7.5, 1.0 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.95 (dt, J = 7.8, 0.8 Hz, 1H), 6.87 (dd, J = 7.9, 1.7 Hz, 1H), 6.37 (ddd, J = 9.9, 4.1, 3.2 Hz, 1H), 5.54 (ddd, J = 9.9, 2.5, 1.8 Hz, 1H), 3.92 (dt, J = 22.7, 2.9 Hz, 1H), 3.74 (ddd, J = 22.6, 4.0, 1.8 Hz, 1H), 3.28 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 154.6, 148.5, 143.5, 134.9, 134.7, 129.9, 128.9, 128.3, 124.7, 124.7, 123.5, 122.0, 108.4, 55.1, 33.0, 26.7 ppm.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{15}N_2O$, 263.1106; found 263.1247.

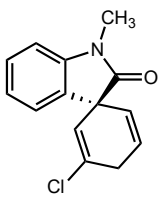


2-chloro-1'-methylspiro[cyclohexane-1,3'-indoline]-2,5-dien-2'-one (27): Prepared according to General Procedure A using 2-chloro-*N*-(2-iodophenyl)-*N*-methylbenzamide (**S28**) (194 mg, 0.52 mmol, 1 equiv), DIPEA (137 µL, 1.5 mmol, 3 equiv), and 3DPAFIPN (19 mg, 6 mol%). After 16 h, the reaction was purified on silica (10–30% EtOAc/hexanes) to provide the desired product as an off-white solid (84 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.23 (t, *J* = 3.7 Hz, 1H), 6.04 (dt, *J* = 9.8, 3.4 Hz, 1H), 5.34 (dt, *J* = 9.8, 2.1 Hz, 1H), 3.25 (s, 3H), 3.16 – 3.05 (m, 1H), 3.05 – 2.95 (m, 1H).

^{13}C NMR (126 MHz, $cdcl_3$) δ 175.4, 143.7, 131.6, 129.1, 128.0, 126.3, 125.5, 124.3, 124.2, 123.1, 108.2, 56.7, 28.3, 26.71.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{13}ClNO$, 246.0607; found 246.0675.

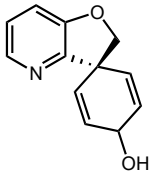


3-chloro-1'-methylspiro[cyclohexane-1,3'-indoline]-2,5-dien-2'-one (28): Prepared according to General Procedure A using 3-chloro-*N*-(2-iodophenyl)-*N*-methylbenzamide (**S30**) (196 mg, 0.5 mmol, 1 equiv). After 16 h, the reaction was purified on silica (10–20% EtOAc/hexanes) to provide the desired product as light yellow solid (95 mg, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (tt, *J* = 7.7, 1.3 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.08 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.88 – 6.82 (m, 1H), 6.06 (dtd, *J* = 9.8, 3.5, 1.0 Hz, 1H), 5.52 (q, *J* = 1.7 Hz, 1H), 5.40 – 5.35 (m, 1H), 3.31 – 3.06 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 142.9, 133.4, 132.5, 128.9, 126.5, 124.9, 123.4, 123.1, 121.21, 121.20, 54.4, 33.2, 26.7.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{13}ClNO$, 246.0607; found 246.0770.



2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-dien-4-ol (29): Prepared according to General Procedure A using 2-bromo-3-((4-chlorobenzyl)oxy)pyridine (**S31**) (149 mL, 0.5 mmol, 1 equiv),) DIPEA(260 μL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol %). After 16 h, the reaction was purified on silica (30 – 100% EtOAc/hexanes to 10% MeOH/EtOAc) to provide the desired products as yellow oils (combined yield 55 mg, 54% yield). Crude reaction mixture indicated 1.6:1 d.r., isolated in a 1.4 (32 mg) : 1 (23 mg) ratio.

Major Diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, J = 4.8, 1.3 Hz, 1H), 7.11 (dd, J = 8.1, 1.4 Hz, 1H), 7.06 (dd, J = 8.1, 4.8 Hz, 1H), 6.20 (dd, J = 9.8, 4.2 Hz, 2H), 5.94 (d, J = 9.1 Hz, 2H), 4.54 (s, 2H), 4.50 (tt, J = 4.1, 0.9 Hz, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.7, 152.1, 142.6, 131.5, 130.2, 123.3, 117.4, 81.7, 60.9, 49.0 ppm.

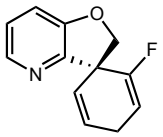
HRMS (ESI) m/z: [M+H] calc'd for $C_{12}H_{13}NO_2$, 202.0790, found 202.0874.

Minor Diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 4.8, 1.3 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.03 (dd, *J* = 8.1, 4.8 Hz, 1H), 6.09 (dd, *J* = 10.1, 3.2 Hz, 2H), 5.88 (dd, *J* = 10.0, 1.5 Hz, 2H), 4.79 (s, 1H), 4.47 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.1, 153.1, 142.9, 129.3, 129.1, 123.2, 117.0, 80.7, 61.7, 48.3.

HRMS (ESI) m/z: [M+H] calc'd for $C_{12}H_{13}NO_2$, 202.0790, found 202.0929.



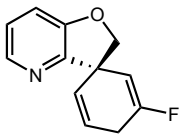
2-fluoro-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (30): Prepared according to General Procedure A using 2-bromo-3-((2-fluorobenzyl)oxy)pyridine (**S32**) (144 mg, 0.5 mmol, 1 equiv)) DIPEA(280 µL, 1.6 mmol, 3 equiv) and 3DPAFIPN (17 mg, 5 mol %). After 16 h, the reaction was purified on silica (20 – 30% EtOAc/hexanes) to provide the desired product as a yellow solid (86 mg, 83% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 3.6, 2.5 Hz, 1H), 7.11 (s, 1H), 7.10 (d, *J* = 1.3 Hz, 1H), 5.95 (dddd, *J* = 10.7, 4.5, 3.4, 1.2 Hz, 1H), 5.69 (tt, *J* = 9.6, 2.0 Hz, 1H), 5.54 (dtd, *J* = 16.7, 3.6, 1.2 Hz, 1H), 4.83 (d, *J* = 9.3 Hz, 1H), 4.45 (d, *J* = 9.3 Hz, 1H), 3.09 (ddtd, *J* = 22.8, 5.4, 3.5, 2.0 Hz, 1H), 2.91 (ddtd, *J* = 22.8, 4.6, 3.5, 2.0 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.2 (d, $^{1}J_{C\text{-}F}$ = 253.6 Hz), 153.6, 151.3, 142.8, 127.1 (d, $^{3}J_{C\text{-}F}$ = 5.8 Hz), 125.3 (d, $^{4}J_{C\text{-}F}$ = 2.4 Hz), 123.5, 116.8, 102.5 (d, $^{2}J_{C\text{-}F}$ = 16.5 Hz), 79.3, 49.8 (d, $^{2}J_{C\text{-}F}$ = 24.5 Hz), 26.4 (d, $^{3}J_{C\text{-}F}$ = 6.7 Hz).

^{19}F NMR (565 MHz, $CDCl_3$) δ -117.94 – -118.05 (1F, m).

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_{11}FNO$, 204.0745; found 204.0956.



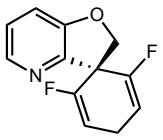
3-fluoro-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (31): Prepared according to General Procedure A using 2-bromo-3-((3-fluorobenzyl)oxy)pyridine (**S33**) (152 mg, 0.5 mmol, 1 equiv),) DIPEA(300 μL, 1.7 mmol, 3 equiv) and 3DPAFIPN (17 mg, 5 mol %). After 16 h, the reaction was purified on silica (20 – 30% EtOAc/hexanes) to provide the desired product as a colorless oil (91 mg, 83% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.14 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.10 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.1, 4.6 Hz, 1H), 5.89 (ddt, *J* = 9.8, 7.7, 3.5 Hz, 2H), 5.73 – 5.69 (m, 2H), 5.32 (dq, *J* = 16.3, 1.5 Hz, 1H), 4.47 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.44 (dd, *J* = 9.2, 0.7 Hz, 1H), 3.10 (ddt, *J* = 22.3, 3.1, 1.5 Hz, 2H), 2.92 (ddt, *J* = 22.3, 3.4, 2.1 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.8 (d, $^1J_{C\text{-}F}$ = 258.2 Hz), 153.9 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 152.5, 142.9, 127.4 (d, $^3J_{C\text{-}F}$ = 2.8 Hz), 123.2, 123.2, 123.1, 116.9, 104.0 (d, $^2J_{C\text{-}F}$ = 16.7 Hz), 82.4 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 50.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 26.8 (d, $^2J_{C\text{-}F}$ = 26.1 Hz).

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.27 (dd, *J* = 16.9, 7.8 Hz).

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_{11}FNO$, 204.0746; found 204.1005.



2,6-difluoro-2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine]-2,5-diene (32): Prepared according to General Procedure A using 2-bromo-3-((2,6-difluorobenzyl)oxy)pyridine (**S34**) (150 mg, 0.5 mmol, 1 equiv),) DIPEA (270 μL, 1.5 mmol, 3 equiv) and 3DPAFIPN (16 mg, 5 mol%).

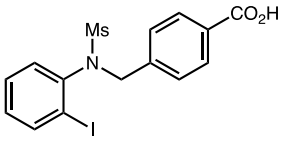
After 16 h, the reaction was purified on silica (20 – 30% EtOAc/hexanes) to provide the desired product as a light yellow solid (78 mg, 70% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 4.4, 1.7 Hz, 1H), 7.16 (dd, *J* = 8.2, 4.4 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.7 Hz, 1H), 5.58 (ddt, *J* = 10.4, 5.3, 3.7 Hz, 2H), 4.80 (s, 2H), 3.07 (dtt, *J* = 22.2, 5.1, 3.7 Hz, 1H), 2.89 (dtt, *J* = 22.3, 4.9, 3.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.4 (dd, $^{1}J_{C\text{-}F}$ = 254.8, $^{3}J_{C\text{-}F}$ = 12.1 Hz), 154.6, 147.7, 142.8, 124.2, 117.0, 102.3 (d, $^{2}J_{C\text{-}F}$ = 14.4 Hz), 75.5, 52.1 (t, $^{2}J_{C\text{-}F}$ = 27.8 Hz), 22.2 (t, $^{3}J_{C\text{-}F}$ = 8.0 Hz).

^{19}F NMR (565 MHz, $CDCl_3$) δ -119.83 (dq, *J* = 10.2, 5.1 Hz).

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{12}H_{10}F_2NO$, 222.0652; found 222.0972.



4-((*N*-(2-iodophenyl)methylsulfonamido)methyl)benzoic acid (**33**)

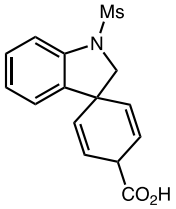
A 100 mL round bottom flask was charged with *N*-(2-iodophenyl)methanesulfonamide (**S1**), (414 mg, 1.4 mmol, 1.0 equiv) and K_2CO_3 (480 mg, 3.5 mmol, 2.2 equiv). DMF was added (50 mL), followed by benzyl bromide (350 µL, 2.4 mmol, 2.3 equiv). The reaction was stirred overnight (ca. 16 h) at 50 °C. The reaction was cooled to room temperature and then partitioned between EtOAc and water. The organic layer was washed with brine 3x, dried with $MgSO_4$ and concentrated. The crude oil was dissolved in THF/H_2O (1:1 v/v) and lithium hydroxide (excess, ca 10 equiv) was added. The reaction was stirred at 50 °C until reaction completion as determined by TLC. The reaction was then cooled to room temperature and partitioned between EtOAc and water. The organic layer was washed 3x with 1M NaOH. The organic layer was then discarded. EtOAc was added and the aqueous layer was re-acidified with HCl. The aqueous layer was extracted 3x wth EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated.

The desired product was purified by trituration with a minimal amount of EtOAc and was collected by filtration as a white solid (371 mg, 62% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.94 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.26 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.05 (td, *J* = 7.5, 1.6 Hz, 1H), 5.16 (d, *J* = 14.9 Hz, 1H), 4.66 (d, *J* = 14.9 Hz, 1H), 3.13 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 141.6, 140.6, 140.2, 134.3, 130.4, 129.7, 129.2, 129.0, 126.6, 101.8, 55.2, 40.4.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{15}INO_4S$ 432.0, found 431.6.



1'-(methylsulfonyl)spiro[cyclohexane-1,3'-indoline]-2,5-diene-4-carboxylic acid (34)

Prepared according to General Procedure A using 4-((*N*-(2-iodophenyl) methylsulfonamido) methyl) benzoic acid **33** (120 mg, 0.28 mmol, 1.0 equiv), DIPEA (244 µL, 1.4 mmol, 5.0 equiv) and 3DPAFIPN (10.1 mg, 5 mol%). After 16 h, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was acidified with 1N HCl and extracted 5x. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. ^{1}H NMR analysis of the crude reaction mixture indicated a 1:1 diastereomeric ratio. Purification of the residue by silica gel chromatography (EtOAc (containing 1% v/v AcOH):Hex, 30–100% gradient) afforded three fractions: the leading fraction contained a single diastereomer (f1: 30.8 mg), followed by two fractions that were enriched in either diastereomer (f2: 176.9 mg, 1.5:1 dr; f3 210.7 mg, 1:2 dr), combined yield: 418.4 mg (95%).

Diastereomer 1 (f1):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 10.1, 3.6 Hz, 1H), 5.91 (dd, *J* = 10.2, 2.1 Hz, 1H), 3.89 (m, 1H), 3.87 (s, 2H), 2.95 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 141.1, 136.2, 130.9, 129.1, 125.8, 124.4, 121.7, 113.3, 62.3, 45.3, 41.8, 34.7.

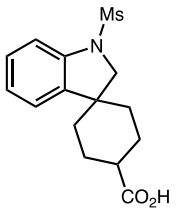
Diastereomer 2 (characteristic peaks):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dd, *J* = 10.1, 3.4 Hz, 1H), 5.92 (dd, *J* = 10.1, 2.2 Hz, 1H), 3.95 – 3.91 (m, 1H).

For the mixture of diastereomers (f2)

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.9, 176.3, 141.9, 136.4, 136.2, 131.0, 130.9, 129.2, 129.1, 125.8, 125.3, 124.4, 124.2, 122.5, 121.7, 113.5, 113.3, 62.3, 62.3, 45.3, 42.4, 41.5, 35.9, 34.7, 32.6.

LRMS (APCI) m/z: $[M-H]^-$ calc'd for $C_{15}H_{14}NO_4S$ 304.1, found 304.1.

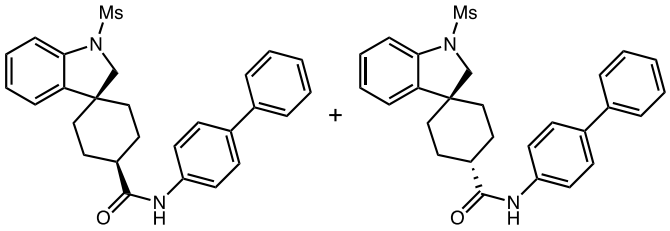


1'-(methylsulfonyl)spiro[cyclohexane-1,3'-indoline]-4-carboxylic acid (S35)

A 4 mL vial was charged with 1'-(methylsulfonyl)spiro[cyclohexane-1,3'-indoline]-2,5-diene-4-carboxylic acid (**S36,** from f2 (1.6:1 dr; 15.4 mg, 0.05 mmol) , 5 mg 5% Pd/C (wet basis), and a stir bar. To the vial was added 2 mL of 200 proof ethanol and the vial was placed in Parr high-pressure reactor. The reactor was sealed, evacuated, and backfilled with hydrogen at 1 PSI. This was repeated for a total of 5 times. The reactor was then pressurized to 40 PSI with hydrogen and stirred for 72 hours. Upon reaction completion, the reactor was depressurized and dismantled. 0.5 mL of water was added to the reaction vial then the reaction mixture was filtered through celite. The filtrate was concentrated then azeotroped with 10 mL of MeCN to remove the remaining

water. Quantitative conversion to the hydrogenated product was detected by ^{1}H NMR and LRMS. The crude residue was used in the next step without further purification.

LRMS (APCI) m/z: $[M-H]^-$ calc'd for $C_{15}H_{18}NO_4S$ 308.1, found 308.1.



***N*-([1,1'-biphenyl]-4-yl)-1'-(methylsulfonyl)spiro[cyclohexane-1,3'-indoline]-4-carboxamide (35)**

In an 8mL reaction tube equipped with a stir bar, 1'-(methylsulfonyl)spiro[cyclohexane-1,3'-indoline]-4-carboxylic acid (S**35**) (15.4 mg, 0.05 mmol, 1.0 equiv) was dissolved in EtOAc to make a 0.1 M solution. 4-aminobiphenyl 10 mg, 0.06 mmol, 1.2 equiv) was added, followed by DIPEA 35 µL, 0.2 mmol, 4.0 equiv). Propanephosphonic acid anhydride (as a 50% w/w solution in EtOAc) 55 µL, 0.08 mmol, 1.6 equiv) was then added in one portion. The reaction mixture was allowed to stir for 3 h before being partitioned between water and EtOAc. The organic layer was washed with 1M HCl 3x then brine 3x. The organic layer was then dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by preparatory TLC in 50% EtOAc/Hex eluent to separate both diastereomers and afford the desired products as white solids: diasteromer 1(R_f 0.47, 50% EtOAc/Hex): 12.0 mg; diastereomer 2 (R_f 0.35, 50% EtOAc/Hex): 5.8 mg; Combined yield: 17.8 mg, 82% over 2-steps).

Diastereomer 1 (R_f 0.47):

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 4H), 7.46 – 7.39 (m, 3H), 7.37 – 7.31 (m, 1H), 7.27 – 7.21 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H),

3.87 (s, 2H), 2.92 (s, 3H), 2.43 – 2.32 (m, 1H), 2.08 (d, *J* = 11.4 Hz, 2H), 1.91 (d, *J* = 11.0 Hz, 2H), 1.83 – 1.71 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 141.4, 140.5, 139.0, 137.8, 137.1, 129.3, 128.3, 127.7, 127.2, 126.9, 123.7, 122.9, 120.7, 115.5, 58.4, 45.8, 44.8, 43.9, 35.9, 34.7, 29.7, 26.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{27}H_{29}N_2O_3S$, 461.1821, found 461.1875.

Diastereomer 2 (R_f 0.35):

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.6 Hz, 2H), 7.61 – 7.56 (m, 4H), 7.48 – 7.38 (m, 4H), 7.36 – 7.31 (m, 1H), 7.29 (s, 1H), 7.23 (ddd, *J* = 8.1, 7.5, 1.3 Hz, 1H), 7.06 (td, *J* = 7.5, 1.1 Hz, 1H), 3.76 (s, 2H), 2.91 (s, 3H), 2.62 – 2.52 (m, 1H), 2.25 – 2.12 (m, 4H), 1.94 – 1.86 (m, 2H), 1.69 – 1.62 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 141.1, 140.5, 139.1, 137.7, 137.1, 128.8, 128.5, 127.7, 127.2, 126.9, 124.9, 123.7, 120.1, 115.3, 61.7, 45.8, 43.3, 42.1, 34.3, 34.1, 30.2, 25.8.

HRMS (ESI) m/z: $[M+H]^+$ calc'd. for $C_{27}H_{29}N_2O_3S$, 461.1821, found 461.1874.

3.4.9 Computational Details

All DFT calculations were carried out using the Gaussian 16 software package[75] at the uM06[76] level of theory with the 6-311+G(d,p)[77] basis set. The CPCM formalism for the Self Consistent Reaction Field (SCRF) model of solvation was employed in calculations to account for solvation in MeCN, and the default parameters as implemented in Gaussian were used. NBO charges were obtained using NBO Version 3.1 in Gaussian 16.[78] Orbitals were visualized using Avagadro version 1.2.0.[79]

Reduction potentials were calculated using a modified procedure as described by Nicewicz and coworkers.[80] Geometry optimizations were carried out for the reduced and neutral forms of each molecule, and frequency calculations were performed on the minimized structures to ensure no imaginary frequencies existed. Gibbs free energies (G_{298}) were obtained from the calculation and employed in the following equation:

$$E_{1/2}^{0,calc} = -\frac{(G_{298}[reduced] - G_{298}[oxidized])}{n_e\mathcal{F}} - E_{1/2}^{0,SHE} + E_{1/2}^{0,SCE}$$

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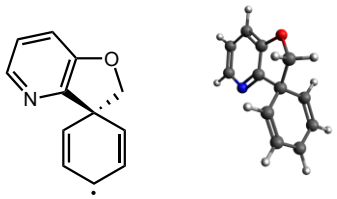
Where n_e is the number of electrons transferred (n_e= 1 for all calculations here), $\mathcal{F}$ is the Faraday constant (value 23.061 kcal mol^{-1} V^{-1}), $E_{1/2}^{0,SHE}$ is the absolute value for the standard hydrogen electrode (SHE, value = 4.281 V) and $E_{1/2}^{0,SCE}$ is the potential of the saturated calomel electrode (SCE) relative to the SHE in MeCN (value = –0.141V)[81], and G_{298}[oxidized] and G_{298}[reduced] are the Gibbs free energies in DMSO obtained from DFT calculations.



Charge: 0

Multiplicity: 2

Number of Imaginary Frequencies: 0

Solvation: MeCN

G_{298}: -592.774968 Hartree

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C	2.9431520	0.3713730	0.1841100
C	1.6254950	0.7551680	0.0419870
C	0.6391270	-0.2082310	-0.1308360
N	0.8577230	-1.5059140	-0.1734550
H	3.7393170	1.0946780	0.3238200

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H	2.3295360	-2.9585960	-0.0925660
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C	-0.2220040	1.9418370	-0.4049320
H	-0.2233980	2.1681040	-1.4787000
H	-0.8062050	2.6922400	0.1295300
C	-0.7197230	0.4922050	-0.1623780
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C	-1.3538670	0.3427030	1.1893470
C	-2.7817220	-0.6228760	-1.0343270
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C	-2.5460480	-0.2838250	1.3700900
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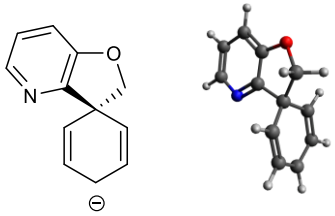

Charge: -1

Multiplicity: 1

Number of Imaginary Frequencies: 0

Solvation: MeCN

C	2.076487	-1.923675	-0.112260
C	3.153155	-1.081021	0.121502
C	2.951311	0.296572	0.212533
C	1.650719	0.725897	0.059913
C	0.621043	-0.189039	-0.156695
N	0.812151	-1.493178	-0.247670
H	3.769359	0.989395	0.383874
H	2.235740	-2.997189	-0.193741
H	4.149697	-1.497808	0.224187
O	1.220503	2.653200	0.102935
C	-0.155812	1.989316	-0.358778
H	-0.152963	2.265084	-1.423647
H	-0.708878	2.739142	0.211695
C	-0.710632	0.558718	-0.164365
C	-1.671897	0.164641	-1.256064
C	-1.383810	0.481000	1.186441
C	-2.795092	-0.578860	-1.972200
H	-1.389390	0.419182	-2.278172
C	-2.512029	-0.354137	1.356645
H	-0.879557	0.854767	2.040930
C	-3.227819	-0.932789	0.286072

H	-3.399656	-0.881098	-1.867266
H	-2.895207	-0.471807	2.372384
H	-4.151973	-1.478266	0.448639

Chapter 4:

Dearomatization of Unactivated Arenes via Catalytic Hydroalkylation

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A. R. Blood synthesized Gabapentin, screened amide R-groups, found conditions for *tert*-butyl deprotection, and contributed to the scope. G. C. Smith conducted DFT calculations.

Abstract: The formation and dearomative spirocyclization of α-acyl radicals has been achieved under mild conditions. In the presence of an organic photoredox catalyst, trialkylamine reductant, and blue light in aqueous acetonitrile, the amine-mediated reduction and cyclization of N-benzylchloroacetamides yields complex spirolactams in a single step. Cyclization of the α-acyl radical is dictated by the amide conformation, while the intermediate reductive radical-polar crossover event proceeds most efficiently if substrate reduction is endergonic. We demonstrate further derivatization of the resulting spirocyclic lactam/1,4-cyclohexadiene, along with the synthesis of the anticonvulsant Gabapentin.

4.1 Introduction

Due to the three-dimensional nature of enzymes, sp^3 character is highly desirable in drug discovery.[82] In this context, spirocyclic compounds are useful because of their ability to access unique three-dimensional space. However, the construction of spirocycles containing all-carbon quaternary centers is a synthetic challenge. An efficient and emerging strategy for the synthesis of these spirocyclic building blocks is the ipso cyclization of carbon-centered radicals onto arenes.[83] In Chapter 3, we reported a system for the synthesis of spirocycles via the dearomative cyclization of aryl radicals onto unactivated arenes.[84] The enabling feature of this system is a reductive radical-

[82] (a) Kingwell, K. Exploring the third dimension. *Nat. Rev. Drug Discov.* **2009,** *8 (12)*, 931. (b) Lovering, F.; Bikker, J.; Humblet, C., Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009,** *52 (21)*, 6752-6.
[83] Yang, W. C.; Zhang, M. M.; Feng, J. G. Recent Advances in the Construction of Spiro Compounds via Radical Dearomatization. *Advanced Synthesis & Catalysis* **2020,** *362 (21)*, 4446-4461.
[84] Flynn, A. R.; McDaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020,** *142 (20)*, 9163-9168.

polar crossover mechanism. The dienyl radical resulting from cyclization is rapidly trapped as the anion, providing high selectivity for the 1,4-diene products and preventing rearrangement pathways leading to the restoration of aromaticity.

We sought to extend these mechanistic principles to the synthesis of spirocyclic lactams, a class of scaffolds that directly translates to many known biologically active compounds, including NMDA modulators, HDAC inhibitors, and angiogenesis inhibitors (Figure 4.1).[85]

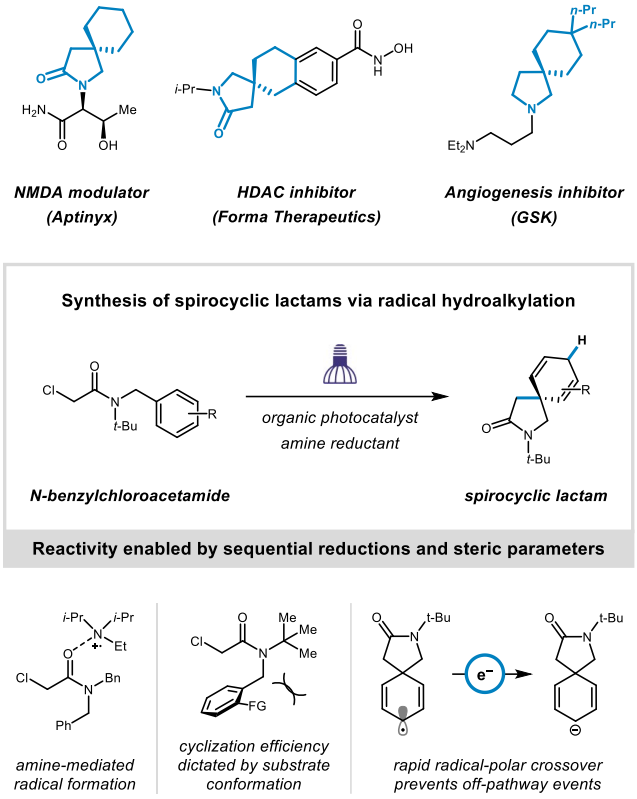


Figure 4.1: Dearomative hydroalkylation strategy for the synthesis of biologically-relevant spirocyclic lactams

Specifically, we pursued the dearomative cyclization of α-acyl radicals accessed via single-electron reduction of *N*-benzylchloroacetamides. This method provides two desirable features in drug discovery, spirocycles and nitrogen-containing heterocycles, under mild, broadly applicable conditions. A few key factors informed the development of this system: reduction of the *N*-benzylchloroacetamide substrates is facilitated by the amine radical cation, the efficiency of radical cyclization is highly-dependent on substrate conformation, which is dictated by steric factors, and rapid radical-polar crossover is essential for the formation of the desired spirocyclic products.

[85] (a) Ng, P. Y.; Davis, H.; Bair, K. W.; Millan, D. S.; Rudnitskaya, A.; Zheng, X.; Han, B.; Barczak, N.; Lancia, D. 3-Spiro-7-hydroxamic acid tetralins as HDAC inhibitors. WO 2016/168660 A1, Oct 20, 2016. (b) Brodowski, M. H.; Denhart, D.; Ashraf, S.; Argentieri, S. R.; Buchman, J. J. Spiro-lactam NMDA receptor modulators and uses thereof. WO 2019/152688, Aug 8 2019. (c) Shailubhai, K.; Dheer, S.; Picker, D.; Kaur, G.; Sausville, E. A.; Jacob, G. S. Atiprimod is an inhibitor of cancer cell proliferation and angiogenesis. *Journal of Experimental Therapeutics and Oncology* **2004,** *4*, 267-279.

Previous methods have shown dearomative spirocyclization of α-acyl radicals; however, these methods operate via alternative mechanistic manifolds, which limits the generality of the reactivity. Atom transfer radical cyclization of trichloroacetamides results in chlorinated cyclohexadiene products, with scopes limited to alkyl and fluorine substituents.[86] Photocatalytic and peroxide-mediated methods require *para*-alkoxy or *para*-fluoro benzenoid precursors and terminate via oxidation to the cyclohexadienone.[87] In contrast, our net-reductive method functions on a broad scope of electronically-varied arenes and does not necessitate the formation of chlorinated or oxidized products.

4.2 Results and Discussion

4.2.1 Mechanistic design of dearomative hydroalkylation system

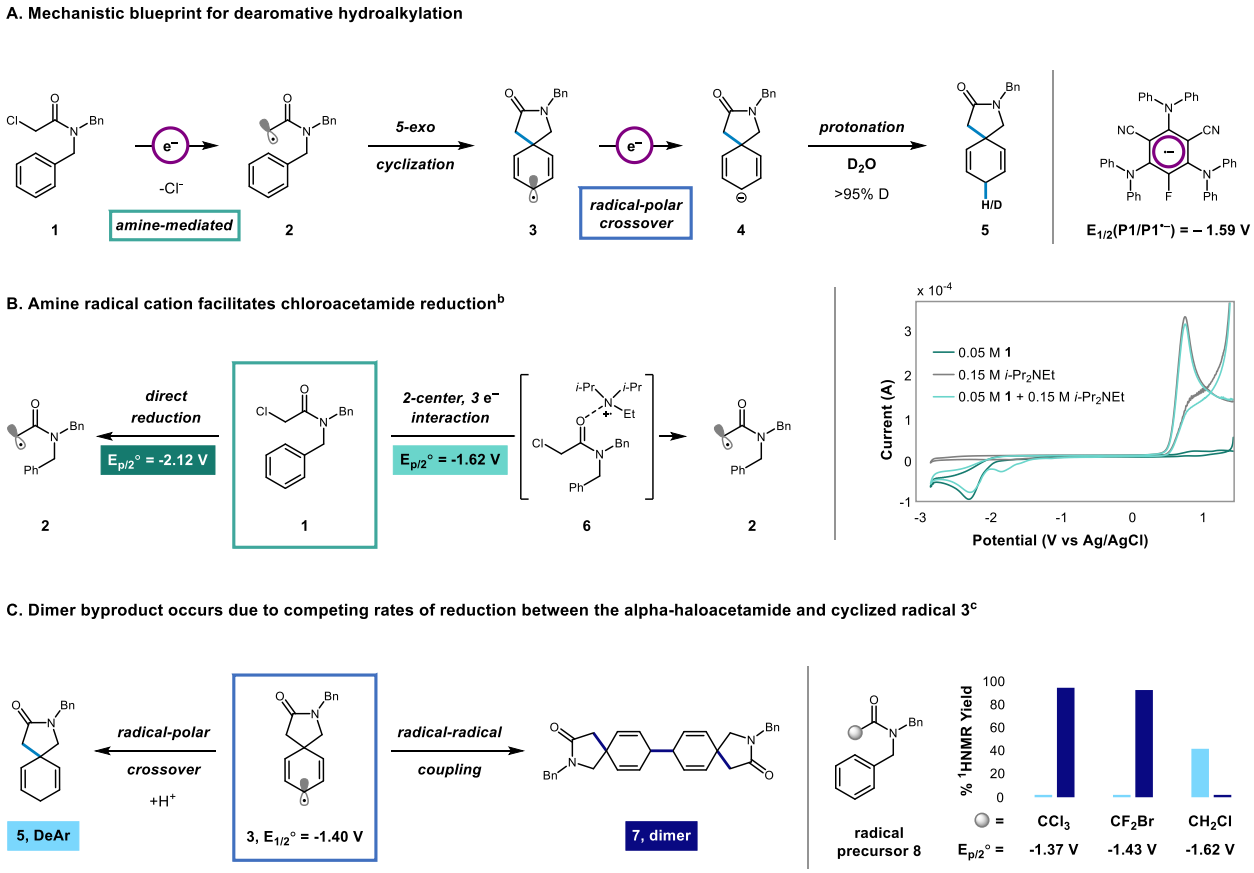
In designing a system for the dearomative synthesis of spirolactams, we envisioned the mechanistic blueprint shown in Scheme 4.1A. Single-electron reduction of chloroacetamide **1** and loss of chloride yields α-acyl radical **2**. Rapid 5-*exo*-cyclization of **2** breaks aromaticity, furnishing the cyclized radical **3**. Reductive radical-polar crossover ($E_{1/2}° = -1.40$ V vs SCE; see SI for details) results in the formation of the dienyl anion **5**, which is protonated by solvent (>95% D incorporation with D_2O solvent; see SI for details) to give the dearomatized spirocyclic lactam

[86] (a) Boivin, J.; Yousfi, M.; Zard, S. Z. Spirolactams by a Novel ipso-Radical Cyclisation and Loss of Aromaticity. *Tetrahedron Lett.* **1997,** *38 (34)*, 5985-5988. (b) Diaba, F.; Montiel, J. A.; Martínez-Laporta, A.; Bonjoch, J. Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes. *Tetrahedron Lett.* **2013,** *54 (21)*, 2619-2622.

[87] (a) Yuan, L.; Jiang, S. M.; Li, Z. Z.; Zhu, Y.; Yu, J.; Li, L.; Li, M. Z.; Tang, S.; Sheng, R. R. Photocatalyzed cascade Meerwein addition/cyclization of N-benzylacrylamides toward azaspirocycles. *Org. Biomol. Chem.* **2018,** *16 (14)*, 2406-2410. (b) Hu, B.; Li, Y.; Dong, W.; Ren, K.; Xie, X.; Wan, J.; Zhang, Z. Visible light-induced intramolecular dearomative cyclization of alpha-bromo-N-benzyl-alkylamides: efficient construction of 2-azaspiro[4.5]decanes. *Chem. Commun.* **2016,** *52 (18)*, 3709-3712. (c) Ibarra-Rivera, T. R.; Gamez-Montano, R.; Miranda, L. D. Efficient oxidative radical spirolactamization. *Chem. Commun.* **2007,** *(33)*, 3485-3487. (d) Gámez-Montaño, R.; Ibarra-Rivera, T.; Kaïm, L.; Miranda, L. Efficient Synthesis of Azaspirodienones by Microwave-Assisted Radical Spirocyclization of Xanthate-Containing Ugi Adducts. *Synthesis* **2010,** *2010 (08)*, 1285-1290.

product **5**. In this net-reductive mechanism, reducing electrons come from photocatalyst 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile (3DPAFIPN, **P1**).[88] Photoexcitation of **P1** followed by reductive quenching from Hünig's base (*i*-Pr_2NEt) yields highly reducing species $\mathbf{P1}^{\bullet-}$ ($E_{1/2}°(\mathbf{P1}/\mathbf{P1}^{\bullet-})$ = -1.59 V vs SCE), which reduces both **1** and **3**.[89]

Scheme 4.1: Design of dearomative spirolactamization reaction and insight into key mechanistic steps[a]



[a]All potentials vs SCE. [b]Cyclic voltammetry conditions: 0.05 M **1**, 0.15 M *i*-Pr_2NEt, and 0.1 M tetrabutylammonium hexafluorophosphate. A glassy carbon working electrode, Ag/AgCl reference electrode, and platinum wire counter electrode were used. The experiment was conducted in MeCN at 23 °C with a scan rate of 100 mV/s. [c]Reaction conditions: *N*-benzylhaloactetamide **8** (1 equiv), 3DPAFIPN (5 mol%), *i*-Pr_2NEt (3 equiv), MeCN:H_2O (1:1 v/v, 0.05 M), blue LEDs, 50 °C, 16 h. Yields determined by ^1H NMR analysis.

[88] Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018,** *140 (45)*, 15353-15365.
[89] *J. Am. Chem. Soc.* **2018,** *140 (45)*, 15353-15365.

Upon examining the reduction of **1** via cyclic voltammetry (CV) (Scheme 4.1B), we found that direct reduction in the absence of amine occurs at $E_{p/2}°$ = -2.12 V vs SCE. This is well out of the range of the reducing power of **P1**$^{\bullet-}$, -1.59 V vs SCE, making direct reduction unlikely. However, upon subjecting **1** to a CV experiment with oxidized *i*-Pr_2NEt present, a new reduction event appeared at $E_{p/2}°$ = -1.62 V vs SCE (Scheme 4.1B). Based on previous reports, this feature can be explained by substrate activation though a 2-center-3-electron interaction between the carbonyl and amine radical cation.[90] The presence of intermediate **6** allows this otherwise unlikely electron transfer event to occur.

Additionally, we found that the second reduction, reductive radical-polar crossover of **3**, is key to achieving the desired reactivity. Under conditions analogous to those previously developed in our lab, the formation of **5** was highly dependent on the identity of the radical precursor (Scheme 4.1C).[91] Trichloro- and bromodifluoroacetamide substrates lead to exclusive formation of the dimer of the cyclized radical, **7**. We postulate that this is due to a competing rates of reduction between the radical precursor **8** and the cyclized radical **3**. Since the reduction potentials of the trichloro- ($E_{p/2}°$ = -1.37 V vs SCE) and bromodifluoroacetamide ($E_{p/2}°$ = -1.43 V vs SCE) substrates are in the same range of that of the cyclized radical **3** ($E_{1/2}°$ = -1.40 V vs SCE; see SI for details), preferential reduction of **8** over **3** leads to a buildup of **3**, which dimerizes via radical-

[90] (a) Humbel, S.; Hoffmann, N.; Cote, I.; Bouquant, J. Substituent Effects on Two-Center Three-Electron Bonds and Hydrogen Bonds Involving Unsaturated Organic Functional Groups and an Ammonia Radical Cation--The Resonance Contribution. *Chem. Eur. J.* **2000,** *6 (9)*, 1592-1600. (b) Humbel, S.; Cote, I.; Hofmann, N.; Bouquant, J. Three-Electron Binding between Carbonyl-like Compounds and Ammonia Radical Cation. Comparison with the Hydrogen Bonded Complex. *J. Am. Chem. Soc.* **1999,** *121 (23)*, 5507-5512. (c) Chen, M.; Zhao, X.; Yang, C.; Xia, W. Visible-Light-Triggered Directly Reductive Arylation of Carbonyl/Iminyl Derivatives through Photocatalytic PCET. *Org. Lett.* **2017,** *19 (14)*, 3807-3810. (d) Fan, X.; Gong, X.; Ma, M.; Wang, R.; Walsh, P. J. Visible light-promoted CO2 fixation with imines to synthesize diaryl alpha-amino acids. *Nat. Commun.* **2018,** *9 (1)*, 4936. (e) Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. Photoredox-Catalyzed Reductive Coupling of Aldehydes, Ketones, and Imines with Visible Light. *Angew. Chem. Int. Ed.* **2015,** *54 (30)*, 8828-8832. (f) Betori, R. C.; Scheidt, K. A. Reductive Arylation of Arylidene Malonates Using Photoredox Catalysis. *ACS Catalysis* **2019,** *9 (11)*, 10350-10357.

[91] Flynn, A. R.; McDaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020,** *142 (20)*, 9163-9168.

radical coupling to form **7**. However, when running the harder to reduce choroacetamide substrate **1** ($E_{p/2}°$ = -1.62 V vs SCE) under the same conditions, we saw the suppression of the dimer byproduct **7** along with formation of the desired product **5** (with the rest of the mass balance consisting of hydrodehalogenation).

In screening a variety of photocatalysts with substrate **1**, we found that, when electron transfer to the substrate is endergonic, the dimer product **7** is fully suppressed. However, when using the strongly reducing photocatalyst 2,4,6-tris(diphenylamino)-3,5-difluorobenzonitrile (3DPA2FBN; $E_{1/2}°(PC/PC^{\bullet-})$ = -1.92 V vs SCE),[92] for which both electron transfer events are exergonic, we saw formation of both the dearomatized product **5** (29%) and the dimer **7** (44%). We believe this results from a buildup of **3** due to rapid reduction of **1**. This is a phenomenon we had previously seen in our dearomative hydroarylation system (Chapter 3), specifically with bromopyridine aryl radical precursors. Formation of dimeric products was seen when highly-reducing photocatalysts were used (3DPA2FBN $E_{1/2}°$ = -1.92 V vs SCE; $Ir(ppy)_3$ $E_{1/2}°$ = -2.19 V vs SCE) or when 2,2,2-trifluoroethanol (TFE) was used as solvent.[93] The solvent effect can be explained by our group's previous discovery that TFE engages in proton-coupled electron transfer (PCET) with bromopyridines, lowering the energy barrier to substrate reduction.[94]

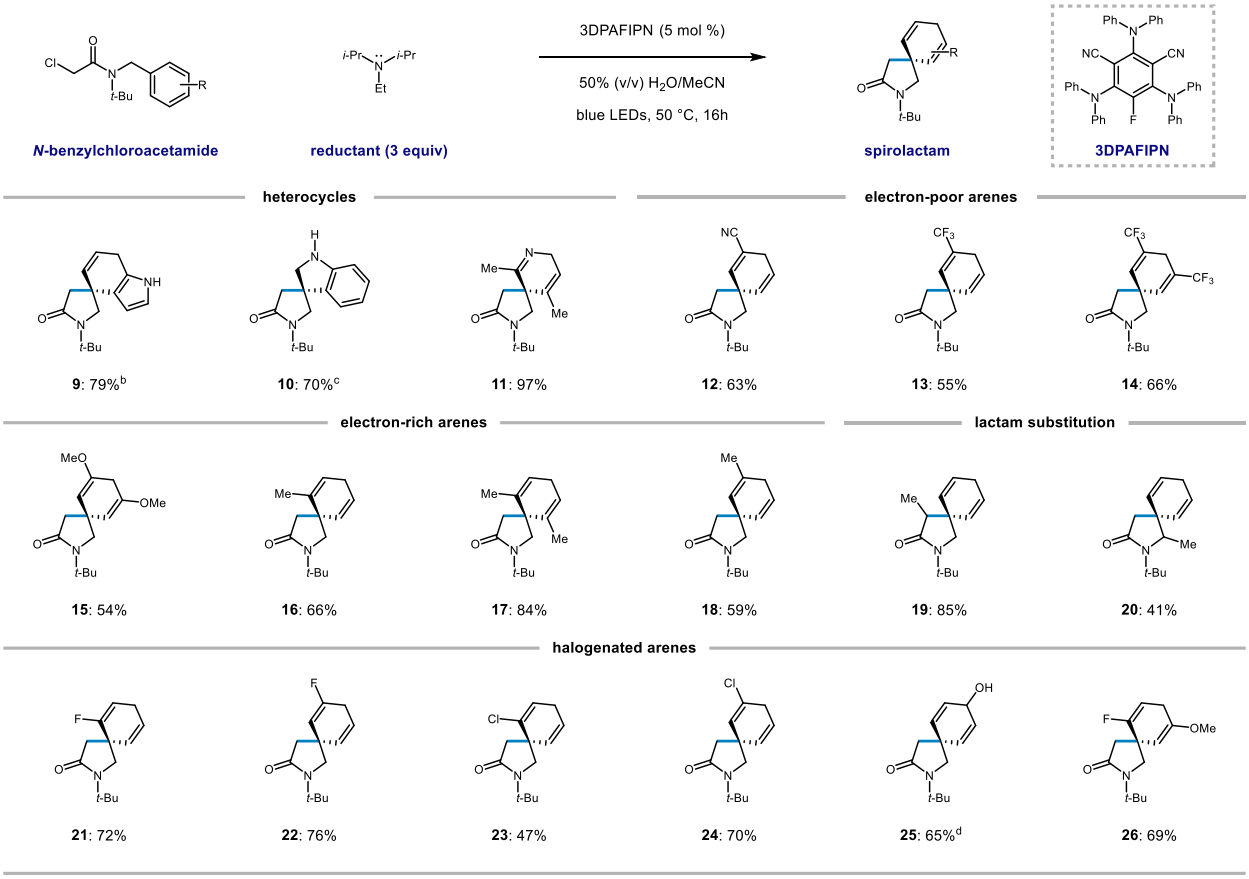
[92] Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018,** *140 (45)*, 15353-15365.
[93] *J. Am. Chem. Soc.* **2018,** *140 (45)*, 15353-15365.
[94] Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018,** *140 (45)*, 15525-15534.

4.2.2 Scope of dearomative hydroalkylation

This reactivity successfully transforms a range of *N*-benzylchloroacetamide structures to complex, spirocyclic lactam products (Table 4.1). In looking at the hydroalkylation of heterocycles, we were able to demonstrate selective dearomatization of either ring of indole derivatives (**9**-**10**, 70-79%). Interestingly, formation of **10** required the addition of polarity-reversal catalyst cyclohexanethiol, suggesting that formation of this product is terminated through hydrogen atom transfer (HAT) rather than reductive radical-polar crossover. A pyridine substate dearomatized in high yield (**11**, 97%), providing a precursor to spirocyclic piperidines, a highly sought-after scaffold in drug discovery. Unfortunately, pyridine substrates were limited by their synthesis: unhindered pyridines polymerized via *N*-alkylation. In contrast to our the previously reported dearomatization methods (Chapters 2 and 3),[95] this method functions with electron-poor acceptor arenes. Benzenoids bearing nitriles and trifluoromethyl substituents cyclized well without evidence of competitive reduction of the electron-poor rings (**12**-**14**, 55-66%). Electron-rich arenes bearing methoxy and methyl groups cyclized in good yields (**15**-**18**, 54-84%). Substitution on the lactam ring is also tolerated, as demonstrated by methyl substituted lactams **19**-**20** (41-85%). This method also functions on halogenated arenes. Substrates bearing aryl fluoride and chloride substituents at the *ortho* and *meta* positions cyclize to give dearomatized products in good yields (**21**-**24**, **26**, 47-76%). A *para*-chloro benzenoid cyclized to give alcohol **25** (65%), which presumably arises from solvolysis of the doubly allylic halide product.

[95] (a) McDaniel, K. A.; Jui, N. T. Dearomatization through Photoredox Hydroarylation: Discovery of a Radical-Polar Crossover Strategy. *Org. Lett.* **2021**, *23*, 5576–5580. (b) Flynn, A. R.; McDaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J. Am. Chem. Soc.* **2020,** *142 (20)*, 9163-9168.

Table 4.1: Photocatalytic radical hydroalkylation of aromatics: Scope of spirocyclic lactam products[a]

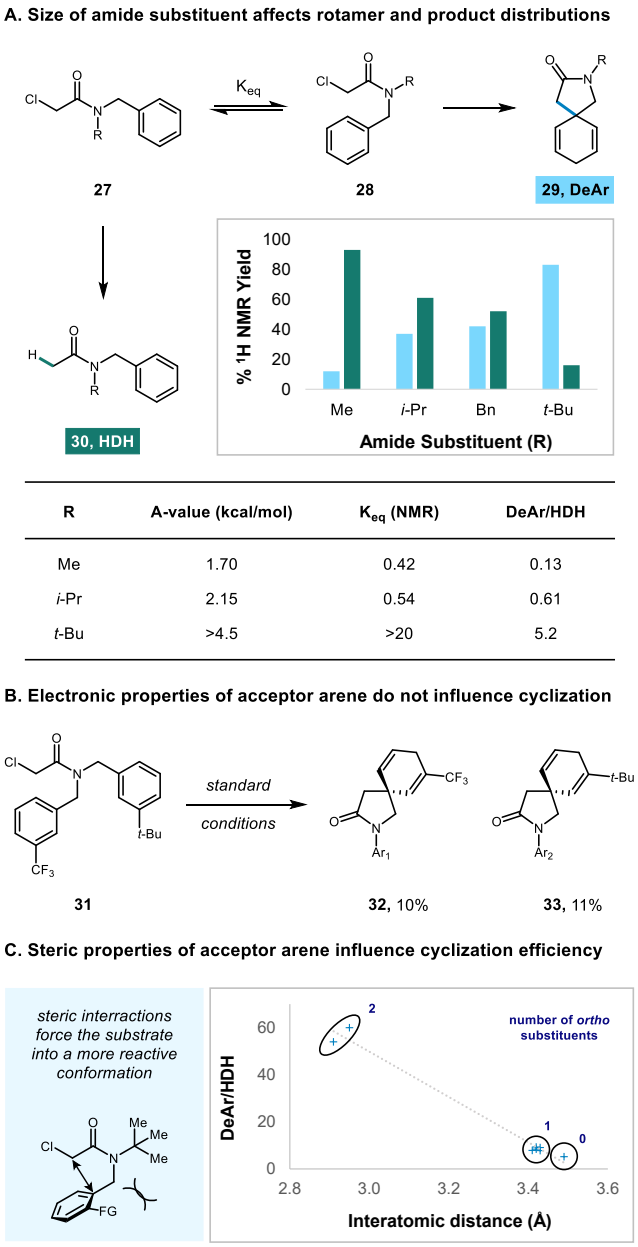


[a]Reaction conditions: *N*-benzylchloroactetamide (1 equiv), 3DPAFIPN (5 mol%), *i*-Pr_2NEt (3 equiv), MeCN:H_2O (1:1 v/v, 0.05 M), blue LEDs, 50 °C, 16 h. Isolated yields shown. [b]Reaction conducted with 9:1 v/v MeCN:H_2O solvent. [c]Reaction conducted with CySH (5 mol%) additive [d]1:1 d.r., isolated yield of combined diastereomers shown; *para*-chlorobenzene dearomatization was followed by chloride solvolysis.

4.2.3 Factors influencing cyclization efficiency

In exploring the factors influencing the efficiency of cyclization, we considered both steric and electronic effects. While cyclization of the trichloro- and bromodifluoroacetamide substrates was highly efficient (presumably due to the highly electrophilic nature of the corresponding α-acyl radicals), cyclization of the monochloroacetamide substrate is highly dependent on the amide substituent (R; Figure 4.2A). Less efficient cyclization results in formation of the hydrodehalogenation (HDH) product **30** via single-electron reduction of α-acyl radical followed

by protonation (for R = Me, 88% D incorporation with D_2O solvent; see SI for details). In line with previous observations by Zard,[96] upon screening R-groups of different sizes, we saw a trend in which smaller amide substituents (Me, *i*-Pr) primarily yielded the HDH product **30**, while bulkier amide substituents (*t*-Bu) led to formation of spirolactam **29** as the major product (83%). We hypothesized that this phenomenon is due to the equilibrium between the two amide rotamers, where rotamer **28** is oriented for cyclization and rotamer **27** is not. Indeed, we found that the size of the amide substituent (A-value), equilibrium constant (K_{eq}) of the amide rotamers (as determined by ^{1}H NMR), and ratio of products of the reaction were correlated (Figure 4.2A). Rotamer **28** is favored only for the large *t*-Bu substituent (A-value > 4.5 kcal/mol; K_{eq} > 20), and thus it provides



R	A-value (kcal/mol)	K_{eq} (NMR)	DeAr/HDH
Me	1.70	0.42	0.13
i-Pr	2.15	0.54	0.61
t-Bu	>4.5	>20	5.2

Figure 4.2: The effect of conformation and electronic factors on cyclization

[96] Boivin, J.; Yousfi, M.; Zard, S. Z. Spirolactams by a Novel ipso-Radical Cyclisation and Loss of Aromaticity. *Tetrahedron Lett.* **1997,** *38 (34)*, 5985-5988.

the highest yield of dearomatized spirocycle **29**. The requirement for a bulky amide substituent is convenient because *tert*-butyl groups are known to be removable amide protecting groups.[97]

We also considered the effect of substituents on the acceptor arene, since we had seen that the philicity of the α-acyl radical impacted the cyclization efficiency. In order to determine whether the electronic properties of the arene affect the efficiency of cyclization, we synthesized unsymmetric *N*,*N*-dibenzyl substrate **31**, in which one of the arenes contains an electron-donating *tert*-butyl group while the other contains an electron-withdrawing trifluoromethyl group. Upon subjecting this substrate to the standard reaction conditions, we saw an even distribution of cyclization into each ring (where the remaining mass balance consisted of HDH), demonstrating that the electronic properties of the arene do not significantly affect the preference for cyclization (Figure 4.2B).

Finally, we investigated the steric effect of the arene substituents on cyclization, postulating that unfavorable interactions between *ortho* substituents and the *tert*-butyl force the substrate into a more reactive conformation. For a sampling of substrates, the structural minima were computationally determined, along with the interatomic distance between the two carbons which form the spirocyclic center (Figure 4.3C; see SI for details). These interatomic distances are strongly correlated to the product distribution (R^2 = 0.98), where substrates with a smaller interatomic distance cyclize in higher yields than those with a larger interatomic distance. For example, substates with two *ortho* substituents have the smallest calculated interatomic distances and the highest experimental ratio of cyclized product to HDH. These data strongly suggest that substrate conformation plays the largest role in the cyclization efficiency of the α-acyl radical. This

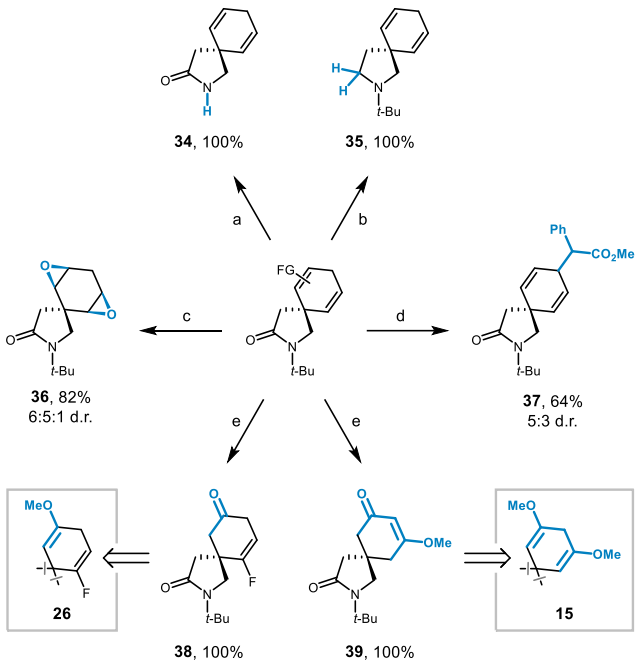
[97] Evans, V.; Mahon, M. F.; Webster, R. L. A mild, copper-catalysed amide deprotection strategy: use of tert-butyl as a protecting group. *Tetrahedron* **2014,** *70 (41)*, 7593-7597.

is notable because it demonstrates the highly efficient formation of sterically encumbered all-carbon quaternary centers.

4.2.4 Derivatization of spirolactam products

To demonstrate the utility of these spirocyclic lactams, we showed modular derivatization of each part of the scaffold (Scheme 4.2). Selective deprotections of the lactam are possible. Deprotection of the *tert*-butyl group proceeds at 150 °C in trifluoroacetic acid (**34**, 100%). An alternative protecting group is the cumyl group (-C(C_6H_5)(CH_3)$_2$). Dearomative cyclization with this protecting group proceeds in comparable yield (59%; see SI for details) and deprotection proceeds at 50 °C in trifluoroacetic acid (**34**, 59%). Removal of the carbonyl is also efficient with lithium aluminum hydride (**35**, 100%).

Scheme 4.2: Derivatization of spirocyclic lactam products



[a]TFA, 150 °C, 16h. [b]$LiAlH_4$ (2 equiv), THF, 16h. [c]*m*CPBA, CH_2Cl_2, 16h. [d]Rh_2(*S*-PTAD)$_4$, methyl 2-diazo-2-phenylacetate, CH_2Cl_2, 3h. [e]TFA/CH_2Cl_2, 16h.

The 1,4-cyclohexadiene moiety is highly functionalizable, as a plethora of olefin functionalization reactions are known.[98] We demonstrated oxidation of both olefins with *m*CPBA, which gives a mixture of three diastereomers in good yield (**36**, 82%, major diastereomer shown; see SI for details), as was expected based on literature reports detailing similar reactivity.[99] This

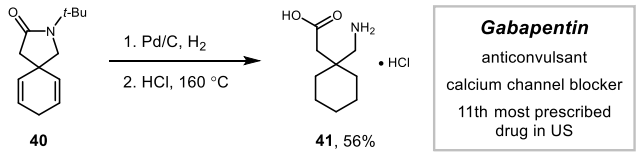
[98] Smith, M. B.; March, J. Addition to Carbon-Carbon Multiple Bonds. In *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2007; pp 999−1250.

[99] (a) Bykova, T.; Al-Maharik, N.; Slawin, A. M. Z.; O'Hagan, D. Fluorinated cyclohexanes: Synthesis of amine building blocks of the all-cis 2,3,5,6-tetrafluorocyclohexylamine motif. *Beilstein J. Org. Chem.* **2017,** *13*, 728-733.

rapidly gives access to four new stereocenters, which can easily be further functionalized through nucleophilic epoxide opening strategies. Functionalization of the doubly-allylic carbon is also possible via C-H functionalization methods.[100] With catalytic Rh_2(*S*-PTAD)$_4$, methyl 2-diazo-2-phenylacetate underwent C- H insertion in good yield (**37**, 64%). Finally, the quantitative hydrolysis of enol ether-containing products further demonstrates the rapid conversion of functionalized arenes to complex cyclohexenes. The 2-fluoro-3-methoxy spirocycle **26** underwent enol ether hydrolysis to give cyclohexanone **38**, which can be further functionalized at any position on the ring. The 3,5-dimethoxy spirocycle **15** underwent enol ether hydrolysis to furnish the β-methoxy α,β-unsaturated ketone **39**, which acts as a useful handle for further functionalization.

To further illustrate the utility of this method, we demonstrate the synthesis of the commonly-prescribed anticonvulsant Gabapentin (Scheme 4.3).[101] The spirolactam precursor **40** is made in three steps via reductive amination, acylation, and dearomative cyclization under our standard conditions (81% over 3 steps; see SI for details). Olefin reduction followed by one-pot *tert*-butyl deprotection/lactam hydrolysis yields Gabapentin as the HCl salt (**41**, 56% over 2 steps).

Scheme 4.3: Synthesis of the anticonvulsant Gabapentin



(b) Bykova, T.; Al-Maharik, N.; Slawin, A. M.; O'Hagan, D. Multicomponent reactions of methyl substituted all-cis tetrafluorocyclohexane aldehydes. *Org. Biomol. Chem.* **2016,** *14 (3)*, 1117-1123. (c) Bykova, T.; Al-Maharik, N.; Slawin, A. M. Z.; O'Hagan, D. Synthesis of selectively fluorinated cyclohexanes: The observation of phenonium rearrangements during deoxyfluorination reactions on cyclohexane rings with a vicinal phenyl substituent. *Journal of Fluorine Chemistry* **2015,** *179*, 188-192.

[100] Denton, J. R.; Davies, H. M. L. Enantioselective Reactions of Donor/Acceptor Carbenoids Derived from α-Aryl-α-Diazoketones. *Org. Lett.* **2009,** *11 (4)*, 787-790.

[101] The Top 200 Drugs of 2018. https://clincalc.com/DrugStats/Top200Drugs.aspx (accessed Dec 04, 2020).

4.3 Conclusions

In conclusion, we have developed a mild and efficient method for the dearomative spirocyclization of *N*-benzylchloroacetamides. In this process, radical formation is enabled by a 2-center-3-electron interaction, and effective radical-polar crossover requires the initial reductive event to be endergonic and slower than the second reduction. Substrate conformation, dictated by rotamer preference and steric interactions, plays an important role in enabling the cyclization event. This method results in a diverse range of spirocyclic lactams that can be easily diversified to even more complex, biologically relevant products.

4.4 Supporting Information

4.4.1 General Information

General Reagent Information

Solvents used in anhydrous reactions were purified by passing over activated alumina and storing under argon. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Astatech, and TCI America and used as received, unless stated otherwise. Organic solutions were concentrated under reduced pressure on a rotary evaporator using a water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on 230–400 mesh silica gel. Preparative thin-layer chromatography (PTLC) separations were carried out on 1000 μm SiliCycle silica gel F-254 plates. Thin-layer chromatography (TLC) was performed on 250 μm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or staining using $KMnO_4$, p-anisaldehyde, or ninhydrin stains. All photoredox reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs, unless stated otherwise (LED wholesalers PAR38 Indoor Outdoor 16-Watt LED Flood Light Bulb, Blue; or Hydrofarm® PPB1002 PowerPAR LED Bulb-Blue 15W/E27 (available from Amazon)). Solvent was degassed by sonication under mild vacuum for 15 minutes. Photoredox catalysts 3DPAFIPN, 3DPA2FBN, 5CzBn, 4CzIPN, and $[Ir(ppy)_2dtbbpy]PF_6$ were prepared according to literature procedures.[102,103]

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[102] Speckmeier, E.; Fischer, T.; Zeitler, K. A Toolbox Approach to Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15354–15365.

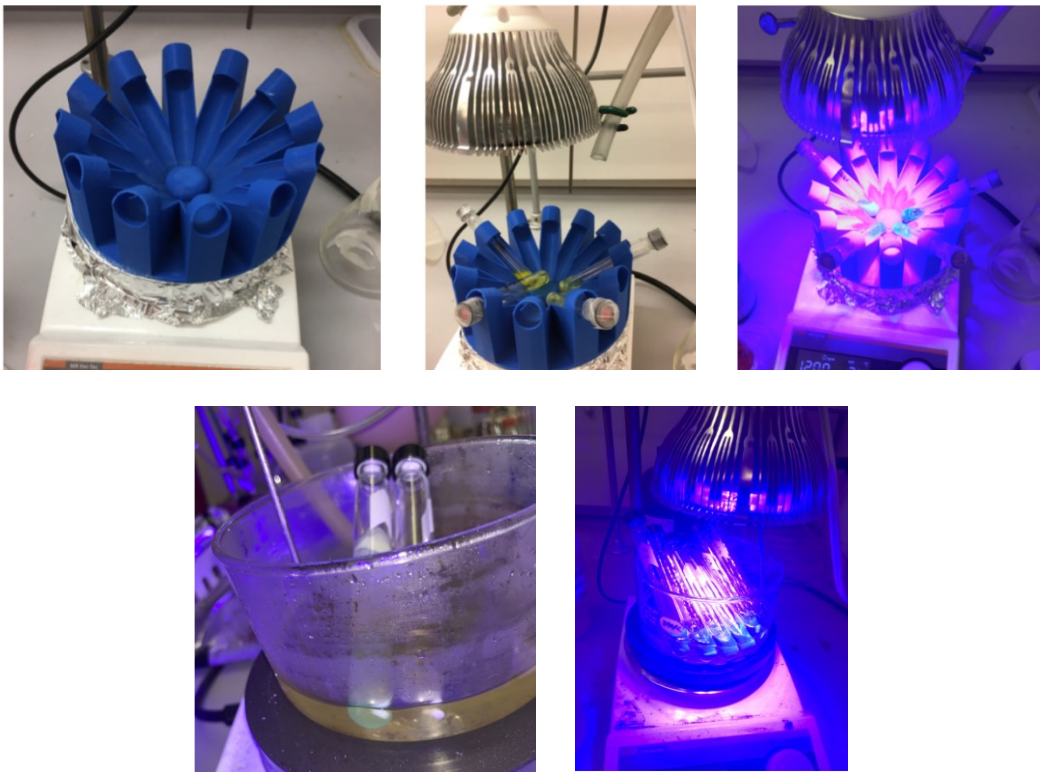
[103] Slinker, J. D.; Gorodetsky, A. A.; Lowry, M. S.; Wang, J.; Parker, S.; Rohl, R.; Bernhard, S.; Malliaras, G. G. Efficient Yellow Electroluminescence from a Single Layer of a Cyclometalated Iridium Complex. *J. Am. Chem. Soc.* **2004**, *126*, 2763-2767.

General Analytical Information

Unless otherwise noted, all yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. New compounds were characterized by ^{1}H NMR, ^{13}C NMR, and LRMS. ^{1}H and ^{13}C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), Bruker NEO 400 (400 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), or VNMR 400 (400 MHz) and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, dtd= doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), integration, and assignment, when applicable. Data for decoupled ^{13}C NMR are reported in terms of chemical shift and multiplicity when applicable. Gas Chromatography Mass Spectrometry (GCMS) was performed on an Agilent 5977A mass spectrometer with an Agilent 7890A gas chromatography inlet. Liquid Chromatography Mass Spectrometry (LCMS) was performed on an Agilent 6120 mass spectrometer with an Agilent 1220 Infinity liquid chromatography inlet.

General Photoredox Reaction Setup

To run multiple reactions (for optimization), an appropriately sized 3D printed carousel was used, which exposed the reactions to the blue light evenly. A 15 W LED array lamp was used as a blue light source. These lamps were routinely used for up to 12 reactions at a time. The reactions were cooled with a line of compressed air. The blue LEDs were positioned approximately 6 cm above the reaction vials to get good light coverage without overheating the reactions. Reactions run at elevated temperatures were irradiated in a shallow oil bath.



4.4.2 General Procedures

General Reductive Amination Procedure

To a round bottomed flask charged with benzaldehyde (1.0 equiv) was added MeOH (0.2 M) and primary amine. After stirring for 2-16 hours, $NaBH_4$ (1.5 equiv) was added slowly, and the resultant mixture was stirred until bubbling ceased. The reaction mixture was quenched with 1 M NaOH (aq) and extracted with EtOAc (3x). The combined organic layers were washed with 1 M HCl (aq), and the resulting aqueous layer was brought to pH 14 with 2 M NaOH (aq) or 50% KOH (aq) and extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ or Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product.

General Acylation Procedure

To a round bottomed flask charged with secondary amine (1.0 equiv) was added CH_2Cl_2 (0.1 M), Et_3N (1.2 equiv), and chloroacetyl chloride (1.2 equiv). After stirring for 1-2 hours, the reaction mixture was quenched with MeOH, diluted with H_2O, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ or Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified on silica using the indicated solvent mixture, if necessary, to afford the desired product.

General Dearomative Spirolactamization Procedure 1

A 20 mL screw-top test tube was charged with 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), and substrate (0.5 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv) was added via syringe, followed by degassed solvent (5 mL of each MeCN and H_2O to give a 0.05 M solution). The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with EtOAc (3x), dried over $MgSO_4$ or Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified as indicated to afford the desired product (1,4-diene products stain strongly with $KMnO_4$).

General Dearomative Spirolactamization Procedure 2

A 20 mL screw-top test tube was charged with 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), and substrate (0.5 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA

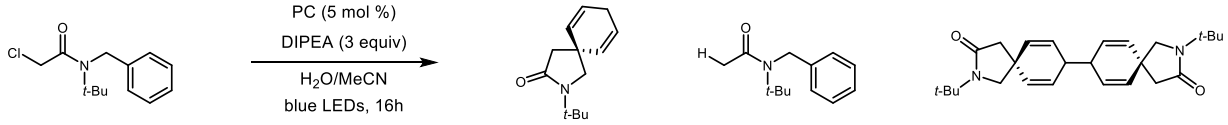
(0.26 mL, 1.5 mmol, 3.0 equiv) was added via syringe, followed by degassed solvent (5 mL of each MeCN and H_2O to give a 0.05 M solution). The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with EtOAc (3x), dried over $MgSO_4$ or Na_2SO_4, and concentrated under reduced pressure. In order to deprotect the HDH byproduct that is sometimes difficult to separate from the dearomatized product via chromatography, the crude residue was dissolved in 50% (v/v) TFA/CH_2Cl_2 (0.1 M) for 16 hours. The reaction was quenched with saturated $NaHCO_3$ (aq) then extracted with EtOAc (3x), dried over $MgSO_4$ or Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified as indicated to afford the desired product (1,4-diene products stain strongly with $KMnO_4$).

4.4.3 Optimization Details

Optimization Procedure

An 8 mL screw-top test tube was charged with photocatalyst (0.005 mmol, 5 mol%) and *N*-benzyl-*N*-(*tert*-butyl)-2-chloroacetamide (**S39**) (24.0 mg, 0.1 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA (52 μL, 0.3 mmol, 3 equiv) was added via syringe, followed by degassed solvent. The resulting mixture was stirred at the indicated temperature for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with ethyl acetate (3x) and concentrated under reduced pressure. $CDCl_3$ and an internal standard of dibromomethane (7 μL, 0.1 mmol) were added. The sample was analyzed by ^1H NMR (d1 = 5 s), and the integral values were used to calculate the data given in Table 4.2.

Table 4.2: Optimization of dearomative spirocyclization and control reactions



S39 **40** **HDH** **Dimer**

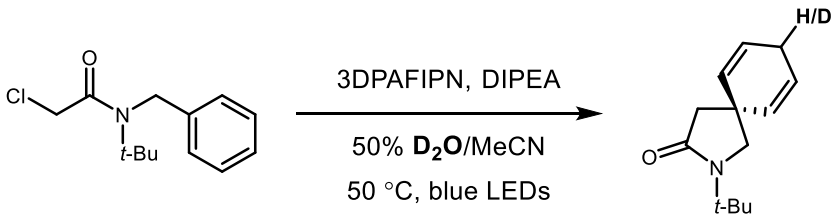
Entry	PC	Concentration	Temperature	% water	S39	40	HDH	Dimer	
1	3DPAFIPN	0.05 M	23 °C	50%	-	74	25	-	
2	3DPA2FBN	0.05 M	23 °C	50%	-	29	14	44	
3	5CzBN	0.05 M	23 °C	50%	-	34	65	-	
4	4CzIPN	0.05 M	23 °C	50%	78	16	7	-	
5	$[Ir(ppy)_2dtbbpy]PF_6$	0.05 M	23 °C	50%	-	42	58	-	
6	3DPAFIPN	0.1 M	23 °C	50%	-	67	31	-	
7	3DPAFIPN	0.033 M	23 °C	50%	-	74	24	-	
8	3DPAFIPN	0.05 M	0 °C	50%	-	52	50	-	
9	3DPAFIPN	0.05 M	40 °C	50%	-	79	21	-	
10	**3DPAFIPN**	**0.05 M**	**50 °C**	**50%**	**-**	**83**	**18**	**-**	**optimized conditions**
11	3DPAFIPN	0.05 M	60 °C	50%	-	79	19	-	
12	3DPAFIPN	0.05 M	50 °C	0%	-	42	57	-	
13	3DPAFIPN	0.05 M	50 °C	10%	-	39	60	-	
14	3DPAFIPN	0.05 M	50 °C	25%	-	54	44	-	
			controls						
15	-	0.05 M	23 °C	25%	100	-	-	-	**no PC**
16	3DPAFIPN	0.05 M	23 °C	25%	97	-	-	-	**no reductant**
17	3DPAFIPN	0.05 M	23 °C	25%	99	-	-	-	**no light**

4.4.4 Deuterium Labeling Study

General Deuterium Labeling Procedure

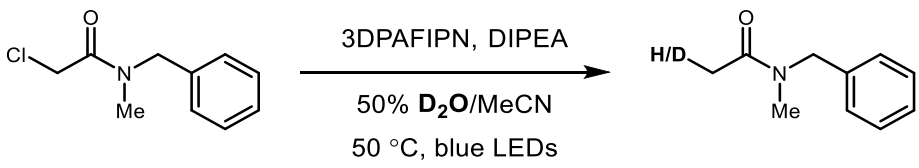
An 8 mL screw-top test tube was charged with 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%) and substrate (0.1 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, degassed solvent was added via syringe (1 mL of each MeCN and **D_2O** to give a 0.05 M solution), followed by DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv). The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs. The reaction was then extracted with ethyl acetate (3x) and concentrated. $CDCl_3$ was added and the sample was analyzed by ^1H NMR (d1 = 5 s) to determine the % D incorporation at the indicated position.

Experiment 1 – Deuterium incorporation in dearomatized spirolactam



N-benzyl-*N*-(*tert*-butyl)-2-chloroacetamide (**S39**) (24.0 mg) was subjected to the General Deuterium Labeling Procedure. ^1H NMR analysis showed >95% deuterium incorporation.

Experiment 2 – Deuterium incorporation in hydrodehalogenation byproduct



N-benzyl-2-chloro-*N*-methylacetamide (**S43**) (24.0 mg) was subjected to the General Deuterium Labeling Procedure. ^1H NMR analysis showed 88% deuterium incorporation.

4.4.5 Electrochemical Measurements

Electrochemical potentials were obtained with a standard set of conditions according to literature procedure.[104] Cyclic voltammograms (CVs) were collected with a VersaSTAT 4 Potentiostat. Samples were prepared with 0.05 mmol of substrate in 10 mL of 0.1 M tetra-*n*-butylammonium hexafluorophosphate in dry, degassed acetonitrile. Measurements employed a glassy carbon working electrode, platinum wire counter electrode, 3 M NaCl silver-silver chloride reference electrode, and a scan rate of 100 mV/s. Reductions were measured by scanning potentials in the negative direction and oxidations in the positive direction; the glassy carbon electrode was polished between each scan. Data was analyzed using Microsoft Excel by subtracting a background current prior to identifying the maximum current (C_p) and determining the potential ($E_{p/2}$) at half this value ($C_{p/2}$). The obtained value was referenced to Ag | AgCl and converted to SCE by subtracting 0.035 V.

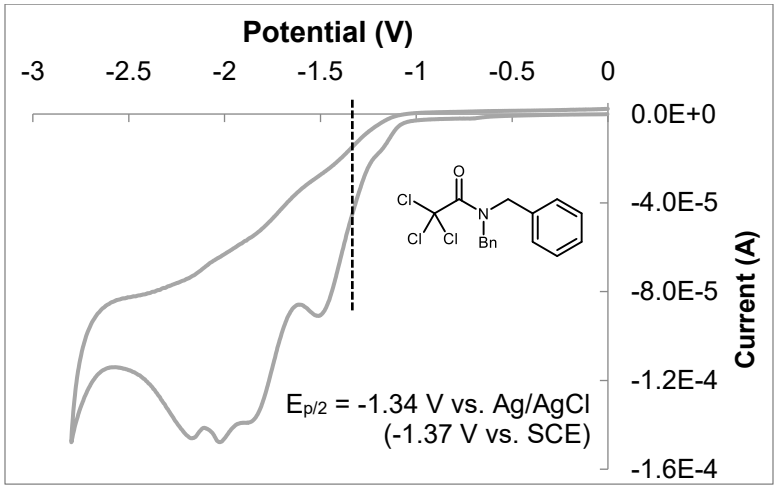


Figure 4.3: CV of *N*,*N*-dibenzyl-2,2,2-trichloroacetamide (S48)

[104] Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett.* **2016**, *27*, 714-723.

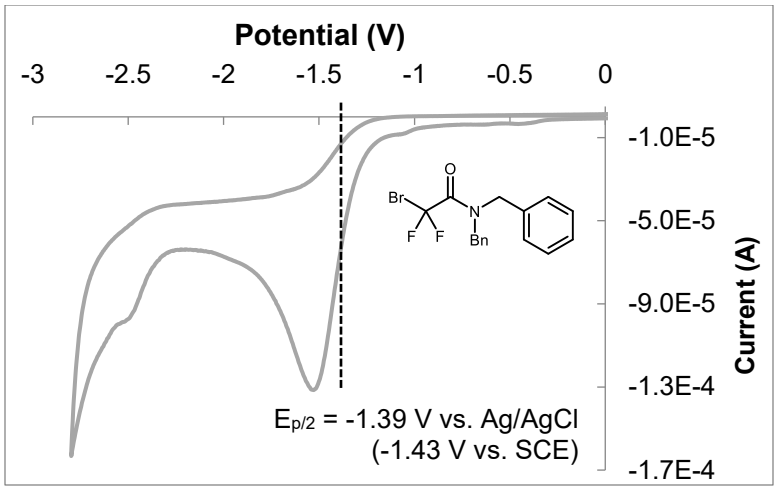


Figure 4.4: CV of *N*,*N*-dibenzyl-2-bromo-2,2-difluoroacetamide (S47)

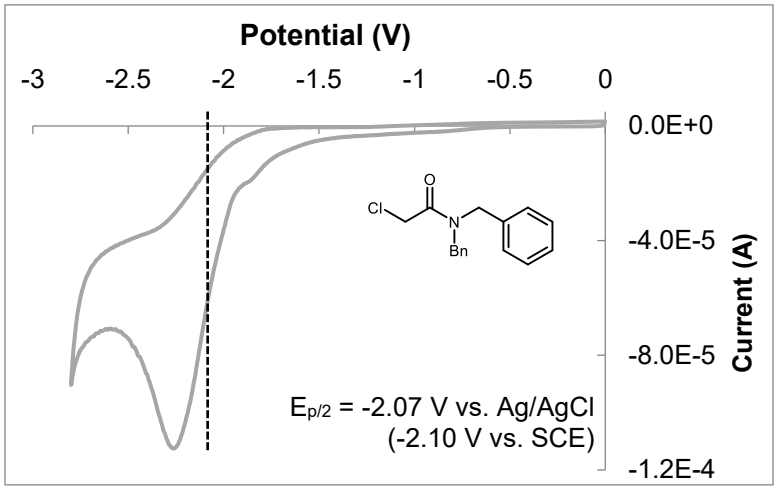


Figure 4.5: CV of *N*,*N*-dibenzyl-2-chloroacetamide (**1**)

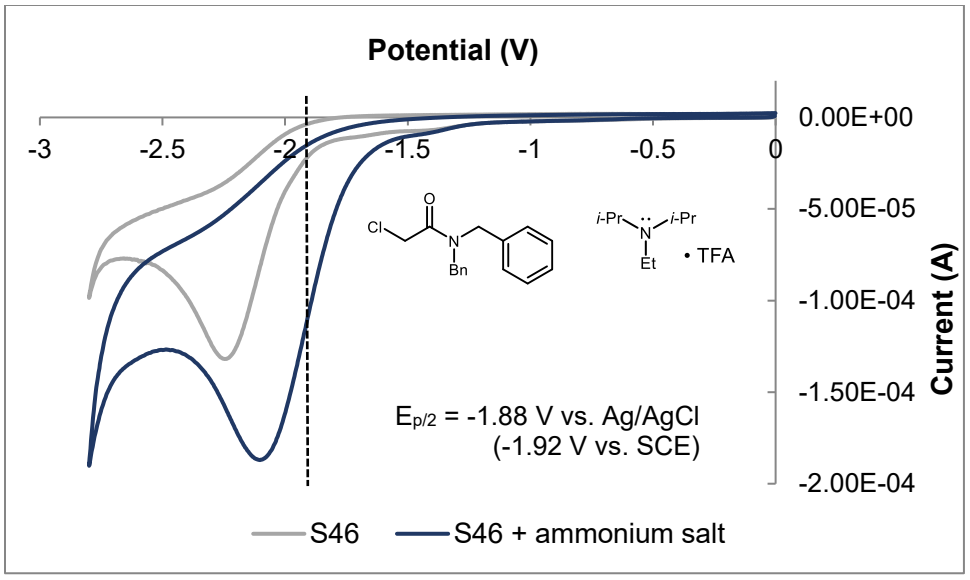


Figure 4.6: CV of *N*,*N*-dibenzyl-2-chloroacetamide (**1**) + *i*-Pr$_2$NEt • TFA (3 equiv)

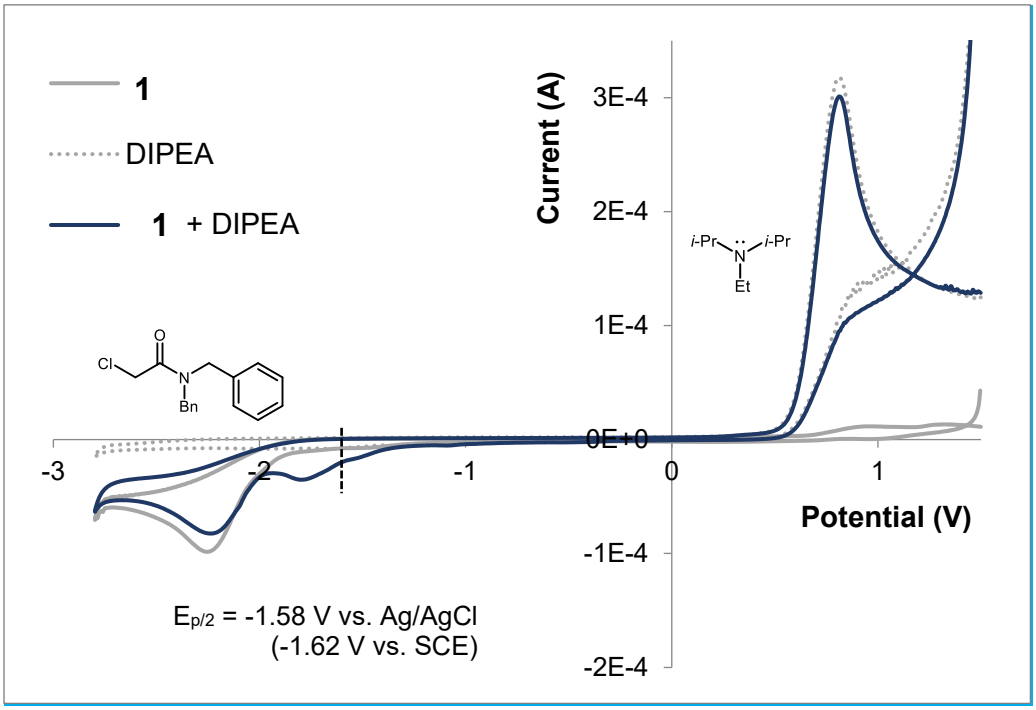


Figure 4.7: CV of *N*,*N*-dibenzyl-2-chloroacetamide (**1**) + *i*-Pr$_2$NEt (3 equiv)

4.4.6 Computational Details

All DFT calculations were carried out using the Gaussian 9 software package[105] at the (U)B3LYP[106] or R(B3LYP)[5] level of theory with the 6-311+G(d,p)[107] basis set. The CPCM formalism for the Self Consistent Reaction Field (SCRF) model of solvation was employed in calculations to account for solvation in MeCN, and the default parameters as implemented in Gaussian were used.

Reduction potentials were calculated using a modified procedure as described by Nicewicz and coworkers.[108] Geometry optimizations were carried out for the reduced and neutral forms of each molecule, and frequency calculations were performed on the minimized structures to ensure no imaginary frequencies existed. Geometry optimizations that did not converge to an energy minimum upon the initial calculation were sequentially optimized using a tight convergence criteria. Gibbs free energies (G_{298}) were obtained from the calculation and employed in the following equation:

$$E_{1/2}^{0,calc} = -\frac{(G_{298}[reduced] - G_{298}[oxidized])}{n_e\mathcal{F}} - E_{1/2}^{0,SHE} + E_{1/2}^{0,SCE}$$

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[105]M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

[106](a) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B,* **1988**, *37* (2), 785–789. (b) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys*. **1993**, *98* (7), 5648–5652.

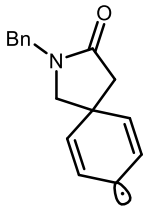
[107] McLean, A. D.; Chandler, G. S. Contracted Gaussian Basis Sets for Molecular Calculations. I. Second Row Atoms, Z=11–18. *J. Chem. Phys*. **1980**, *72*, 5639– 5648.

[7] Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to SingleElectron Redox Chemistry. *Synlett* **2016**, *27* (05), 714–723.

Where n_e is the number of electrons transferred (n_e= 1 for all calculations here), $\mathcal{F}$ is the Faraday constant (value 23.061 kcal mol^{-1} V^{-1}), $E_{1/2}^{0,SHE}$ is the absolute value for the standard hydrogen electrode (SHE, value = 4.281 V) and $E_{1/2}^{0,SCE}$ is the potential of the saturated calomel electrode (SCE) relative to the SHE in MeCN (value = –0.141V)[109], and G_{298}[oxidized] and G_{298}[reduced] are the Gibbs free energies in MeCN obtained from DFT calculations.

Steric effects of the arene substituents on cyclization were observed from the minimized geometries of the relevant compounds. The structural minima were visualized using GaussView 5[9] allowing the interatomic distances between the two carbons which form the spirocyclic center to be obtained.

Molecular coordinates of optimized structures:



Charge: 0

Multiplicity: 2

Number of imaginary frequencies: 0

Solvation: MeCN

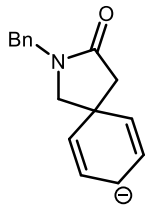
G_{298} = -749.250858 Hartree

C	-0.67021525	1.67383904	-3.52647222
C	1.62256455	1.29631778	-3.73626915
C	0.07672390	2.37458623	-2.38022356
H	-1.57793076	2.15145972	-3.83115408

[8] Isse, A. A.; Gennaro, A. Absolute Potential of the Standard Hydrogen Electrode and the Problem of Interconversion of Potentials in Different Solvents. *J. Phys. Chem. B* **2010**, *114* (23), 7894–7899.
[9] Roy Dennington TK and JM. GaussView, Version 5, Semichem Inc, Shawnee Mission KS, **2009**.

H	-0.90383945	0.67001427	-3.23897339
H	1.48810123	0.31261662	-3.33733101
H	2.55355683	1.31829279	-4.26321362
O	-0.45691413	2.90442774	-1.37122951
N	1.53966646	2.32415369	-2.66562245
C	1.99332151	3.62922748	-3.16749843
H	1.41849308	3.89967664	-4.02850339
H	3.02787126	3.56890337	-3.43389629
C	1.80692420	4.69402465	-2.07065614
C	2.83996131	4.94875764	-1.15858849
C	0.60426554	5.40825710	-1.98459730
C	2.67034073	5.91772490	-0.16046362
H	3.75821850	4.40342648	-1.22429734
C	0.43464415	6.37722284	-0.98647109
H	-0.18448079	5.21376361	-2.68098190
C	1.46768203	6.63195728	-0.07440472
H	3.45908884	6.11222174	0.53591803
H	-0.48361187	6.92255620	-0.92076418
H	1.33817319	7.37178573	0.68768538
C	0.41715892	1.68130187	-4.58869847
C	0.60945176	3.15768691	-5.12274815
C	0.13949927	0.65242991	-5.75754249
C	0.94414182	3.32317391	-6.39869152

H	0.51126987	3.99542129	-4.46437028
C	-0.31675236	1.12588223	-6.91301264
H	0.27797525	-0.39785205	-5.60710243
C	0.27516439	2.42711245	-7.42686688
H	1.69198010	4.03440692	-6.68115480
H	-1.10493686	0.62654268	-7.43677329
H	0.22350066	2.69870937	-8.46053316



Charge: -1

Multiplicity: 1

Number of imaginary frequencies: 0

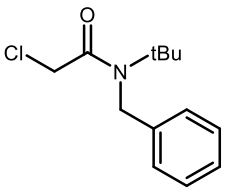
Solvation: MeCN

G_{298} = -749.361362 Hartree

C	-0.67021525	1.67383904	-3.52647222
C	1.62256455	1.29631778	-3.73626915
C	0.07672390	2.37458623	-2.38022356
H	-1.57793076	2.15145972	-3.83115408
H	-0.90383945	0.67001427	-3.23897339
H	1.48810123	0.31261662	-3.33733101
H	2.55355683	1.31829279	-4.26321362
O	-0.45691413	2.90442774	-1.37122951
N	1.53966646	2.32415369	-2.66562245
C	1.99332151	3.62922748	-3.16749843

H	1.41849308	3.89967664	-4.02850339
H	3.02787126	3.56890337	-3.43389629
C	1.80692420	4.69402465	-2.07065614
C	2.83996131	4.94875764	-1.15858849
C	0.60426554	5.40825710	-1.98459730
C	2.67034073	5.91772490	-0.16046362
H	3.75821850	4.40342648	-1.22429734
C	0.43464415	6.37722284	-0.98647109
H	-0.18448079	5.21376361	-2.68098190
C	1.46768203	6.63195728	-0.07440472
H	3.45908884	6.11222174	0.53591803
H	-0.48361187	6.92255620	-0.92076418
H	1.33817319	7.37178573	0.68768538
C	0.41715892	1.68130187	-4.58869847
C	0.60945176	3.15768691	-5.12274815
C	0.13949927	0.65242991	-5.75754249
C	0.94414182	3.32317391	-6.39869152
H	0.51126987	3.99542129	-4.46437028
C	-0.31675236	1.12588223	-6.91301264
H	0.27797525	-0.39785205	-5.60710243
C	0.27516439	2.42711245	-7.42686688
H	1.69198010	4.03440692	-6.68115480
H	-1.10493686	0.62654268	-7.43677329

H	0.22350066	2.69870937	-8.46053316



Charge: 0

Multiplicity: 1

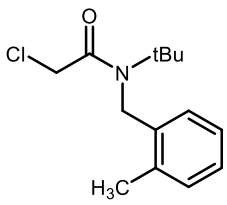
Solvation: MeCN

Number of imaginary frequencies: 0

Interatomic Distance: 3.49 Å

C	-1.42928837	1.11221039	0.41076646
O	-1.33747937	1.09112177	1.66563575
N	-0.21375667	1.09002359	-0.41560538
C	-2.81505622	1.16126145	-0.25918986
H	-3.16450854	0.16432840	-0.42921214
H	-2.74146226	1.67760837	-1.19346486
Cl	-3.94504256	2.00781660	0.79155999
C	0.84595957	0.35633052	0.29121565
C	0.38046073	-1.08711028	0.55840376
H	1.15181881	-1.62115898	1.07289253
H	0.17044641	-1.57212133	-0.37195008
H	-0.50431405	-1.07096071	1.15991251
C	1.14822317	1.05438379	1.63022959
H	1.91958125	0.52033510	2.14471837
H	0.26344839	1.07053337	2.23173835
H	1.47165419	2.05729396	1.44458591

C	2.11937374	0.33308720	-0.57450723
H	2.89073182	-0.20096150	-0.06001846
H	2.44280476	1.33599736	-0.76015092
H	1.90935943	-0.15192384	-1.50486107
C	-0.50228101	0.42370000	-1.69375505
H	0.38249377	0.40755043	-2.29526381
H	-0.82571202	-0.57921016	-1.50811136
C	-1.61245993	1.19233084	-2.43423422
C	-2.48811378	0.50857202	-3.28841580
C	-1.74706889	2.57554372	-2.25388869
C	-3.49837493	1.20802651	-3.96225391
H	-2.38533832	-0.54754210	-3.42611180
C	-2.75733089	3.27499799	-2.92772574
H	-1.07848790	3.09760871	-1.60170192
C	-3.63298329	2.59123954	-3.78190911
H	-4.16695566	0.68596158	-4.61444100
H	-2.86010661	4.33111204	-2.79002943
H	-4.40433884	3.12528890	-4.29640101



Charge: 0

Multiplicity: 1

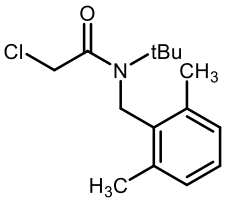
Number of imaginary frequencies: 0

Solvation: MeCN

Interatomic Distance: 3.42 Å

C	-0.43282831	-0.79332914	0.01121010
O	-1.15350877	-1.79569780	-0.23260806
N	1.03169377	-0.91818165	-0.01085634
C	-1.08513793	0.56414367	0.33270619
H	-1.23097314	1.11340606	-0.57390449
H	-0.44744177	1.12003940	0.98785774
Cl	-2.63967693	0.29771101	1.11374532
C	1.42013417	-1.96127084	-0.97105371
C	2.95439540	-2.09206871	-0.99417094
H	3.23713774	-2.85132411	-1.69309011
H	3.30449213	-2.35723106	-0.01845520
H	3.38756900	-1.15853001	-1.28702948
C	0.91625664	-1.57963532	-2.37535488
H	1.19899898	-2.33889072	-3.07427405
H	1.34943024	-0.64609662	-2.66821341
H	-0.14975603	-1.48875628	-2.35929291
C	0.79668805	-3.30486860	-0.54955638
H	1.07943039	-4.06412400	-1.24847556
H	-0.26932462	-3.21398956	-0.53349441
H	1.14678478	-3.57003094	0.42615936
C	1.62680143	0.36434348	-0.41319471
H	1.27670470	0.62950582	-1.38891045

H	2.69281410	0.27346444	-0.42925668
C	1.21986386	1.45710358	0.59272635
C	1.09241111	2.78690766	0.16928938
C	0.97700342	1.12171120	1.93155147
C	0.72209430	3.78131876	1.08467673
C	0.60668597	2.11612218	2.84693868
H	1.07431902	0.10637671	2.25485557
C	0.47923215	3.44592608	2.42350147
H	0.62478130	4.79665368	0.76137321
H	0.42125398	1.86004221	3.86916078
H	0.19648575	4.20518080	3.12241974
C	1.35929469	3.15547139	-1.30194613
H	1.72782650	4.15848454	-1.35716320
H	0.44934096	3.07862445	-1.85960082
H	2.08614872	2.48538517	-1.71129646



Charge: 0

Multiplicity: 1

Number of imaginary frequencies: 0

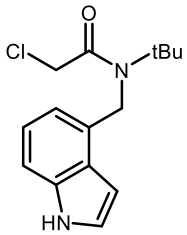
Solvation: MeCN

Interatomic Distance: 2.91 Å

C	-0.46509528	0.55862783	0.17643923
O	-1.11792889	-0.50351715	0.00548049

N	0.99291720	0.56343212	-0.01084802
C	-1.19361469	1.85342254	0.58186015
H	-1.48812414	2.38725389	-0.29745111
H	-0.53748551	2.46370861	1.16662114
Cl	-2.62102207	1.45127518	1.52969224
C	1.36083931	-0.44177984	-1.01836092
C	0.67065848	-0.10673774	-2.35365012
H	0.93846576	-0.83842258	-3.08700986
H	0.98458438	0.86123309	-2.68438097
H	-0.39061595	-0.11023476	-2.21732540
C	0.90902068	-1.83493418	-0.54235572
H	1.17682788	-2.56661908	-1.27571541
H	-0.15225374	-1.83843116	-0.40603096
H	1.38856193	-2.06772318	0.38541010
C	2.88828097	-0.43674675	-1.21456659
H	3.15608824	-1.16843160	-1.94792629
H	3.36782219	-0.66953570	-0.28680076
H	3.20220688	0.53122407	-1.54529744
C	1.42419860	1.89326126	-0.46521659
H	0.94465737	2.12605024	-1.39298246
H	2.48547299	1.89675826	-0.60154133
C	1.03875641	2.94634046	0.59027312
C	0.74834651	4.25951975	0.19638959

C	0.97841390	2.59146326	1.94465228
C	0.39759530	5.21782213	1.15688535
C	0.62766535	3.54976632	2.90514834
C	0.33725629	4.86294581	2.51126490
H	0.17586062	6.22046358	0.85614650
H	0.58159357	3.27880998	3.93924700
H	0.06944982	5.59463092	3.24462471
C	0.81465566	4.64949437	-1.29193930
H	1.08524402	5.68107847	-1.37863557
H	-0.14199254	4.49242142	-1.74476641
H	1.54678741	4.04593963	-1.78651457
C	1.29754143	1.14840803	2.37749085
H	1.70949193	1.15507812	3.36498888
H	2.00541810	0.72069865	1.69861295
H	0.39944568	0.56680505	2.3696092



Charge: 0

Multiplicity: 1

Number of imaginary frequencies: 0

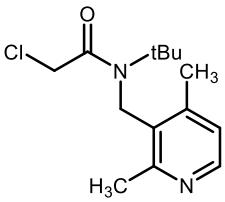
Solvation: MeCN

Interatomic Distance: 3.41 Å

C	-0.50779625	1.50532687	0.33496392
O	-1.15791776	0.45474692	0.09581049

N	0.95129954	1.44454317	0.50302599
C	-1.24076953	2.85467982	0.45156918
H	-1.29019019	3.31812571	-0.51158995
H	-0.70944740	3.49197138	1.12718464
Cl	-2.87111364	2.58623869	1.05780137
C	1.49214433	0.34225853	-0.30527808
C	1.15581445	0.58071586	-1.78906391
H	1.54949055	-0.22162741	-2.37742131
H	1.59051752	1.50449655	-2.10931771
H	0.09375155	0.62495983	-1.91139483
C	0.86649699	-0.98729501	0.15564797
H	1.26017309	-1.78963827	-0.43270941
H	-0.19556591	-0.94305104	0.03331709
H	1.10018077	-1.15297640	1.18659006
C	3.02072084	0.27858039	-0.12921309
H	3.41439695	-0.52376286	-0.71757049
H	3.25440467	0.11289902	0.90172898
H	3.45542381	1.20236111	-0.44946690
C	1.54850833	2.71366245	0.06305114
H	1.31482454	2.87934380	-0.96789094
H	2.61057125	2.66941854	0.18538202
C	0.98190907	3.86843687	0.90984587
C	0.85691106	5.15148359	0.38937984

C	0.57797504	3.66702136	2.24537631
C	0.28995697	6.17897067	1.08982434
C	0.07149149	4.75199263	3.00918067
H	0.65659470	2.69506976	2.68586357
C	-0.07451198	6.02921740	2.42534016
H	-0.20387837	4.59989838	4.03189215
H	-0.45919004	6.85348853	2.98881146
C	1.30281089	5.70566587	-0.95218599
H	1.77466013	5.16100102	-1.74313384
C	1.00986056	7.03255115	-0.94292059
H	1.35306981	7.73623853	-1.67225692
N	0.14972544	7.37497755	0.22779087
H	-0.80086996	7.48509673	-0.06245413



Charge: 0

Multiplicity: 1

Number of imaginary frequencies: 0

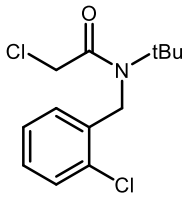
Solvation: MeCN

Interatomic Distance: 2.95 Å

C	2.18821795	1.15575564	-1.92603099
O	2.78368334	0.66024971	-2.91772923
N	2.95555049	1.83421108	-0.87161220
C	0.65562940	1.05138115	-1.81704346

H	0.20600082	1.90176989	-2.28562977
H	0.37263454	1.02133901	-0.78558266
Cl	0.10916246	-0.41725914	-2.61833592
C	2.12875659	2.88700819	-0.26421602
H	2.68729115	3.38084986	0.50328614
H	1.84790004	3.59695636	-1.01387807
C	4.16382720	2.43521874	-1.45449914
C	5.02999225	1.33228845	-2.09081892
H	5.90948618	1.76975660	-2.51509717
H	4.47145770	0.83844672	-2.85832104
H	5.31084886	0.62234032	-1.34115685
C	3.75960369	3.45701324	-2.53345204
H	4.63909764	3.89448139	-2.95773029
H	3.15778772	4.22333495	-2.09133377
H	3.20106914	2.96317151	-3.30095416
C	4.96769935	3.14598163	-0.34986994
H	5.84719328	3.58344980	-0.77414818
H	5.24855595	2.43603351	0.39979215
H	4.36588336	3.91230333	0.09224833
C	0.86294285	2.25738114	0.34642737
C	-0.32966103	2.99049776	0.41391645
C	0.89268568	0.95148609	0.83775696
C	-0.27219432	0.41145146	1.38462852

C	-1.43705684	1.18968051	1.42674257
H	-0.27597075	-0.58743090	1.76819045
H	-2.33361790	0.78175801	1.84468694
N	-1.43592273	2.44433269	0.94602106
C	-0.37241114	4.43225234	-0.12563537
H	-1.09216047	4.99884195	0.42739004
H	-0.64768225	4.41814592	-1.15952455
H	0.59290631	4.88150770	-0.01965502
C	2.18814983	0.12097726	0.77752642
H	2.20814867	-0.56851182	1.59551472
H	3.03358497	0.77379063	0.84056721
H	2.22281108	-0.41938888	-0.14535116



Charge: 0

Multiplicity: 1

Number of imaginary frequencies: 0

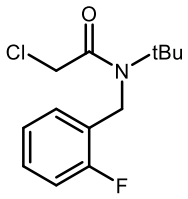
Solvation: MeCN

Interatomic Distance: 3.42 Å

C	-0.99633452	0.18519537	-0.16020934
O	-1.62020267	-0.87186988	-0.43764791
N	0.46878452	0.16454722	-0.04231174
C	-1.76774614	1.50043808	0.05580161
H	-1.86432111	2.01469876	-0.87753071

H	-1.23465676	2.11684354	0.74917022
Cl	-3.36736441	1.14378531	0.69737794
C	1.01711452	-0.87224924	-0.92847612
C	0.62362710	-0.56330213	-2.38495109
H	1.02275166	-1.31797710	-3.02998230
H	1.01755263	0.39100131	-2.66606963
H	-0.44282009	-0.54827252	-2.47076771
C	0.45015628	-2.24573269	-0.52387561
H	0.84928084	-3.00040766	-1.16890682
H	-0.61629092	-2.23070308	-0.60969223
H	0.72355338	-2.46039075	0.48809077
C	2.55200114	-0.89388064	-0.80496435
H	2.95112570	-1.64855561	-1.44999557
H	2.82539824	-1.10853870	0.20700202
H	2.94592667	0.06042280	-1.08608289
C	1.00997194	1.47559960	-0.42852132
H	0.73657483	1.69025766	-1.44048770
H	2.07641913	1.46056999	-0.34270470
C	0.43553098	2.56176732	0.49984136
C	0.25787743	3.86791526	0.02409065
C	0.09044326	2.24403201	1.82040211
C	-0.26486135	4.85632852	0.86890149
C	-0.43229680	3.23244494	2.66521254

H	0.22608547	1.24675902	2.18364826
C	-0.60994818	4.53859343	2.18946253
H	-0.40050316	5.85360161	0.50565546
H	-0.69577712	2.98984744	3.67349056
H	-1.00906898	5.29326936	2.83449495
Cl	0.69126501	4.26695399	-1.63438555



Charge: 0

Multiplicity: 1

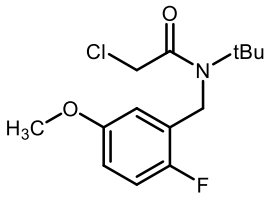
Number of imaginary frequencies: 0

Solvation: MeCN

Interatomic Distance: 3.43 Å

C	-0.61568894	0.26849260	0.52217769
O	-1.18280256	-0.82303094	0.78775079
N	0.85162121	0.35651459	0.53454962
C	1.42378791	-0.94638530	0.16579882
C	0.94481915	-1.33665208	-1.24483252
H	1.36129423	-2.28502138	-1.51324297
H	1.26359618	-0.59537172	-1.94753064
H	-0.12322293	-1.40072250	-1.25383794
C	0.96498733	-2.01327478	1.17715873
H	1.38146241	-2.96164409	0.90874829
H	-0.10305474	-2.07734521	1.16815331

H	1.29777731	-1.74211540	2.15727271
C	2.96096997	-0.85417179	0.17875989
H	3.37744504	-1.80254109	-0.08965056
H	3.29375994	-0.58301240	1.15887387
H	3.27974699	-0.11289143	-0.52393824
C	1.28956721	1.37490909	-0.43083939
H	0.95677723	1.10374971	-1.41095337
H	2.35760929	1.43897952	-0.42183398
C	-1.45885082	1.51205963	0.18421457
H	-1.63090453	1.55026933	-0.87117045
H	-0.93494532	2.39269024	0.49229369
Cl	-3.00121129	1.42191558	1.02718446
C	0.69015448	2.73985183	-0.04452903
C	0.40768852	3.68743915	-1.03761171
C	0.42715486	3.03436241	1.30009608
C	-0.13777457	4.92953807	-0.68606902
C	-0.11830950	4.27646080	1.65163863
H	0.64282365	2.31085836	2.05833672
C	-0.40077329	5.22404901	0.65855618
H	-0.35344298	5.65304227	-1.44430962
H	-0.31911375	4.50132690	2.67828993
H	-0.81724459	6.17241986	0.92696703
F	0.66103916	3.40372938	-2.33291948



Charge: 0

Multiplicity: 1

Number of imaginary frequencies: 0

Solvation: MeCN

Interatomic Distance: 3.43 Å

C	-0.53706787	0.37443739	0.68435628
O	-1.11307434	-0.69793748	1.00341623
N	0.92925254	0.42180201	0.59183032
C	1.43849310	-0.90045013	0.20039280
C	0.85021447	-1.29270053	-1.16769633
H	1.22088617	-2.25515616	-1.45262024
H	1.13812537	-0.56830622	-1.90067668
H	-0.21710719	-1.32717681	-1.10034750
C	1.02411667	-1.94303633	1.25533649
H	1.39478838	-2.90549196	0.97041258
H	-0.04320499	-1.97751261	1.32268532
H	1.43285572	-1.67049871	2.20589192
C	2.97463829	-0.85083005	0.10346084
H	3.34531000	-1.81328569	-0.18146307
H	3.38337735	-0.57829243	1.05401628
H	3.26254919	-0.12643574	-0.62951951
C	1.32479368	1.41699793	-0.41516138

H	0.91605462	1.14446031	-1.36571682
H	2.39211534	1.45147421	-0.48251022
C	-1.36831004	1.63716418	0.39083027
H	-1.61379233	1.66856837	-0.65015591
H	-0.80032440	2.50622755	0.64971473
Cl	-2.84877388	1.59913760	1.34181965
C	0.79130357	2.80221445	-0.00508398
C	0.46464029	3.74634028	-0.98785532
C	0.63249084	3.11863567	1.35085779
C	-0.02083759	5.00688661	-0.61468493
C	0.14701590	4.37918311	1.72402826
C	-0.17964861	5.32330846	0.74125689
H	-0.27025496	5.72774660	-1.36505274
H	-0.55031993	6.28576425	1.02618081
F	0.61762651	3.44152402	-2.29406443
H	0.88190600	2.39777484	2.10122553
O	-0.01503554	4.70206279	3.10764239
C	0.17093435	6.10760855	3.29407287
H	0.04967908	6.34920383	4.32936456
H	-0.55284110	6.64295259	2.71575130
H	1.15511737	6.38237129	2.97659970

Ratio of cyclized product to hydrodehalogenation

A screw-top test tube was charged with 3DPAFIPN (5 mol%) and the substrate (1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA (3 equiv) was added via syringe, followed by degassed solvent. The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs. The reaction was then extracted with ethyl acetate (3x) and concentrated under reduced pressure. $CDCl_3$ and an internal standard of dibromomethane (1 equiv) were added. The sample was analyzed by ^1H NMR (d1 = 5 s), and the integral values were used to calculate the ratio of dearomatized product to hydrodehalogenation.

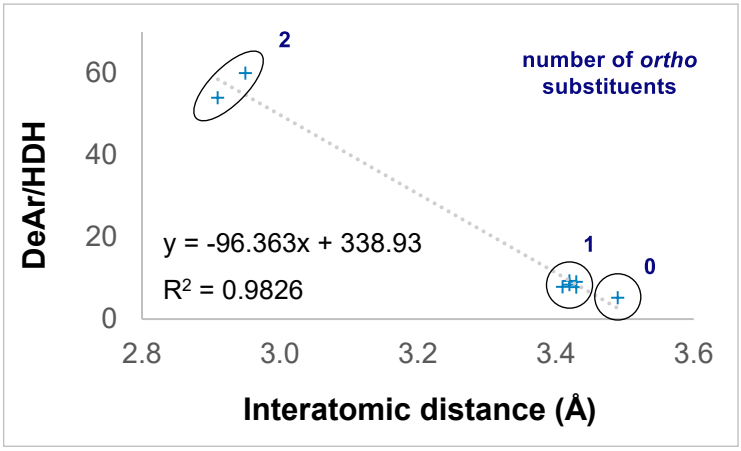
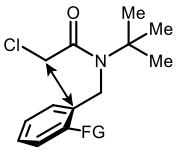
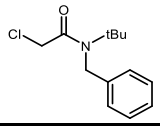
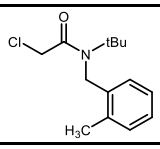
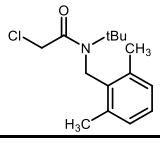
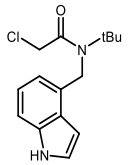
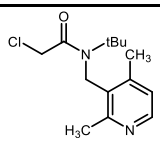
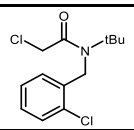
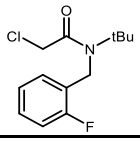
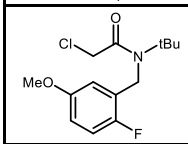
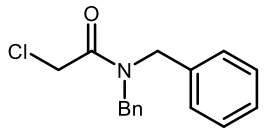


Figure 4.8: Ratio of dearomatized product to hydrodehalogenation vs computationally-determined interatomic distance

Table 4.3: Computationally-determined interatomic distance and DeAr/HDH ratio for a range of substrates

Substrate	 Interatomic distance (Å)	DeAr/HDH (^{1}H NMR)
	3.49	5.2
	3.42	9.3
	2.91	54
	3.41	7.9
	2.95	60
	3.42	8.4
	3.43	9.1
	3.43	7.8

4.4.7 Preparation of Starting Materials

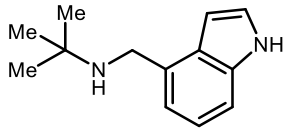


***N*,*N*-dibenzyl-2-chloroacetamide (1):**

Prepared according to General Acylation Procedure. Dibenzylamine (0.22 mL, 2.0 mmol, 1.0 equiv), Et_3N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (20 mL, 0.1 M) for 20 min. Purification on silica gel (10-30% EtOAc/hexanes) afforded the title compound as a colorless oil. (307 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 6H), 7.23 (d, J = 6.4 Hz, 2H), 7.18 – 7.15 (d, J = 6.4 Hz, 2H), 4.62 (s, 2H), 4.52 (s, 2H), 4.15 (s, 2H).

^{1}H NMR spectrum is consistent with reported values.[110]



***N*-((1*H*-indol-4-yl)methyl)-2-methylpropan-2-amine (S1):**

Prepared according to General Reductive Amination Procedure. Indole-4-carboxaldehyde (435 mg, 3.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.38 mL, 3.6 mmol, 1.2 equiv) were stirred in MeOH (15 mL, 0.2 M) for 16 hours. After $NaBH_4$ (170 mg, 4.5 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a light-brown amorphous solid (607 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.29 (d, J = 7.8 Hz, 1fH), 7.24 – 7.17 (m, 1H), 7.18 – 7.08 (m, 2H), 6.65 (ddd, J = 3.2, 2.1, 1.0 Hz, 1H), 4.04 (s, 2H), 1.25 (s, 9H) ppm.

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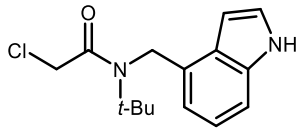
[110] Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp^3)-H Alkylation. *Angew. Chem. Int. Ed.* **2014**, *126*, 9210-9213.

^{13}C NMR (151 MHz, $CDCl_3$) δ 136.1, 133.3, 127.1, 124.0, 122.4, 119.40 110.0, 100.9, 51.0, 45.3, 29.3 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{13}H_{18}N_2$, 202.2, found 202.2.



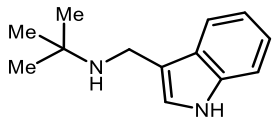
***N*-((1*H*-indol-4-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (S2):**

Prepared according to General Acylation Procedure. *N*-((1*H*-indol-4-yl)methyl)-2-methylpropan-2-amine (**S1**) (474 mg, 2.3 mmol, 1.0 equiv), Et_3N (0.39 mL, 2.8 mmol, 1.2 equiv), and chloroacetyl chloride (0.19 mL, 2.3 mmol, 1.0 equiv) were stirred in CH_2Cl_2 (23 mL, 0.1 M) for 30 minutes. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as a light-brown amorphous solid (535 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 7.36 (dt, J = 8.2, 0.9 Hz, 1H), 7.29 (dd, J = 3.3, 2.4 Hz, 1H), 7.21 (dd, J = 8.2, 7.3 Hz, 1H), 6.98 (dq, J = 7.2, 1.0 Hz, 1H), 6.56 (ddd, J = 3.1, 2.0, 1.0 Hz, 1H), 4.92 (s, 2H), 4.01 (s, 2H), 1.51 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 135.9, 130.4, 124.7, 124.7, 122.6, 116.1, 110.6, 99.9, 58.8, 46.9, 44.5, 28.5 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{15}H_{19}ClN_2O$, 278.1, found 278.1.



***N*-((1*H*-indol-3-yl)methyl)-2-methylpropan-2-amine (S3):**

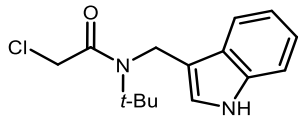
Prepared according to General Reductive Amination Procedure. Indole-3-carbaldehyde (871 mg, 6.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.76 mL, 7.2 mmol, 1.2 equiv) were stirred in MeOH (30 mL, 0.2 M) for 16 hours. After $NaBH_4$ (340 mg, 9.0 mmol, 1.5 equiv) was added, the reaction

was stirred for an additional 4 hours. The title compound was obtained as an off-white amorphous solid (627 mg, 52%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 3.96 (s, 2H), 1.25 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 136.6, 127.2, 122. 5, 122.2, 119.6, 118.9, 115.9, 111.4, 50.8, 38.1, 29.2 ppm.

LRMS (APCI) m/z: $[M+1]^+$ calc'd. for $C_{13}H_{18}N_2$, 203.2, found 203.2.

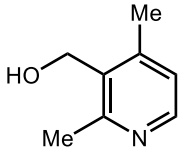


***N*-((1*H*-indol-3-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (S4):**

Prepared according to General Acylation Procedure. *N*-((1*H*-indol-3-yl)methyl)-2-methylpropan-2-amine (**S3**) (506 mg, 2.5 mmol, 1.0 equiv), Et_3N (0.35 mL, 2.5 mmol, 1.0 equiv), and chloroacetyl chloride (0.20 mL, 2.5 mmol, 1.0 equiv) were stirred in CH_2Cl_2 (25 mL, 0.1 M) for 18 hours. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as an off-white amorphous solid (534 mg, 77%).

^{1}H NMR (600 MHz, C_6D_6) δ 7.55 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.20 – 7.14 (m, 2H), 6.51 (s, 1H), 4.35 (s, 2H), 3.80 (s, 2H), 1.39 (s, 9H) ppm.

^{13}C NMR (151 MHz, C_6D_6) δ 13C NMR (151 MHz, C6D6) δ 167.4, 137.2, 125.7, 123.0, 121.8, 120.1, 118.6, 114.7, 111.9, 58.1, 44.3, 41.8, 28.4 ppm.



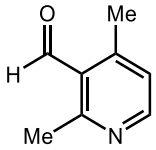
(2,4-dimethylpyridin-3-yl)methanol (S5):

Lithium aluminum hydride (4.0 M in ether, 7.5 mL, 10.0 mmol, 2.0 equiv) was added to cold, dry THF (12 mL). Ethyl 2,4-dimethylnicotinate (896.1 mg, 5.0 mmol, 1.0 equiv) was dissolved in dry THF (3 mL) and slowly added to the lithium aluminum hydride solution at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 hours, then cooled to 0°C, diluted with water, quenched with 1 M NaOH (aq), filtered through a plug of celite, and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a tan amorphous solid (519 mg, 76%).

^{1}H NMR (600 MHz, CDCl3) δ 8.26 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 5.1 Hz, 1H), 4.77 (s, 2H), 2.63 (s, 3H), 2.42 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 157.7, 148.4, 147.0, 132.2, 124.0, 59.0, 22.4, 19.1 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_8H_{11}NO$, 137.1, found 137.0.



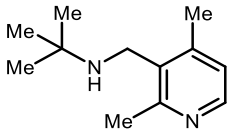
2,4-dimethylnicotinaldehyde (S6):

(2,4-dimethylpyridin-3-yl)methanol (**S5**) (478.8 mg, 3.5 mmol, 1.0 equiv), and manganese dioxide (1520 mg, 20.0 mmol, 5.0 equiv) were dissolved in CH_2Cl_2 (32 mL, 0.15 M) and refluxed at 40°C for 18 hours. The reaction mixture was cooled to room temperature and filtered through a plug of celite. Purification on silica gel (20-50% EtOAc/hexanes) afforded the title compound as a brown amorphous solid (263 mg, 56%).

^{1}H NMR (600 MHz, CDCl3) δ 10.64 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 7.06 (d, J = 5.2 Hz, 1H), 2.83 (s, 3H), 2.61 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 192.7, 160.9, 152.2, 150.1, 128.6, 125.3, 23.3, 20.4 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for C_8H_9NO, 135.1, found 135.0.



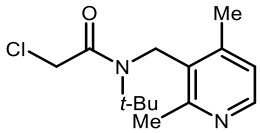
***N*-((2,4-dimethylpyridin-3-yl)methyl)-2-methylpropan-2-amine (S7):**

Prepared according to General Reductive Amination Procedure. 2,4-dimethylnicotinaldehyde (**S6**) (237 mg, 1.8 mmol, 1.0 equiv) and *tert*-butyl amine (0.28 mL, 2.6 mmol, 1.5 equiv) were stirred in MeOH (9 mL, 0.2 M) for 16 hours. After $NaBH_4$ (100 mg, 2.6 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1 hour. The title compound was obtained as a white amorphous solid (316 mg, 94%).

^{1}H NMR (600 MHz, CDCl3) δ 8.22 (d, J = 5.0 Hz, 1H), 6.92 (d, J = 5.0 Hz, 1H), 3.72 (s, 2H), 2.61 (s, 3H), 2.38 (s, 3H), 1.20 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 157.2, 147.3, 146.4, 132.7, 123.7, 50.7, 40.4, 28.9, 22.1, 18.9 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{12}H_{20}N_2$, 192.2, found 192.2.



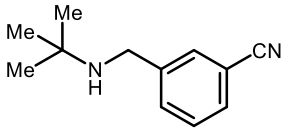
***N*-(*tert*-butyl)-2-chloro-*N*-((2,4-dimethylpyridin-3-yl)methyl)acetamide (S8):**

Prepared according to General Acylation Procedure. *N*-((2,4-dimethylpyridin-3-yl)methyl)-2-methylpropan-2-amine (**S7**) (289 mg, 1.5 mmol, 1.0 equiv), Et_3N (0.23 mL, 1.7 mmol, 1.1 equiv), and chloroacetyl chloride (0.13 mL, 1.7 mmol, 1.1 equiv) were stirred in THF (15 mL, 0.1 M) for 3 hours. The title compound was afforded as a white amorphous solid (148 mg, 37%).

^{1}H NMR (600 MHz, CDCl3) δ 8.28 (d, J = 5.0 Hz, 1H), 6.94 (d, J = 4.9 Hz, 1H), 4.69 (s, 2H), 4.15 (s, 2H), 2.59 (s, 3H), 2.38 (s, 3H), 1.38 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 168.6, 155.9, 147.6, 145.4, 130.9, 125.2, 59.4, 46.0, 44.9, 28.4, 23.9, 20.5 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{21}ClN_2O$, 268.1, found 268.1.



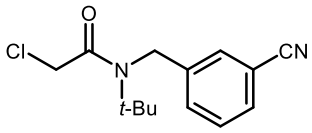
3-((*tert*-butylamino)methyl)benzonitrile (S9):

Prepared according to General Reductive Amination Procedure. 3-formylbenzonitrile (525 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 12 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a colorless oil (694 mg, 92%).

^{1}H NMR (600 MHz, CDCl3) δ 7.65 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 3.73 (s, 2H), 1.14 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 143.4, 132.7, 131.8, 130.5, 129.1, 119.1, 112.3, 50.9, 46.5, 29.2 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{12}H_{16}N_2$, 188.1, found 188.2.



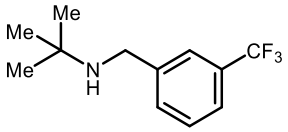
***N*-(*tert*-butyl)-2-chloro-*N*-(3-cyanobenzyl)acetamide (S10):**

Prepared according to General Acylation Procedure. 3-((*tert*-butylamino)methyl)benzonitrile (**S9**) (377 mg, 2.0 mmol, 1.0 equiv), Et_3N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (20 mL, 0.1 M) for 3 hours. The title compound was afforded as a tan soid (526 mg, 99%).

^{1}H NMR (600 MHz, CDCl3) δ 7.59 (d, J = 7.6 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 4.69 (s, 2H), 3.92 (s, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 167.7, 140.7, 131.4, 130.1, 130.0, 129.2, 118.5, 113.5, 59.1, 48.4, 44.0, 28.6 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{17}ClN_2O$, 264.1, found 264.1.



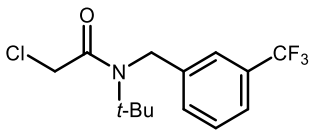
2-methyl-*N*-(3-(trifluoromethyl)benzyl)propan-2-amine (S11):

Prepared according to General Reductive Amination Procedure. 3-(trifluoromethyl)benzaldehyde (0.54 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 26 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a light-yellow oil (590 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.54 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.44 – 7.39 (m, 1H), 3.79 (s, 2H), 1.18 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) 142.5, 131.7, 130.7 (q, $^2J_{C\text{-}F}$ = 32.1 Hz), 128.8, 125.0 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 272.2 Hz), 123.7 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 50.9, 46.8, 29.2 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{12}H_{16}F_3N$, 231.1, found 231.2.



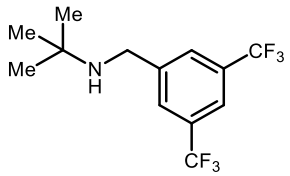
***N*-(*tert*-butyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (S12):**

Prepared according to General Acylation Procedure. 2-methyl-*N*-(3-(trifluoromethyl)benzyl)propan-2-amine (**S11**) (490 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.50 mL, 3.6

mmol, 1.2 equiv), and chloroacetyl chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 1 hour. The title compound afforded as a light-yellow amorphous solid (685 mg, 95%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.47 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 4.73 (s, 2H), 3.94 (s, 2H), 1.46 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[111]



***N*-(3,5-bis(trifluoromethyl)benzyl)-2-methylpropan-2-amine (S13):**

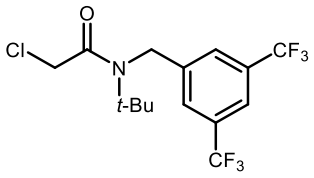
Prepared according to General Reductive Amination Procedure. 3,5-bis(trifluoromethyl)benzaldehyde (0.66 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 17 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a colorless oil (164 mg, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.74 (s, 1H), 3.86 (s, 2H), 1.18 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 131.6 (q, $^2J_{C\text{-}F}$ = 33.1 Hz), 128.6, 123.6 (q, $^1J_{C\text{-}F}$ = 272.5 Hz), 121.0, 51.4, 46.5, 29.2 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{13}H_{15}F_6N$, 299.1, found 299.1.

[111] Yanagita, H.; Urano, E.; Matsumoto, K.; Ichikawa, R.; Takaesu, Y.; Ogata, M.; Murakami, T.; Wu, H.; Chiba, J.; Komano, J.; Hoshino, T. Structural and biochemical study on the inhibitory activity of derivatives of 5-nitro-furan-2-carboxylic acid for RNase H function of HIV-1 reverse transcriptase. *Bioorg. Med. Chem.* **2011**, *19*, 816-825.



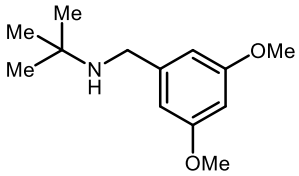
_N_-(3,5-bis(trifluoromethyl)benzyl)-_N_-(*tert*-butyl)-2-chloroacetamide (S14):

Prepared according to General Acylation Procedure. *N*-(3,5-bis(trifluoromethyl)benzyl)-2-methylpropan-2-amine (**S13**) (157 mg, 0.52 mmol, 1.0 equiv), Et_3N (84 µL, 0.62 mmol, 1.2 equiv), and chloroacetyl chloride (49 µL, 0.62 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (5 mL, 0.1 M) for 1 hour. The title compound afforded as a light-yellow amorphous solid (180 mg, 92%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.69 (s, 2H), 4.80 (s, 2H), 3.92 (s, 2H), 1.45 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ167.8, 142.0, 132.8 (q, $^2J_{C\text{-}F}$ = 33.5 Hz), 125.9 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.2 (q, $^1J_{C\text{-}F}$ = 272.9 Hz), 121.8 (hept, $^3J_{C\text{-}F}$ = 3.8 Hz), 59.2, 48.6, 43.8, 28.6 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{15}H_{16}ClF_6NO$, 375.1, found 375.1.

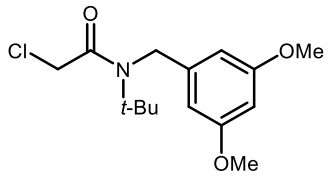


_N_-(3,5-dimethoxybenzyl)-2-methylpropan-2-amine (S15):

Prepared according to General Reductive Amination Procedure. 3,5-dimethoxybenzaldehyde (665 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 2 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1 hour. The title compound was obtained as a white amorphous solid (701 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, J = 2.1 Hz, 2H), 6.34 (t, J = 2.3 Hz, 1H), 3.79 (s, 6H), 3.67 (s, 2H), 1.17 (s, 9H) ppm.

^{1}H NMR is consistent with reported values.[112]

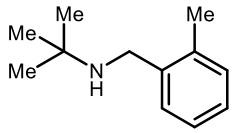


_N_-(_tert_-butyl)-2-chloro-_N_-(3,5-dimethoxybenzyl)acetamide (S16):

Prepared according to General Acylation Procedure. _N_-(3,5-dimethoxybenzyl)-2-methylpropan-2-amine (**S15**) (670 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.50 mL, 3.6 mmol, 1.2 equiv), and chloroacetyl chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 1 hour. The title compound was obtained as a light-brown amorphous solid (899 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (t, J = 2.2 Hz, 1H), 6.34 (d, J = 2.2 Hz, 2H), 4.59 (d, J = 0.8 Hz, 2H), 3.97 (s, 2H), 3.78 (s, 6H), 1.47 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[113]



2-methyl-_N_-(2-methylbenzyl)propan-2-amine (S17):

Prepared according to General Reductive Amination Procedure. 2-methylbenzaldehyde (0.46 mL, 4.0 mmol, 1.0 equiv) and _tert_-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a white amorphous solid (546 mg, 77%).

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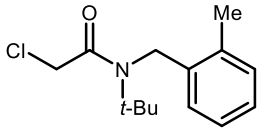
[112] Padwa, A.; Kuethe, J. T. Additive and Vinylogous Pummerer Reactions of Amido Sulfoxides and Their Use in the Preparation of Nitrogen Containing Heterocycles. *J. Org. Chem.* **1998**, *63*, 4256-4268.

[113] Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. Photochemical Synthesis of 1,2,3,4-Tetrahydroisoquinolin-3-ones and Oxindoles from N-Chloroacetyl Derivatives of Benzylamines and Anilines. Role of Intramolecular Exciplex Formation and cis Conformation of Amide Bonds. *Chem. Pharm. Bull.* **1981**, *29*, 128-136.

^{1}H NMR (400 MHz, cdcl3) δ 7.33 – 7.24 (m, 1H), 7.21 – 7.11 (m, 3H), 3.70 (s, 2H), 2.37 (s, 3H), 1.20 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[114]



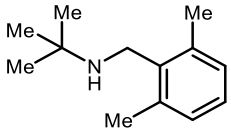
***N*-(*tert*-butyl)-2-chloro-*N*-(2-methylbenzyl)acetamide (S18):**

Prepared according to General Acylation Procedure. 2-methyl-*N*-(2-methylbenzyl)propan-2-amine (**S17**) (319 mg, 1.8 mmol, 1.0 equiv), Et_3N (0.28 mL, 2.0 mmol, 1.1 equiv), and chloroacetyl chloride (0.16 mL, 2.0 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (18 mL, 0.1 M) for 3.5 hours, which afforded the title compound as a white amorphous solid (401 mg, 88%).

^{1}H NMR (600 MHz, CDCl3) δ 7.25 – 7.15 (m, 4H), 4.54 (s, 2H), 3.89 (s, 2H), 2.29 (s, 3H), 1.46 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 167.8, 136.3, 134.3, 130.7, 127.3, 127.3, 126.7, 124.6, 58.6, 46.7, 44.1, 28.3, 19.1 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{20}ClNO$, 253.1, found 253.2.



***N*-(2,6-dimethylbenzyl)-2-methylpropan-2-amine (S19):**

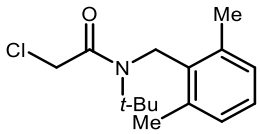
Prepared according to General Reductive Amination Procedure. 2,6-dimethylbenzaldehyde (537 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (1.20 mL, 8.0 mmol, 2.0 equiv) were stirred in MeOH (20 mL, 0.2 M) for 6 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the

[114] Franchi, P.; Casati, C.; Mezzina, E.; Lucarini, M. Kinetic control of the direction of inclusion of nitroxide cyclodextrines. *Org. Biomol. Chem.*, **2011**, *9*, 6396-6401.

reaction was stirred for an additional 1.5 hours. The title compound was obtained as a white amorphous solid (708 mg, 93%).

^{1}H NMR (600 MHz, CDCl3) δ 7.07 – 6.98 (m, 3H), 3.72 (s, 2H), 2.39 (s, 6H), 1.45 (s, 1H), 1.21 (s, 9H).

^{1}H NMR spectrum is consistent with reported values.[115]



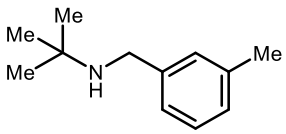
***N*-(*tert*-butyl)-2-chloro-*N*-(2,6-dimethylbenzyl)acetamide (S20):**

Prepared according to General Acylation Procedure. *N*-(2,6-dimethylbenzyl)-2-methylpropan-2-amine (**S19**) (574 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.46 mL, 3.3 mmol, 1.1 equiv), and chloroacetyl chloride (0.26 mL, 3.3 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 14 hours, which afforded the title compound as a yellow amorphous solid (654 mg, 81%).

^{1}H NMR (600 MHz, CDCl3) δ 7.08 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 2H), 4.65 (s, 2H), 4.11 (s, 2H), 2.36 (s, 6H), 1.39 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 168.6, 136.0, 134.8, 130.1, 127.4, 59.5, 46.8, 45.2, 28.3, 28.3, 21.1 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{15}H_{22}ClNO$, 267.1, found 267.1.



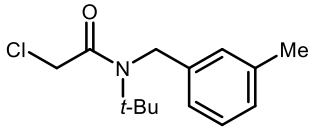
2-methyl-*N*-(3-methylbenzyl)propan-2-amine (S21):

[115] Franchi, P.; Casati, C.; Mezzina, E.; Lucarini, M. Kinetic control of the direction of inclusion of nitroxide cyclodextrines. *Org. Biomol. Chem.*, **2011**, *9*, 6396-6401.

Prepared according to General Reductive Amination Procedure. 3-methylbenzaldehyde (0.71 mL, 6.0 mmol, 1.0 equiv) and *tert*-butyl amine (1.10 mL, 7.2 mmol, 1.2 equiv) were stirred in MeOH (30 mL, 0.2 M) for 15 hours. After $NaBH_4$ (340 mg, 9.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a light-yellow oil (990 mg, 93%).

^{1}H NMR (400 MHz, CDCl3) δ 7.23 – 7.10 (m, 3H), 7.04 (d, J = 7.5 Hz, 1H), 3.69 (s, 2H), 2.34 (d, J = 0.7 Hz, 3H), 1.18 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[116]



***N*-(*tert*-butyl)-2-chloro-*N*-(3-methylbenzyl)acetamide (S22):**

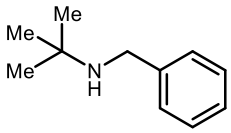
Prepared according to General Reductive Amination Procedure. 2-methyl-*N*-(3-methylbenzyl)propan-2-amine (**S21**) (443 mg, 2.5 mmol, 1.0 equiv) Et_3N (0.38 mL, 2.8 mmol, 1.1 equiv), and chloroacetyl chloride (0.22 mL, 2.8 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (25 mL, 0.1 M) for 1 hour, which afforded the title compound as a white amorphous solid (593 mg, 94%).

^{1}H NMR (600 MHz, CDCl3) δ 7.21 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.96 (d, J = 8.5 Hz, 1H), 4.59 (s, 2H), 3.95 (s, 2H), 2.31 (s, 3H), 1.42 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 167.5, 138.7, 138.4, 128.9, 128.1, 126.0, 122.3, 58.6, 48.6, 44.2, 28.3, 21.4 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{20}ClNO$, 253.1, found 253.2.

[116] Jankowski, K.; Harvey, R. A general one-pot, three-component mono N-alkylation of amines and amine derivatives in lithium perchlorate/diethyl ether solution. *Synthesis*, **2005**, *4*, 627-633.

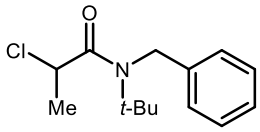


***N*-benzyl-2-methylpropan-2-amine (S23):**

Prepared according to General Reductive Amination Procedure. Benzaldehyde (1.02 mL, 10.0 mmol, 1.0 equiv) and *tert*-butyl amine (1.26 mL, 12.0 mmol, 1.2 equiv) were stirred in MeOH (50 mL, 0.2 M) for 4 hours. After $NaBH_4$ (567 mg, 15.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1 hour. The title compound was obtained as a colorless oil (1061 mg, 100%).

^{1}H NMR (400 MHz, cdcl3) δ 7.38 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 3.73 (s, 2H), 1.18 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[117]



***N*-benzyl-*N*-(*tert*-butyl)-2-chloropropanamide (S24):**

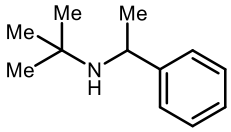
Prepared according to General Acylation Procedure. *N*-benzyl-2-methylpropan-2-amine (**S23**) (264 mg, 1.6 mmol, 1.0 equiv), Et_3N (0.26 mL, 1.9 mmol, 1.2 equiv), and 2-chloropropionyl chloride (0.18 mL, 1.9 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (16 mL, 0.1 M) for 1 hour. Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (276 mg, 68%).

[117] Niu, Z.; Zhang, W.; Lan, P. C.; Aguila, B.; Ma, S. Promoting frustrated lewis pairs for heterogeneous chemoselective hydrogenation via the tailored pore environment within metal-organic frameworks. *Angew. Chem. Int. Ed*. **2019**, *58*, 7420-7424.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, J = 7.7 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 7.2 Hz, 2H), 4.82 (d, J = 18.9 Hz, 1H), 4.62 (d, J = 18.9 Hz, 1H), 4.32 (q, J = 6.4 Hz, 1H), 1.60 (d, J = 6.4 Hz, 3H), 1.45 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 139.2, 129.1, 127.3, 125.3, 58.5, 52.1, 48.3, 28.4, 21.4 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{20}ClNO$, 253.1, found 253.2.

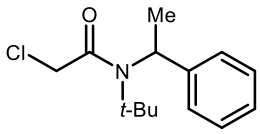


2-methyl-*N*-(1-phenylethyl)propan-2-amine (S25):

To a round bottomed flask charged with (1-bromoethyl)benzene (0.41 mL, 3.0 mmol, 1.0 equiv) was added MeCN (15 mL, 0.2 M), *tert*-butylamine (0.38 mL, 3.6 mmol, 1.2 equiv), and K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv). The resulting suspension was heated at reflux for 16 hours. After cooling to room temperature, the reaction was quenched with H_2O and extracted with EtOAc (3x). The combined organic layers were washed with 1 M HCl (aq), and the resulting aqueous layer was brought to pH 14 with 2 M NaOH (aq) extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound as a colorless oil (363 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.33 – 7.23 (m, 2H), 7.23 – 7.14 (m, 1H), 3.95 (q, J = 6.7 Hz, 1H), 1.31 (d, J = 6.7 Hz, 3H), 1.02 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[118]



[118] Cliffe, I. A.; Crossley, R.; Shepherd, R. G. Sterically Hindered Lithium Dialkylamides; A Novel Synthesis of Lithium Dialkylamides from *N*-*t*-Alkyl-*N*-benzylideneamines and the Isolation of Highly Hindered *s*-Alkyl-*t*-alkylamines. *Synthesis* **1985**, *12*, 1138-1140.

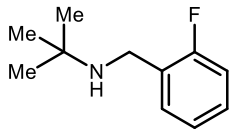
***N*-(*tert*-butyl)-2-chloro-*N*-(1-phenylethyl)acetamide (S26):**

Prepared according to General Acylation Procedure. 2-methyl-*N*-(1-phenylethyl)propan-2-amine (**S25**) (266 mg, 1.5 mmol, 1.0 equiv), Et_3N (0.25 mL, 1.8 mmol, 1.2 equiv), and chloroacetyl chloride (0.14 mL, 1.8 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (15 mL, 0.1 M) for 4 hours. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as a light-yellow oil (292 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 8.3, 7.2 Hz, 2H), 7.33 – 7.26 (m, 3H), 5.13 (q, J = 7.0 Hz, 1H), 3.76 (d, J = 12.7 Hz, 1H), 3.45 (d, J = 11.9 Hz, 1H), 1.79 (d, J = 7.1 Hz, 3H), 1.56 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 143.1, 129.3, 127.3, 125.6, 60.0, 53.0, 44.7, 29.4, 21.0 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{20}ClNO$, 253.1, found 253.1.



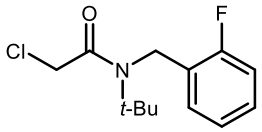
***N*-(2-fluorobenzyl)-2-methylpropan-2-amine (S27):**

Prepared according to General Reductive Amination Procedure. 2-fluorobenzaldehyde (0.42 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After $NaBH_4$ (227 mg, 4.8 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1.5 hours. The title compound was obtained as a colorless oil (508 mg, 70%).

^{1}H NMR (600 MHz, CDCl3) δ 7.39 (td, J = 7.6, 1.8 Hz, 1H), 7.21 (tdd, J = 7.5, 5.2, 1.8 Hz, 1H), 7.09 (td, J = 7.5, 1.2 Hz, 1H), 7.01 (ddd, J = 9.8, 8.2, 1.2 Hz, 1H), 3.78 (s, 2H), 1.19 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 161.3 (d, $^{1}J_{C\text{-}F}$ = 245.0 Hz), 130.6 (d, $^{3}J_{C\text{-}F}$ = 4.9 Hz), 128.6 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 128.5, 124.3 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz), 115.4 (d, $^{2}J_{C\text{-}F}$ = 21.9 Hz), 51.0, 40.9 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 29.3 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{11}H_{16}FN$, 181.1, found 181.2.



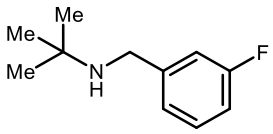
***N*-(*tert*-butyl)-2-chloro-*N*-(2-fluorobenzyl)acetamide (S28):**

Prepared according to General Acylation Procedure. *N*-(2-fluorobenzyl)-2-methylpropan-2-amine (**S27**) (399 mg, 2.0 mmol, 1.0 equiv), Et_3N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.16 mL, 2.0 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (20 mL, 0.1 M) for 3 hours. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as a white amorphous solid (473 mg, 92%).

^{1}H NMR (600 MHz, CDCl3) δ 7.29 (dtd, J = 7.4, 6.3, 5.2, 1.8 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.21 – 7.15 (t, J = 7.2 Hz, 1H), 7.08 (ddd, J = 10.3, 8.2, 1.2 Hz, 1H), 4.69 (s, 2H), 3.98 (s, 2H), 1.46 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 167.77, 159.79 (d, $^{1}J_{C\text{-}F}$ = 245.8 Hz), 129.21 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 127.06 (d, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 125.87 (d, $^{2}J_{C\text{-}F}$ = 13.9 Hz), 124.74 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 115.80 (d, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 58.89, 44.15, 42.99 (d, $^{3}J_{C\text{-}F}$ = 5.9 Hz), 28.40.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{13}H_{17}ClFNO$, 257.1, found 257.1.



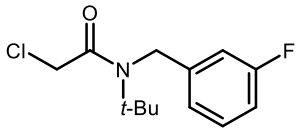
***N*-(3-fluorobenzyl)-2-methylpropan-2-amine (S29):**

Prepared according to General Reductive Amination Procedure. 3-Fluorobenzaldehyde (0.42 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 14 hours. The title compound was obtained as a white amorphous solid (633 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 1H), 7.19 – 7.10 (m, 2H), 6.96 – 6.88 (m, 1H), 3.75 (s, 2H), 1.20 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{C\text{-}F}$ = 245.6 Hz), 130.0 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 124.3, 122.4 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 114.1 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 64.7, 46.7, 28.9 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{11}H_{16}FN$, 181.1, found 181.0.



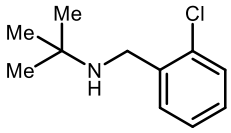
***N*-(*tert*-butyl)-2-chloro-*N*-(3-fluorobenzyl)acetamide (S30):**

Prepared according to General Acylation Procedure. *N*-(3-fluorobenzyl)-2-methylpropan-2-amine (**S29**) (544 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.50 mL, 3.6 mmol, 1.2 equiv), and chloroacetyl chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 2 hours. Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a white amorphous solid (601 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (td, J = 8.0, 5.8 Hz, 1H), 7.03 – 6.95 (m, 2H), 6.95 – 6.87 (m, 1H), 4.65 (s, 2H), 3.95 (s, 2H), 1.45 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.7, 163.5 (d, $^1J_{C\text{-}F}$ = 247.7 Hz), 141.7 (d, $^3J_{C\text{-}F}$ = 6.6 Hz), 130.9 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 121.1 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 114.6 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 112.7 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 59.0, 48.6 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 44.2, 28.6 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{13}H_{17}ClFNO$, 257.1, found 257.1.

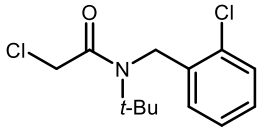


***N*-(2-chlorobenzyl)-2-methylpropan-2-amine (S31):**

Prepared according to General Reductive Amination Procedure. 2-chlorobenzaldehyde (0.45 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 4 hours. The title compound was obtained as a colorless oil (515 mg, 65%).

^{1}H NMR (600 MHz, CDCl3) δ 7.45 (dd, J = 7.5, 1.7 Hz, 1H), 7.33 (dd, J = 7.9, 1.4 Hz, 1H), 7.22 (td, J = 7.5, 1.4 Hz, 1H), 7.17 (td, J = 7.6, 1.8 Hz, 1H), 3.82 (s, 2H), 1.20 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[119]



***N*-(*tert*-butyl)-2-chloro-*N*-(2-chlorobenzyl)acetamide (S32):**

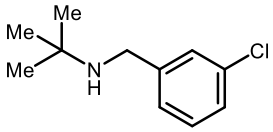
Prepared according to General Acylation Procedure. *N*-(2-chlorobenzyl)-2-methylpropan-2-amine (**S31**) (395 mg, 2.0 mmol, 1.0 equiv), Et_3N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (20 mL, 0.1 M) for 3.5 hours. Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a light yellow oil (435 mg, 79%).

[119] Franchi, P.; Casati, C.; Mezzina, E.; Lucarini, M. Kinetic control of the direction of inclusion of nitroxide cyclodextrines. *Org. Biomol. Chem.*, **2011**, *9*, 6396-6401.

^{1}H NMR (600 MHz, CDCl3) δ 7.40 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.29 – 7.23 (m, 2H), 4.67 (s, 2H), 3.92 (s, 2H), 1.46 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 167.8, 136.0, 132.1, 130.1, 128.9, 127.5, 126.8, 59.0, 47.0, 44.1, 28.4 ppm.

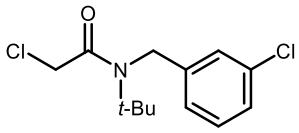
LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{13}H_{17}Cl_2NO$, 273.1, found 273.1.



***N*-(3-chlorobenzyl)-2-methylpropan-2-amine (S33):**

Prepared according to General Reductive Amination Procedure. 3-chlorobenzaldehyde (0.45 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 4.5 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1.5 hours. The title compound was obtained as a light-yellow oil (744 mg, 94%).

^{1}H NMR (400 MHz, CDCl3) δ 7.36 (s, 1H), 7.24 – 7.14 (m, 3H), 3.70 (s, 2H), 1.17 (s, 9H) ppm. ^{1}H NMR spectrum is consistent with reported values.[120]



***N*-(*tert*-butyl)-2-chloro-*N*-(3-chlorobenzyl)acetamide (S34):**

Prepared according to General Acylation Procedure. *N*-(3-chlorobenzyl)-2-methylpropan-2-amine (**S33**) (395 mg, 2.0 mmol, 1.0 equiv), Et_3N (0.15 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl

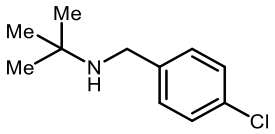
[120] Jiang, G.; Chen, J.; Huang, J-S.; Che, C-M. Highly efficient oxidation of amines to imines by singlet oxygen and its application in ugi-type reactions. *Org. Lett*., **2009**, *11*, 4568-4571.

chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (20 mL, 0.1 M) for 3.5 hours, which afforded the title compound as a white amorphous solid (436 mg, 72%).

^{1}H NMR (400 MHz, CDCl3) δ 7.36 – 7.23 (m, 2H), 7.19 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 4.64 (s, 2H), 3.95 (s, 2H), 1.45 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ 167.6, 140.9, 135.2, 130.4, 127.8, 125.7, 123.5, 58.9, 48.4, 44.0, 28.4 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{13}H_{17}Cl_2NO$, 273.1, found 273.1.



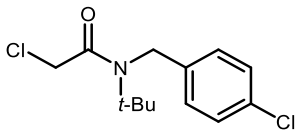
***N*-(4-chlorobenzyl)-2-methylpropan-2-amine (S35):**

Prepared according to General Reductive Amination Procedure. 4-Chlorobenzaldehyde (562 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 17 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a white amorphous solid (676 mg, 85%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 4H), 3.70 (s, 2H), 1.17 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.2, 132.6, 129.8, 128.6, 51.0, 46.7, 29.3 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{11}H_{16}ClN$, 197.1, found 197.1.



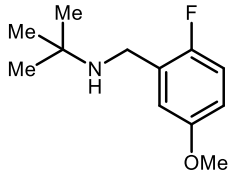
***N*-(*tert*-butyl)-2-chloro-*N*-(4-chlorobenzyl)acetamide (S36):**

Prepared according to General Acylation Procedure. *N*-(4-chlorobenzyl)-2-methylpropan-2-amine (**S35**) (593 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.50 mL, 3.6 mmol, 1.2 equiv), and chloroacetyl

chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 1 hour. The title compound was obtained as a yellow oil (823 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 4.65 (s, 2H), 3.97 (s, 2H), 1.46 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[121]



***N*-(2-fluoro-5-methoxybenzyl)-2-methylpropan-2-amine (S37):**

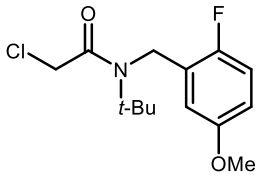
Prepared according to General Reductive Amination Procedure. 2-fluoro-5-methoxybenzaldehyde (0.25 mL, 2.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.41 mL, 2.4 mmol, 1.2 equiv) were stirred in MeOH (4 mL, 0.5 M) for 14 hours. After $NaBH_4$ (114 mg, 3.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1 hour. The title compound was obtained as a light-yellow oil (386 mg, 46%).

^{1}H NMR (400 MHz, CDCl3) δ 6.95 – 6.86 (m, 2H), 6.69 (ddd, J = 8.9, 4.0, 3.2 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 2H), 1.17 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ 155.8 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 155.5 (d, $^1J_{C\text{-}F}$ = 237.4 Hz), 129.1 (d, $^2J_{C\text{-}F}$ = 16.8 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 23.8 Hz), 115.4 (d, $^3J_{C\text{-}F}$ = 4.7 Hz), 113.2 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 55.8, 50.9, 41.0 (d, $^3J_{C\text{-}F}$ = 2.9 Hz), 29.1 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{12}H_{18}FNO$, 211.1, found 211.2.

[121] Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp^3)—H Alkylation. *Angew. Chem. Int. Ed.* **2014**, *53*, 9064-9067.



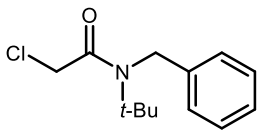
***N*-(tert-butyl)-2-chloro-*N*-(2-fluoro-5-methoxybenzyl)acetamide (S38):**

Prepared according to General Acylation Procedure. *N*-(2-fluoro-5-methoxybenzyl)-2-methylpropan-2-amine (**S37**) (211 mg, 1.0 mmol, 1.0 equiv), Et_3N (0.15 mL, 1.1 mmol, 1.1 equiv), and chloroacetyl chloride (0.09 mL, 1.1 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (10 mL, 0.1 M) for 4.5 hours, which afforded the title compound as a tan amorphous solid (263 mg, 91%).

^{1}H NMR 1H NMR (400 MHz, CDCl3) δ 6.99 (t, J = 9.1 Hz, 1H), 6.80 – 6.72 (m, 1H), 6.76 – 6.70 (m, 1H), 4.64 (s, 2H), 3.98 (s, 2H), 3.76 (s, 3H), 1.46 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ 167.8, 156.4 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 154.0 (d, $^1J_{C\text{-}F}$ = 238.2 Hz), 126.8 (d, $^2J_{C\text{-}F}$ = 15.7 Hz), 116.4 (d, $^2J_{C\text{-}F}$ = 22.9 Hz), 113.3 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 112.6 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 58.9, 55.9, 44.1, 43.2 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 28.4 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{14}H_{19}ClFNO_2$, 287.1, found 287.1.

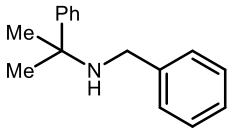


***N*-benzyl-*N*-(*tert*-butyl)-2-chloroacetamide (S39):**

Prepared according to General Acylation Procedure. *N*-benzyl-2-methylpropan-2-amine (**S23**) (688 mg, 4.2 mmol, 1.0 equiv), Et_3N (0.64 mL, 4.6 mmol, 1.1 equiv), and chloroacetyl chloride (0.37 mL, 4.6 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (42 mL, 0.1 M) for 3.5 hours. The title compound was afforded as a white amorphous solid (946 mg, 99%).

^{1}H NMR (400 MHz, cdcl3) δ 7.38 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.20 (d, J = 6.9 Hz, 2H), 4.66 (s, 2H), 3.98 (s, 2H), 1.46 (s, 9H) ppm.

^{1}H NMR spectrum is consistent with reported values.[122]

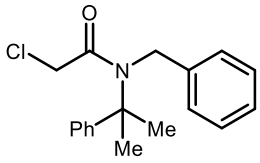


***N*-benzyl-2-phenylpropan-2-amine (S40):**

Prepared according to General Reductive Amination Procedure. Benzaldehyde (0.20 mL, 2.0 mmol, 1.0 equiv) and 2-phenylpropan-2-amine (0.35 mL, 2.4 mmol, 1.2 equiv) were stirred in MeOH (10 mL, 0.2 M) for 14 hours. After $NaBH_4$ (114 mg, 3.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a colorless oil (414 mg, 92%).

^{1}H NMR (600 MHz, CDCl3) δ 7.49 (d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.28 – 7.22 (m, 4H), 7.21 – 7.15 (m, 2H), 3.44 (s, 2H), 1.49 (s, 6H) ppm.

^{1}H NMR spectrum is consistent with reported values.[123]



***N*-benzyl-2-chloro-*N*-(2-phenylpropan-2-yl)acetamide (S41):**

Prepared according to General Acylation Procedure. *N*-benzyl-2-phenylpropan-2-amine (**S40**) (225 mg, 1.0 mmol, 1.0 equiv), Et_3N (0.15 mL, 1.1 mmol, 1.1 equiv), and chloroacetyl chloride (0.09 mL, 1.1 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (10 mL, 0.1 M) for 16 hours. Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (138 mg, 46%).

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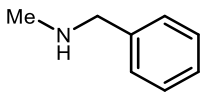
[122] Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp^3)-H Alkylation. *Angew. Chem. Int. Ed.* **2014**, *126*, 9210-9213.

[123] Milburn, R. R.; Snieckus, V. *ortho*-Anisylsufonyl as a protecting group for secondary amines: mild Ni^0-catalyzed hydrodesulfonylation. *Angew. Chem. Int. Ed*. **2004**, *43*, 892-893.

^{1}H NMR (600 MHz, CDCl3) δ 7.40 (t, J = 7.5 Hz, 2H), 7.32 (dd, J = 9.4, 5.9 Hz, 7H), 7.22 (hept, J = 4.2 Hz, 1H), 4.92 (s, 2H), 3.89 (s, 2H), 1.70 (s, 6H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 167.9, 148.1, 138.7, 129.2, 128.7, 127.7, 126.8, 126.4, 124.4, 63.1, 49.5, 43.7, 29.4 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{18}H_{20}ClNO$, 301.1, found 301.1.

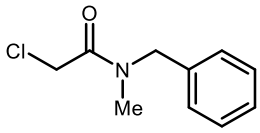


***N*-methyl-1-phenylmethanamine (S42):**

Prepared according to General Reductive Amination Procedure. Benzaldehyde (0.41 mL, 4.0 mmol, 1.0 equiv) and methanamine (0.37 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 2 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a white amorphous solid (479 mg, 99%).

^{1}H NMR (400 MHz, CDCl3) δ 7.36 – 7.30 (m, 4H), 7.29 – 7.22 (m, 1H), 3.75 (s, 2H), 2.46 (s, 3H), 1.59 (s, 1H) ppm.

^{1}H NMR spectrum is consistent with reported values.[124]



***N*-benzyl-2-chloro-*N*-methylacetamide (S43):**

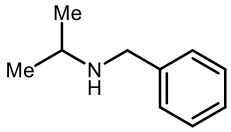
Prepared according to General Acylation Procedure. *N-methyl*-1-phenylmethanamine (**S42**) (364 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.46 mL, 3.3 mmol, 1.1 equiv), and chloroacetyl chloride (0.26

[124] Ji, P.; Manna, K.; Lin, Z.; Feng, X.; Urban, A.; Song, Y.; Lin, W. Single-site cobalt catalysts at new $Zr_{12}(\mu_3\text{-}O)_8(\mu_3\text{-}OH)_8(\mu_2\text{-}OH)_6$ metal-organic framework nodes for highly active hydrogenation of nitroarenes, nitriles and isocyanides. *J. Am. Chem. Soc.* **2017**, *139*, 7004-7011.

mL, 1.1 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 30 min. Purification on silica gel (10-30% EtOAc/hexanes) afforded the title compound as a colorless oil (401 mg, 68%).

^{1}H NMR (600 MHz, CDCl3) δ 7.40 – 7.26 (m, 3H), 7.26 – 7.24 (m, 1H), 7.19 (d, J = 7.5 Hz, 1H), 4.60 (s, 2H), 4.12 (d, J = 22.3 Hz, 2H), 2.99 (d, J = 16.5 Hz, 3H) ppm.

^{1}H NMR spectrum is consistent with reported values.[125]

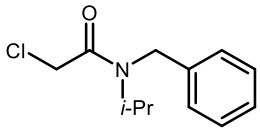


***N*-benzylpropan-2-amine (S44):**

Prepared according to General Reductive Amination Procedure. Benzaldehyde (0.41 mL, 4.0 mmol, 1.0 equiv) and propan-2-amine (0.39 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 2 hours. After $NaBH_4$ (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a yellow amorphous solid (557 mg, 93%).

^{1}H NMR (400 MHz, CDCl3) δ 7.32 (d, J = 4.4 Hz, 4H), 7.26 – 7.22 (m, 1H), 3.78 (s, 2H), 2.85 (h, J = 6.2 Hz, 1H), 1.10 (d, J = 6.2 Hz, 6H) ppm.

^{1}H NMR spectrum is consistent with reported values.[126]



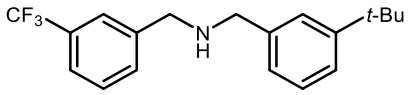
***N*-benzyl-2-chloro-*N*-isopropylacetamide (S45):**

[125] Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp^3)-H Alkylation. *Angew. Chem. Int. Ed.* **2014**, *126*, 9210-9213.
[126] Rauser, M.; Eckert, R.; Gerbershagen, M.; Niggemann, M. Catalyst-free reductive coupling of aromatic and aliphatic nitro compounds with organohalides. *Angew. Chem. Int. Ed*. **2019**, *58*, 6713-6717.

Prepared according to General Acylation Procedure. *N*-benzylpropan-2-amine (**S44**) (448 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.46 mL, 3.3 mmol, 1.1 equiv), and chloroacetyl chloride (0.26 mL, 3.3 mmol, 1.1 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 30 min. Purification on silica gel (10-30% EtOAc/hexanes) afforded the title compound as a colorless oil (414 mg, 61%). Mixture of rotamers (H* denotes major rotamer and H denotes minor rotamer).

^{1}H NMR (600 MHz, CDCl3) δ 7.36 (t, J = 7.6 Hz, 2(H+H*)), 7.29 (t, J = 7.7 Hz, 4(H+H*)), 7.22 (t, J = 8.1 Hz, 4(H+H*)), 4.79 (spt, J = 6.8 Hz, 1H*), 4.54 (m, 4(H+H*)), 4.22 (spt, J = 6.8 Hz, 1H), 4.20 (s, 2H*), 3.91 (s, 2H), 1.20 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H*) ppm.

^{1}H NMR spectrum is consistent with reported values.[22]



***N*-(3-(*tert*-butyl)benzyl)-1-(3-(trifluoromethyl)phenyl)methanamine (S46):**

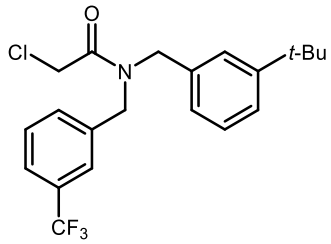
3-(trifluoromethyl)benzylamine (0.29 mL, 2.0 mmol, 1.0 equiv) was dissolved in DCM (8 mL, 0.25 M). 3-*tert*-butylbenzaldehyde (324 mg, 2.0 mmol, 1.0 equiv), AcOH (0.11 mL, 2.0 mmol, 1.0 equiv), and sodium triacetoxyborohydride (593 mg, 2.8 mmol, 1.4 equiv) were added and reaction was stirred for 16 hours. $NaBH_4$ (76 mg, 2.0 mmol, 1.0 equiv) was added and the reaction was stirred for an additional 4 hours. The reaction was quenched with 1 M NaOH (aq), extracted with DCM (3x), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (50% EtOAc/hexanes) afforded the title compound as a colorless oil (361 mg, 56%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.35 (s, 1H), 7.32 – 7.27 (m, 2H), 7.16 (dt, J = 7.0, 1.7 Hz, 1H), 3.88 (s, 2H), 3.81 (s, 2H), 1.33 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.6, 141.5, 139.7, 131.7, 130.9 (q, $^2J_{C-F}$ = 32.0 Hz), 129.0, 128.4, 125.5, 125.3, 125.3 (q, $^1J_{C-F}$ = 272.0 Hz), 125.1 (q, $^3J_{C-F}$ = 3.8 Hz), 124.3, 124.0 (q, $^3J_{C-F}$ = 3.8 Hz), 53.6, 52.7, 34.9, 31.6 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{19}H_{22}F_3N$, 321.2, found 321.3.

^{1}H NMR spectrum is consistent with reported values.[127]



***N*-(3-(*tert*-butyl)benzyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (31):**

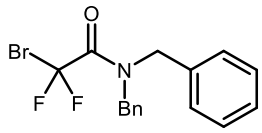
Prepared according to General Acylation Procedure. *N*-(3-(*tert*-butyl)benzyl)-1-(3-(trifluoromethyl)phenyl)methanamine (**S47**) (321 mg, 1.0 mmol, 1.0 equiv), Et_3N (0.17 mL, 1.2 mmol, 1.2 equiv), and chloroacetyl chloride (0.10 mL, 1.2 mmol, 1.2 equiv) were stirred in CH_2Cl_2 (10 mL, 0.1 M) for 16 hours. The title compound was obtained as a colorless oil (390 mg, 98%). Mixture of rotamers (* denotes major rotamer $^{\#}$ denotes minor isomer).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 – 7.27$^{(*+\#)}$ (m, 6H), 7.16$^{(*+\#)}$ (d, J = 27.3 Hz, 1H), 7.00$^{(*+\#)}$ (dd, J = 23.3, 7.5 Hz, 1H), 4.65* (s, 1H), 4.61$^{\#}$ (s, 1H), 4.58$^{\#}$ (s, 1H), 4.54* (s, 1H), 4.18* (s, 1H), 4.13$^{\#}$ (s, 1H), 1.30* (s, 9H), 1.29$^{\#}$ (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.7*, 167.4$^{\#}$, 152.6*, 152.1$^{\#}$, 137.8*, 137.2$^{\#}$, 135.7$^{\#}$, 135.0*, 131.7*, 131.3$^{\#}$, 130.0$^{\#}$, 129.8$^{\#}$, 129.5*, 129.1*, 128.8$^{\#}$, 125.5$^{\#}$, 125.4*, 125.4$^{\#}$, 125.1 (m), 124.67 (q, $^3J_{C-F}$ = 3.8 Hz), 123.9*, 123.7*, 51.4*, 50.2$^{\#}$, 49.1$^{\#}$, 48.6*, 41.4$^{(*+\#)}$, 34.9*, 34.8$^{\#}$, 31.5$^{(*+\#)}$ ppm.

[127] Diaba, F.; Montiel, J.A.; Martínez-Laporta, A.; Bonjoch, J. Dearomative radical spirocyclization from N-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes. *Tetrahedron Lett.* **2013**, 5*4*, 2619-2622.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{21}H_{24}F_3NO$, 398.1, found 398.2.



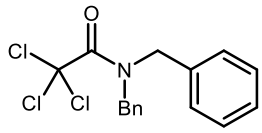
***N*,*N*-dibenzyl-2-bromo-2,2-difluoroacetamide (S47):**

An oven-dried reaction vial was cooled under N_2. Dibenzylamine (0.19 mL, 1.0 mmol, 1.0 equiv), ethyl bromodifluoroacetate (0.15 mL, 1.2 mmol, 1.2 equiv), and $La(OTf)_3$ (59 mg, 0.1 mmol, 10 mol %) were added sequentially. The reaction was stirred for 20 hours then quenched with 1 M HCl (aq), extracted with EtOAc (3x), filtered through a plug of silica with EtOAc, and concentrated under reduced pressure. The crude residue was purified on silica gel (20% EtOAc/hexanes) to afford the title compound as a white amorphous solid (104 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 6H), 7.19 (ddd, J = 7.4, 5.5, 1.6 Hz, 4H), 4.63 (s, 2H), 4.55 (s, 2H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ160.1 (t, $^2J_{C\text{-}F}$ = 26.3 Hz), 135.5, 134.8, 129.2, 129.1, 128.4, 128.4, 128.2, 127.5, 111.3 (t, $^1J_{C\text{-}F}$ = 315.1 Hz), 50.6 (t, $^4J_{C\text{-}F}$ = 3.8 Hz), 48.8 ppm.

LRMS (EI) m/z: $[M]^+$ calc'd. for $C_{16}H_{14}BrF_2NO$, 353.0, found 353.1.

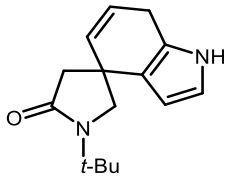


***N*,*N*-dibenzyl-2,2,2-trichloroacetamide (S48):**

Prepared according to General Acylation Procedure. Dibenzylamine (0.66 mL, 3.3 mmol, 1.1 equiv), Et_3N (0.46 mL, 3.3 mmol, 1.1 equiv), and trichloroacetyl chloride (0.33 mL, 3.0 mmol, 1.0 equiv) were stirred in CH_2Cl_2 (30 mL, 0.1 M) for 23 hours. Purification on silica gel (0-10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (654 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 6H), 7.24 (d, J = 6.9 Hz, 2H), 7.16 (d, J = 6.9 Hz, 2H), 4.91 (s, 2H), 4.58 (s, 2H) ppm.

4.4.8 Preparation of Spirolactam Products



1'-(*tert*-butyl)-1,7-dihydrospiro[indole-4,3'-pyrrolidin]-5'-one (9):

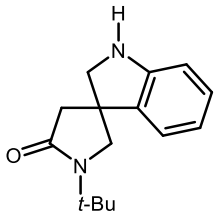
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-((1*H*-indol-4-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (**S2**) (139 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 10% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (0-10% acetone/CH_2Cl_2) afforded the title compound as a yellow oil (96.3 mg, 79%).

R_f: 0.21 (5% acetone/DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 6.72 (dd, J = 3.0, 2.4 Hz, 1H), 6.16 (t, J = 2.7 Hz, 1H), 5.86 (dt, J = 10.0, 3.0 Hz, 1H), 5.81 (dt, J = 10.0, 1.8 Hz, 1H), 3.59 (d, J = 9.6 Hz, 1H), 3.44 (d, J = 9.7 Hz, 1H), 3.28 – 3.22 (m, 2H), 2.64 (d, J = 16.4 Hz, 1H), 2.48 (d, J = 16.5 Hz, 1H), 1.43 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 132.4, 124.1, 122.6, 120.9, 117.3, 104.4, 59.9, 54.2, 48.7, 37.3, 28.0, 24.1 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{21}N_2O$, 245.16484, found 245.16491.



1'-(*tert*-butyl)spiro[indoline-3,3'-pyrrolidin]-5'-one (10):

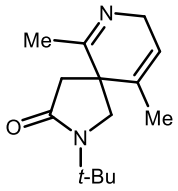
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-((1*H*-indol-3-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (**S4**) (56 mg, 0.2 mmol, 1.0 equiv), 3DPAFIPN (6.5 mg, 0.01 mmol, 5 mol%), DIPEA (0.10 mL, 0.6 mmol, 3.0 equiv), cyclohexanethiol (1.2 µL, 0.01 mmol, 5 mol%), and 50% H_2O/MeCN (4 mL, 0.05 M). Purification on silica gel (10-50% EtOAc/hexanes) afforded the title compound as a yellow oil (34.4 mg, 70%).

R_f: 0.15 (30% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, J = 7.4 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.83 – 6.77 (m, 1H), 6.71 (d, J = 7.8 Hz, 1H), 3.63 (d, J = 9.8 Hz, 1H), 3.58 (d, J = 9.1 Hz, 1H), 3.51 (d, J = 9.1 Hz, 1H), 3.49 (d, J = 9.8 Hz, 1H), 2.80 (d, J = 16.7 Hz, 1H), 2.52 (d, J = 16.7 Hz, 1H), 1.42 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 150.4, 133.3, 128.8, 122.4, 119.9, 110.5, 60.2, 57.7, 54.4, 45.6, 45.5, 28.0 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{21}N_2O$, 245.16484, found 245.16487.



2-(*tert*-butyl)-6,10-dimethyl-2,7-diazaspiro[4.5]deca-6,9-dien-3-one (11):

Prepared according to General Dearomative Spirolactamization Procedure 1 using N-(tert-butyl)-2-chloro-N-((2,4-dimethylpyridin-3-yl)methyl)acetamide (**S8**) (26.9 mg, 0.1 mmol, 1.0 equiv),

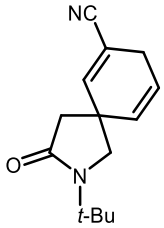
3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (0.05 mL, 0.3 mmol, 3.0 equiv), and 50% H_2O/MeCN (2 mL, 0.05 M). Purification on silica gel (50-70% acetone/DCM) afforded the title compound as a white amorphous solid (23 mg, 97%).

R_f: 0.24 (50% acetone/DCM)

^{1}H NMR (500 MHz, CDCl3) δ 5.55 (dq, J = 3.1, 1.5 Hz, 1H), 4.16 – 4.08 (m, 2H), 3.49 (d, J = 10.9 Hz, 1H), 3.42 (d, J = 10.9 Hz, 1H), 2.55 (d, J = 9.6 Hz, 2H), 2.06 (d, J = 1.8 Hz, 3H), 1.73 (t, J = 1.8 Hz, 3H), 1.42 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ 173.0, 167.0, 131.7, 121.4, 54.7, 54.3, 50.3, 41.6, 39.1, 27.8, 22.3, 18.2 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{23}N_2O$, 235.18049, found 235.18090.



2-(*tert*-butyl)-3-oxo-2-azaspiro[4.5]deca-6,9-diene-7-carbonitrile (12):

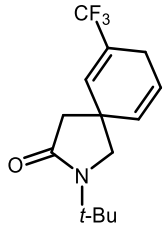
Prepared according to General Dearomative Spirolactamization Procedure 2 using N-(tert-butyl)-2-chloro-N-(3-cyanobenzyl)acetamide (**S10**) (132.4 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (0-30% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (73 mg, 63%).

R_f: 0.13 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 6.50 (q, J = 2.0 Hz, 1H), 5.77 (dt, J = 10.3, 3.4 Hz, 1H), 5.67 (dq, J = 10.2, 2.2 Hz, 1H), 3.33 (q, J = 12 Hz, 2H), 2.85 (dq, J = 3.4, 1.7 Hz, 2H), 2.35 (d, J = 1.6 Hz, 2H), 1.37 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 172.0, 145.4, 145.4, 128.8, 122.6, 122.6, 118.5, 110.8, 57.3, 54.4, 46.7, 37.6, 27.8, 278, 27.8, 27.8, 27.7 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{19}N_2O$, 231.14919, found 231.14940.



2-(*tert*-butyl)-7-(trifluoromethyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (13):

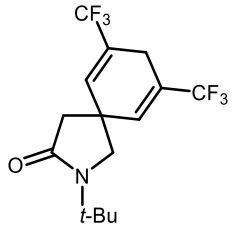
Prepared according to General Dearomative Spirolactamization Procedure 2 using *N*-(*tert*-butyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (**S12**) (120 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (75 mg, 55%).

R_f: 0.27 (20% EtOAc/hexanes)

^{z1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (p, J = 1.7 Hz, 1H), 5.83 (dt, J = 10.1, 3.4 Hz, 1H), 5.70 (dq, J = 10.0, 2.1 Hz, 1H), 3.36 (d, J = 10.1 Hz, 1H), 3.33 (d, J = 10.3 Hz, 1H), 2.84 – 2.77 (m, 2H), 2.38 (s, 2H), 1.40 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 72.7, 132.1 (q, $^3J_{C-F}$ = 5.6 Hz), 129.2, 126.6 (q, $^2J_{C-F}$ = 31.2 Hz), 123.5 (q, $^1J_{C-F}$ = 272.1 Hz), 122.8, 57.7, 54.4, 47.0, 37.0, 27.9, 23.7 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{19}F_3NO$, 274.14133, found 274.14162.



2-(*tert*-butyl)-7,9-bis(trifluoromethyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (14):

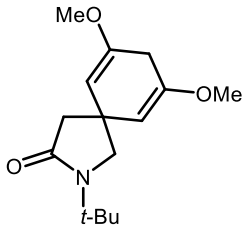
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-(*tert*-butyl)-2-chloroacetamide (**S14**) (174 mg, 0.46 mmol, 1.0 equiv), 3DPAFIPN (14.9 mg, 0.023 mmol, 5 mol%), DIPEA (0.24 mL, 1.38 mmol, 3.0 equiv), and 50% H_2O/MeCN (9 mL, 0.05 M). Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (103 mg, 66%).

R_f: 0.46 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (p, J = 1.8 Hz, 2H), 3.41 (s, 2H), 2.97 (s, 2H), 2.45 (s, 2H), 1.41 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 131.2 (q, $^3J_{C\text{-}F}$ = 5.4 Hz), 125.4 (q, $^2J_{C\text{-}F}$ = 31.8 Hz), 123.0 (q, $^1J_{C\text{-}F}$ = 272.4 Hz), 56.7, 54.7, 46.1, 37.8, 27.8, 21.4 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{18}F_6NO$, 342.12871, found 342.12899.



2-(*tert*-butyl)-7,9-dimethoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (15):

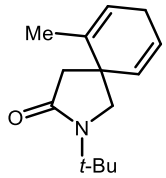
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(3,5-dimethoxybenzyl)-2-methylpropan-2-amine (**S16**) (60 mg, 0.2 mmol, 1.0 equiv), 3DPAFIPN (6.5 mg, 0.01 mmol, 5 mol%), DIPEA (0.10 mL, 0.6 mmol, 3.0 equiv), and 50% H_2O/MeCN (4 mL, 0.05 M). Purification by preparatory TLC (20% acetone/hexanes eluent) afforded the title compound as an off-white amorphous solid (28 mg, 54%).

R_f: 0.29 (20% acetone/hexanes)

^{1}H NMR (600 MHz, C_6D_6) δ 4.45 (t, J = 1.3 Hz, 2H), 3.13 (s, 6H), 3.03 (s, 2H), 2.95 (qt, J = 8.0, 1.3 Hz, 2H), 2.35 (s, 2H), 1.40 (s, 9H) ppm.

^{13}C NMR (151z MHz, C_6D_6) δ 173.3, 152.9, 98.4, 60.1, 54.0, 53.6, 49.5, 39.4, 32.0, 28.0 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{24}NO_3$, 266.17507, found 266.17541.



2-(*tert*-butyl)-6-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (16):

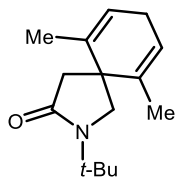
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2-methylbenzyl)acetamide (**S18**) (126.6 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (5-10% acetone/hexanes) afforded the title compound as a yellow oil (72 mg, 66%).

R_f: 0.27 (10% acetone/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 5.70 (dtd, J = 9.8, 3.3, 1.5 Hz, 1H), 5.57 (dt, J = 9.9, 2.1 Hz, 1H), 5.46 (tt, J = 3.4, 1.6 Hz, 1H), 3.45 (d, J = 10.2 Hz, 1H), 3.21 (d, J = 10.2 Hz, 1H), 2.59 (tq, J = 3.7, 1.9 Hz, 2H), 2.49 (d, J = 17.1 Hz, 1H), 2.23 (d, J = 17.1 Hz, 1H), 1.72 (q, J = 1.8 Hz, 3H), 1.37 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 173.7, 134.7, 131.9, 123.6, 121.6, 57.4, 54.2, 45.8, 37.9, 27.8, 27.0, 19.0 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{22}NO$, 220.16959, found 220.16959.



2-(*tert*-butyl)-6,10-dimethyl-2-azaspiro[4.5]deca-6,9-dien-3-one (17):

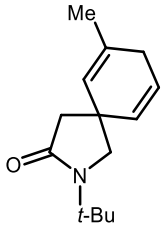
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2,6-dimethylbenzyl)acetamide (**S20**) (133.9 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-15% acetone/hexanes) afforded the title compound as a yellow oil (98 mg, 84%).

R_f: 0.24 (10% acetone/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 5.47 (t, J = 3.5 Hz, 2H), 3.39 (s, 2H), 2.59 (tt, J = 3.7, 1.9 Hz, 2H), 2.47 (s, 2H), 1.75 – 1.72 (m, 6H), 1.41 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 174.1, 134.8, 121.3, 55.6, 54.5, 42.5, 39.8, 27.8, 27.3, 18.9 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{15}H_{24}NO$, 234.18524, found 234.18562.



2-(*tert*-butyl)-7-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (18):

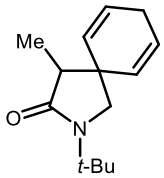
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-N-(3-methylbenzyl)acetamide (**S22**) (126.9 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow oil (65 mg, 59%).

R_f: 0.34 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 5.74 (dt, J = 10.0, 3.3 Hz, 1H), 5.65 (dq, J = 10.0, 2.1 Hz, 1H), 5.35 (s, 1H), 3.24 (s, 2H), 2.54 – 2.50 (m, 2H), 2.26 (s, 2H), 1.69 (s, 3H), 1.37 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 173.8, 132.1, 130.2, 125.0, 124.3, 58.7, 54.0, 47.9, 37.6, 31.2, 27.9, 23.2 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{22}NO$, 220.16959, found 220.16966.



2-(*tert*-butyl)-4-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (19):

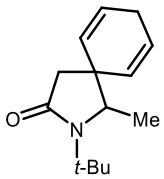
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-*N*-(*tert*-butyl)-2-chloropropanamide (**S24**) (127 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (2-3% acetone/hexanes) afforded the title compound as an off-white amorphous solid (94 mg, 85%).

R_f: 0.26 (5% acetone/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 – 5.81 (m, 2H), 5.55 (dq, J = 9.6, 1.9 Hz, 1H), 5.48 (dq, J = 10.0, 2.1 Hz, 1H), 3.24 (d, J = 9.7 Hz, 1H), 3.19 (d, J = 9.8 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.24 (q, J = 7.3 Hz, 1H), 1.38 (s, 9H), 0.94 (d, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ175.9, 130.0, 127.2, 127.0, 125.8, 56.6, 53.9, 49.3, 41.9, 27.9, 26.8, 9.7 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{22}NO$, 220.16959, found 220.16969.



2-(*tert*-butyl)-1-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (20):

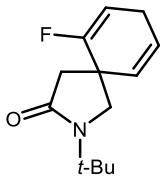
Prepared according to General Dearomative Spirolactamization Procedure 2 using *N*-(*tert*-butyl)-2-chloro-*N*-(1-phenylethyl)acetamide (**S26**) (254 mg, 1.0 mmol, 1.0 equiv), 3DPAFIPN (32.4 mg, 0.05 mmol, 5 mol%), DIPEA (0.52 mL, 3.0 mmol, 3.0 equiv), and 50% H_2O/MeCN (20 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (89.7 mg, 41%).

R_f: 0.45 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dtd, J = 10.3, 3.4, 1.7 Hz, 1H), 5.81 (dq, J = 10.2, 2.0 Hz, 1H), 5.72 (dtd, J = 10.2, 3.3, 1.7 Hz, 1H), 5.60 (dq, J = 10.3, 2.1 Hz, 1H), 3.49 (q, J = 6.5 Hz, 1H), 2.64 (m, 2H), 2.51 (d, J = 16.6 Hz, 1H), 2.11 (d, J = 16.6 Hz, 1H), 1.43 (s, 9H), 1.20 (d, J = 6.4 Hz, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 73.0, 131.3, 127.9, 127.0, 123.3, 64.9, 54.2, 45.5, 40.2, 28.4, 26.7, 17.7 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{22}NO$, 220.16959, found 220.16983.



2-(*tert*-butyl)-6-fluoro-2-azaspiro[4.5]deca-6,9-dien-3-one (21):

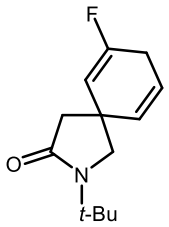
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2-fluorobenzyl)acetamide (**S28**) (128.6 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (0-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (81 mg, 72%).

R_f: 0.32 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 5.72 – 5.64 (m, 2H), 5.33 (dt, J = 17.5, 3.9 Hz, 1H), 3.71 (d, J = 9.8 Hz, 1H), 3.27 (d, J = 9.9 Hz, 1H), 2.83 – 2.77 (m, 3H), 2.25 (d, J = 16.7 Hz, 1H), 1.40 (d, J = 0.8 Hz, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 172.6, 158.4 (d, $^1J_{C-F}$ = 254.7 Hz), 130.2 (d, $^3J_{C-F}$ = 6.4 Hz), 123.2 (d, $^4J_{C-F}$ = 2.7 Hz), 101.7 (d, $^2J_{C-F}$ = 17.2 Hz), 55.4, 54.4, 43.6, 37.8 (d, $^2J_{C-F}$ = 23.2 Hz), 27.8, 26.4 (d, $^3J_{C-F}$ = 7.0 Hz) ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{19}FNO$, 224.14452, found 224.14472.



2-(*tert*-butyl)-7-fluoro-2-azaspiro[4.5]deca-6,9-dien-3-one (22):

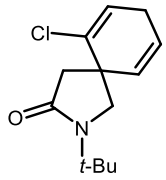
Prepared according to General Dearomative Spirolactamization Procedure 2 using *N*-(*tert*-butyl)-2-chloro-*N*-(3-fluorobenzyl)acetamide (**S30**) (129 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (84.7 mg, 76%).

R_f: 0.26 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (ddt, J = 9.9, 7.8, 3.3 Hz, 1H), 5.64 (ddq, J = 9.8, 3.7, 1.9 Hz, 1H), 5.24 (dq, J = 17.0, 1.5 Hz, 1H), 3.34 (dd, J = 9.9, 1.1 Hz, 1H), 3.32 (d, J = 9.9 Hz, 1H), 2.86 – 2.82 (m, 2H), 2.36 (d, J = 1.0 Hz, 1H), 2.35 (d, J = 16.6 Hz, 1H), 1.39 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 158.5 (d, $^1J_{C-F}$ = 256.0 Hz), 130.5 (d, $^4J_{C-F}$ = 2.8 Hz), 121.9 (d, $^3J_{C-F}$ = 10.6 Hz), 106.3 (d, $^2J_{C-F}$ = 15.0 Hz), 58.4 (d, $^4J_{C-F}$ = 2.6 Hz), 54.2, 47.6 (d, $^4J_{C-F}$ = 2.0 Hz), 39.5 (d, $^3J_{C-F}$ = 7.8 Hz), 27.9, 27.2 (d, $^2J_{C-F}$ = 26.4 Hz) ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{19}FNO$, 224.14452, found 224.14468.



2-(*tert*-butyl)-6-chloro-2-azaspiro[4.5]deca-6,9-dien-3-one (23):

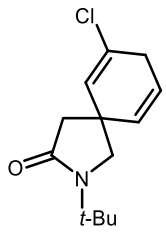
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2-chlorobenzyl)acetamide (**S32**) (137.1 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (5-10% acetone/hexanes) afforded the title compound as a yellow oil (57 mg, 47%).

R_f: 0.22 (10% acetone/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 5.93 (t, J = 3.7 Hz, 1H), 5.75 – 5.67 (m, 2H), 3.79 (d, J = 10.1 Hz, 1H), 3.27 (d, J = 10.1 Hz, 1H), 2.92 (d, J = 17.0 Hz, 1H), 2.79 (dq, J = 4.0, 2.4, 2.0 Hz, 2H), 2.27 (d, J = 16.9 Hz, 1H), 1.41 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 172.8, 134.4, 130.9, 124.8, 122.0, 56.82, 54.5, 45.2, 40.4, 28.5, 27.8 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{19}ClNO$, 240.11497, found 240.11541.



2-(*tert*-butyl)-7-chloro-2-azaspiro[4.5]deca-6,9-dien-3-one (24):

Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(3-chlorobenzyl)acetamide (**S34**) (137.1 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2

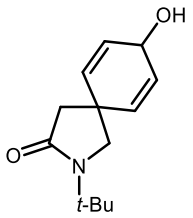
mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (84 mg, 70%).

R_f: 0.31 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 5.78 (q, J = 1.8 Hz, 1H), 5.69 (dt, J = 10.0, 3.3 Hz, 1H), 5.63 (dq, J = 10.0, 2.0 Hz, 1H), 3.30 (dd, J = 18.0, 12.0 Hz, 2H), 2.89 (dt, J = 3.4, 2.0 Hz, 2H), 2.33 (d, J = 1.9 Hz, 2H), 1.36 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 173.0, 131.0, 129.4, 127.2, 123.4, 57.9, 54.3, 47.1, 40.0, 33.6, 27.8 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{19}ClNO$, 240.11497, found 240.11508.



2-(*tert*-butyl)-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (25):

Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(*tert*-butyl)-2-chloro-*N*-(4-chlorobenzyl)acetamide (**S36**) (137 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (50-75% EtOAc/hexanes) afforded the title compound (72.2 mg, 65%, 1:1 d.r.).

Diastereomer 1 (elutes first, 36.2 mg, yellow amorphous solid):

R_f: 0.30 (75% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (dq, J = 10.3, 3.0 Hz, 2H), 5.88 (dd, J = 10.3, 1.3 Hz, 2H), 4.54 (s, 1H), 3.33 (s, 2H), 2.32 (s, 2H), 1.39 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 132.9, 128.1, 62.3, 56.5, 54.3, 46.2, 37.2, 27.9 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{20}NO_2$, 222.14886, found 222.14877.

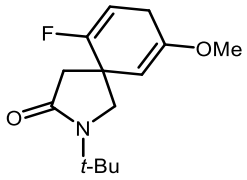
Diastereomer 2 (elutes second, 36.0 mg, yellow amorphous solid):

R_f: 0.22 (75% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (dq, J = 10.3, 3.1 Hz, 2H), 5.87 (dq, J = 10.2, 1.5 Hz, 2H), 4.51 (s, 1H), 3.28 (s, 2H), 2.37 (s, 2H), 1.39 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 132.9, 128.2, 62.2, 57.0, 54.3, 45.7, 37.2, 27.9 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{20}NO_2$, 222.14886, found 222.14897.



2-(*tert*-butyl)-6-fluoro-9-methoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (26):

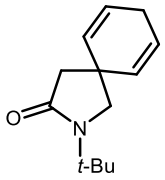
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2-fluoro-5-methoxybenzyl)acetamide (**S38**) (143.9 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow oil (88 mg, 69%).

R_f: 0.26 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, C6D6) δ 4.86 (dt, J = 16.1, 3.7 Hz, 1H), 4.36 (d, J = 7.3 Hz, 1H), 3.52 (dd, J = 9.6, 1.0 Hz, 1H), 3.01 (s, 3H), 2.95 (d, J = 9.6 Hz, 1H), 2.87 (d, J = 16.5 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.23 (d, J = 16.5 Hz, 1H), 1.32 (s, 9H) ppm.

^{13}C NMR (151 MHz, C6D6) δ 172.0, 159.1 (d, $^1J_{C\text{-}F}$ = 254.5 Hz), 153.3 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 99.8 (d, $^2J_{C\text{-}F}$ = 20.1 Hz), 98.5 (d, $^3J_{C\text{-}F}$ = 7.4 Hz), 56.39, 54.2, 44.7, 38.8 (d, $^2J_{C\text{-}F}$ = 23.8 Hz), 28.3 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 27.7 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{21}FNO_2$, 254.15508, found 254.15549.



2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (40):

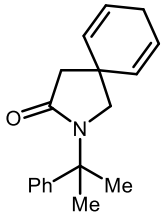
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-*N*-(*tert*-butyl)-2-chloroacetamide (**S39**) (120 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H_2O/MeCN (10 mL, 0.05 M). Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (103 mg, 73%).

R_f: 0.28 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 5.77 (dt, J = 10.1, 3.3 Hz, 2H), 5.66 (dt, J = 10.3, 2.1 Hz, 2H), 3.28 (s, 2H), 2.63 (p, J = 2.7 Hz, 2H), 2.31 (s, 2H), 1.38 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 173.7, 130.3, 124.7, 58.8, 54.1, 48.0, 36.4, 27.9, 26.4 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{20}NO$, 206.15394, found 206.15423.



2-(2-phenylpropan-2-yl)-2-azaspiro[4.5]deca-6,9-dien-3-one (S49):

Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-2-chloro-*N*-(2-phenylpropan-2-yl)acetamide (**S41**) (121 mg, 0.4 mmol, 1.0 equiv), 3DPAFIPN (13.0 mg, 0.020 mmol, 5 mol%), DIPEA (0.21 mL, 1.2 mmol, 3.0 equiv), and 50% H_2O/MeCN (8 mL,

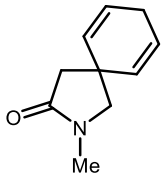
0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a white amorphous solid (63 mg, 59%).

R_f: 0.36 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, CDCl3) δ 7.37 – 7.28 (m, 4H), 7.23 (tt, J = 6.6, 2.1 Hz, 1H), 5.78 (dt, J = 10.3, 3.3 Hz, 2H), 5.70 (dt, J = 10.3, 2.1 Hz, 2H), 3.22 (s, 2H), 2.63 (dh, J = 7.4, 2.2 Hz, 2H), 2.36 (s, 2H), 1.75 (s, 6H) ppm.

^{13}C NMR (151 MHz, CDCl3) δ 173.5, 146.7, 130.2, 128.5, 126.9, 125.2, 124.8, 59.6, 59.0, 47.9, 36.7, 27.9, 26.4.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{18}H_{22}NO$, 268.16959, found 268.17006.



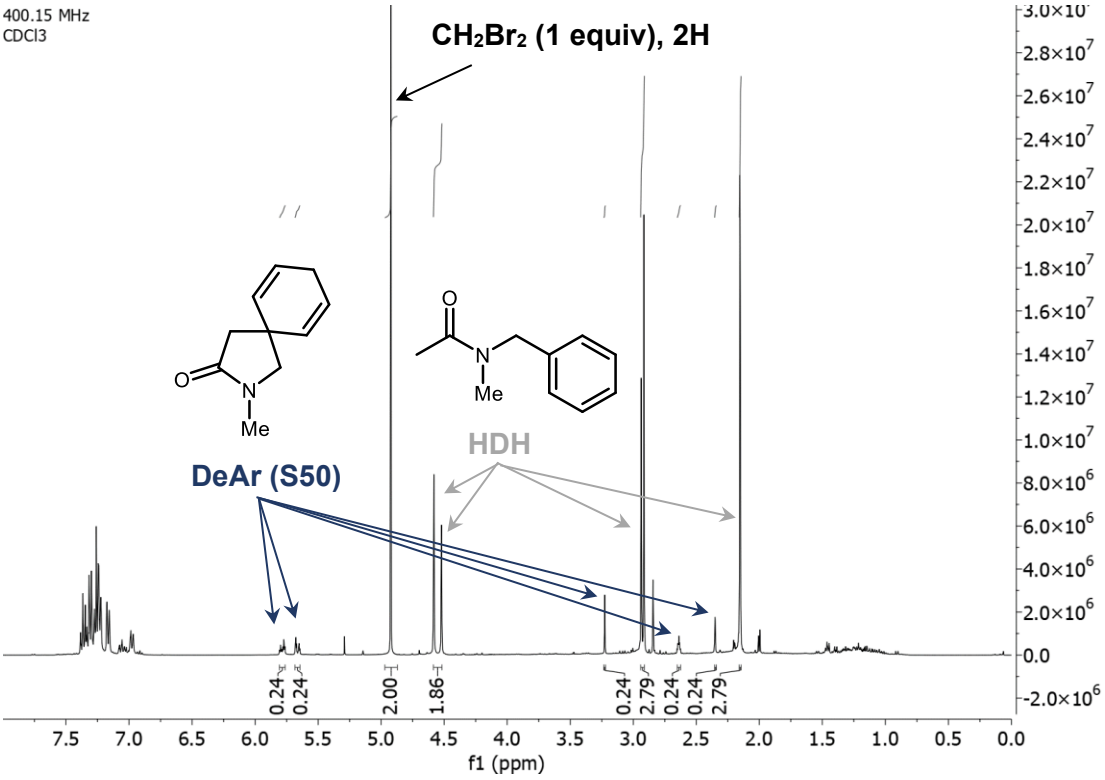
2-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (S50):

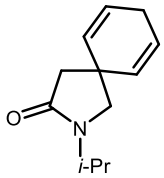
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-2-chloro-*N*-methylacetamide (**S43**) (20 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52 μL, 0.3 mmol, 3.0 equiv), and 50% H_2O/MeCN (2 mL, 0.05 M). $CDCl_3$ and an internal standard of dibromomethane (7 μL, 0.1 mmol) were added to the crude residue. The sample was analyzed by ^{1}H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (12%) and the hydrodehalogenation byproduct (93%). ^{1}H NMR spectrum of HDH byproduct is consistent with reported values.[128]

Characteristic peaks

[128] Rauser, M.; Ascheberg, A.; Niggemann, M. Direct Reductive *N*-Functionalization of Aliphatic Nitro Compounds. *Chem. Eur. J.* **2018**, *24*, 3970-3974.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.75 (m, 2H), 5.66 (dt, J = 10.3, 2.0 Hz, 2H), 3.23 (s, 2H), 2.84 (t, J = 0.8 Hz, 3H), 2.64 (ddd, J = 5.4, 3.4, 2.0 Hz, 2H), 2.35 (d, J = 0.9 Hz, 2H) ppm.





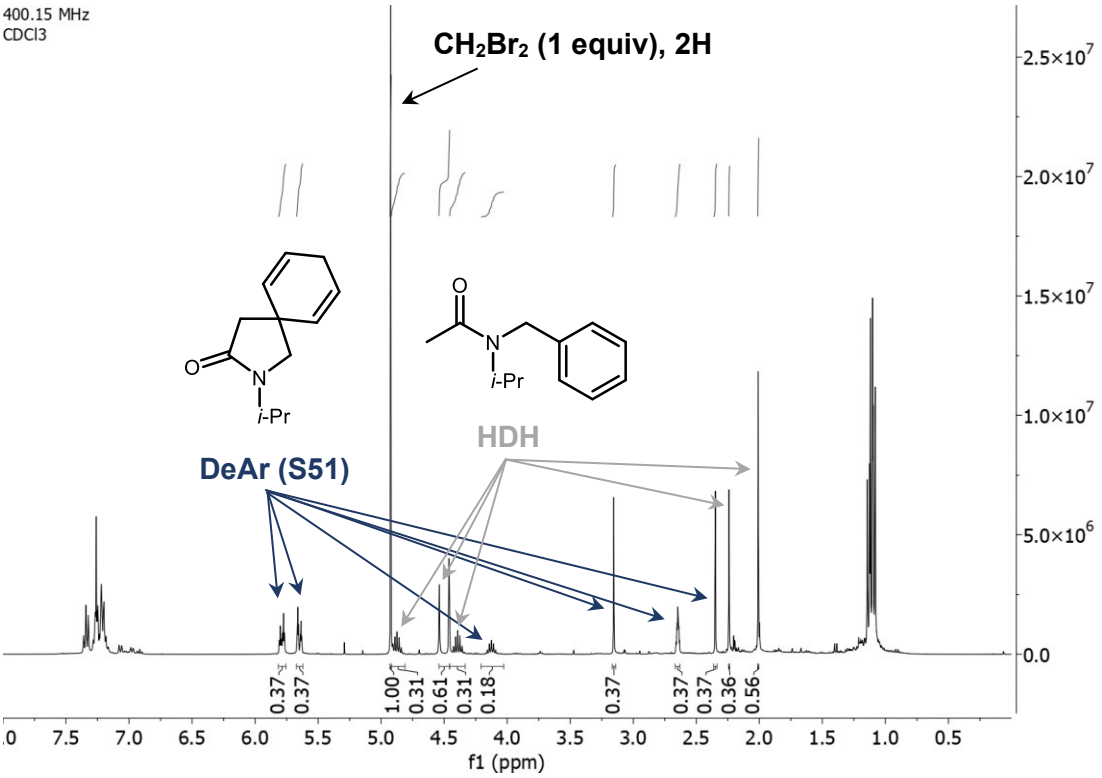
2-isopropyl-2-azaspiro[4.5]deca-6,9-dien-3-one (S51):

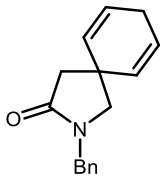
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-2-chloro-*N*-isopropylacetamide (**S45**) (23 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52 µL, 0.3 mmol, 3.0 equiv), and 50% H_2O/MeCN (2 mL, 0.05 M). $CDCl_3$ and an internal standard of dibromomethane (7 µL, 0.1 mmol) were added to the crude residue. The sample was analyzed by ^{1}H NMR (d1 = 5 s), and the integral values were used to

calculate the yield of the title compound (37%) and the hydrodehalogenation byproduct (61%). ^{1}H NMR spectrum of HDH byproduct is consistent with reported values.[129]

Characteristic peaks

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 – 5.74 (m, 2H), 5.65 (dt, J = 10.4, 2.0 Hz, 2H), 4.12 (p, J = 6.7 Hz, 1H), 3.15 (s, 2H), 2.65 (tt, J = 3.4, 2.0 Hz, 2H), 2.35 (s, 2H) ppm.





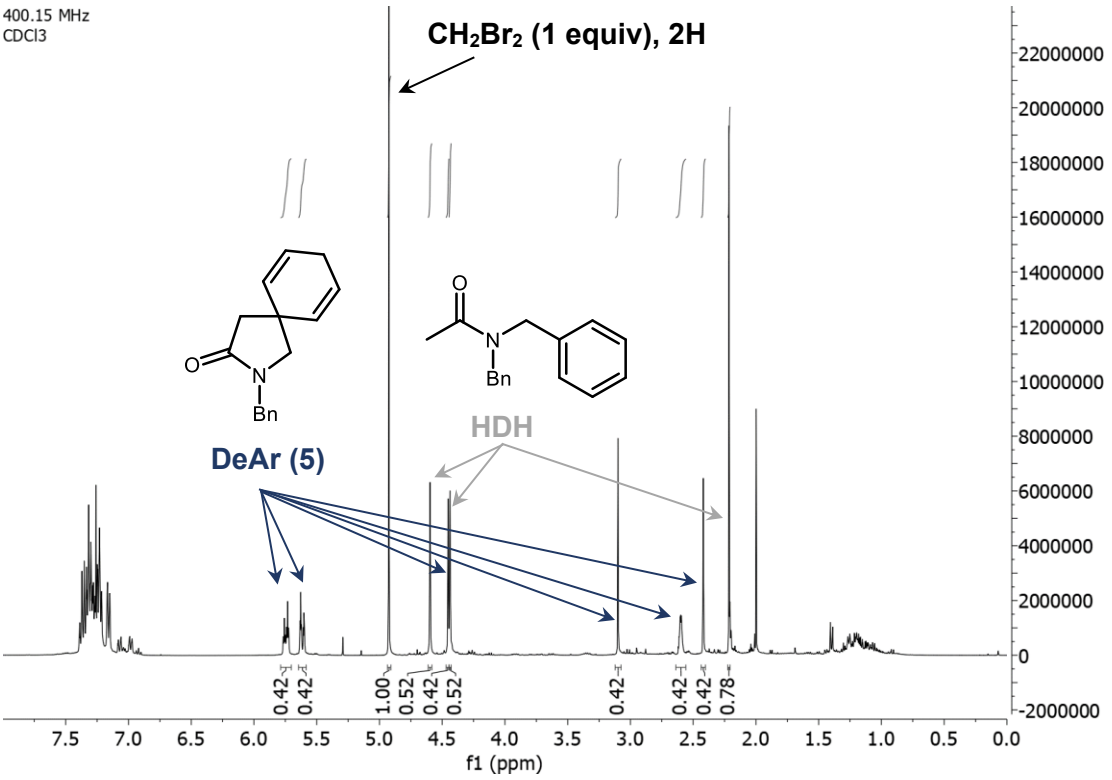
2-benzyl-2-azaspiro[4.5]deca-6,9-dien-3-one (5):

[129] Rauser, M.; Ascheberg, A.; Niggemann, M. Direct Reductive *N*-Functionalization of Aliphatic Nitro Compounds. *Chem. Eur. J.* **2018**, *24*, 3970-3974.

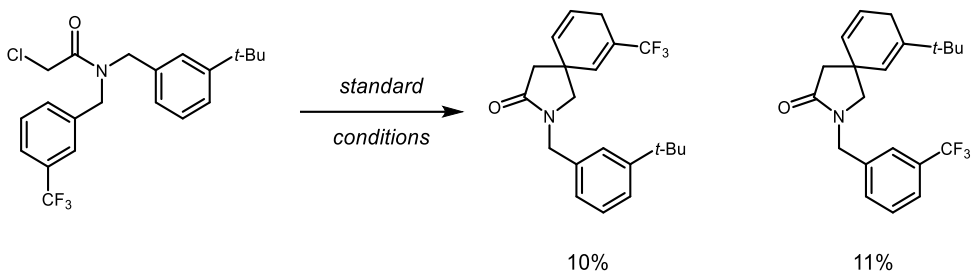
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N,N*-dibenzyl-2-chloroacetamide (27 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52 µL, 0.3 mmol, 3.0 equiv), and 50% H_2O/MeCN (2 mL, 0.05 M). $CDCl_3$ and an internal standard of dibromomethane (7 µL, 0.1 mmol) were added to the crude residue. The sample was analyzed by ^1H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (42%) and the hydrodehalogenation byproduct (52%). ^1H NMR spectrum of HDH byproduct is consistent with reported values.[130]

Characteristic peaks

^1H NMR (400 MHz, $CDCl_3$) δ 5.77 – 5.69 (m, 2H), 5.61 (dt, J = 10.4, 2.0 Hz, 2H), 4.45 (s, 2H), 3.10 (s, 2H), 2.60 (dtt, J = 4.1, 3.3, 2.1 Hz, 2H), 2.42 (s, 2H) ppm.



[130] Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. A Convenient and General Iron-Catalyzed Reduction of Amides to Amines. *Angew. Chem. Int. Ed.* **2009**, *48*, 9507-9510.



2-(3-*tert*-butylbenzyl)-7-(trifluoromethyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (32) and 7-*tert*-butyl-2-(3-(trifluoromethyl)benzyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (33):

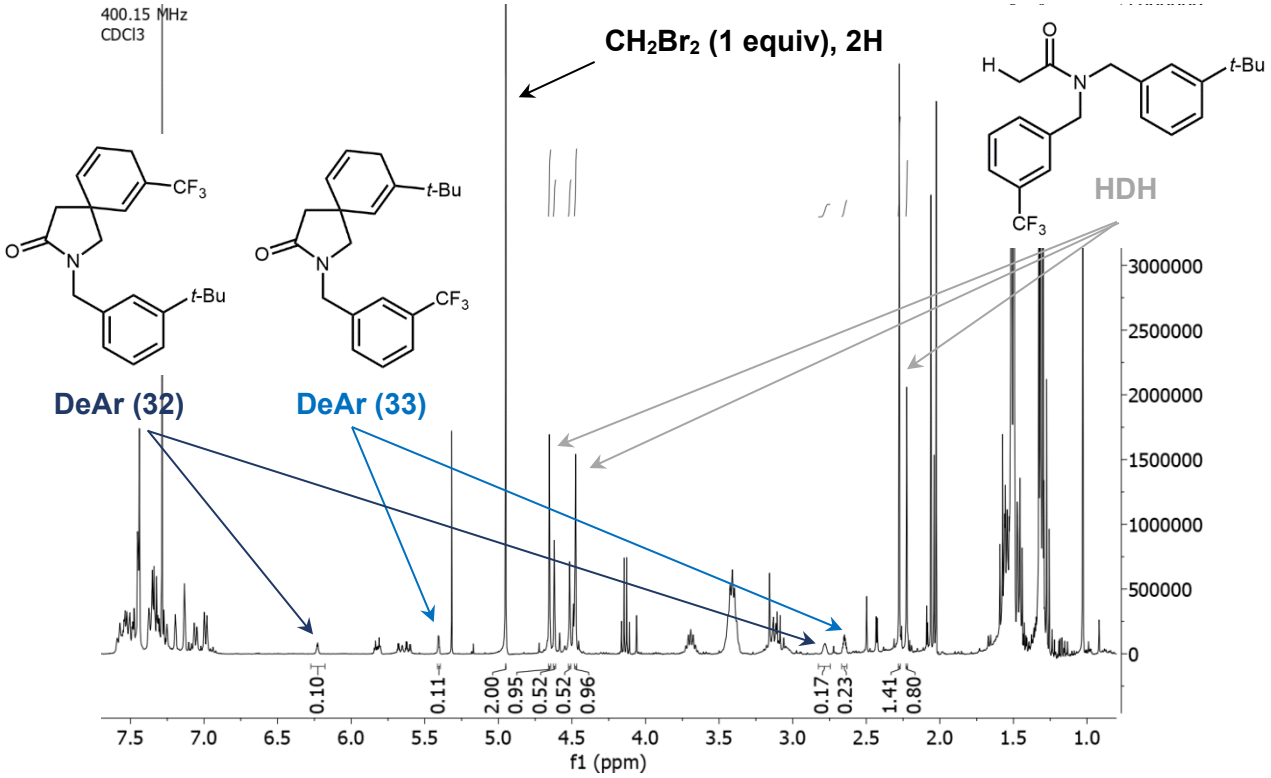
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(3-(*tert*-butyl)benzyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (**31**) (39.8 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52 μL, 0.3 mmol, 3.0 equiv), and 50% H_2O/MeCN (2 mL, 0.05 M). $CDCl_3$ and an internal standard of dibromomethane (7 μL, 0.1 mmol) were added to the crude residue. The sample was analyzed by ^1H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compounds (10%, 11%) and the hydrodehalogenation byproduct (74%).

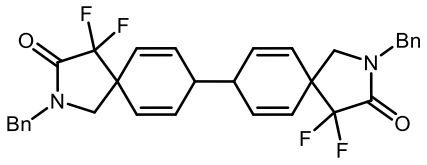
32 (characteristic peaks):

^1H NMR (400 MHz, $CDCl_3$) δ 6.26 – 6.18 (m, 1H), 2.81 – 2.74 (m, 2H) ppm.

33 (characteristic peaks):

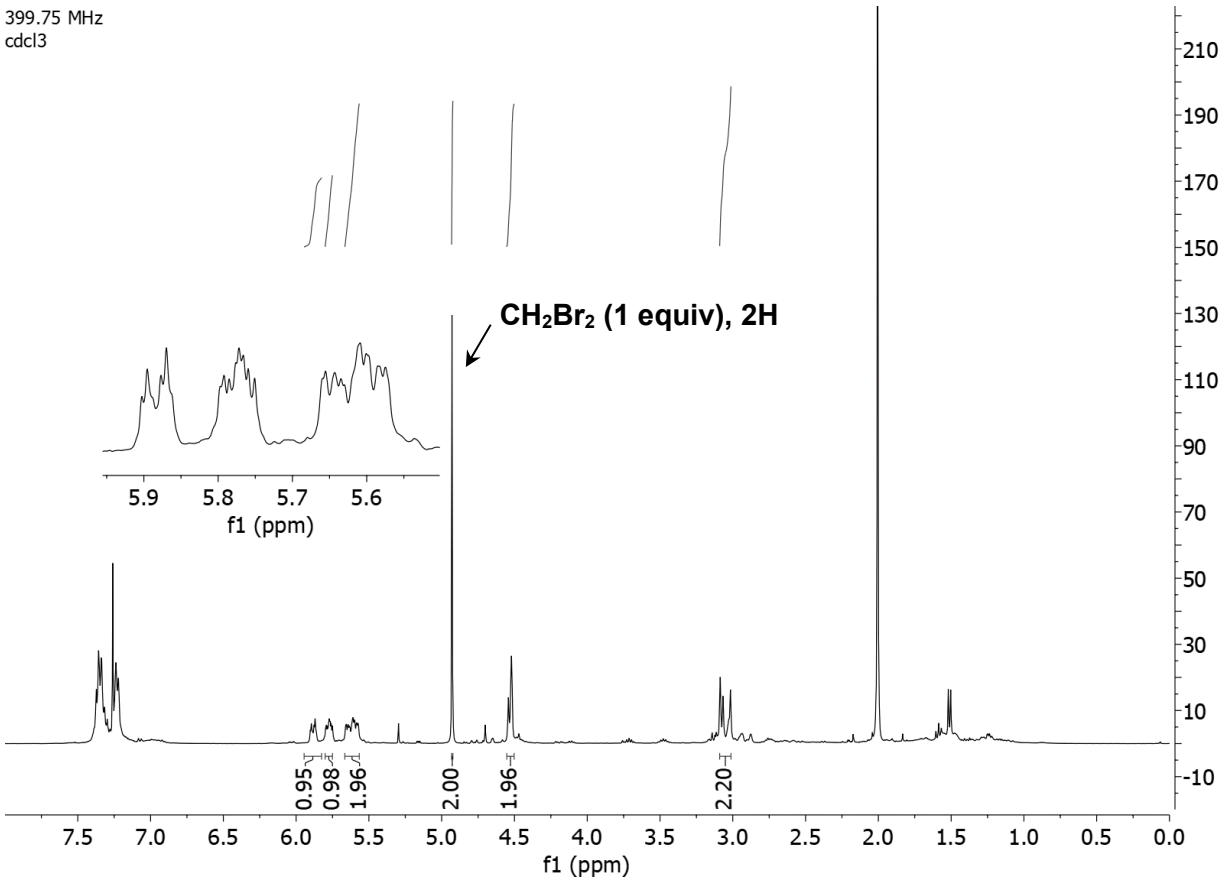
^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (q, J = 1.7 Hz, 1H), 2.65 (tt, J = 3.8, 1.9 Hz, 2H) ppm.

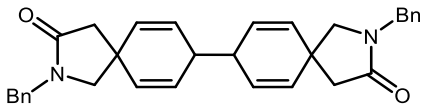

400.15 MHz
CDCl3
CH2Br2 (1 equiv), 2H
HDH
DeAr (32)
DeAr (33)
t-Bu
CF3
0.10
0.11
2.00
0.95
0.52
0.52
0.96
0.17
0.23
1.41
0.80
f1 (ppm)



2,2'-dibenzyl-4,4,4',4'-tetrafluoro-2,2'-diaza[8,8'-bispiro[4.5]decane-6,6',9,9'-tetraene]-3,3'-dione (S52):

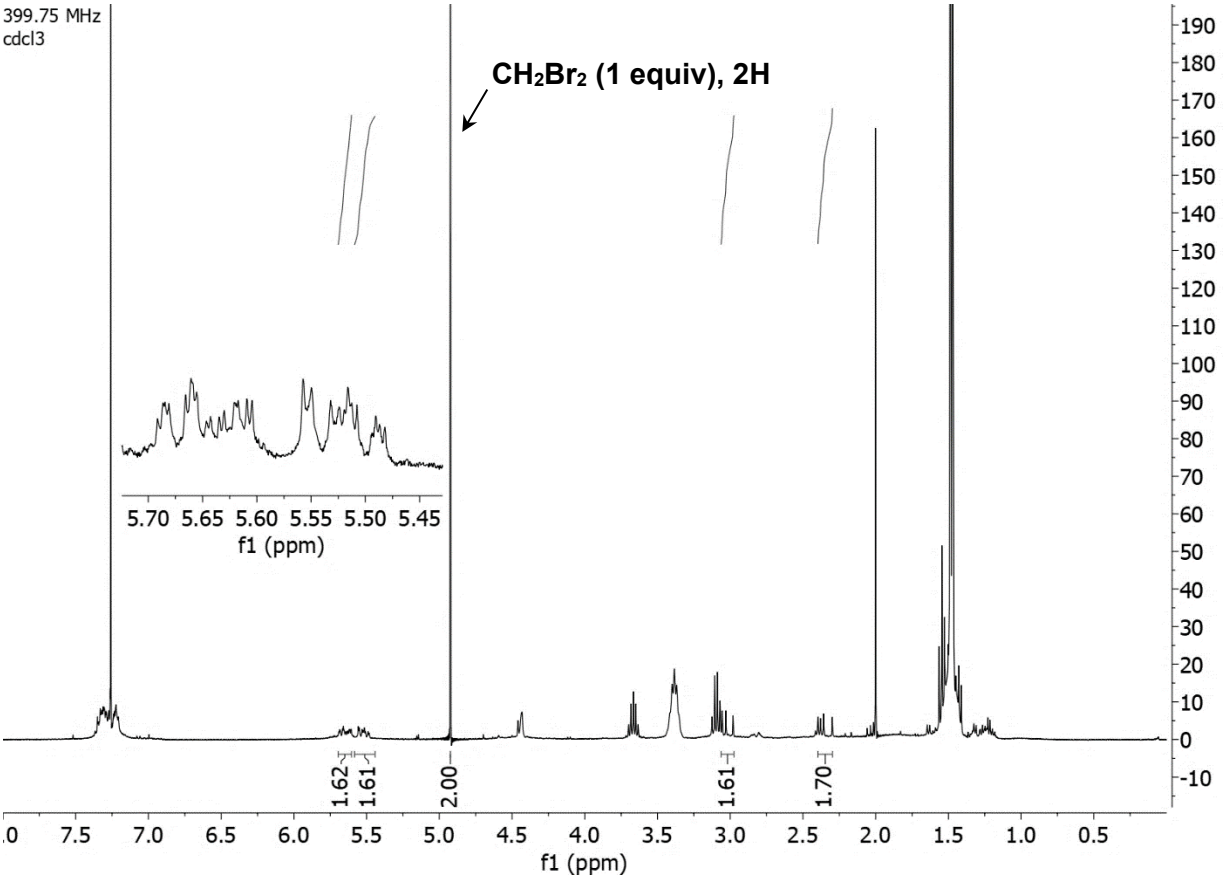
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*,*N*-dibenzyl-2-bromo-2,2-difluoroacetamide (**S49**) (35.4 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52 μL, 0.3 mmol, 3.0 equiv), and 50% H_2O/MeCN (2 mL, 0.05 M). $CDCl_3$ and an internal standard of dibromomethane (7 μL, 0.1 mmol) were added to the crude residue. The sample was analyzed by ^1H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (98%).



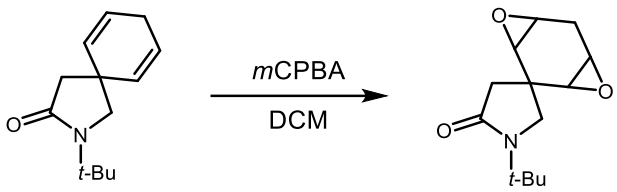


2,2'-dibenzyl-2,2'-diaza[8,8'-bispiro[4.5]decane-6,6',9,9'-tetraene]-3,3'-dione (S53):

Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*,*N*-dibenzyl-2,2,2-trichloroacetamide (**S50**) (34.3 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52 μL, 0.3 mmol, 3.0 equiv), and 50% H_2O/MeCN (2 mL, 0.05 M). $CDCl_3$ and an internal standard of dibromomethane (7 μL, 0.1 mmol) were added to the crude residue. The sample was analyzed by ^1H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (81%).

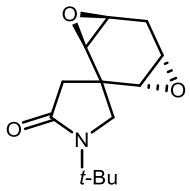


Derivatization



1-(*tert*-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0^{3,5}]octan]-5-one (36):

To an reaction vial charged with 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**40**) (62 mg, 0.3 mmol, 1.0 equiv) cooled to 0 °C was added CH_2Cl_2 (6 mL, 0.05 M) and *m*CPBA (75%, 172 mg, 0.75 mmol, 2.5 equiv). The resulting solution was allowed to stir at 23 °C for 17 hours. The precipitate was filtered and washed with CH_2Cl_2 and 1 M NaOH (aq). The filtrate was extracted with CH_2Cl_2 (3x), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified on silica gel (10-50% acetone/hexanes) to yield the title compound (57.0 mg, 82%, 5:6:1 d.r.; diastereomers 2 and 3 isolated as a mixture).



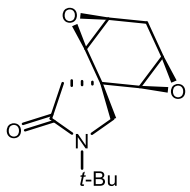
Diastereomer 1 (elutes first, 23.8 mg, white amorphous solid): (1'R,3'R,5'S,7'S)-1-(tert-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0^{3,5}]octan]-5-one:

R$_f$: 0.55 (50% acetone/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (d, J = 10.5 Hz, 1H), 3.37 (d, J = 10.5 Hz, 1H), 3.18 (tq, J = 4.0, 1.8 Hz, 2H), 2.94 (dt, J = 5.8, 2.9 Hz, 2H), 2.71 (d, J = 17.0 Hz, 1H), 2.42 (d, J = 16.9 Hz, 1H), 2.34 (t, J = 2.3 Hz, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 56.5, 55.9, 54.5, 52.4, 51.0, 50.8, 41.6, 34.8, 27.9, 23.9 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{20}NO_3$, 238.14377, found 238.14375.



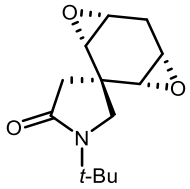
Diastereomer 2 (elutes second, 29.0 mg, white amorphous solid): (1'R,3r,3'S,5'R,7'S)-1-(tert-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0^{3,5}]octan]-5-one one:

R_f: 0.35 (50% acetone/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 2H), 3.23 (ddd, J = 4.1, 2.9, 1.2 Hz, 2H), 3.05 – 3.01 (m, 2H), 2.76 (dt, J = 17.3, 1.3 Hz, 1H), 2.43 (s, 2H), 2.24 (dt, J = 17.3, 3.0 Hz, 1H), 1.44 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.0, 55.8, 54.7, 53.1, 51.3, 41.0, 34.4, 27.9, 23.0 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{20}NO_3$, 238.14377, found 238.14384.



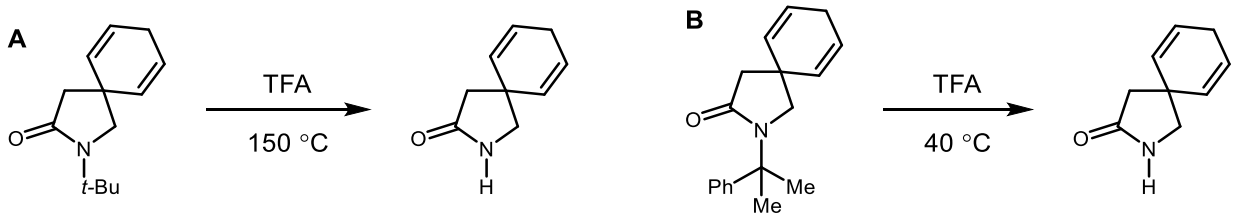
Diastereomer 3 (elutes second, 5.1 mg, white amorphous solid): (1'R,3s,3'S,5'R,7'S)-1-(tert-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0^{3,5}]octan]-5-one one *(characteristic peaks):*

R_f: 0.35 (50% acetone/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 2H), 3.20 (ddd, J = 3.9, 2.9, 1.2 Hz, 2H), 3.01 – 2.99 (m, 2H), 2.79 (s, 2H), 2.21 (dt, J = 17.2, 3.0 Hz, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 56.0, 54.5, 52.0, 41.6, 34.2, 27.9 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{20}NO_3$, 238.14377, found 238.14384.



2-azaspiro[4.5]deca-6,9-dien-3-one (34):

Procedure A: Dissolved 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**40**) (20.5 mg, 0.1 mmol, 1.0 equiv) in TFA (4 mL). The reaction was heated to 150 ºC in a pressure tube. After 16 hours, quenched with 1 M NaOH (aq), extracted with CH_2Cl_2 (3x) and concentrated under reduced pressure. The crude residue was purified on silica gel (10-100% ethyl acetate/hexanes) to yield the title compound as an off-white amorphous solid (14.9 mg, 100%).

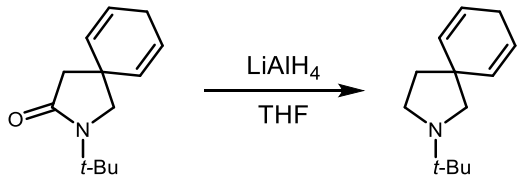
Procedure B: Dissolved 2-(2-phenylpropan-2-yl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**S41**) (57.8 mg, 0.22 mmol, 1.0 equiv) in TFA (1 mL). The reaction was heated to 40 ºC. After 2 hours, quenched with 1 M NaOH (aq), extracted with CH_2Cl_2 (3x) and concentrated under reduced pressure. The crude residue was purified on silica gel (20-100% ethyl acetate/hexanes) to yield the title compound as an off-white amorphous solid (19.0 mg, 59%).

R_f: 0.29 (100% EtOAc)

^{1}H NMR (600 MHz, CDCl3) δ 6.55 (s, 1H), 5.78 (dt, J = 10.4, 3.3 Hz, 2H), 5.72 (dt, J = 10.4, 2.0 Hz, 2H), 3.24 (s, 2H), 2.64 (tt, J = 3.5, 1.9 Hz, 2H), 2.28 (s, 2H) ppm.

^{13}C NMR 13C NMR (151 MHz, CDCl3) δ 177.3, 130.1, 124.7, 55.4, 45.3, 39.9, 26.3 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_9H_{12}NO$, 150.09134, found 150.09157.



2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-diene (35):

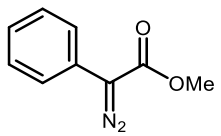
To an oven-dried reaction vial charged with 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**40**) (20.5 mg, 0.1 mmol, 1.0 equiv) was added THF (1 mL, 0.1 M). The solution was cooled to 0 °C and $LiAlH_4$ (1 M in THF, 0.25 mL, 0.25 mmol, 2.5 equiv) was added dropwise. The resulting solution was allowed to warm to 23 °C and stir for 20 hours. The reaction was cooled to 0 °C and diluted with Et_2O. Then 0.01 mL H_2O, 0.01 mL 15% NaOH (aq), and 0.03 mL H_2O were added sequentially, and the resulting solution was stirred for 15 minutes at 23 °C. Anhydrous $MgSO_4$ was added and the resulting suspension was stirred for an additional 15 minutes. After filtration and concentration under reduced pressure, the title compound was obtained as a white amorphous solid (19.1 mg, 100%).

R_f: 0.19 (5% MeOH/DCM)

^{1}H NMR (600 MHz, C_6D_6) δ 5.83 (dt, J = 10.4, 2.1 Hz, 2H), 5.60 (dt, J = 10.2, 3.3 Hz, 2H), 2.66 (t, J = 7.0 Hz, 2H), 2.63 (s, 2H), 2.49 (tt, J = 3.5, 2.1 Hz, 2H), 1.75 (t, J = 7.0 Hz, 2H), 1.00 (s, 9H) ppm.

^{13}C NMR (151 MHz, C_6D_6) δ 134.2, 122.0, 60.8, 52.0, 45.6, 42.1, 41.3, 26.8, 26.2 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{22}N$, 192.17468, found 192.17484.



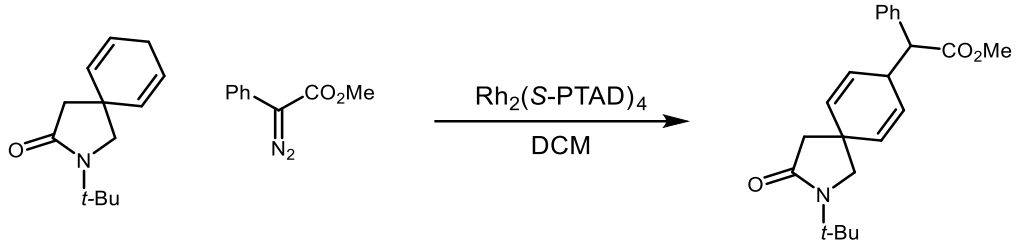
Methyl 2-diazo-2-phenylacetate (S54):

To a flame-dried round bottomed flask charged with methyl phenylacetate (601 mg, 4.0 mmol, 1.0 equiv) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA; 1.15 g, 4.8 mmol, 1.2 equiv) was added MeCN (40 mL, 0.1 M) followed by DBU (0.84 mL, 5.6 mmol, 1.4 equiv) dropwise. After stirring for 17 hours, the reaction was diluted with H_2O, extracted with EtOAc (3x), washed with saturated NH_4Cl (aq) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude

residue was purified on silica gel (1-5% EtOAc/hexanes) to afford the title compound as an orange oil (363 mg, 51%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 7.1 Hz, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 3.87 (s, 3H) ppm.

^{1}H NMR spectrum is consistent with reported values.[131]



Methyl 2-(2-(*tert*-butyl)-3-oxo-2-azaspiro[4.5]deca-6,9-dien-8-yl)-2-phenylacetate (37):

To an oven-dried reaction vial charged with 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**40**) (82 mg, 0.4 mmol, 2.0 equiv) and Rh_2(*S*-PTAD)$_4$ (1.6 mg, 0.001 mmol, 0.5 mol%) was added CH_2Cl_2 (0.5 mL). A solution of methyl 2-diazo-2-phenylacetate (**S54**) (35 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (3.0 mL) was added over 3 hours via syringe pump. The reaction was concentrated under reduced pressure. Purification of the crude residue on silica gel (10-20% EtOAc/hexanes) afforded title compound as a colorless oil (45.6 mg, 64%, 5:3 d.r.). An analytically pure fraction of each diastereomer was obtained.

Diastereomer 1 (elutes first, minor, 4.4 mg, colorless oil):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 5H), 5.77 (ddd, J = 10.1, 2.9, 1.8 Hz, 1H), 5.75 – 5.70 (m, 1H), 5.64 (dt, J = 10.1, 1.9 Hz, 1H), 5.46 (ddd, J = 10.2, 3.3, 1.8 Hz, 1H), 3.68 (s, 3H), 3.46 (ddq, J = 9.1, 3.1, 1.6 Hz, 1H), 3.39 (d, J = 9.1 Hz, 1H), 3.25 (d, J = 10.0 Hz, 1H), 3.22 (d, J = 10.0 Hz, 1H), 2.08 (s, 2H), 1.36 (s, 9H) ppm.

[131] Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. Copper(II) Triflate Catalyzed Intermolecular Aromatic Substitution of *N*,*N*-Disubstituted Anilines with Diazo Esters. *Eur. J. Org. Chem.* **2010**, *35*, 6719-6721.

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 173.3, 136.2, 132.0, 131.8, 128.9, 128.7, 127.8, 127.1, 126.1, 58.1, 57.4, 54.1, 52.3, 47.1, 39.1, 37.0, 29.9, 27.9 ppm.

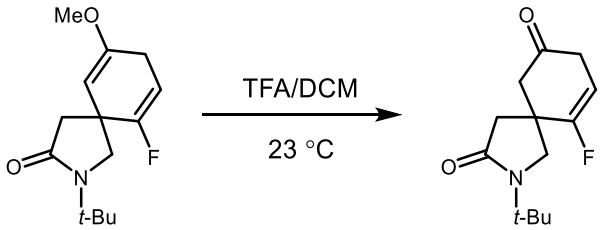
LRMS (APCI) m/z: $[M+1]^+$ calc'd. for $C_{22}H_{28}NO_3$, 354.2, found 354.2.

Diastereomer 2 (elutes second, major, 2.4 mg, colorless oil):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 5H), 5.78 – 5.72 (m, 1H), 5.72 – 5.67 (m, 1H), 5.63 (dt, J = 10.2, 1.7 Hz, 1H), 5.57 (ddd, J = 10.2, 2.9, 1.8 Hz, 1H), 3.70 (s, 3H), 3.51 – 3.47 (m, 1H), 3.45 (d, J = 8.2 Hz, 1H), 2.86 (d, J = 10.0 Hz, 1H), 2.82 (d, J = 10.0 Hz, 1H), 2.25 (s, 2H), 1.32 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 173.2, 136.1, 132.2, 132.2, 129.3, 128.4, 127.7, 126.9, 126.0, 57.8, 57.3, 54.2, 52.3, 47.4, 39.2, 36.8, 29.9, 27.9 ppm.

LRMS (APCI) m/z: $[M+1]^+$ calc'd. for $C_{22}H_{28}NO_3$, 354.2, found 354.2.



2-(*tert*-butyl)-10-fluoro-2-azaspiro[4.5]dec-9-ene-3,7-dione (38):

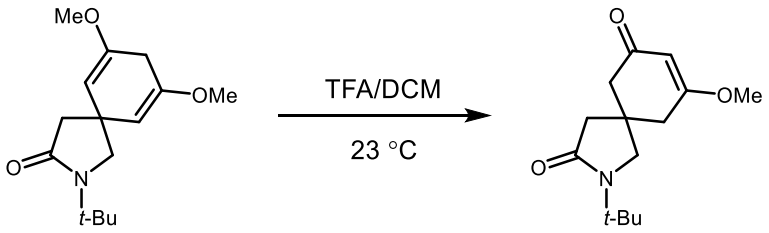
Dissolved 2-(tert-butyl)-6-fluoro-9-methoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (**26**) (6.0 mg, 0.024 mmol) in CH_2Cl_2 (1.0 mL) and added TFA (0.2 mL). After 16 hours, quenched with 1M NaOH (aq), extracted with DCM (3x) and concentrated under reduced pressure to obtain the title compound as a yellow oil (5.7 mg, 100%).

R_f: 0.58 (100% EtOAc)

^{1}H NMR (400 MHz, CDCl3) δ 5.40 (dt, J = 15.5, 3.9 Hz, 1H), 3.58 (dt, J = 10.0, 0.8 Hz, 1H), 3.21 (dt, J = 10.1, 0.6 Hz, 1H), 3.05 (ddd, J = 20.9, 5.5, 3.6 Hz, 1H), 2.93 (d, J = 16.6 Hz, 1H), 2.89 (dt, J = 20.9, 4.6 Hz, 1H), 2.77 – 2.62 (m, 2H), 2.19 (d, J = 16.6 Hz, 1H), 1.38 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ 204.6 (d, $^{4}J_{C-F}$ = 2.5 Hz), 171.8, 158.6 (d, $^{1}J_{C-F}$ = 260.1 Hz), 101.8 (d, $^{2}J_{C-F}$ = 22.2 Hz), 54.6, 53.4 (d, $^{3}J_{C-F}$ = 1.5 Hz), 50.0 (d, $^{3}J_{C-F}$ = 5.3 Hz), 42.2 (d, $^{3}J_{C-F}$ = 2.5 Hz), 40.6 (d, $^{2}J_{C-F}$ = 23.9 Hz), 37.4 (d, $^{3}J_{C-F}$ = 8.1 Hz), 27.8 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{19}FNO_2$, 240.13943, found 240.13983.



2-(*tert*-butyl)-9-methoxy-2-azaspiro[4.5]dec-8-ene-3,7-dione (39):

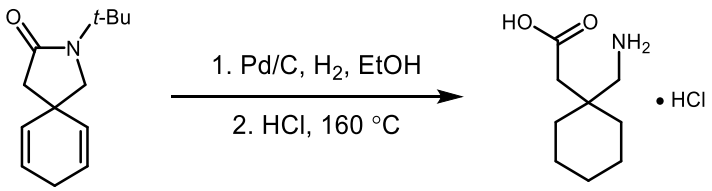
Dissolved 2-(*tert*-butyl)-7,9-dimethoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (**15**) (2.8 mg, 0.011 mmol) in CH_2Cl_2 (0.5 mL) and added TFA (0.1 mL). After 18 hours, quenched with saturated $NaHCO_3$ (aq), extracted with EtOAc (3x) and concentrated under reduced pressure to obtain the title compound as a yellow oil (2.7 mg, 100%).

R_f: 0.14 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (s, 1H), 3.75 (s, 3H), 3.34 (s, 2H), 2.60 – 2.43 (m, 4H), 2.47 (s, 2H), 1.39 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 197.6, 176.6, 174.2, 102.2, 56.7, 56.5, 55.3, 47.2, 44.9, 40.0, 36.2, 27.9 ppm.

HRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{14}H_{22}NO_3$, 252.15942, found 252.15975.



2-(1-(aminomethyl)cyclohexyl)acetic acid hydrochloride (41):

Dissolved 2-(tert-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**40**) (102.6 mg, 0.50 mmol, 1.0 equiv) in methanol (20 mL, 0.025 M). Added palladium (5% on carbon, wet basis, 5 mg), and evacuated and backfilled with hydrogen. After 16 hours, the reaction mixture was filtered through a plug of celite to afford a white solid, which was added to a microwave vial with hydrochloric acid (37% in water, 5 mL), and microwaved at 160°C for 16 hours. The resulting reaction mixture was extracted with CH_2Cl_2 (4x) and Et_2O (1x). The aqueous phase was azeotroped with acetonitrile under reduced pressure. The resulting white solid was sonicated in Et_2O and vacuum filtered to afford the title compound as a white solid (103 mg, 52%).

^{1}H NMR (600 MHz, D_2O) δ 3.12 (s, 2H), 2.56 (s, 2H), 1.57 – 1.35 (m, 10H) ppm.

^{1}H NMR spectrum is consistent with reported values.[132]

[132] Nagatomo, M.; Nishiyama, H.; Fujino, M. Decarbonylative Radical Coupling of α-Aminoacyl Tellurides: Single-Step Preparation of γ-Amino and α,β-Diamino Acids and Rapid Synthesis of Gabapentin and Manzacidin A. *Angew. Chem. Int. Ed.* **2015**, *54*, 1537-1541.