LATE-STAGE C(sp^3)–H HYDROXYLATION, AMINATION, AND METHYLATION IN NITROGEN-CONTAINING MOLECULES

BY

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DISSERTATION

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ABSTRACT

Direct installation of oxygen, nitrogen, and methyl functionalities into C(sp^3)–H bonds is a topic of significant synthetic and medicinal interest. These modifications have the potential to drastically change a molecule's physical and biological properties, which could lead to the discovery of new medications. Among FDA-approved small-molecule drugs, 84% contain at least one nitrogen atom. Functionalization of these molecules via transition metal catalysis faced substantial challenges, as the strongly Lewis basic nitrogen is prone to bind to the Lewis acidic metal center, thereby either shutting down the catalysis or limiting functionalization to sites proximal to itself as a directing group. Consequently, functionalizations at sites remote from nitrogen and mediated by ligated transition metal catalysts were elusive. On the other hand, functionalizations alpha to nitrogen via hydroxylation have been demonstrated, but the hydroxylated intermediates are by nature more hyperconjugatively activated than the substrates and promote overoxidation, thus requiring reduction before further derivatization. In this dissertation, I describe new methods that address these issues and selectively functionalize these nitrogen-containing molecules both at sites remote from nitrogen and alpha to nitrogen to install hydroxyl, amino, and methyl groups at late stages.

The first chapter of this dissertation focuses on the development of a remote oxidation strategy using small-molecule iron catalysts Fe(PDP) and Fe(CF_3PDP). These catalysts have shown excellent regioselectivity in oxidizing complex molecules based on the electronic, steric, and stereoelectronic environments of their aliphatic C–H bonds, but were previously unreactive toward amines and pyridines due to nitrogen-metal binding. Key to the success of this new strategy was the use of a strong Brønsted acid (HBF_4) or azaphilic Lewis acid (BF_3), which

irreversibly protonates or binds with the basic nitrogen, thus stripping its ability to bind with the iron center. This protection simultaneously renders the nitrogen motif a strong electron-withdrawing group, inductively deactivating its proximal sites and promoting remote oxidation. For tertiary amines and pyridines, the HBF_4 protection rendered optimal yields of remotely oxidized products. For sterically unhindered secondary and primary amines, complexation with BF_3 is preferred, as it produced stable complexes that can be readily oxidized in good yields and purified via silica chromatography. A site-selective late-stage hydroxylation was demonstrated on an analogue of prostate cancer drug abiraterone. A previously reported computational model was expanded to include nitrogen-containing substrates, and accurately predicted the site of oxidation among fifteen possible sites.

In the second chapter, I describe the expansion of the nitrogen protecting strategy to enable late-stage benzylic amination in amines, pyridines, imide, and benzimidazole. Although preparative benzylic amination is achievable with rhodium catalysis, its functionalization of basic amines either only occur alpha to nitrogen and on nitrogen, or does not occur at all when the nitrogen is acid-protected, likely because of the labile ligand. Using a highly acid-stable and easily obtainable catalyst, $[Mn^{III}(ClPc)]$, and an inert polar solvent, 1,2-dichloroethane, remote amination was achieved on a series of basic-nitrogen-containing molecules with high chemoselectivity and site-selectivity. In general, HBF_4 protection gave higher yields, but BF_3 is preferable when the HBF_4 protonation results in low solubility. Imide nitrogens are already deactivated by its carbonyls and need no acid protection. Late-stage amination was demonstrated in six derivatives of drugs and natural products containing competing sites, where only the most electron-rich and sterically accessible secondary benzylic site was aminated. The sulfonamide products can be easily deprotected using zinc-copper couple to produce the free amines.

In the final chapter, I discuss the development of a late-stage methylation strategy. Frequently referred to as the "magic methyl" effect, installation of methyl groups adjacent to heteroatoms is especially desirable for medicinal chemists, as this modification often leads to significant potency boost. Traditional alkylation methods rely on metalation followed by treatment with alkyl electrophiles. This process is unselective and has very a limited heterocycle scope. This work describes a different approach via oxidized hemiaminal intermediates, which significantly expanded the substrate scope. Key challenges addressed include chemoselectivity, overoxidation, elimination, and functional group tolerance. A small-molecule manganese catalyst, Mn(CF_3PDP), was previously introduced for selective methylene oxidation and tolerates electron-poor arenes. By significantly lowering its catalyst loading to a 200:1 substrate to catalyst ratio, deleterious aromatic oxidation and overoxidation to imides were suppressed and unprecedented tolerance for electron-rich and electron-neutral arenes was established. The use of the commercial mild nucleophile, trimethylaluminum, along with one of three mild hemiaminal activation methods (BF_3, DAST, TFAA/TMSOTf), enabled late-stage methylation on nine derivatives of drugs and natural products without eroding electrophilic functional groups or causing elimination. Additionally, methylation of a secondary aniline and remote methylation of the same abiraterone analogue can be achieved by altering the reaction conditions to include a stronger nucleophile or activation method. Collectively, these methods now provide rapid access to metabolites and drug derivatives while reducing synthetic effort, time, and cost, and I expect their wide applications in the discovery research for novel therapeutics.

Soli Deo gloria

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CHAPTER 1: REMOTE OXIDATION OF ALIPHATIC C–H BONDS IN NITROGEN-CONTAINING MOLECULES

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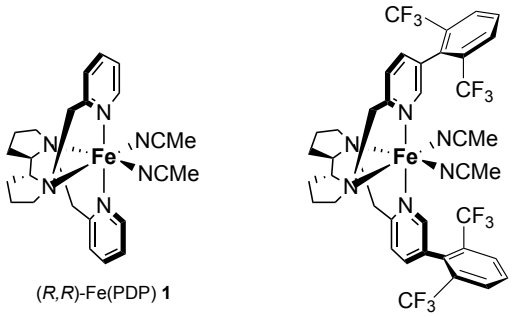
1.1 Introduction

The direct transformation of a C–H bond into a C–O bond is of substantial interest among medicinal chemists.[1] Aliphatic C–H bonds are ubiquitous across all classes of organic molecules, including natural products and pharmaceuticals. Introduction of oxygen functionalities could dramatically change the physical and biological properties of these molecules, such as flavor and toxicity.[1] However, one significant challenge in drug discovery is the synthesis of these oxygenated derivatives, in which chemists traditionally rely on either functional group manipulations or de novo synthesis. These processes significantly lengthen the synthetic sequence, leading to low overall yields. Conversely, a method that enables direct and preparative hydroxylation of C–H bonds at late stages would significantly expedite the process of studying metabolites and optimizing drug leads, reduce cost, and facilitate drug discovery.

Figure 1. Non-Heme Small-Molecule Iron Catalysts



(*R*,*R*)-Fe(PDP) **1**

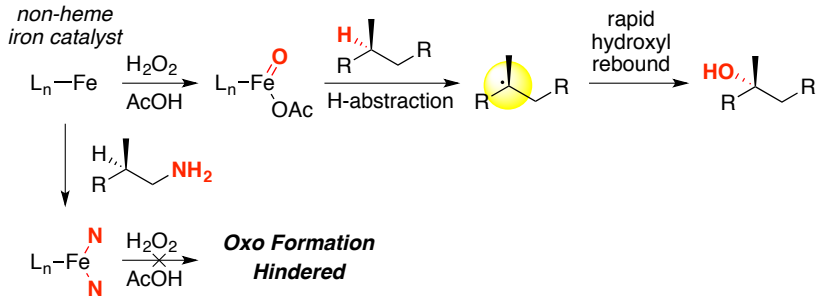
(*R*,*R*)-Fe(CF_3PDP) **2**

This type of C(sp^3)–H oxidations are efficiently and selectively performed in nature by cytochrome P450 enzymes. One prominent example of this is its selective oxidation of taxadiene to paclitaxel,[2] which requires a substantial effort to obtain synthetically.[3] Mimicking the function of nature's enzymatic machinery, cytochrome P450, with a small-molecule catalyst had been a great challenge.[4] Since 2007, our group has developed a suite of tunable, non-heme, small-molecule iron catalysts, Fe(PDP) and Fe(CF_3PDP) (Figure 1).[5] These catalysts selectively and preparatively hydroxylate molecules via high-valent iron-oxo intermediates, differentiating different C–H bonds based on their electronic, steric, and stereoelectronic properties.

However, nature encounters a limit in C–H oxidation when facing molecules with more electron-rich functional groups, such as amines. The basic nitrogen atom is proposed to bind to the iron center in cytochrome P450, resulting in C–C bond cleavage α to the nitrogen with no hydroxylation occurring.[6] Likewise, these non-heme iron catalysts were not able to tolerate basic nitrogen functionality (Figure 2). This poses a significant limitation to the application of iron-catalyzed C–H oxidation as approximately 84% of small-molecule drugs contain at least one nitrogen atom, 70% in which contain a nitrogen heterocycle.[7] Although primary and secondary amines can be protected by acyl or sulfonyl protecting groups, this strategy is not applicable on tertiary amines and pyridines with no replaceable N–H. Moreover, in acyl or sulfonyl protected

primary and secondary amines, the hyperconjugative ability of the nitrogen atom activates the C–H bond α to the nitrogen and results solely in α-functionalization.[8] Similarly, strategies using nitrogen as a directing group in primary and secondary amines only lead to functionalization proximal (i.e., α, β, γ) to the nitrogen functionality.[9] With a ligated, tunable transition metal catalyst, remote C(sp^3)–H oxidation in nitrogen containing molecules has never been achieved prior to our work. We sought to develop a general nitrogen protection strategy that would enable remote, non-directed C–H oxidation employing non-heme iron catalysts.

Figure 2. Proposed C–H Hydroxylation Mechanism



Considering the strong basicity of nitrogen, we envisioned by applying a Lewis or Brønsted acid to the substrate prior to oxidation, the nitrogen will lose its lone pair and be deactivated while rendered a strong electron-withdrawing group.[10] As the highly electrophilic iron oxo strongly disfavors electron-deficient C(sp^3)–H bonds, we envisioned that this strategy will also deactivate all C–H bonds proximal to the protonated nitrogen, thus affording remote site-selectivity.

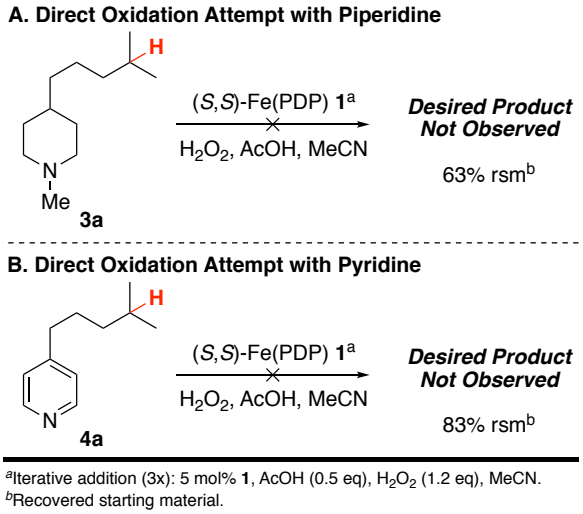
1.2 Results and Discussion

1.2.1 Initial Studies and Reaction Optimization

Initial investigations evaluated the oxidation of tertiary piperidine **3a** and pyridine **4a**, two of the most prevalent nitrogen heterocycles in FDA-approved drugs (Figure 3).[7] These

attempts proved unfruitful and no product was observed, showing a protection strategy is necessary. Inspired by previous studies regarding Lewis acid boron trifluoride (BF_3), which is prone to form amine-BF_3 complexes[11] and has some precedents in palladium-catalyzed allylic C–H acetoxylations,[12] we envisioned that by pre-complexing the amine substrates with BF_3 we would be able to achieve aliphatic C(sp^3)–H oxidation with our catalysts.

Figure 3. Initial Direct Oxidation Attempts on Nitrogen Heterocycles

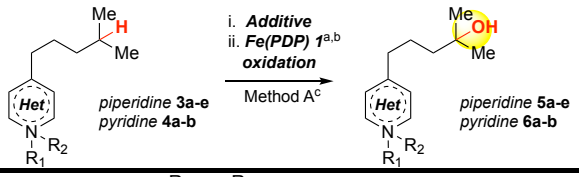


[a]Iterative addition (3x): 5 mol% **1**, AcOH (0.5 eq), H_2O_2 (1.2 eq), MeCN.
[b]Recovered starting material.

Encouragingly, we observed oxidation with both **3a** and **4a** in moderate yields (Table 1, entries 1, 2).[13] We reasoned that the steric bulk and modest basicity could render BF_3 binding reversible and cause yield diminishment.[14] Therefore, alternative strategies providing stronger nitrogen binding were explored. Irreversible protonation with a strong Brønsted acid has been previously used as a protection strategy in olefin oxidation and metathesis, as well as methyl(trifluoromethyl)dioxirane (TFDO) and a Shilov oxidation that was investigated concurrent with our study.[15] By employing tetrafluoroboric acid (HBF_4), a strong Brønsted acid (pK_a = -0.4) with a non-coordinating counterion, we were able to oxidize both **3a** and **4a** in greatly improved yields (entries 3, 7). Trifluoroacetic acid (pK_a = 0.2) and sulfuric acid[15e] (pK_{a1} = -3.0, pK_{a2} = 2.0), while also efficiently strong acids, both generate counterions capable of

catalyst binding, and afforded minimal yields (entries 4, 5). An in situ protocol with HBF_4 leaves excessive acid in the reaction system, which may cause ligand protonation and proved non-beneficial for the oxidation (entry 6). Pyridine *N*-oxides, although proved a successful protection strategy in the palladium catalysis,[12] did not afford the desired product (entry 8).

Table 1. Reaction Optimization



Entry	Heterocycle	R_1	R_2	Additive (equiv)	Yield (%) (rsm)[d]
1	**3a**	Me	-	BF_3•OEt_2 (1.1)	46 (28)
2	**4a**	-	-	BF_3•OEt_2 (1.1)	27 (67)
3	**3a**	Me	-	HBF_4•OEt_2 (1.1)	56 (29)
4	**3a**	Me	-	F_3CCO_2H (1.1)	5 (74)
5[e]	**3a**	Me	-	H_2SO_4 (1.1)	0 (76)
6[f]	**3a**	Me	-	HBF_4•H_2O (1.1)	43 (40)
7	**4a**	-	-	HBF_4•OEt_2 (1.1)	57 (23)
8[a]	**4b**	O	-	-	0 (65)
9[a]	**3b**	Boc	-	-	n.d. (37)
10[a]	**3c**	TFA	-	-	n.d. (11)
11	**3d**	H	-	HBF_4•OEt_2 (1.1)	40 (26)
12[a,g]	**3e**	H	BF_3	-	44 (22)

[a]Iterative addition (3x): 5 mol% **1**, AcOH (0.5 equiv), H_2O_2 (1.2 equiv), MeCN. [b]Catalyst enantiomers used interchangeably. [c]Method A: (i) Additive (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Iterative addition, (iii) 1M NaOH. [d]Isolated yields, % recovered starting material (rsm). [e]No product observed with H_2SO_4 (0.55 equiv). [f]In situ addition of HBF_4 (1.1 equiv). [g]2° Piperidine-BF_3 complex **3e** isolated and purified. Product **5e** isolated/purified as 2° piperidine-BF_3 complex.

For secondary piperidines, common acyl-protecting groups failed to deliver C–H oxidation in a site-selective manner and resulted in multiple products, possibly due to *N*-dealkylation pathways (entries 9, 10). The HBF_4 protection strategy was viable and afforded moderate yield (entry 11). However, due to the strong basicity and polarity of the substrates and products, purification and storage can be problematic. Primary and secondary amines are known to absorb carbon dioxide from the atmosphere to form carbamates.[16] We hypothesized that the stronger basicity and reduced steric hindrance would result a stronger N–BF_3 interaction that would persist under the oxidative reaction conditions, and afford the product as a stable,

nonpolar, and isolable complex. Encouragingly, we were able to observe a slightly increased yield using the BF_3-protection strategy (entry 12).

Table 2. Site-Selectivity Study

Entry	Heterocycle	R	Yield (%) (rsm)[c]	Selectivity[d]
1	**7a**	Me	57 (4)	1:1 δ/mixture
2	**7b**	-	53 (10)	2.6:1 δ/γ

[a]Catalyst enantiomers used interchangeably. [b]Method B: (i) Additive (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Slow addition: 25 mol% **2**, AcOH (5.0 equiv), H_2O_2 (9.0 equiv), MeCN, (iii) 1M NaOH. [c]Isolated yields, % recovered starting material (rsm). [d]Based on isolation.

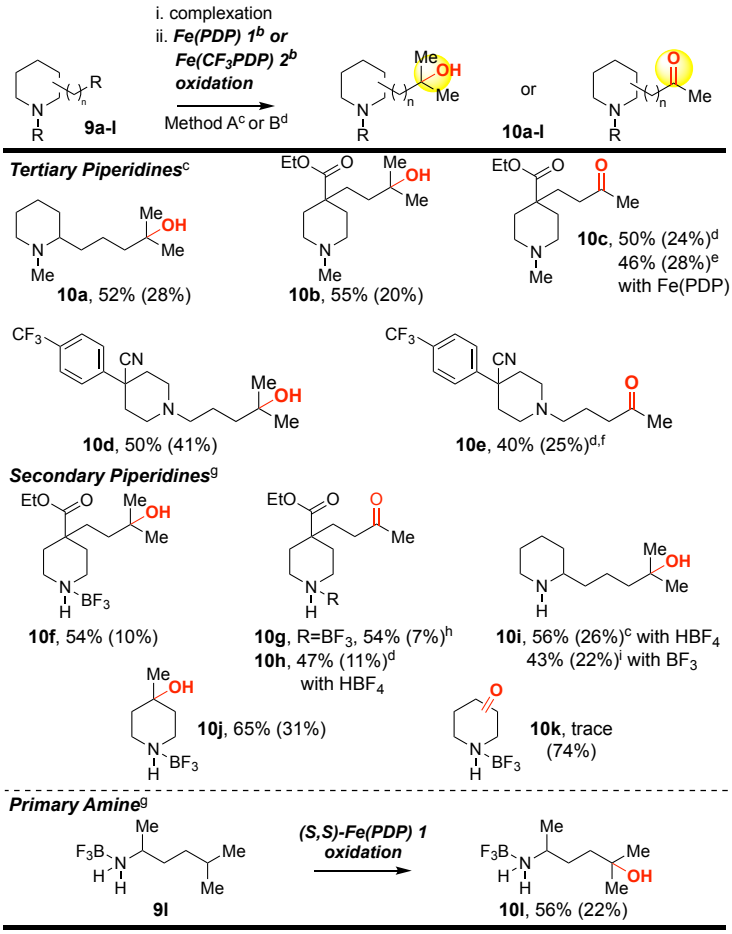
We next sought to examine the remote site-selectivity limit of the electron-withdrawing effect rendered by nitrogen complexation. Piperidine **7a** and pyridine **7b** have long linear alkyl chains. Their potential sites for oxidation are sterically near identical and differentiated only by their electronic properties. Since all the potential sites are unactivated secondary sites, their electron density difference will largely depend on the electron-withdrawing ability of the protonated remote nitrogen atom. Piperidine **7a** was oxidized in good overall yields but with no selectivity, whereas the oxidation of pyridine **7b** was moderately selective in a 2.6:1 ratio favoring the most remote secondary site (Table 2). Significantly, no isolable amount of benzylic oxidation was observed. This study suggests that protonation of the pyridine renders the aromatic system a stronger electron-withdrawing group than the saturated protonated piperidine, and can more effectively deactivate remote sites.

1.2.2 Reaction Scope and Site-Selectivity

Piperidine is the most prevalent nitrogen heterocycle in FDA approved drugs, with substitutions mostly seen on N, C4 and C2 positions.[7] We examined HBF_4 protonation strategy on a series of piperidine substrates with substitution on these sites. Notably, under Fe(PDP)

catalysis, all *N*-methyl and *N*-alkyl substrates were oxidized in preparative yields with excellent site-selectivity (Figure 4).

Figure 4. Oxidation of Basic Amines



[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Catalyst enantiomers used interchangeably. [c]Method A with HBF_4•Et_2O (1.1 equiv). [d]Method B. [e]Method B with **1**. [f]Starting material recycled 1x. [g]Method A with BF_3•Et_2O (1.1 equiv) concd and purified prior to use. Isolated as BF_3-complex, no NaOH workup. [h]Method B with BF_3•Et_2O (1.1 equiv) concd and purified prior to use. [i]Method A with BF_3•Et_2O (1.1 equiv). Isolated as BF_3-complex, no NaOH workup.

The HBF_4 protection strategy was beneficial in the sterically encumbered substrate **9a**, which proceeded efficiently and afforded **10a** in 52% yield. Ester and nitrile functionalities are well tolerated in the oxidation, despite potential competition of hydrolysis and functional group oxidation (**10b**, **c**). Fe(CF_3PDP) has proven to be a better catalyst for methylene oxidations,[6c] as the small cone-angle of this catalyst prevents off-site oxidation and generally affords higher yields, as seen in the oxidation of **9c**. Electron-deficient aromatic rings are also tolerated. In 4-

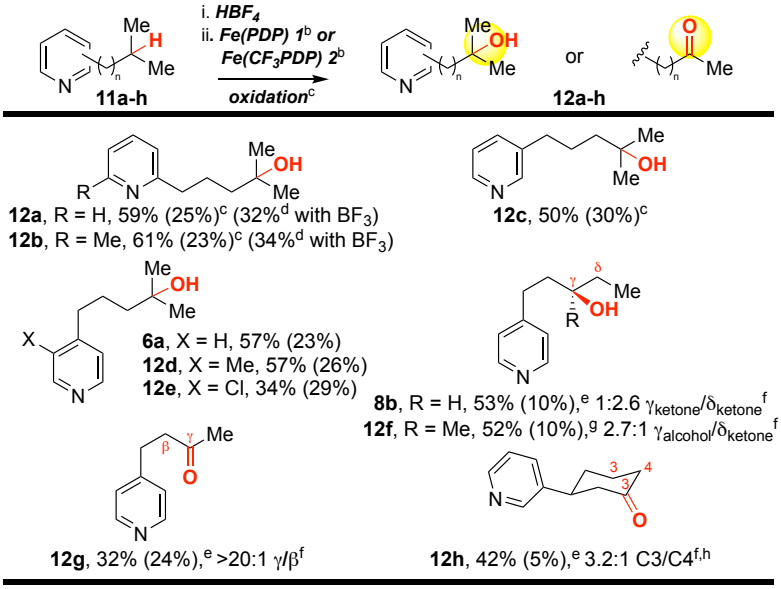
phenylpiperidine substrates representing a pharmacophore found in opioids,[17] the 4-(trifluoromethyl)phenyl ring persisted through oxidation (**10d**, **e**). Encouragingly, **9c** and **9e** were oxidized in synthetically useful yields, demonstrating that closer proximity to nitrogen and electron-withdrawing groups improves site-selectivity.

In secondary piperidines, the BF_3 protection strategy was proven effective: oxidation of **9f** afforded preparative yields. When the nitrogen is sterically unencumbered and substitution is farther away, the BF_3 protection strategy is beneficial for isolation/purification and afforded higher yields (**10g** vs **10h**). However, in cases with sterically encumbered substrates, BF_3 protection is less effective due to the bulky size of BF_3. Protection with HBF_4 is preferable in this case, as in the oxidation of **9i** (43% with BF_3 and 56% with HBF_4, respectively). Notably, despite the close distance to nitrogen, 4-methylpiperidine **9j** was oxidized in 65% yield, generating the corresponding alcohol, while oxidation of piperidine **9k** with secondary sites only afforded trace product. This further stressed the electronic difference and reactivity between tertiary and secondary C–H bonds. The BF_3 complexation strategy is also competent for primary amines, and afforded **10l** in 56% yield. The BF_3 complex can be readily converted to the corresponding free amine, either by base-mediated hydrolysis or exposure to a nucleophilic fluoride source.

Pyridine is the second most common nitrogen heterocycle in FDA approved pharmaceuticals and the most prevalent among aromatics.[7] The oxidation challenge associated with pyridine-based substrates is two-fold: the lower basicity may cause weaker binding or reversible protonation, and the aromatic ring may suffer from oxidative destruction.[6] Despite these challenges, the protonation/oxidation of both mono- and disubstituted 2-alkylpyridines proceeded in good yields (Figure 5, **12a**, **b**). The HBF_4 protection method again proves beneficial for sterically encumbered substrates, as BF_3 protection afforded diminished yields.

Long-chain 3-alkylpyridine is the most prevalent in natural products.[18] Encouragingly, the oxidation proceeded smoothly in 50% yield (**12c**). While the oxidation worked well with electron-rich pyridines (**6a**, **12d**), the yield and mass balance decreased when the substrate contains electron-withdrawing groups, such as a chlorine atom (**11e**), possibly due to lowered basicity of the pyridine ring. While the aforementioned oxidation of **7b** rendered a distal preference (**8b**, 1:2.6 γ/δ), oxidation of its analogue **11f** with a methyl at *γ* position reversed the selectivity favoring the exposed tertiary site (**12f**, 2.7:1 γ/δ). Analogue **11g**, being one carbon shorter than **7b**, afforded diminished yield due to lower electron density, but with greatly improved site-selectivity (>20:1 γ/β, **12g**). In a cyclohexane-derived substrate **11h**, the sterically bulky pyridyl group rendered stereoelectronic preference for the C3 position, and overrode electronically preferred C4 in oxidation (**12h**, 1.6:1 C3/C4) to produce ketone products in 42% overall yield.

Figure 5. Oxidation of Pyridines

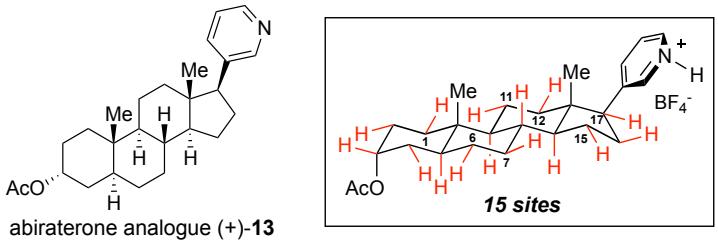


[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Catalyst enantiomers used interchangeably. [c]Method A with HBF_4•Et_2O (1.1 equiv). [d]Method B with BF_3•OEt_2 (1.1 equiv), catalyst **1** and 20% NaOH workup. [e]Method B. [f]Based on isolation. [g]Starting material recycled 1x. [h]1.6:1 C3/C4 adjusted for number of hydrogens.

1.2.3 Application in Late-Stage Derivatization

Having evaluated the protection strategies on simple molecules with positive outcomes, we next sought to apply these strategies on the late-stage diversification of complex molecules. I selected an analogue of abiraterone, a steroidal antiandrogen drug for treatment of prostate cancer. The abiraterone analogue (+)-**13** contains 15 possible sites open for oxidation, including aromatic rings, benzylic sites, and numerous secondary and tertiary sites (Figure 6). I hypothesized the pyridine ring will be deactivated by the electron-withdrawing effect of protonation, but the possibility of other sites being oxidized are hard to visually differentiate.

Figure 6. Abiraterone Analogue (+)-**13**

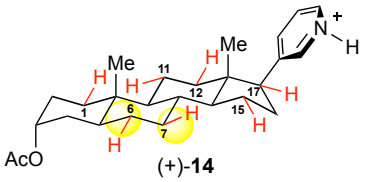


In 2013, Gormisky and White reported a quantitative, predictive model for Fe(PDP) and Fe(CF_3PDP) for predicting potential sites for oxidation in complex molecules.[5c] However, this model is mostly built on substrates with known oxidation results, and has never been applied in the nitrogen protection system. The protonated substrate differs from the substrates studied in the model in the overall charge of the molecule and the strong inductive effect of the protonated nitrogen. I sought to employ this model in predicting the oxidation outcome on the HBF_4 protected abiraterone analogue.

By applying the electronic- and steric-based site filter in both protonated molecules according to procedures described by Gormisky and White,[5c] I was able to downscale the number of potentially oxidizable sites. The electronic factors were obtained through calculation of natural partial atomic charges (NPA, B3LYP/6-311++G(d,p)). The steric factors were

calculated by considering the local and through-space steric, as well as stereoelectronic effect. In addition to the certain approximations previously applied to simplify the calculation (e.g., methylene as ethyl, methine as isopropyl, quaternary carbon as *t*-butyl),[6c] I considered aromatic rings (e.g., phenyl, protonated pyridine) as phenyl groups when they are free to rotate, and as acetyl groups when their positions are constrained in the molecule. Smaller numbers indicate less partial positive charge or steric hindrance and are therefore more oxidatively preferable. From the site filter analysis, electronically or sterically unflavored sites were eliminated for HBF_4-protonated substrates (+)-**14** (Table 3).[19]

Table 3. Oxidation Site Filter for Protonated Abiraterone Analogue (+)-**14**



(+)-**14**

Site (H_{eq} atom)	Electronic Parameter (E)	Steric/ Stereoelectronic Parameter (S)
C1	0.2013	9.41
C6*	0.2098	5.82
C7	0.2030	6.90
C11	0.2147	7.44
C12	0.1957	9.49
C15	0.2201	6.72
C17	0.2212	12.59

Red = highly reactive, purple = moderately reactive, blue = unreactive.

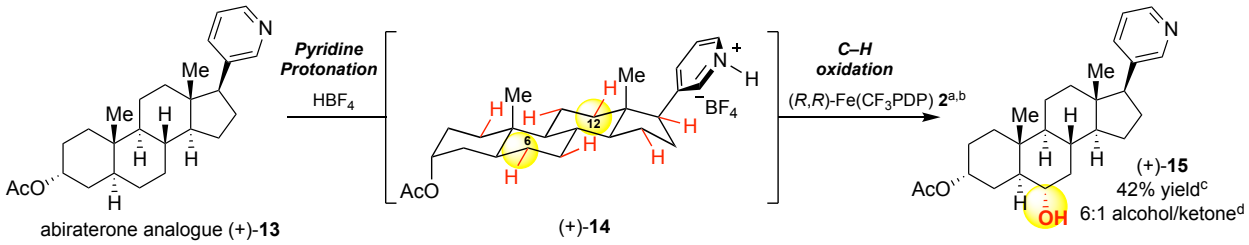
Sites with one blue parameter or two purple parameters were immediately eliminated due to their unlikeness to be chosen by the catalyst. Notably, in this case the benzylic site was suggested electronically unfavorable and eliminated by the site filter, indicating the strong electron withdrawing effect has turned the normally activated site into an unfavored site for oxidation.

The selection of reference site is important in the calculation process. When the model was being built, the most oxidatively favored sites were selected as the reference sites.[6c]

However, such strategy does not apply for prediction of molecules with unknown oxidative outcomes. Experimentally, steric factor contributes the largest in site-selectivity with Fe(CF_3PDP).[5c] Therefore, the least sterically hindered C–H bond was used as the reference site. In (+)-**14**, C6 is the least hindered site (S = 5.82) and the corresponding equatorial hydrogen was chosen as the reference.

Sterically, C6 is the most favored site. In comparison, C12 is the most electronically favored (0.1957 versus 0.2098) but sterically more encumbered (9.49 versus 5.82). All other sites are either less electron-rich or more hindered for oxidation. The calculation suggests a predominant preference on C6 (Figure 7). Consistent with the calculation, the oxidation afforded 42% oxidation product at C6 as 6:1 alcohol/ketone, while no significant amount of C12 oxidation product was detected. This again signified the strong preference of Fe(CF_3PDP) over the steric environment of the C–H bonds.

Figure 7. Oxidation of Abiraterone Analogue (+)-**13**



Sites (*a*:*b*)	ΔE_{ab}	ΔS_{ab}
C6:C12	-1.02	1.36

Input into Structure-Based Reactivity Model

Sites (*a*:*b*)	Calc'd $\Delta\Delta G^{\ddagger}$ (kcal/mol)	Calc'd Ratio	Observed Ratio
C6:C12	10.04	>20:1	>20:1

[a]Substrates containing chirality demonstrated matched/mis-matched reactivity with catalyst enantiomers. [b](i) HBF_4•Et_2O (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Iterative addition with **2**, (iii) $NaHCO_3$. [c]Starting material recycled 2x. [d]Based on isolation.

Significantly, this is the first example of transition-metal-mediated remote C(sp^3)–H oxidation on nitrogen-containing steroid skeletons. These results show that by employing the nitrogen protection strategy, site-selective oxidation can be achieved in complex molecules at

sites remote from nitrogen similar to in the more simple molecules. The site and selectivity of oxidation can be predicted through the computation model with predictable outcomes.

1.3 Conclusion

This work enables aliphatic C–H oxidation of nitrogen-containing molecules at sites remote to nitrogen. Basic nitrogen atoms can be tamed by employing Lewis/Brønsted acids and rendered strong electron-withdrawing groups. In contrast of common practice using nitrogen as a directing group to install functional groups in the proximal sites (α, β, γ), this strategy inverted the electronic nature of nitrogen and afforded remote site-selectivity. Oxidation on HBF_4/BF_3 protected simple and complex piperidines, amines (3°, 2°, 1°) and pyridines generally proceeded in good selectivity and preparative yields (≥50% mono-oxidized product). The quantitative model simplifies late-stage diversification with predictively oxidative outcome. The application of these strategies has the potential to greatly broaden the scope of iron-catalyzed $C(sp^3)$–H oxidation and enable a new approach to rapidly diversify nitrogen-containing complex molecules for medicinal chemists.

1.4. Experimental Section

1.4.1 General Methods

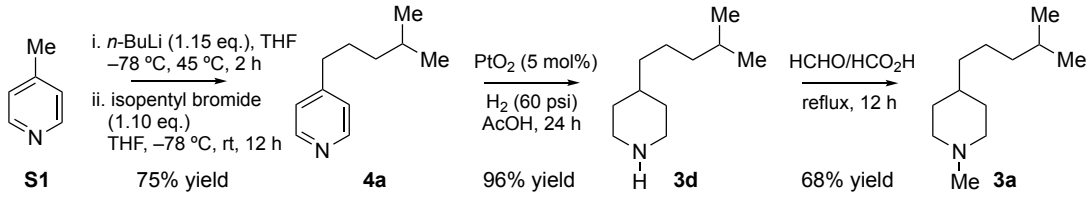
Experimental. All C–H oxidations were run under air with no precautions taken to exclude moisture. All other reactions were run under an Ar or N_2 atmosphere with dry solvent in flame dried glassware unless otherwise noted. Dry solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), dimethylsulfoxide (DMSO) and acetonitrile (MeCN) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna

Beach, CA). Triethylamine and pyridine were distilled from calcium hydride. Commercially available reagents that were used as received are noted in the individual reaction procedures. (*S,S*)- and (*R,R*)-2,2'-bispyrrolidine tartrate were prepared according to the literature procedure.[20] The ee of the diamine was checked by conversion to the dibenzoate and analysis by reverse phase HPLC; obtained either enantiomer in >99% ee (Chiralpak AD-RH, 35:60:5 MeCN:H_2O:*i*-PrOH, 0.8 mL/min., 30℃, t_R(*S,S*)=10.803 min., t_R(*R,R*)=13.240 min.). (*S,S*)- and (*R,R*)- Fe(PDP) **1**[5a] and Fe(CF_3PDP) **2**[5c] were prepared according to literature procedures and stored at 4 °C in a desiccator, prior to use catalysts were warmed to room temperature and weighed out in air. Thin-layer chromatography (TLC) was conducted with E. Merck TLC silica gel 60 F_{254} pre-coated plates (0.25 mm) or E. Merck TLC aluminum oxide 60 F_{254}, basic, pre-coated glass backed plates. Visualization was conducted with UV, ninhydrin and potassium permanganate ($KMnO_4$) stain. Flash chromatography was performed as described by Still[21] using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.) or basic aluminum oxide, Brockmann grade III (6% H_2O added to Brockmann grade I) prepared from Alfa Aesar aluminum oxide, activated, basic, Brockmann grade I, 58 angstroms, 60 mesh power, S.A. 150m^2/g, CAS: 1344-28-1. Medium pressure liquid chromatography was performed on a Teledyne Isco CombiFlash Rf machine using pre-packed RediSep columns (12 g SiO_2).

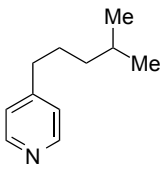
Structural analysis. ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Inova-500 (500 MHz), Varian Unity-500 (500 MHz), Varian Unity-600 (600 MHz) and a Varian 750 (750 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CHCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, hept = heptet, m = multiplet, br = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100

MHz), Varian Unity-500 (125 MHz) and Varian Inova-500 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). ^{19}F spectra were recorded on Varian Untiy 500 (470 MHz) or Varian VXR 500 (470 MHz) and are reported in ppm using $FCCl_3$ (0 ppm) as an external standard. The ^{13}C NMR spectra will contain the same impurities as the ^{1}H NMR spectra as they were generally obtained from the same sample. Impurities were calculated out when reporting isolated yields. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX FT-IR and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectrometry (HRMS) performed by Dr. Furong Sun, Dr. Kevin Tucker, Dr. Haijun Yao and Dr. Elizabeth Eves at the University of Illinois Mass Spectrometry Laboratory. X-ray crystallographic analysis carried out by Dr. Jeffery Bertke and Dr. Danielle Gray at the University of Illinois George L. Clark X-Ray Facility. Optical rotations were measured in a 1 mL cell with with 50 mm path length on a Jasco P2000 digital polarimeter, sodium lamp and are reported as follows: $[a]_{\lambda}^{T\,^{\circ}C}$ concentration (c = g / 100 mL, solvent).

1.4.2 Synthesis of Substrates and Characterization for Table 1



General Pyridine Alkylation Procedure



4-(4-Methylpentyl)pyridine [4a] The known compound was prepared following the published procedure and the ^{1}H NMR spectra matched that reported.[22] To a flame dried two-neck round bottom flask equipped with an addition funnel and magnetic stir bar was added 4-picoline **S1** (5.4 mL, 55.01 mmol, 1.00 equiv.) dissolved in THF (25 mL) and the solution was cooled to -78 ºC via an acetone/dry ice bath. *n*-Butyllithium (39.5

mL, 63.26 mmol, 1.15 equiv., 1.6 M in Hex) was added slowly, upon complete addition the reaction was removed from the -78 ºC bath and warmed to room temperature and stirred at 45 ºC for 2 hours. The resultant 4-picolyllithium salt slurry was dissolved with THF (25 mL) to give a deep red homogeneous solution. The solution was cooled to 0 ºC and slowly transferred via cannula to a solution of isopentyl bromide (9.14 g, 7.3 mL, 60.51 mmol, 1.10 equiv.) in THF (10 mL) cooled to -78 ºC. The reaction solution was gradually warmed to room temperature and stirred overnight. Reaction was quenched at room temperature with the addition of H_2O (3 mL). Reaction was filtered through a SiO_2 (250 mL)/sand plug and rinsed with EtOAc (1.5 L, volume = 6 x SiO_2 volume) and the solvent was evaporated. The residue was further purified by flash chromatography (500 mL SiO_2, gradient elution 20→40% EtOAc/Hex) to afford 4-(4-methylpentyl)pyridine **4a** as a dark orange oil (6.77 g, 41.47 mmol, 75% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.47 (d, *J* = 6.0 Hz, 2H), 7.09 (d, *J* = 5.7 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 4H), 1.65 – 1.51 (m, 3H), 1.24 – 1.17 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H);

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.83, 149.77, 124.02, 38.56, 35.60, 28.29, 27.96, 22.66;

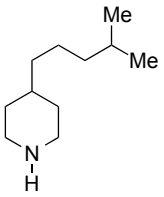
IR: (ATR, neat, cm^{-1})

3068, 3025, 2956, 2869, 1932, 1602, 1558, 1496, 1467, 1415, 1384, 1367, 1218, 1168, 1070, 993, 813, 792, 734;

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{18}N$ 164.1439; Found 164.1438

General Pyridine Hydrogenation Procedure



4-(4-Methylpentyl)piperidine [3d] To a 100 mL round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)pyridine **4a** (2.3 g, 14.09 mmol, 1.00 equiv.), AcOH (30 mL, 0.47 M) and PtO_2 (159 mg, 0.70 mmol, 5 mol%); rinsed catalyst from side of round bottom flask with AcOH (2 mL). The reaction was placed into a metal pressure reactor, sealed and purged with H_2 (3 x ~70 psi). After purging the metal pressure reactor was pressurized with H_2 (~70 psi) and stirred overnight at room temperature. Upon completion of the reaction as monitored by TLC analysis the reaction solution color changed from red to colorless. The reaction was filtered through a celite/cotton plug, rinsing with AcOH (100 mL) and concentrated via rotary evaporation. The resultant residue was diluted with H_2O (150 mL) and basified by the addition of 50% aq. NaOH (pH = 10-11). The basic aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layer was washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated via rotary evaporation to afford 4-(4-methylpentyl)piperidine **3d** as a yellow oil (2.3 g, 13.58 mmol, 96% yield), no further purification required. ***Important Note:*** *4-(4-methylpentyl)piperidine **3d** readily forms carbamic acid upon exposure to air at room temperature. The carbamic acid was a crystalline solid and was confirmed by ^{1}H NMR. Material was moved forward immediately to the next step or stored under an argon atmosphere at –20 ºC.*

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.03 (dt, *J* = 12.5, 3.2 Hz, 2H), 2.56 (td, *J* = 11.9, 2.4 Hz, 2H), 1.64 (br d, *J* = 12.2 Hz, 2H), 1.51 (dp, *J* = 13.2, 6.5 Hz, 1H), 1.44 (br s, 1H), 1.36 – 1.23 (m, 3H), 1.21 – 1.14 (m, 2H), 1.17 – 1.08 (m, 2H), 1.05 (qd, *J* = 11.9, 11.4, 4.0 Hz, 2H), 0.85 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

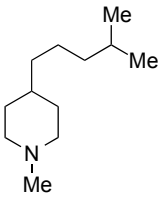
δ 47.11, 39.34, 37.68, 36.47, 33.98, 28.11, 24.38, 22.78;

IR: (ATR, neat, cm^{-1})

3272, 2904, 2805, 2732, 1743, 1650, 1465, 1444, 1384, 1365, 1319, 1255, 1145, 1124, 1101, 1047, 1006, 987, 950, 917, 904, 759

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{24}N$ 170.1909; Found 170.1906



1-Methyl-4-(4-methylpentyl)piperidine [3a] Prepared following the published procedure.[23] To a round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)piperidine **3d** (1.54 g, 9.10 mmol, 1.00 equiv.), formaldehyde (2.2 g, 2.0 mL, 27.30 mmol, 3.00 equiv., 37% w/w in H_2O) and formic acid (2.5 g, 2 mL, 54.60 mmol, 6.00 equiv.). Round bottom was fitted with a condenser and placed in a preheated oil bath (100-110 ºC). Reaction was refluxed overnight. Reaction progress was monitored by TLC analysis. Upon completion the reaction solution was cooled to 0 ºC and basified with 50% aq. NaOH (pH = 10-11). The basic aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated via rotoevaporation. The crude material was purified by flash chromatography (170 mL SiO_2, gradient elution 5% MeOH/CH_2Cl_2 doped with 1% NH_4OH→10% MeOH/CH_2Cl_2 doped with 2% NH_4OH). Fractions were combined and concentrated to an oil that was taken up in CH_2Cl_2 and washed with an equal volume of 1M NaOH to remove residual NH_4OH and water. Dried over anhydrous Na_2SO_4, filtered and concentrated to afford 1-methyl-4-(4-methylpentyl)piperidine **3a** as a yellow oil (1.13 g, 6.16 mmol, 68% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.83 (d, *J* = 12.1 Hz, 2H), 2.25 (s, 3H), 1.88 (t, *J* = 11.7 Hz, 2H), 1.66 (d, *J* = 10.4 Hz, 2H), 1.51 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.33 – 1.21 (m, 3H), 1.24 – 1.15 (m, 4H), 1.17 – 1.09 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

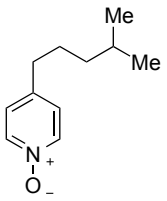
δ 56.24, 46.64, 39.35, 36.98, 35.27, 32.65, 28.13, 24.66, 22.79

IR: (ATR, neat, cm^{-1})

2912, 2778, 2734, 2680, 1712, 1677, 1643, 1573, 1556, 1463, 1378, 1367, 1280, 1199, 1145, 1112, 1072, 981, 767

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{12}H_{26}N$ 184.2065; Found 184.2063



4-(4-Methylpentyl)pyridine 1-oxide [4b] To a 100 mL round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)pyridine **4a** (653 mg, 4.00 mmol, 1.0 equiv.), *meta*-chloroperoxybenzoic acid (1.18 g, 4.80 mmol, 1.2 equiv., 70 wt.% in H_2O) and CH_2Cl_2 (40 mL). The reaction mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (SiO_2, gradient elution 40% EtOAc/Hex→10% MeOH/CH_2Cl_2) afforded pyridine *N*-oxide **4b** as a yellow oil (583.3 mg, 3.25 mmol, 81% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

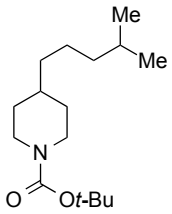
δ 8.12 (d, *J* = 6.9 Hz, 2H), 7.07 (d, *J* = 6.7 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.65-1.49 (m, 3H), 1.24-1.15 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (100 MHz, $CDCl_3$)

δ 142.76, 138.87, 126.07, 38.33, 34.73, 28.14, 27.91, 22.63

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{18}NO$ 180.1388; Found 180.1394



***Tert*-butyl 4-(4-methylpentyl)piperidine-1-carboxylate [3b]** Prepared following the published procedure.[24] To a solution of 4-(4-methylpentyl)piperidine **3d** (500 mg, 2.953 mmol, 1.00 equiv.) in dioxane-water (1:1 dioxane/H_2O, 1 M) was added Et_3N (415 mL, 2.953 mmol, 1.00 equiv.) followed by di-*tert*-butylcarbonate (882 mL, 3.839 mmol, 1.30 equiv.) at room temperature and the resulting reaction solution was stirred overnight. The product was then extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with 1 M HCl (1 x 30 mL) and brine (1 x 30 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (60 mL SiO_2, gradient elution 2→5→10% EtOAc/Hex, 1 column volume each) to afford *tert*-butyl 4-(4-methylpentyl)piperidine-1-carboxylate **3b** as a colorless oil (686.0 mg, 2.546 mg, 86% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

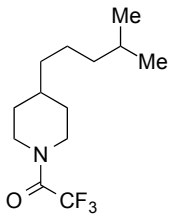
δ 4.06 (br s, 2H), 2.66 (t, *J* = 12.6 Hz, 2H), 1.64 (dd, *J* = 13.4, 3.5 Hz, 2H), 1.52 (tt, *J* = 12.3, 6.1 Hz, 1H), 1.45 (s, 9H), 1.36 (ddq, *J* = 14.9, 7.8, 4.4, 3.9 Hz, 1H), 1.33 – 1.24 (m, 2H), 1.24 – 1.15 (m, 2H), 1.18 – 1.10 (m, 2H), 1.06 (qd, *J* = 12.4, 4.4 Hz, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 155.06, 79.23, 44.27, 39.28, 36.92, 36.13, 32.39, 28.63, 28.08, 24.49, 22.76

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{16}H_{32}NO_2$ 270.2433; Found 270.2434



2,2,2-Trifluoro-1-(4-(4-methylpentyl)piperidin-1-yl)ethan-1-one [3c] Prepared following the published procedure.[25] To a flame-dried 50 mL round bottom flask was added 4-(4-methylpentyl)piperidine **3d** (500 mg, 2.953 mmol, 1.00 equiv.), CH_2Cl_2 (15 mL, 0.2 M) and Et_3N (617 mL, 4.430 mmol, 1.50 equiv.), the solution was cooled to 0 ºC and trifluoroacetic anhydride (616 mL, 4.430 mmol, 1.50 equiv.) was added. Reaction solution was gradually warmed to room temperature and stirred 12 hours. The reaction solution was poured slowly into aqueous saturated $NaHCO_3$ solution (50 mL) at 0 ºC. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). Combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography (60 mL SiO_2, gradient elution 2→5→10% EtOAc/Hex, 1 column volume each) to afford 2,2,2-trifluoro-1-(4-(4-methylpentyl)piperidin-1-yl)ethan-1-one **3c** as a colorless oil (686.4 mg, 2.587 mmol, 88% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.51 (ddt, *J* = 13.2, 4.4, 2.6 Hz, 1H), 3.99 (dd, *J* = 12.9, 4.0 Hz, 1H), 3.08 (td, *J* = 13.5, 2.6 Hz, 1H), 2.74 (td, *J* = 12.6, 2.8 Hz, 1H), 1.80 (dd, *J* = 13.1, 1.9 Hz, 2H), 1.58 – 1.48 (m, 2H), 1.34 – 1.26 (m, 2H), 1.26 – 1.20 (m, 2H), 1.20 – 1.11 (m, 4H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

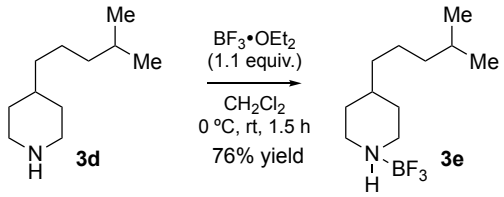
δ 155.29, 116.79 (q, *J* = 286.0 Hz), 46.29 (q, *J* = 3.6 Hz), 44.16, 39.16, 36.48, 35.97, 32.85, 31.87, 28.05, 24.42, 22.73

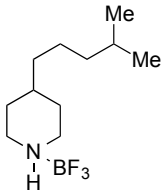
^{19}F NMR: (470 MHz, $CDCl_3$)

δ -69.27

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{13}H_{23}NOF_3$ 266.1732; Found 266.1736





Trifluoro(4-(4-methylpentyl)piperidine-1-ium-1-yl)borate [3e] To a flame-dried 50 mL round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)piperidine **3d** (637 mg, 3.76 mmol, 1.00 equiv.) and CH_2Cl_2. The solution was cooled to 0 ºC and BF_3•OEt_2 (511 mL, 4.13 mmol, 1.10 equiv.) was added. The solution was stirred at 0 ºC for 30 minutes followed by 1 hour room temperature. Solvent was removed via rotoevaporation. The crude material was purified by flash chromatography (70 mL SiO_2, gradient elution 15→20→25→50→75→100% EtOAc/Hex, 1 column volume each) to afford trifluoro(4-(4-methylpentyl)piperidine-1-ium-1-yl)borate **3e** as a white crystalline solid (675.8 mg, 2.850 mmol, 76% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.47 (br s, 1H), 3.41 (d, *J* = 13.4 Hz, 2H), 2.72 (tdd, *J* = 13.7, 11.6, 2.8 Hz, 2H), 1.95 (d, *J* = 14.8 Hz, 2H), 1.56 – 1.43 (m, 2H), 1.33 – 1.10 (m, 8H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 46.05, 39.08, 36.62, 34.65, 31.31, 28.03, 24.25, 22.72

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.29 (q, J = 16.0 Hz)

HRMS: (ESI-TOF MS ES-)

m/z: $[M–H]^-$ calculated for $C_{11}H_{22}NBF_3$ 236.1797; Found 236.1800

1.4.3 Experimental Procedures and Characterization for Table 1

General screening procedure to evaluate heterocycle protecting groups for remote aliphatic C–H oxidation (Table 1, entries 1-6 and 10) (GSP1). To a flame-dried 40 mL vial equipped with a stir bar was added heterocycle (0.50 mmol, 1.0 equiv.) and CH_2Cl_2 (2.0 mL, 0.25 M) the vial was flushed with a N_2 stream and then cooled to 0 ºC. The additive (BF_3•OEt_2, HBF_4•OEt_2 or F_3CCO_2H) (0.55 mmol, 1.1 equiv.) was added dropwise via syringe. The reaction mixture was stirred for 30 minutes at 0 ºC and then warmed to room temperature and stirred for an additional hour. The reaction solution was concentrated in vacuo and left on high vacuum overnight (12–24 hours). Resultant heterocycle complexes or salts were then subjected to the iterative oxidation protocol (**IOP**).

Iterative oxidation protocol (IOP). Protecting groups were evaluated under the standard iterative addition oxidation protocol, previously described in the literature.[5] The heterocycle complex or salt was dissolved in MeCN (746 mL, 0.67 M to substrate). A solution of Fe(PDP) (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 15.0 mg, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)) was added. A solution of H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. ***Significant decreases in yield were noted when the***

peroxide solution was added rapidly. After 10 min, a second portion of Fe(PDP) and AcOH dissolved in MeCN was added to the reaction mixture, followed by the dropwise addition of a second portion of H_2O_2 solution in MeCN as described above. After an additional 10 minutes, a third portion of Fe(PDP) and AcOH dissolved in MeCN were added followed by the dropwise addition of a third portion of H_2O_2 solution in MeCN as described above. The reaction solution was stirred for 10 minutes after the last iterative addition, for a total reaction time of approximately 36 minutes.

BF_3-pyrdine (BF_3-4a) complex reaction workup (W1). MeCN volume was reduced to approximately 1–2 mL via rotoevaporation and diluted with Et_2O (10 mL). Aqueous NaOH solution (10 mL, 20 wt.%) was added and the hydrolysis was stirred vigorously for 2 hours. The organic layer was separated, and the aqueous layer was filtered through a Celite® plug and extracted with Et_2O (3 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated via rotoevaporation. Purification by flash chromatography (50 mL SiO_2, gradient elution 2→5→10% MeOH/CH_2Cl_2) afforded 2-methyl-5-(pyridin-4-yl)pentan-2-ol **6a** as a colorless oil.

BF_3-Me-piperidine (BF_3-3a) complex, HBF_4-Me-piperidine (HBF_4-3a) salt, F_3CCO_2H-Me-piperidine (F_3CCO_2H-3a) salt, and HBF_4-pyrdine (HBF_4-4a) reaction workup (W2). MeCN volume was reduced to approximately 1–2 mL via rotoevaporation and diluted with CH_2Cl_2 (10 mL). Aqueous NaOH solution (10 mL, 1 M) was added to basify or hydrolyze and stirred vigorously for 10 minutes. The hydrolysis was poured into aq. NaOH (30 mL, 1 M) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine (1 x 60 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated via rotoevaporation. Purification by flash chromatography (25 mL, basic Al_2O_3 Brockmann grade III, gradient elution

10→20→40→80→100% EtOAc/Hex, 1 column volume of each) afforded the desired tertiary alcohol.

Entry 1. According to **GSP1** 1-methyl-4-(4-methylpentyl)piperidine **3a** (91.7 mg, 0.500 mmol, 1.0 equiv.) was complexed with BF_3•OEt_2 (67.9 mL, 0.550 mmol, 1.1 equiv.) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant **BF_3-3a** complex. The oxidation was carried out in iterative fashion with (*S,S*)- Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 15.0 mg, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol **5a** was isolated according to the reaction workup and purification described in **W2**.

Run 1 (49.2 mg, 0.247 mmol, 49% yield; 35.9 mg, 0.196 mmol; 39% rsm)

Run 1 (42.9 mg, 0.215 mmol, 43% yield; 15.0 mg, 0.082 mmol; 16% rsm)

Average yield: 46% (28% rsm)

Entry 2. According to **GSP1** 4-(4-methylpentyl)pyridine **4a** (81.6 mg, 0.500 mmol, 1.0 equiv.) was complexed with BF_3•OEt_2 (67.9 mL, 0.550 mmol, 1.1 equiv.) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant **BF_3-4a** complex. The oxidation was carried out in iterative fashion with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 15.0 mg, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes.

2-Methyl-5-(pyridin-4-yl)pentan-2-ol **6a** was isolated according to the reaction workup and purification described in **W1**.

Run 1 (21.0 mg, 0.117 mmol, 23% yield; 51.4 mg, 0.315 mmol, 63% rsm)

Run 2 (26.9 mg, 0.150 mmol, 30% yield; 56.9 mg, 0.349 mmol, 70% rsm)

Average yield: 27% (67% rsm)

Entry 3. According to **GSP1** 1-methyl-4-(4-methylpentyl)piperidine **3a** (91.7 mg, 0.500 mmol, 1.0 equiv.) was protonated with HBF_4•OEt_2 (75.8 mL, 0.550 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-3a** salt. The oxidation was carried out in iterative fashion with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol **5a** was isolated according to the reaction workup and purification described in **W2**.

Run 1 (56.0 mg, 0.281 mmol, 56% yield; 15.5 mg, 0.085 mmol, 40% rsm)

Run 2 (54.8 mg, 0.275 mmol, 55% yield; 37.0 mg, 0.202 mmol, 17% rsm)

Average yield: 56% (29% rsm)

Entry 4. According to **GSP1** 1-methyl-4-(4-methylpentyl)piperidine **3a** (91.7 mg, 0.500 mmol, 1.0 equiv.) was protonated with F_3CCO_2H (550 mL, 0.550 mmol, 1.1 equiv., 1 M F_3CCO_2H in CH_2Cl_2) in CH_2Cl_2 (1.5 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant **F_3CCO_2H-3a** salt. The oxidation was carried out in iterative fashion with (*R,R*)-

$Fe(PDP)(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol **5a** was isolated according to the reaction workup and purification described in **W2**.

Run 1 (4.8 mg, 0.0242 mmol, 5% yield; 67.6 mg, 0.369 mmol, 74% rsm)

Entry 5. According to **GSP1** 1-methyl-4-(4-methylpentyl)piperidine **3a** (91.7 mg, 0.500 mmol, 1.0 equiv.) was protonated with concentrated H_2SO_4 (30.6 mL, 0.550 mmol, 1.1 equiv., 18 M) in CH_2Cl_2 (2.0 mL, 0.25 M). Solvent was removed and the **H_2SO_4-3a** salt was placed on a high vacuum for 1-12 hours. MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant **H_2SO_4-3a** salt. The oxidation was carried out in iterative fashion with (*S,S*)-$Fe(PDP)(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 1-Methyl-4-(4-methylpentyl)piperidine **3a** was recovered according to the reaction workup and purification described in **W2**.

Run 1 (74.3 mg, 0.405 mmol, 81% rsm)

Run 2 (66.2 mg, 0.361 mmol, 72% rsm)

Average: 76% rsm

Entry 6. ***In situ protection/oxidation procedure.*** To a 40 mL vial equipped with a magnetic stir bar was added 1-methyl-4-(4-methylpentyl)piperidine **3a** (91.7 mg, 0.500 mmol, 1.0 equiv.) and

MeCN (746 mL, 0.67 M to substrate) the solution was cooled to 0 ºC and HBF_4 (71.9 mL, 0.550 mmol, 1.1 equiv., 48 wt.% in H_2O) was added. The solution was stirred for 10 minutes at 0 ºC then at room temperature for 30 minutes. The iterative oxidation protocol (**IOP**) was then carried out with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 µL, 15.0 mg, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 µL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol **5a** was isolated according to the reaction workup and purification described in **W2**.

Run 1 (42.9 mg, 0.215 mmol, 43% yield; 41.8 mg, 0.228 mmol; 46% rsm)

Run 2 (42.3 mg, 0.212 mmol, 42% yield; 31.0 mg, 0.169 mmol; 34% rsm)

Average overall yield: 43% (40% rsm)

Entry 7. According to **GSP1** 4-(4-methylpentyl)pyridine **4a** (81.6 mg, 0.500 mmol, 1.0 equiv.) was protonated with HBF_4•OEt_2 (75.8 mL, 0.550 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-4a** salt. The oxidation was carried out in iterative fashion with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 µL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 µL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(pyridin-4-yl)pentan-2-ol **6a** was isolated according to the reaction workup and purification described in **W2**.

Run 1 (50.1 mg, 0.280 mmol, 56% yield; 19.9 mg, 0.120 mmol, 24% rsm)

Run 2 (51.3 mg, 0.286 mmol, 57% yield; 18.0 mg, 0.110 mmol, 22% rsm)

Average yield: 57% (23% rsm)

Entry 8. To a 40 mL vial equipped with a magnetic stir bar was added 4-(4-methylpentyl)pyridine 1-oxide **4b** (53.8 mg, 0.300 mmol, 1.0 equiv.) and MeCN (450 mL, 0.67 M to substrate). The iterative oxidation protocol (**IOP**) was then carried out with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (14.0 mg, 0.015 mmol, 0.05 equiv.) and AcOH (8.6 μL, 0.15 mmol, 0.5 equiv.) dissolved in MeCN (300 mL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.36 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (2.7 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. By TLC analysis there was no evidence of desired product. The MeCN volume was concentrated and purified directly by flash chromatography (50 mL SiO_2, gradient elution with 5→10% MeOH/CH_2Cl_2) to recover starting material **4b**.

Run 1 (33.6 mg, 0.187 mmol, 62% rsm)

Run 2 (36.3 mg, 0.202 mmol, 67% rsm)

Average recovered starting material: 65% rsm

Entry 9. To a 40 mL vial equipped with a magnetic stir bar was added *tert*-butyl 4-(4-methylpentyl)piperidine-1-carboxylate **3b** (80.8 mg, 0.300 mmol, 1.0 equiv.) and MeCN (448 mL, 0.67 M to substrate). The iterative oxidation protocol (**IOP**) was then carried out with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (14.0 mg, 0.015 mmol, 0.05 equiv.) and AcOH (8.9 μL, 0.15 mmol, 0.5 equiv.) dissolved in MeCN (300 mL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.36 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (2.8 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. It was evident by TLC that there was over oxidation. The reaction was directly concentrated onto SiO_2 and purified by flash chromatography (20 mL SiO_2, gradient

elution 10→20→40→80→100% EtOAc/Hex, 1 column volume each, approximately 30 mL) to recover **3b** and an intractable mixture of over oxidized products.

Run 1 (29.8 mg, 0.111 mmol, 37% rsm)

Entry 10. To a 40 mL vial equipped with a magnetic stir bar was added 2,2,2-trifluoro-1-(4-(4-methylpentyl)piperidin-1-yl)ethan-1-one **3c** (79.6 mg, 0.300 mmol, 1.0 equiv.) and MeCN (447 mL, 0.67 M to substrate). The iterative oxidation protocol (**IOP**) was then carried out with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (14.0 mg, 0.015 mmol, 0.05 equiv.) and AcOH (8.9 μL, 0.15 mmol, 0.5 equiv.) dissolved in MeCN (300 mL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.36 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (2.8 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. It was evident by TLC that there was over oxidation. The reaction was directly concentrated onto SiO_2 and purified by flash chromatography (100:1 SiO_2/theoretical yield, 20 mL SiO_2, gradient elution 10→20→30→40→50→60→70→80→90→100% EtOAc/Hex, 1 column volume each, approximately 30 mL) to recover **3c** and an intractable mixture of over oxidized products.

Run 1 (8.8 mg, 0.033 mmol, 11% rsm)

Entry 11. According to **GSP1** 4-(4-methylpentyl)piperidine **3d** (84.7 mg, 0.500 mmol, 1.0 equiv.) was protonated with HBF_4•OEt_2 (75.8 mL, 0.550 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant **HBF_4•3d** salt. The oxidation was carried out in iterative fashion with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2

equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(piperidin-4-yl)pentan-2-ol **5d** was isolated according to the reaction workup described in **W2**. Purification by flash chromatography (25 mL, basic Al_2O_3 Brockmann grade III, gradient elution 0→2→5→10% MeOH/DCM, 2 column volume of each) afforded the desired tertiary alcohol **5d**.

Run 1 (37.6 mg, 0.203 mmol, 41% yield; 21.0 mg, 0.124 mmol, 25% rsm)

Run 2 (36.0 mg, 0.194 mmol, 39% yield; 23.9 mg, 0.141 mmol, 28% rsm)

Average yield: 40% (26% rsm)

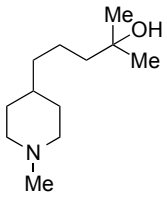
Entry 12. To a 40 mL vial equipped with a magnetic stir bar was added trifluoro(4-(4-methylpentyl)piperidine-1-ium-1-yl)borate **3e** (118.6 mg, 0.500 mmol, 1.0 equiv.) and MeCN (746 mL, 0.67 M to substrate). The iterative oxidation protocol (**IOP**) was then carried out with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The MeCN volume was concentrated to approximately 0.5–1 mL and purified directly by flash chromatography (25 mL SiO_2, gradient elution 25→35→45→55→65→75→85→100% EtOAc/Hex, 1 column volume each, approximately 35 mL) to afford alcohol **5e**.

Run 1 (54.5 mg, 0.215 mmol, 43% yield; 26.7 mg, 0.113 mmol, 23% rsm)

Run 2 (56.3 mg, 0.222 mmol, 44% yield; 24.1 mg, 0.102 mmol, 20% rsm)

Average yield: 44% (22% rsm)

2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol [5a]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.82 (dd, *J* = 11.7, 3.8 Hz, 2H), 2.23 (s, 3H), 1.87 (t, *J* = 11.4 Hz, 2H), 1.66 (d, *J* = 9.8 Hz, 2H), 1.45 – 1.39 (m, 2H), 1.34 (ddd, *J* = 12.8, 9.2, 5.7 Hz, 2H), 1.28 – 1.20 (m, 5H), 1.19 (s, 6H)

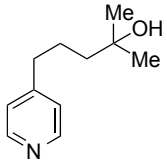
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.10, 56.16, 46.59, 44.25, 37.16, 35.23, 32.54, 29.38, 21.64

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{12}H_{26}NO$ 200.2014, found 200.2016

2-Methyl-5-(pyridin-4-yl)pentan-2-ol [6a]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.43 (dd, *J* = 4.6, 1.3 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.16 (br s, 1H), 1.74-1.69 (m, 2H), 1.49-1.45 (m, 2H), 1.19 (s, 6H)

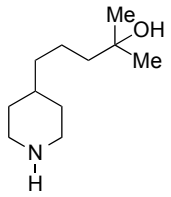
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.57, 149.55, 124.02, 70.58, 43.30, 35.65, 29.40, 25.10

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{18}NO$ 180.1388, found 180.1393

2-Methyl-5-(piperidin-4-yl)pentan-2-ol [5d]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.05 (dt, *J* = 12.4, 3.2 Hz, 2H), 2.57 (td, *J* = 12.3, 2.6 Hz, 2H), 1.82 (br s, 1H), 1.67 (d, *J* = 13.1 Hz, 2H), 1.47 – 1.38 (m, 3H), 1.41 – 1.29 (m, 3H), 1.20 (s, 6H), 1.14 – 1.04 (m, 2H)

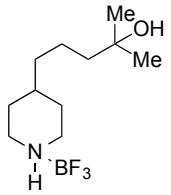
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.09, 46.89, 44.26, 37.82, 36.35, 33.69, 29.41, 21.37

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{23}NO$ 186.1858, found 186.1863

2-Methyl-5-(piperidin-4-yl)pentan-2-ol boron trifluoride complex [5e]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.63 (br s, 1H), 3.40 (ddd, *J* = 13.8, 4.3, 2.2 Hz, 2H), 2.72 (tdd, *J* = 13.5, 11.3, 2.8 Hz, 2H), 1.95 (d, *J* = 13.5 Hz, 2H), 1.50 (dddd, *J* = 15.1, 8.5, 6.9, 3.3 Hz, 1H), 1.46 – 1.34 (m, 5H), 1.31 – 1.23 (m, 4H), 1.21 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.10, 45.96, 43.89, 36.84, 34.66, 31.19, 29.46, 21.23

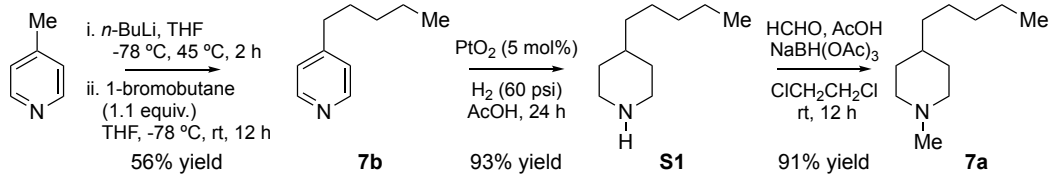
^{19}F NMR: (470 MHz, $CDCl_3$)

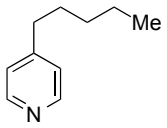
δ -158.20 (q, J = 16.6 Hz)

HRMS: (ESI-TOF MS ES-)

m/z: $[M–H]^-$ calculated for $C_{11}H_{22}NOF_3B$ 252.1747, found 252.1749

1.4.4 Synthesis of Substrates and Characterization for Figure 4





4-Pentylpyridine [7b] Following the general pyrdine alkylation procedrue, 4-picoline (2.7 mL, 2.56 g, 27.50 mmol, 1.0 equiv.) was reacted with 1-bromobutane (3.3 mL, 4.15 g, 30.26 mmol, 1.1 equiv.). Purification by flash chromatography (SiO_2, eluting with 20→40% EtOAc/hexanes) afforded 4-pentylpyridine **7b** as a yellow oil (2.30 g, 15.4 mmol, 56% yield).

^{1}H NMR: (400 MHz, $CDCl_3$)

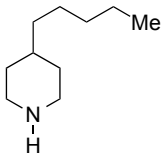
δ 8.47 (d, J = 5.3 Hz, 2H), 7.09 (d, J = 5.6 Hz, 2H), 2.58 (t, J = 7.8 Hz, 2H), 1.62 (p, J = 7.7 Hz, 2H), 1.40-1.24 (m, 4H), 0.89 (d, J = 6.9 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.86, 149.75, 124.02, 35.34, 31.47, 30.10, 22.57, 14.08

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{10}H_{16}N$ 150.1283, found 150.1281.

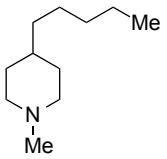


4-Pentylpiperidine [S1] Following the general pyridine hydrogenation procedure, 4-pentylpyridine **4c** (924.0 mg, 6.19 mmol, 1.0 equiv.) was reacted with H_2 (60 psi) and PtO_2 (70.3 mg, 0.310 mmol, 0.05 equiv.) in acetic acid (13.2 mL). 4-Pentylpiperidine **S2** was obtained as a colorless oil (891.1 mg, 5.74 mmol, 93% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.04 (dt, *J* = 12.1, 2.7 Hz, 2H), 2.56 (dt, *J* = 12.1, 2.5 Hz, 2H), 1.65 (d, *J* = 13.7 Hz, 2H), 1.55 (br s, 1H), 1.36-1.16 (m, 9H), 1.05 (qd, *J* = 12.1, 4.0 Hz, 2H), 0.88 (t, *J* = 7.1 Hz, 3H)

General Reductive Amination Procedure for Piperidine Substrates



1-Methyl-4-pentylpiperidine [7a] To a round bottom flask equipped with a magnetic stir bar was added 4-pentylpiperidine **S1** (581 mg, 3.74 mmol, 1.0 equiv.), 1,2-dichloroethane (37.4 mL, 0.1 M), AcOH (750 mL, 1% v/v) and formaldehyde (1.4 mL, 562 mg, 18.7 mmol, 5.0 equiv., 37% wt. in H_2O), solution was stirred at room temperature for 30 minutes. $NaBH(OAc)_3$ (1.19 g, 5.61 mmol, 1.5 equiv.) was added in one portion and reaction solution was stirred overnight at room temperature. Reaction was quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layer was washed with $NaHCO_3$ solution saturated (100 mL) and brine (100 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography (basic Al_2O_3 Brockmann grade III, eluted with 20% EtOAc/Hex) to afford 1-methyl-4-pentylpiperidine **7a** as a colorless oil (571.3 mg, 3.38 mmol, 91% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.81 (d, *J* = 11.6 Hz, 2H), 2.24 (s, 3H), 1.35-1.10 (m, 11H), 0.87 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 56.32, 46.73, 36.75, 35.32, 32.75, 32.26, 26.61, 22.83, 14.22

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{24}N$ 170.1909; found 170.1912

1.4.5 Experimental Procedures and Characterization for Figure 4

Entry 1. According to GSP1 1-methyl-4-pentylpiperidine **[7a]** (0.300 mmol, 50.8 mg) was protonated with HBF_4•OEt_2 (45.5 mL, 0.330 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 ml, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-7a** salt. Following slow addition protocol: H_2O_2 (153 μL, 2.7 mmol, 9.0 equiv., 50 wt.% in H_2O) in MeCN (3.0 mL) in 10 mL syringe and AcOH (86 μL, 90 mg, 1.5 mmol, 5.0 equiv.) mixed together with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (14.0 mg, 0.015 mmol, 0.05 equiv.) in MeCN (0.3 mL) and filled in 1 mL syringe were added simultaneously via a syringe pump to the substrate/MeCN solution (6.0 mL/min).

Run 1 (major ketone - 16.9 mg, 0.092 mmol, 31% yield; 2.8 mg, 0.017 mmol, 6% rsm; combined minor ketones - 17.2 mg, 0.094 mmol, 31% yield)

Run 2 (major ketone - 13.8 mg, 0.075 mmol, 25% yield; 1.2 mg, 0.007 mmol, 2% rsm; combined minor ketones - 14.9 mg, 0.081 mmol, 27% yield)

Average overall yield: 28% yield major ketone 8a, 29% combined minor ketones (4% rsm)

Entry 2. According to GSP1 1-methyl-4-pentylpiperidine 4-pentylpyridine [**7b**] (0.3 mmol, 44.8 mg) was protonated with HBF_4•OEt_2 (45.5 mL, 0.330 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 ml, 0.67 M to substrate) was used to dissolve the resultant **HBF_4•7b**

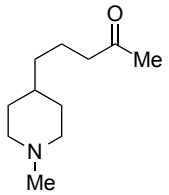
salt. Following slow addition protocol: H_2O_2 (153 μL, 2.7 mmol, 9.0 equiv., 50 wt.% in H_2O) in MeCN (3.0 mL) in 10 mL syringe and AcOH (86 μL, 90 mg, 1.5 mmol, 5.0 equiv.) mixed together with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (14.0 mg, 0.015 mmol, 0.05 equiv.) in MeCN (0.3 mL) and filled in 1 mL syringe were added simultaneously via a syringe pump to the substrate/MeCN solution (6.0 mL/min). Reaction was worked up according to W1 and purified by flash chromatography (50 mL, SiO_2, eluting with 80% EtOAc/hexanes) to afford as 5-(pyridin-4-yl)pentan-2-one **8b** and 1-(pyridin-4-yl)pentan-3-one **8c** both as colorless oils.

Run 1 (18.9 mg, 0.116 mmol, 39% yield **8b**; 7.2 mg, 0.044 mmol, 15% yield **8c**; 4.3 mg, 0.029 mmol, 10% rsm)

Run 2 (18.3 mg, 0.112 mmol, 37% yield **8b**; 7.0 mg, 0.043 mmol, 14% yield **8c**; 5.0 mg, 0.034 mmol, 11% rsm)

Average overall: 38% yield 6c and 15% yield 6d (10% rsm)

5-(1-Methylpiperidin-4-yl)pentan-2-one [8a]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.82 (d, *J* = 11.6 Hz, 2H), 2.45-2.37 (m, 2H), 2.24 (s, 3H), 2.13 (s, 3H), 1.86 (t, *J* = 11.2 Hz, 2H), 1.67 (d, *J* = 11.2 Hz, 2H), 1.63-1.49 (m, 2H), 1.27-1.15 (m, 5H)

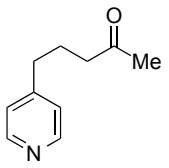
^{13}C NMR: (101 MHz, $CDCl_3$)

δ 209.27, 55.90, 46.20, 44.00, 35.97, 34.96, 31.98, 30.08, 21.19

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{22}NO$ 184.1701, found 184.1705

5-(Pyridin-4-yl)pentan-2-one [8b]



^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.46 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.88 (p, *J* = 7.4 Hz, 2H)

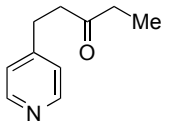
^{13}C NMR: (101 MHz, $CDCl_3$)

δ 208.20, 150.60, 149.84, 123.94, 42.56, 34.31, 30.12, 24.00

HRMS: (EI+)

m/z: $[M+H]^+$ calculated for 164.1075, found 164.1082

1-(Pyridin-4-yl)pentan-3-one [8c]



^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.48 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.11 (d, *J* = 5.9 Hz, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 2.75 (t, *J* = 7.4 Hz, 2H), 2.42 (q, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.3 Hz, 3H)

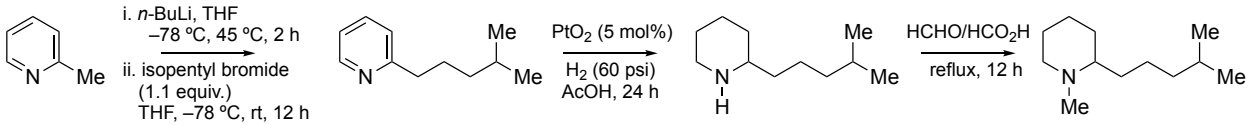
^{13}C NMR: (101 MHz, $CDCl_3$)

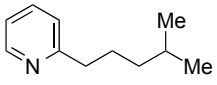
δ 209.74, 150.30, 149.96, 123.92, 42.47, 36.24, 28.98, 7.84

HRMS: (EI+)

m/z: $[M+H]^+$ calculated for $C_{10}H_{14}NO$ 164.1075, found 164.1080

1.4.6 Synthesis of Substrates and Characterization for Figure 5





2-(4-Methylpentyl)pyridine [11a] Following the general pyridine alkylation procedure, 2-picoline (1.4 mL, 1.28 g, 13.75 mmol, 1.0 equiv.) was reacted with isopentyl bromide (1.9 mL, 2.33 g, 15.13 mmol, 1.1 equiv.). Purification by flash chromatography (SiO_2, eluting with 10→25% EtOAc/Hex) afforded 2-(4-methylpentyl)pyridine **11a** as a light yellow oil (1.77 g, 10.80 mmol, 74% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

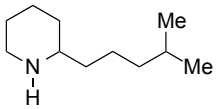
δ 8.51 (d, *J* = 4.2 Hz, 1H), 7.56 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.1, 5.1 Hz, 1H), 2.75 (t, *J* = 7.8 Hz, 2H), 1.76-1.66 (m, 2H), 1.56 (hept, *J* = 6.6 Hz, 2H), 1.27-1.19 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.68, 149.33, 136.31, 122.77, 120.95, 38.86, 28.06, 27.95, 22.72

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{18}N$ 164.1439, found 164.1445



2-(4-Methylpentyl)piperidine [9i] Following the general pyridine hydrogenation procedure, 2-(4-methylpentyl)pyridine **11a** (863.0 mg, 5.29 mmol, 1.0 equiv.) was reacted with hydrogen gas (60 psi) and platinum dioxide (60.0 mg, 0.264 mmol, 0.05 equiv.) in acetic acid (11.3 mL). 2-(4-methylpentyl)piperidine **9i** was obtained as a colorless oil (750.8 mg, 4.43 mmol, 84% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

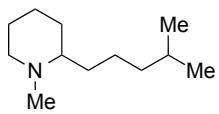
δ 3.05 (ddt, *J* = 12.0, 4.1, 2.1 Hz, 1H), 2.61 (td, *J* = 11.7, 2.7 Hz, 1H), 2.47-2.36 (m, 1H), 1.81-1.72 (m, 1H), 1.69-1.46 (m, 4H), 1.46-1.22 (m, 6H), 1.21-1.11 (m, 2H), 1.10-0.98 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 57.10, 47.43, 39.32, 37.93, 33.18, 28.06, 26.83, 25.09, 23.81, 22.76

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{24}N$ 170.1909, found 170.1906



1-Methyl-2-(4-methylpentyl)piperidine [9a] Prepared following the published procedure.[23] To a round bottom flask equipped with a magnetic stir bar was added 2-(4-methylpentyl)piperidine **9i** (535 mg, 3.16 mmol, 1.00 equiv.), formaldehyde (3.0 mL, 40.00 mmol, 13.0 equiv., 37% w/w in H_2O) and formic acid (3 mL, 79.51 mmol, 25.16 equiv.). Round bottom was fitted with a condenser and placed in a preheated oil bath (100-110 ºC). Reaction was refluxed overnight. Reaction progress was monitored by TLC analysis. Upon completion the reaction solution was cooled to 0 ºC and basified with 50% aq. NaOH (pH = 10-11). The basic aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated via rotoevaporation. The crude material was purified by flash chromatography (Brockmann grade III basic Al_2O_3, gradient elution 2→5→10% EtOAc/Hex) to afford 1-methyl-2-(4-methylpentyl)piperidine **9a** as a yellow oil (325.2 mg, 1.77 mmol, 56% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.83 (dtd, *J* = 11.6, 3.6, 1.5 Hz, 1H), 2.24 (s, 3H), 2.09 – 2.00 (m, 1H), 1.79 (tt, *J* = 7.5, 3.2 Hz, 1H), 1.71 (dtd, *J* = 8.7, 3.6, 1.6 Hz, 1H), 1.68 – 1.60 (m, 1H), 1.61 – 1.47

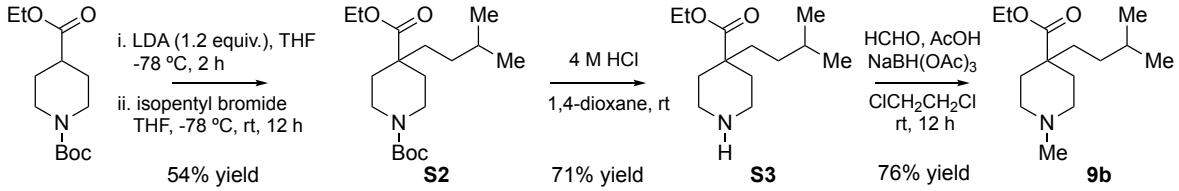
(m, 4H), 1.34 (m, 2H), 1.31 – 1.16 (m, 3H), 1.19 – 1.11 (m, 2H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

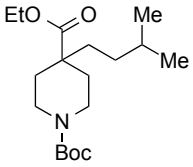
δ 64.14, 57.48, 43.14, 39.69, 33.37, 30.96, 28.13, 26.06, 24.63, 23.15, 22.91, 22.68

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{12}H_{26}N$ 184.2065; found 184.2069



General Piperidine Alkylation Procedure



1-(*tert*-Butyl) 4-ethyl 4-isopentylpiperidine-1,4-dicarboxylate [S2] To a flame dried 500 mL round bottom flask equipped with a magnetic stir bar was added diisopropylamine (6.1 mL, 43.85 mmol) and THF (48 mL, 0.5 M to *n*-BuLi), the solution was cooled to -78 ºC and *n*-BuLi was added; stirred 1 hour at -78 ºC. A solution of 1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate[24] (8.55g, 33.22 mmol, 1.00 equiv.) in THF (20 mL, 1.7 M to substrate) was added to the LDA solution via cannula at -78 ºC, solution was stirred at -78 ºC for 2 hours. Isopentyl bromide (6 mL, 49.83 mmol, 1.5 equiv.) was added in one portion, dropwise (moderate rate) at -78 ºC. The reaction solution was warmed slowly to room temperature and stirred overnight. Reaction was cooled to 0 ºC and quenched with 10% aqueous citric acid solution (50 mL). The quenched reaction solution was poured into brine (200 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material

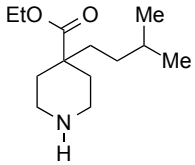
was purified by flash chromatography (25:1 SiO_2/theoretical yield, gradient elution 0→2→5→10→15→20→25% EtOAc/Hex, 1 column volume each) to afford 1-(*tert*-butyl) 4-ethyl 4-isopentylpiperidine-1,4-dicarboxylate **S2** as a viscous colorless oil (5.88 g, 17.96 mmol, 54% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (br s, 2H), 2.87 (br s, 2H), 2.08 (d, *J* = 13.3 Hz, 2H), 1.52 – 1.44 (m, 2H), 1.44 (s, 9H), 1.44 – 1.38 (m, 1H), 1.38 – 1.28 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.11 – 1.02 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 175.77, 155.03, 79.48, 60.51, 45.60, 38.23, 33.54, 32.93, 28.60, 28.57, 28.45, 22.63, 14.50



Ethyl 4-isopentylpiperidine-4-carboxylate [S3] To a 100 mL round bottom flask equipped with a magnetic stir bar was added 1-(*tert*-butyl) 4-ethyl 4-isopentylpiperidine-1,4-dicarboxylate **S2** (1.96 g, 6.00 mmol, 1.00 equiv.), 1,4-dioxane (24 mL, 0.25 M) and 4 M HCl (15 mL, 60.00 mmol, 10.00 equiv.). Reaction was stirred at room temperature and TLC was employed to monitor conversion. Upon completion 1,4-dioxane was removed via rotoevaporation. Solution was basified with 1 M NaOH (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford ethyl 4-isopentylpiperidine-4-carboxylate **S6** as a yellow oil (975 mg, 4.29 mmol, 71% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.13 (q, *J* = 7.3 Hz, 2H), 2.89 (dt, *J* = 12.8, 4.0 Hz, 2H), 2.67 – 2.57 (m, 2H), 2.06 (d, *J* = 13.1 Hz, 2H), 1.59 (s, 1H), 1.48 – 1.37 (m, 3H), 1.30 (ddd, *J* = 13.0, 11.3, 4.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.06 – 1.00 (m, 2H), 0.82 (d, *J* = 6.9 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 176.29, 60.22, 45.75, 44.08, 38.79, 34.86, 32.73, 28.41, 22.59, 14.45

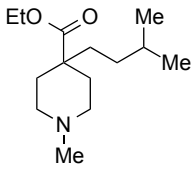
IR: (ATR, neat, cm^{-1})

2953, 2870, 1722, 1467, 1451, 1386, 1367, 1321, 1281, 1201, 1178, 1146, 1096, 1081, 1026, 981, 860, 761

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{13}H_{26}NO_2$ 228.1964; found 228.1968

General Procedure for Reductive Amination of Piperidine Substrates



Ethyl 4-isopentyl-1-methylpiperidine-4-carboxylate [9b] To a round bottom flask equipped with a magnetic stir bar was added ethyl 4-isopentylpiperidine-4-carboxylate **S3** (560 mg, 2.46 mmol, 1.00 equiv.), 1,2-dichloroethane (25 mL, 0.1 M), AcOH (250 mL, 1% v/v) and formaldehyde (366 mL, 4.92 mmol, 2.00 equiv., 37% wt. in H_2O), solution was stirred at room temperature for 30 minutes. $NaBH(OAc)_3$ (782 mg, 3.69 mmol, 1.5 equiv.) was added in one portion and reaction solution was stirred overnight at room temperature. Reaction was quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layer was washed with $NaHCO_3$ solution saturated (50 mL) and brine (50 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography (Brockmann grade III basic Al_2O_3,

eluted with 10% EtOAc/Hex) to afford ethyl 4-isopentyl-1-methylpiperidine-4-carboxylate **9b** (449 mg, 1.86 mmol, 76% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

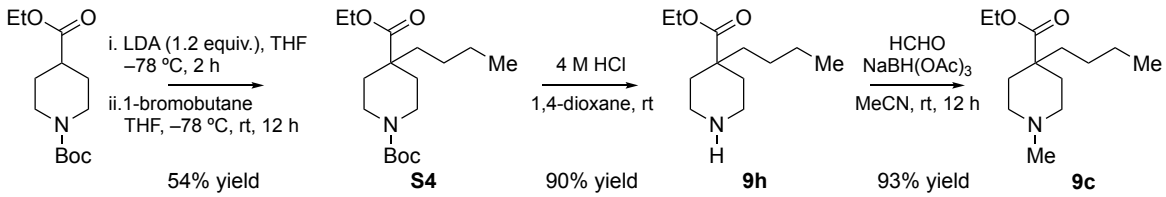
δ 4.11 (q, *J* = 7.1 Hz, 2H), 2.61 (d, *J* = 12.1 Hz, 2H), 2.19 (s, 3H), 2.09 (ddd, *J* = 13.8, 4.6, 2.4 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.46 – 1.34 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.04 – 0.98 (m, 2H), 0.80 (d, *J* = 6.6 Hz, 6H)

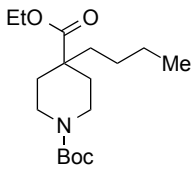
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 176.10, 60.19, 53.39, 46.46, 44.69, 38.44, 33.80, 32.97, 28.40, 22.58, 14.44

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{14}H_{28}NO_2$ 242.2120; found 242.2115

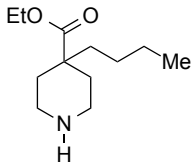




1-(*tert*-Butyl) 4-ethyl 4-butylpiperidine-1,4-dicarboxylate [S4] According to the general piperidine alkylation procedure 1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate[24] (10.3 g, 33.2 mmol, 1.00 equiv.) and 1-bromobutane (5.4 mL, 49.83 mmol, 1.5 equiv.) were reacted. Crude material was purified by flash chromatography (SiO_2, eluting with 15% EtOAc/Hex) to afford 1-(*tert*-butyl) 4-ethyl 4-butylpiperidine-1,4-dicarboxylate **S4** (5.63 g, 18.0 mmol, 54% yield) as a colorless oil.

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (br s, 2H), 2.87 (br s, 2H), 2.13 – 2.04 (m, 2H), 1.48 (dt, *J* = 12.0, 4.2 Hz, 2H), 1.46 (s, 9H), 1.38 – 1.28 (m, 2H), 1.29 – 1.22 (m, 5H), 1.22 – 1.11 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H)



Ethyl 4-butylpiperidine-4-carboxylate [9h] To round bottom flask was added 1-(*tert*-butyl) 4-ethyl 4-butylpiperidine-1,4-dicarboxylate **S4** (1.9 g, 6.06 mmol, 1.00 equiv.) and 4 M HCl in dioxane (15 mL, 60.62 mmol, 10.00 equiv.) and reaction solution was stirred at room temperature. TLC was used to monitor reaction progress. Upon complete conversion of starting material reaction was concentrated via rotoevaporation. Residue was basified with 1 M NaOH (100 mL) and extracted with CH_2CL_2 (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Crude material was purified by flash chromatography (Brockmann grade III basic Al_2O_3, eluted with 10% MeOH/DCM) to afford ethyl 4-butylpiperidine-4-carboxylate **9h** as a colorless oil (1.16 g, 5.44 mmol, 90% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

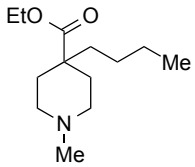
δ 4.16 (q, *J* = 7.1 Hz, 2H), 2.92 (dt, *J* = 12.9, 3.8 Hz, 2H), 2.69-2.59 (m, 2H), 2.10 (d, *J* = 13.2 Hz, 2H), 1.64 (br s, 1H), 1.52-1.45 (m, 2H), 1.33 (ddd, *J* = 13.6, 11.5, 4.0 Hz, 2H), 1.29-1.21 (m, 5H), 1.21-1.12 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 176.39, 60.33, 45.87, 44.12, 40.87, 34.87, 26.05, 23.21, 14.51, 14.08

HRMS (ESI)

m/z: $[M+H]^+$ calculated for $C_{12}H_{24}NO_2$ 214.1807; found 214.1806.



Ethyl 4-butyl-1-methylpiperidine-4-carboxylate [9c] Following general piperidine reductive amination procedure ethyl 4-butylpiperidine-4-carboxylate **9h** (456.8 mg, 2.14 mmol, 1.0 equiv.) was reacted with formaldehyde (797 µL, 321.5 mg, 10.7 mmol, 5.0 eq, 37 wt% in water) and $NaBH(OAc)_3$ (680 mg, 3.21 mmol, 1.5 equiv.) in acetic acid (0.43 mL) and 1,2-dichloroethane (42.4 mL). Purification by flash chromatography (20 mL Brockmann grade III basic Al_2O_3, eluting with 80% EtOAc/Hex) yielded ethyl 4-butyl-1-methylpiperidine-4-carboxylate **9c** as a colorless oil (452.3 mg, 1.99 mmol, 93% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

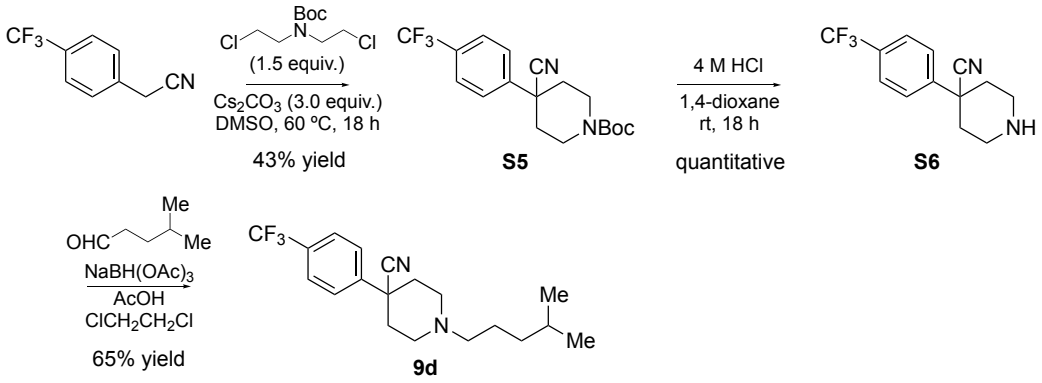
δ 4.15 (q, *J* = 7.1 Hz, 2H), 2.64 (d, *J* = 11.9 Hz, 2H), 2.22 (s, 3H), 2.14 (d, *J* = 13.2 Hz, 2H), 1.98 (t, *J* = 11.5 Hz, 2H), 1.51-1.42 (m, 4H), 1.30-1.10 (m, 7H), 0.86 (t, *J* = 7.2 Hz, 3H)

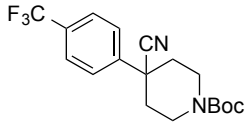
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 176.22, 60.28, 53.48, 46.53, 44.84, 40.53, 33.87, 26.31, 23.21, 14.48, 14.08

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{13}H_{26}NO_2$ 228.1964; found 228.1962





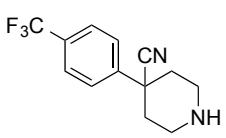
***tert*-Butyl 4-cyano-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate [S5]** To a flame-dried two neck round bottom flask equipped with a magnetic stir bar was added Cs_2CO_3 (17.9 g, 55.09 mmol, 3.00 equiv.) and DMSO (40 mL) to this heterogeneous solution was added 4-(trifluoromethyl)phenyl acetonitrile (3.4 g, 18.36 mmol, 1.00 equiv.) dissolved in DMSO (20 mL) via cannula (rinsed with 10 mL of DMSO to ensure complete material transfer); reaction solution turned yellow. Bis-(2-chloroethyl)carbamic acid *tert*-butyl ester[26] (6.7 g, 27.55 mmol, 1.50 equiv.) dissolved in DMSO (10 mL) via cannula (rinsed with 10 mL of DMSO). The reaction solution was transferred to a 60 ºC oil bath and stirred for 18 hours. The reaction solution turned dark purple. TLC analysis and GC were employed to monitor reaction progress. Reaction solution was cooled to room temperature, diluted with Et_2O (200 mL) and H_2O (200 mL). Upon sitting in separatory funnel emulsion separated. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layer was washed with H_2O (2 x 300 mL) and brine (1 x 300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (400 mL SiO_2, gradient elution 100% Hex→2→5→10→15% EtOAc/Hex) afforded *tert*-butyl 4-cyano-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate **S5** as a viscous orange oil (2.79 g, 7.87 mmol, 43% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 4.31 (br s, 2H), 3.21 (br s, 2H), 2.10 (d, *J* = 13.2 Hz, 2H), 1.96 (dt, *J* = 12.8, 6.3 Hz, 2H), 1.48 (s, 9H)

HRMS: (ESI-TOF MS ES+)

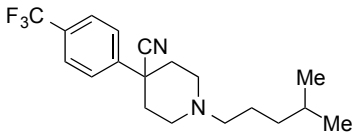
m/z: $[(M–Boc)+2H]^+$ calculated for $C_{13}H_{14}N_2F_3$ 255.1109; Found 255.1112



4-(4-(Trifluoromethyl)phenyl)piperidine-4-carbonitrile [S6] To a round bottom flask equipped with a magnetic stir bar was added *tert*-butyl 4-cyano-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate **S5** (636 mg, 1.795 mmol, 1.0 equiv.), 1,4-dioxane (2 mL, 0.9 M) and 4 M HCl in 1,4-dioxane (3.6 mL, 14.360 mmol, 8.0 equiv.). Reaction solution was stirred at room temperature over night (18 h). Reaction solution was concentrated and basified with 1 M NaOH (50 mL) to pH = 10-11. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford 4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **S6** as a pink crystalline solid. No further purification was required and material was taken directly on to reductive amination (457 mg, 1.80 mmol, quantitative).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.68 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 3.24 – 3.11 (m, 4H), 2.10 (dt, *J* = 13.4, 2.5 Hz, 2H), 2.00 (ddd, *J* = 13.3, 11.5, 4.5 Hz, 2H), 1.68 (s, 1H)



1-(4-Methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile [9d] To a round bottom flask equipped with a magnetic stir bar was added 4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **S6** (499 mg, 1.963 mmol, 1.0 equiv.), 1,2-dichloroethane (20 mL, 0.1 M), 4-methylpentanal[27] (295 mg, 2.945 mmol, 1.5 equiv.) and acetic acid (0.2 mL, 1% v/v). The reaction solution was stirred for 30 minutes at room temperature. $NaBH(OAc)_3$ (624.2 mg, 2.945 mmol, 1.5 equiv.) was added in one portion and the interior of the flask rinsed with 1,2-dichloroethane (2 mL). The reaction solution was stirred overnight (18 h) at room temperature. The reaction was quenched at room temperature by the addition of sat.

$NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with sat. $NaHCO_3$ solution (50 mL) and brine (50 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Crude material was purified by flash chromatography (50:1 SiO_2/theoretical yield, 80 mL SiO_2, gradient elution Hex→2→4→6→8→10→20→30% EtOAc/Hex) afforded 1-(4-methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **9d** as a light orange oil (433 mg, 1.28 mmol, 65% yield)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.67 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.9 Hz, 2H), 3.06 (d, *J* = 12.5 Hz, 2H), 2.48 (ddd, *J* = 12.3, 10.0, 4.5 Hz, 2H), 2.47 – 2.39 (m, 2H), 2.16 – 2.09 (m, 4H), 1.62 – 1.47 (m, 3H), 1.20 (dd, *J* = 15.9, 6.8 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

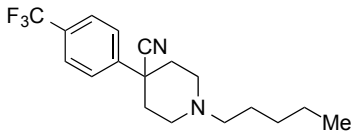
δ 144.29, 130.60 (q, *J* = 32.8 Hz), 126.34, 126.18 (q, *J* = 3.6 Hz), 125.01 (q, *J* = 275.6), 121.55, 59.00, 50.82, 43.23, 36.88, 36.70, 28.12, 24.97, 22.75

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.11

HRMS: (ESI-TOF MS ES+)

m/z:$[M+H]^+$ calculated for $C_{19}H_{26}N_2F_3$ 339.2048; found 339.2047



1-Pentyl-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile [9e] To a round bottom flask equipped with a magnetic stir bar was added 4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **S5** (713.2 mg, 2.805 mmol, 1.0 equiv.), 1,2-dichloroethane (56 mL, 0.05 M), valeraldehyde (1.5 mL, 14.025

mmol, 5.0 equiv.) and acetic acid (0.56 mL, 1% v/v). The reaction solution was stirred for 30 minutes at room temperature. $NaBH(OAc)_3$ (892 mg, 4.208 mmol, 1.5 equiv.) was added in one portion and the interior of the flask rinsed with 1,2-dichloroethane (2 mL). The reaction solution was stirred overnight (18 h) at room temperature. The reaction was quenched at room temperature by the addition of saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Crude material was purified by flash chromatography (50:1 SiO_2/theoretical yield, 100 mL SiO_2, gradient elution CH_2Cl_2→5% MeOH/CH_2Cl_2) afforded 1-pentyl-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **9e** as a light orange oil (493 mg, 1.52 mmol, 54% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 3.09 – 3.03 (m, 2H), 2.51 – 2.41 (m, 4H), 2.18 – 2.07 (m, 4H), 1.57 – 1.47 (m, 2H), 1.39 – 1.26 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

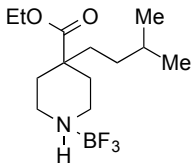
δ 144.31, 130.59 (q, *J* = 32.8 Hz), 126.34, 126.17 (q, *J* = 3.7 Hz), 123.93 (q, *J* = 272.2 Hz), 121.55, 58.71, 50.79, 43.23, 36.70, 29.89, 26.81, 22.75, 14.20

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.11

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{18}H_{24}N_2F_3$ 325.1892; found 325.1894



Ethyl 4-isopentylpiperidine-4-carboxylate boron trifluoride complex [9f] Following the general BF_3 protection procedure ethyl 4-isopentylpiperidine-4-carboxylate **S3** (974.9 mg, 4.29 mmol, 1.00 equiv.) in CH_2Cl_2 (17 mL, 0.25 M) was cooled to 0 ºC and BF_3•OEt_2 (582 mL, 4.72 mmol, 1.10 equiv.) was added. The solution was stirred at 0 ºC for 30 minutes followed by 1 hour room temperature. Solvent was removed via rotoevaporation. The crude material was purified by flash chromatography (25:1 SiO_2/theoretical yield, gradient elution 20→40→60% EtOAc/Hex, 1 column volume of each) to afford **9f** as a white crystalline solid (933.3 mg, 3.16 mmol, 74% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.21 (q, *J* = 7.1 Hz, 2H), 3.55 (br s, 1H), 3.32 (ddd, *J* = 14.1, 4.3, 2.2 Hz, 2H), 2.77 (tdd, *J* = 14.1, 11.8, 2.6 Hz, 2H), 2.41 (d, *J* = 15.1 Hz, 2H), 1.55 – 1.48 (m, 2H), 1.50 – 1.35 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.10 – 1.04 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.46, 61.21, 44.75, 43.65, 39.09, 32.65, 32.47, 28.29, 22.53, 14.41, 14.37

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.12 (q, *J* = 15.5 Hz)

^{11}B NMR: (128 MHz, $CDCl_3$)

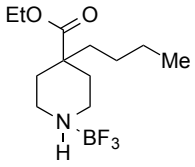
δ -0.36 (br q, *J* = 15.9 Hz)

IR: (ATR, neat, cm^{-1})

3244, 2959, 2933, 2871, 1726, 1473, 1457, 1404, 1368, 1348, 1320, 1301, 1290, 1248, 1204, 1158, 1122, 1096, 1063, 1031, 1006, 990, 979, 963, 946, 929, 874, 804, 777, 746

HRMS: (ESI-TOF MS ES+)

m/z: $[(M–H)+Na]^+$ calculated for $C_{13}H_{25}BNO_2F_3Na$ 318.1828; found 318.1830



Ethyl 4-butylpiperidine-4-carboxylate boron trifluoride complex [9g] Following the general BF_3 protection procedure piperidine **9h** (426.6 mg, 2.00 mmol, 1.0 equiv.) was reacted with BF_3•OEt_2 (272 μL, 2.20 mmol, 1.1 equiv.). Purification by flash chromatography (20 mL SiO_2, eluting with 40% EtOAc/Hex) yielded **9g** as a white solid (328.6 mg, 1.17 mmol, 58% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.21 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 1H), 3.30 (d, *J* = 15.5 Hz, 2H), 2.80 – 2.68 (m, 2H), 2.40 (d, *J* = 15.3 Hz, 2H), 1.55 – 1.47 (m, 2H), 1.42 (td, *J* = 14.2, 4.2 Hz, 2H), 1.34 – 1.22 (m, 6H), 1.17 (ddd, *J* = 13.4, 6.9, 3.5 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

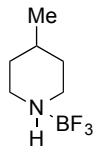
δ 174.45, 61.29, 44.82, 43.65, 41.03, 32.54, 25.95, 22.99, 14.40, 14.00

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -157.83 (q, *J* = 16.0 Hz)

HRMS: (ESI-TOF MS ES-)

m/z: $[M–H]^-$ calculated for $C_{12}H_{22}NO_2F_3B$ 280.1696; found 280.1698



4-Methylpiperidine boron trifluoride complex [9j] Following the general BF_3 protection procedure 4-methylpiperidine (1.2 mL, 10.00 mmol, 1.00 equiv.) was reacted with BF_3•OEt_2 (1.4 mL, 11.00 mmol, 1.10 equiv.) in CH_2Cl_2 (40 mL, 0.25 M). Crude material was purified by flash chromatography (25:1 SiO_2/theoretical yield, gradient elution 10→20% EtOAc/Hex) to afford **9j** a white solid (1.40 g, 8.38 mmol, 84% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.44 (br s, 1H), 3.40 (ddd, *J* = 13.9, 4.4, 2.1 Hz, 2H), 2.73 (tdd, *J* = 13.7, 11.6, 2.8 Hz, 2H), 1.95 – 1.83 (m, 2H), 1.62 (dddd, *J* = 15.4, 12.4, 7.0, 3.6 Hz, 1H), 1.29 – 1.17 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

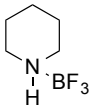
δ 45.90, 32.75, 29.69, 21.72

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -157.99 (q, *J* = 16.6 Hz)

HRMS: (ESI-TOF MS ES-)

m/z: $[M–H]^-$ calculated for $C_6H_{12}BNF_3$ 166.1015, found 166.1014



Piperidine boron trifluoride complex [9k] Following the general BF_3 protection procedure piperidine (494 μL, 425.8 mg, 5.00 mmol, 1.0 equiv.) was reacted with BF_3•OEt_2 (678 μL, 5.50 mmol, 1.1 equiv.). Purification by flash chromatography (25:1 SiO_2/theoretical yield, eluting with 40% EtOAc/Hex) yielded **9k** as a white solid (592.1 mg, 3.87 mmol, 77% yield).

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 3.82 (br s, 1H), 3.34 (d, *J* = 12.9 Hz, 2H), 2.68 (q, *J* = 11.4 Hz, 2H), 1.85 (t, *J* = 16.6 Hz, 3H), 1.67-1.52 (m, 2H), 1.42 (qt, *J* = 12.8, 3.5 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

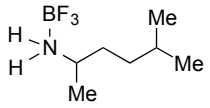
δ 46.13, 24.51, 22.77

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.22 (app t, *J* = 15.4)

HRMS: (ESI-TOF MS ES-)

m/z: [M–H]$^-$ calculated for $C_5H_{10}NF_3B$ 152.0858; found 152.0856



5-Methylhexan-2-amine boron trifluoride complex [9l] Following the general BF_3 protection procedure 2-amino-5-methylhexane (2.5 g, 3.3 mL, 21.70 mmol, 1.00 equiv.) in CH_2Cl_2 (25 mL, 0.9 M) was cooled to 0 ºC and BF_3•OEt_2 (2.3 mL, 23.87 mmol, 1.10 equiv.) was added. The solution was stirred at 0 ºC for 30 minutes followed by 1 hour room temperature. Solvent was removed via rotoevaporation. The crude material was purified by flash chromatography (150 mL SiO_2, gradient elution 25→50 % EtOAc/Hex, 2 column volumes of each) to afford **9l** as a white solid (2.52 g, 13.77 mmol, 63% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.98 (br s, 1H), 3.87 (br s, 1H), 3.25 (dq, *J* = 12.4, 6.4 Hz, 1H), 1.72-1.62 (m, 1H), 1.61-1.52 (m, 1H), 1.48 (ddd, *J* = 16.1, 13.0, 6.7 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.21 (ddd, *J* = 10.0, 7.9, 6.4 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 49.68, 34.34, 34.23, 27.94, 22.62, 22.37, 19.30

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -147.66 (q, *J* = 16.7 Hz)

HRMS: (ESI-TOF MS ES-)

m/z: [M–H]$^-$ calculated for $C_7H_{16}BNF_3$ 182.1328; found 182.1328

1.4.7 Experimental Procedures and Characterization for Figure 5

General procedure for the remote aliphatic C–H oxidation of amines (1°, 2°, 3°) and pyridines: To a flame-dried 40 mL vial equipped with a stir bar was added amine (0.50 mmol,

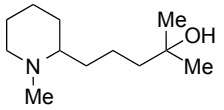
1.0 equiv.) and CH_2Cl_2 (2.0 mL, 0.25 M) the vial was flushed with a N_2 stream and then cooled to 0 ºC. HBF_4•OEt_2 (75.8 mL, 0.55 mmol, 1.1 equiv.) was added dropwise via syringe. The reaction solution was stirred at 0 ºC for 30 minutes followed by warming to room temperature and stirring for 1 hour. The reaction solution was concentrated in vacuo and left on high vacuum overnight (12–24 hours). The resultant amine-HBF_4 salts were then subjected to the iterative oxidation protocol or the slow addition oxidation protocol.

Iterative oxidation protocol. The amine-HBF_4 (0.50 mmol, 1.0 equiv.) was dissolved in MeCN (746 mL, 0.67 M to substrate). A solution of Fe(PDP) (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 µL, 15.0 mg, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)) was added. A solution of H_2O_2 (34.1 µL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. ***Significant decreases in yield were noted when the peroxide solution was added rapidly.*** After 10 min, a second portion of Fe(PDP) and AcOH dissolved in MeCN was added to the reaction mixture, followed by the dropwise addition of a second portion of H_2O_2 solution in MeCN as described above. After an additional 10 minutes, a third portion of Fe(PDP) and AcOH dissolved in MeCN were added followed by the dropwise addition of a third portion of H_2O_2 solution in MeCN as described above. The reaction solution was stirred for 10 minutes after the last iterative addition, for a total reaction time of approximately 36 minutes.

Slow addition oxidation protocol. Starting material (0.50 mmol, 1.0 equiv.) was dissolved in MeCN (0.75 mL, 0.67 M). A 1 mL syringe was charged with a solution of Fe(CF_3PDP) (0.125 mmol, 0.25 equiv.), MeCN (0.55 mL, 0.23 M to Fe catalyst) and AcOH (143 µL, 2.50 mmol, 5.0 equiv.). A 10 mL syringe was charged with a solution of H_2O_2 (256 µL, 4.50 mmol, 9.0 equiv., 50 wt.% in H_2O) in MeCN (6.0 mL, 0.75 M). Both syringes were fitted with 25G needles and

solutions were added simultaneously into the stirring reaction mixture via a syringe pump at 6 mL/h.

Reaction workup. MeCN volume was reduced to approximately 1–2 mL via rotary evaporation and diluted with CH_2Cl_2 (10 mL). Aqueous 1 M NaOH solution (10 mL) was added to basify and stirred vigorously for 10 minutes. The hydrolysis was poured into aqueous 1 M NaOH (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine (1 x 60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated via rotary evaporation. The crude material was purified by flash chromatography to affords the oxidation product.



2-Methyl-5-(1-methylpiperidin-2-yl)pentan-2-ol [10a] According to the general procedure, 1-methyl-2-(4-methylpentyl)piperidine **9a** (91.7 mg, 0.500 mmol, 1.0 equiv.) treated with HBF_4•OEt_2 (75.8 mL, 0.550 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (15 mL basic Al_2O_3 Brockmann grade III, gradient elution 10→20→40→80→100% EtOAc/Hex, 1 column volume each) afforded 2-methyl-5-(1-methylpiperidin-2-yl)pentan-2-ol **10a** as a colorless oil.

Run 1 (49.5 mg, 0.248 mmol, 50% yield; 24.1 mg, 0.131 mmol, 26% rsm)

Run 2 (52.7 mg, 0.264 mmol, 53% yield; 27.7 mg, 0.151 mmol, 30% rsm)

Average yield: 52% (28% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

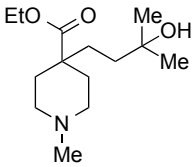
δ 2.84 (dtd, *J* = 11.8, 3.7, 1.5 Hz, 1H), 2.24 (s, 3H), 2.10 – 2.02 (m, 1H), 1.89 – 1.81 (m, 1H), 1.75 – 1.68 (m, 1H), 1.68 – 1.62 (m, 1H), 1.56 (ddt, *J* = 11.0, 8.0, 4.1 Hz, 3H), 1.49 – 1.35 (m, 4H), 1.34 – 1.22 (m, 4H), 1.21 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.08, 63.95, 57.43, 44.52, 43.05, 33.61, 30.86, 29.41, 25.93, 24.59, 20.02

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{12}H_{26}NO$ 200.2014, found 200.2009



Ethyl 4-(3-hydroxy-3-methylbutyl)-1-methylpiperidine-4-carboxylate [10b]

According to the general procedure, ethyl 4-isopentyl-1-methylpiperidine-4-carboxylate **9b** (120.7 mg, 0.500 mmol, 1.0 equiv.) treated with HBF_4•OEt_2 (75.8 mL, 0.550 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL basic Al_2O_3 Brockmann grade III, gradient elution 40→80% EtOAc/Hex→100% EtOAc→1% MeOH/EtOAc→10% MeOH/EtOAc, 1 column volume each) afforded ethyl 4-(3-hydroxy-3-methylbutyl)-1-methylpiperidine-4-carboxylate **10b** as a colorless oil.

Run 1 (70.4 mg, 0.274 mmol, 55% yield; 25.2 mg, 0.104 mmol, 21% rsm)

Run 2 (70.9 mg, 0.275 mmol, 55% yield; 22.7 mg, 0.094 mmol, 19% rsm)

Average yield: 55% (20% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

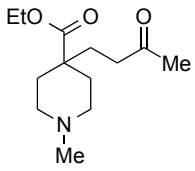
δ 4.16 (q, *J* = 7.1 Hz, 2H), 2.65 (d, *J* = 11.6 Hz, 2H), 2.23 (s, 3H), 2.14 (d, *J* = 13.3 Hz, 2H), 2.02 (t, *J* = 10.3 Hz, 2H), 1.82 (br s, 1H), 1.62 – 1.54 (m, 2H), 1.49 (ddd, *J* = 13.6, 11.5, 3.9 Hz, 2H), 1.39 – 1.32 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 175.99, 70.68, 60.44, 53.33, 46.47, 44.48, 37.85, 35.24, 33.78, 29.32, 14.53

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{14}H_{28}NO_3$ 258.2069, found 258.2017



Ethyl 1-methyl-4-(3-oxobutyl)piperidine-4-carboxylate [10c] According to the general procedure, ethyl 4-butyl-1-methylpiperidine-4-carboxylate **1f** (0.3 mmol, 68.2 mg) treated with HBF_4•OEt_2 (45.5 mL, 0.330 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 mL, 0.67 M to substrate) was used to dissolve the resultant salt. Following the addition protocol, oxidation was carried out with (*R,R*)-Fe(CF_3PDP)(MeCN)$_2$(SbF_6)$_2$ **2** (101.7 mg, 0.075 mmol, 0.25 equiv.) and AcOH (85.9 μL, 1.50 mmol, 5.0 equiv.) dissolved in MeCN (336 mL, 0.23 M to Fe(PDP)). H_2O_2 (153.4 μL, 2.70 mmol, 9.0 equiv., 50 wt.% in H_2O) in MeCN (3.6 mL, 0.75 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL basic Al_2O_3 Brockmann III, eluting with 40%→80% EtOAc/Hex→100% EtOAc→10% MeOH/EtOAc) to afford ethyl 1-methyl-4-(3-oxobutyl)piperidine-4-carboxylate **10c** as a colorless oil.

Run 1 (50% yield, 35.9 mg, 0.15 mmol; 25% rsm, 17.0 mg, 0.075 mmol)

Run 2 (49% yield, 35.7 mg, 0.15 mmol; 23% rsm, 15.7 mg, 0.069 mmol)

Average overall yield: 50% (24% rsm)

Oxidation with (*R*,*R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** same procedure as above: (46% yield, 33.3 mg, 0.14 mmol; 28% rsm, 19.4 mg, 0.085 mmol)

^{1}H NMR: (500 MHz, $CDCl_3$)

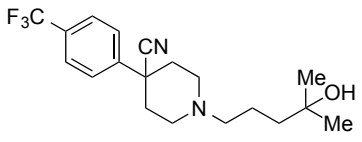
δ 4.12 (q, *J* = 7.1, 2H), 2.63 (d, *J* = 11.9 Hz, 2H), 2.38-2.32 (m, 2H), 2.20 (s, 3H), 2.15-2.07 (m, 5H), 1.96 (t, *J* = 11.4 Hz, 2H), 1.79-1.73 (m, 2H), 1.48-1.40 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 207.97, 175.54, 60.61, 53.20, 46.39, 44.01, 38.36, 33.57, 30.12, 14.40, 14.38

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{13}H_{24}NO_3$ 242.1756, found 242.1753



1-(4-Methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile [10d] According to the general procedure, 1-(4-methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **9d** (101.5 mg, 0.3 mmol, 1.0 equiv.) treated with HBF_4•OEt_2 (45.5 mL, 0.330 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 mL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (14.0 mg, 0.015 mmol, 0.05 equiv.) and AcOH (8.6 µL, 0.150 mmol, 0.5 equiv.) dissolved in MeCN (300 mL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 µL, 0.360 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (2.8 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL SiO_2, eluting with 2→5→10% MeOH/CH_2Cl_2)

afforded 1-(4-methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **10d** as a light yellow oil.

Run 1 (55.7 mg, 0.16 mmol, 52% yield; 39.8 mg, 0.12 mmol, 39% rsm)

Run 2 (50.3 mg, 0.14 mmol, 47% yield; 42.9 mg, 0.13 mmol, 42% rsm)

Average overall yield: 50% (41% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.65 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 3.13 (d, *J* = 12.4 Hz, 2H), 2.59-2.46 (m, 4H), 2.12 (dd, *J* = 7.3, 3.0 Hz, 4H), 1.72-1.60 (m, 4H), 1.20 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

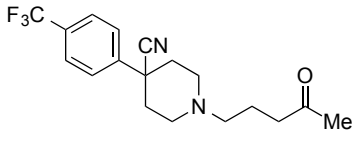
δ 143.65, 130.71 (q, *J* = 32.9 Hz), 126.38, 126.13 (q, *J* = 3.8 Hz), 123.86 (q, *J* = 272.3 Hz), 121.27, 69.08, 59.21, 50.64, 43.25, 42.97, 36.21, 29.84, 21.68

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.24 (s, 3F)

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{19}H_{26}N_2OF_3$ 355.1997, found 355.1990



1-(4-Oxopentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile [10e] According to the general procedure, 1-pentyl-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **9e** (97.3 mg, 0.3 mmol, 1.0 equiv.) treated with HBF_4•OEt_2 (45.5 mL, 0.330 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 mL, 0.67 M to substrate) was used to dissolve the resultant salt. Following the slow addition protocol, oxidation was carried out with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (101.7 mg, 0.075 mmol, 0.25 equiv.) and AcOH (85.9 μL, 1.50

mmol, 5.0 equiv.) dissolved in MeCN (336 mL, 0.23 M to Fe(PDP)). H_2O_2 (153.4 μL, 2.70 mmol, 9.0 equiv., 50 wt.% in H_2O) in MeCN (3.6 mL, 0.75 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL SiO_2, eluting with 2% MeOH/CH_2Cl_2) to afford 1-(4-oxopentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile **10e** as a colorless oil.

Run 1 (cycle 1: 24% yield, 24.3 mg, 0.072 mmol; 56% rsm, 54.6 mg, 0.17 mmol; cycle 2: 28% yield, 16.0 mg, 0.047 mmol; 45% rsm, 24.3 mg, 0.075 mmol; overall: 40% yield, 40.3 mg, 0.12 mmol; 25% rsm, 24.3 mg, 0.075 mmol)

Run 2 (cycle 1: 26% yield, 26.7 mg, 0.079 mmol; 57% rsm, 55.7 mg, 0.17 mmol; cycle 2: 25% yield, 14.7 mg, 0.043 mmol; 45% rsm, 25.3 mg, 0.078 mmol; overall: 41% yield, 41.4 mg, 0.12 mmol; 26% rsm, 25.3 mg, 0.078 mmol)

Average overall yield: 40% (25% rsm).

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.66 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 3.01 (d, *J* = 12.5 Hz, 2H), 2.55-2.37 (m, 6H), 2.16 (s, 3H), 2.14-2.00 (m, 4H), 1.80 (p, *J* = 7.1 Hz, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$)

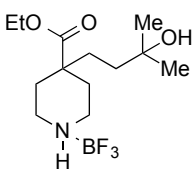
δ 208.52, 144.14, 130.59 (q, *J* = 32.9 Hz), 126.31, 126.16 (q, *J* = 3.6 Hz), 123.89 (q, *J* = 272.3 Hz), 121.42, 57.58, 50.63, 43.03, 41.40, 36.51, 30.31, 21.15

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.21

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{18}H_{22}N_2OF_3$ 339.1684, found 339.1684



Ethyl 4-(3-hydroxy-3-methylbutyl)piperidine-4-carboxylate boron trifluoride complex [10f] According to the iterative oxidation protocol, ethyl 4-isopentylpiperidine-4-carboxylate boron trifluoride complex **9f** (147.6 mg, 0.500 mmol, 1.0 equiv.) was oxidized with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and the crude material was purified by flash chromatography (50 mL SiO_2, gradient elution 30→40→50→60% EtOAc/Hex) to afford alcohol **10f** as a white solid.

Run 1 (81.5 mg, 0.262 mmol, 52% yield; 17.6 mg, 0.060 mmol, 12% rsm)

Run 2 on 0.3 mmol scale (52.3 mg, 0.168 mmol, 56% yield; 6.6 mg, 0.224 mmol, 7% rsm)

Average overall yield: 54% (10% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.22 (q, *J* = 7.1 Hz, 2H), 3.50 (br s, 1H), 3.34 (ddd, *J* = 14.2, 4.4, 2.3 Hz, 2H), 2.79 (tdd, *J* = 14.0, 11.7, 2.6 Hz, 2H), 2.43 (d, *J* = 14.0 Hz, 2H), 1.66 – 1.61 (m, 2H), 1.59 (br s, 1H), 1.43 (td, *J* = 14.2, 4.2 Hz, 2H), 1.39 – 1.34 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

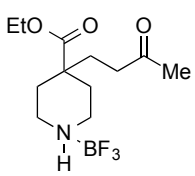
δ 174.13, 70.52, 61.45, 44.46, 43.63, 37.27, 35.67, 32.66, 29.42, 14.45

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.16 (q, *J* = 15.1 Hz)

HRMS: (ESI-TOF MS ES-)

m/z: $[M–H]^-$ calculated for $C_{13}H_{24}BNO_3F_3$ 310.1801, found 310.1800



Ethyl 4-(3-oxobutyl)piperidine-4-carboxylate boron trifluoride complex [10g] Following the slow addition protocol, ethyl 4-butylpiperidine-4-carboxylate boron trifluoride complex **9g** (88.5 mg, 0.300 mmol, 1.0 equiv.) was dissolved in MeCN (447 mL, 0.67 M to substrate). Oxidation was carried out with (*R,R*)-Fe(CF_3PDP)(MeCN)$_2$(SbF_6)$_2$ **2** (107.5 mg, 0.079 mmol, 0.25 equiv.) and AcOH (90.7 μL, 1.56 mmol, 5.0 equiv.) dissolved in MeCN (345 mL, 0.23 M to Fe(CF_3PDP)). H_2O_2 (162.1 μL, 2.85 mmol, 9.0 equiv., 50 wt.% in H_2O) in MeCN (3.8 mL, 0.75 M to H_2O_2). Reaction was concentrated and purified by flash chromatography (25 mL SiO_2, eluting with 20→40→50→60→70→80→90→100% EtOAc/Hex) to afford **10g** as a white solid.

Run 1 (45.8 mg, 0.155 mmol, 52% yield; 7.4 mg, 0.026 mmol, 9% rsm)

Run 2 (48.5 mg, 0.164 mmol, 55% yield; 3.7 mg, 0.013 mmol, 4% rsm)

Average overall yield: 54% (7% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.19 (q, *J* = 7.1 Hz, 2H), 4.07 (br s, 1H), 3.33 – 3.25 (m, 2H), 2.75 – 2.64 (m, 2H), 2.44 – 2.28 (m, 4H), 2.13 (s, 3H), 1.81 (t, *J* = 7.8 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.27 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

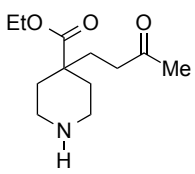
δ 207.85, 173.95, 61.63, 44.03, 43.40, 37.76, 33.91, 32.10, 30.20, 14.31

^{19}F NMR (470 MHz, $CDCl_3$)

δ -157.83 (q, *J* = 15.8 Hz)

HRMS: (ESI-TOF MS ES-)

m/z: $[M–H]^-$ calculated for $C_{12}H_{20}NO_3F_3B$ 294.1488, found 294.1493



Ethyl 4-(3-oxobutyl)piperidine-4-carboxylate [10h] According to the general procedure, ethyl 4-butylpiperidine-4-carboxylate **9h** (64.0 mg, 0.300 mmol, 1.0 equiv.) was treated with HBF_4•OEt_2 (44.9 mL, 0.330 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (447 mL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out according to the slow addition protocol with (*R,R*)-Fe(CF_3PDP)(MeCN)$_2$(SbF_6)$_2$ **2** (101.7 mg, 0.075 mmol, 0.25 equiv.) and AcOH (86 μL, 1.5 mmol, 5.0 equiv.) dissolved in MeCN (345 mL, 0.22 M to Fe(CF_3PDP)). H_2O_2 (153 μL, 2.70 mmol, 9.0 equiv., 50 wt.% in H_2O) in MeCN (3.8 mL, 0.71 M to H_2O_2). Reaction was concentrated and purified by flash chromatography (20 mL basic Al_2O_3 Brockmann grade III, eluting with 2→5→10% MeOH/CH_2Cl_2) to afford ketone **10h** as an inseperable mixture with the starting material as a colorless oil.

Run 1 (33.6 mg, 0.148 mmol, 49% yield; 6.9 mg, 0.032 mmol, 11% rsm)

Run 2 (30.3 mg, 0.133 mmol, 44% yield; 7.7 mg, 0.036 mmol, 12% rsm)

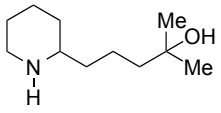
Average overall yield: 47% (11% rsm)

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 4.16 (q, *J* = 7.1 Hz, 2H), 2.94 (dt, *J* = 12.6, 4.1 Hz, 2H), 2.63 (td, *J* = 12.5, 2.5 Hz, 2H), 2.38 (app t, *J* = 8.0 Hz, 2H), 2.13 (s, 3H), 2.10 (app d, *J* = 15.6 Hz, 2H), 1.80 (app t, *J* = 8.0 Hz, 2H), 1.38 – 1.29 (m, 2H), 1.27 (app t, *J* = 7.1 Hz, 4H)

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^-$ calculated for $C_{12}H_{22}NO_3$ 228.1600, found 228.1598



2-Methyl-5-(piperidin-2-yl)pentan-2-ol [10i] According to the iterative oxidation protocol, 2-(4-methylpentyl)piperidine **9i** (84.7 mg, 0.500 mmol,

1.0 equiv.) treated with HBF_4•OEt_2 (75.8 mL, 0.550 mmol, 1.1 equiv., 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 mL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (25 mL basic Al_2O_3 Brockmann grade III, gradient elution 100% CH_2Cl_2→2→5→10% MeOH/CH_2Cl_2, 2 column volume each) afforded 2-methyl-5-(piperidin-2-yl)pentan-2-ol **10i** as a colorless oil.

Run 1 (54.1 mg, 0.292 mmol, 58% yield; 22.9 mg, 0.135 mmol, 27% rsm)

Run 2 (49.9 mg, 0.269 mmol, 54% yield, 21.8 mg, 0.129 mmol, 26% rsm)

Average yield: 56% (26% rsm)

Same procedure as above used BF_3•OEt_2 (67.9 mL, 0.550 mmol, 1.1 equiv.) for complexation.

Run 1 (39.2 mg, 0.212 mmol, 42% yield; 16.1 mg, 0.095 mmol, 19% rsm)

Run 2 (40.8 mg, 0.220 mmol, 44% yield, 21.5 mg, 0.127 mmol, 25% rsm)

Average yield: 43% (22% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

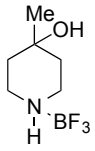
δ 3.03 (ddt, *J* = 12.2, 4.1, 2.1 Hz, 1H), 2.59 (td, *J* = 11.8, 2.9 Hz, 1H), 2.43 (dtd, *J* = 12.9, 6.2, 2.6 Hz, 1H), 1.86 – 1.65 (m, 2H), 1.67 – 1.58 (m, 1H), 1.60 – 1.51 (m, 1H), 1.50 – 1.24 (m, 9H), 1.18 (s, 6H), 1.04 (tdd, *J* = 12.5, 10.7, 3.8 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 70.88, 56.87, 47.27, 44.08, 38.02, 33.15, 29.49, 29.32, 26.77, 24.98, 20.69

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for $C_{11}H_{24}NO$ 186.1858, found 186.1857



4-Methylpiperidin-4-ol boron trifluoride complex [10j] According to the iterative oxidation protocol, 4-methylpiperidine boron trifluoride complex **9j** (100.2 mg, 0.500 mmol, 1.0 equiv.) was oxidized with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and the crude material was purified by flash chromatography (15 mL SiO_2, gradient elution 25→50→75% EtOAc/Hex, 2 column volumes each) to afford alcohol **10j** as a white solid.

Run 1 (55.5 mg, 0.303 mmol, 61% yield; 31.0 mg, 0.186 mmol, 37% rsm)

Run 2 (62.2 mg, 0.340 mmol, 68% yield; 20.9 mg, 0.125 mmol, 25% rsm)

Average overall yield: 65% (31% rsm)

^{1}H NMR: (500 MHz, CD_3CN)

δ 4.52 (br s, 1H), 3.05 (d, *J* = 12.8 Hz, 2H), 2.94 (qd, *J* = 12.4, 11.7, 6.5 Hz, 2H), 2.67 (br s, 1H), 1.64 (dd, *J* = 9.7, 4.1 Hz, 4H), 1.22 (s, 3H)

^{13}C NMR: (126 MHz, CD_3CN)

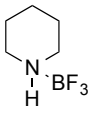
δ 66.02, 41.87, 36.71, 30.63.

^{19}F NMR: (470 MHz, CD_3CN)

δ -158.74 (q, *J* = 16.5 Hz).

HRMS: (ESI-TOF MS ES-)

m/z: $[M–H]^-$ calculated for $C_6H_{12}BNOF_3$ 182.0964, found 182.0969



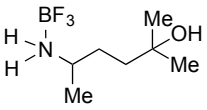
Piperidine boron trifluoride complex [9k] According to the iterative oxidation protocol, piperidine boron trifluoride complex (76.5 mg, 0.500 mmol, 1.0 equiv.) was oxidized with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and the crude material was purified by flash chromatography (20 mL SiO_2, gradient elution 30→40→50→60→80% EtOAc/Hex) to afford recovered starting material **9k**.

Trace ketones **10k** were observed as an intractable mixture.

Run 1 (57.1 mg, 0.373 mmol, 75% rsm)

Run 2 (56.5 mg, 0.369 mmol, 74% rsm)

Average overall rsm: 74%



5-Amino-2-methylhexan-2-ol boron trifluoride complex [10l] According to the iterative oxidation protocol, 5-methylhexan-2-amine boron trifluoride complex **9l** (91.5 mg, 0.5 mmol) was oxidized with (*S,S*)-(FePDP)$(MeCN)_2(SbF_6)_2$ **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv.) dissolved in MeCN (500 mL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv., 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and purified by flash chromatography (20 mL SiO_2 eluting with 20→40→60→80% EtOAc/Hex) to afford alcohol **9l** as a white solid.

Run 1 (57.6 mg, 0.29 mmol, 58% yield; 19.7 mg, 0.11 mmol, 22% rsm)

Run 2 (54.2 mg, 0.27 mmol, 54% yield; 19.6 mg, 0.11 mmol, 21% rsm)

Average overall yield: 56% (22% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.47 (br s, 1H), 3.92 (br s, 1H), 3.24 (br s, 1H), 2.35 (br s, 1H), 1.76-1.67 (m, 2H), 1.67-1.50 (m, 2H), 1.30 (d, J = 6.6 Hz, 3H), 1.26 (s, 3H), 1.24 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.14, 49.51, 38.76, 30.84, 30.03, 29.08, 19.80

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -147.71 (q, J = 16.5 Hz)

HRMS: (ESI-TOF MS ES-)

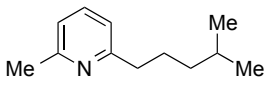
m/z: $[M-H]^-$ calculated for $C_7H_{16}BNOF_3$ 198.1277, found 198.1278

1.4.8 Synthesis of Substrates and Characterization for Figure 6

Pyridine alkylation procedure (Method A). A flame-dried 100 mL round bottom flask was charged with methylpyridine (13.75 mmol, 1.0 equiv.), tetrahydrofuran (THF) (6.3 mL) and a magnetic stir bar. The mixture was stirred and cooled down to -78 °C, and *n*-butyllithium (1.6 M, 9.9 mL, 15.81 mmol, 1.15 equiv.) was added dropwise via syringe. Upon completion of addition the flask was allowed to warm to ambient temperature and placed in 45 °C oil bath and stirred for 2 h. Another portion of THF (6.3 mL) was then added to fully dissolve the orange organolithium salt formed. The solution was then placed in an ice bath. In a separate flame-dried 200 mL round bottom flask was charged alkyl bromide (15.13 mmol, 1.10 equiv.), THF (2.5 mL) and a magnetic stir bar. The mixture was stirred and cooled down to -78 °C, and the organolithium solution was transferred via cannula into the reaction mixture containing the alkyl bromide. The reaction mixture was then allowed to warm to ambient temperature and stirred overnight. Water (0.5 mL) was added to quench the reaction, and the mixture was passed through

a silica plug (50 mL), and flushed with EtOAc (300 mL). The filtrate was concentrated in vacuo. Purification by flash chromatography provided the pure product.

Negishi cross-coupling for alkyl pyridine preparation (Method B). A flame-dried 50 mL flask was charged with zinc powder (1.51 g, 23.09 mmol, 1.5 equiv.) and a magnetic stir bar. The flask was stirred and heated to 70 °C in oil bath in vacuo for 0.5 h. The mixture was then taken out of oil bath, and dimethylacetamide (DMA) (15 mL, freshly distilled over CaH_2) and iodine (97.7 mg, 0.38 mmol, 0.025 equiv.) were added. The mixture was stirred until the brown color disappeared. Alkyl bromide (15.39 mmol, 1.0 equiv.) was then added via syringe, and the flask was placed back in the 70 °C oil bath and stirred overnight. The mixture was filtered through a Schlenk filter into a flame-dried 50 mL three neck flask, and the zinc reagent was stored under nitrogen. A separate flame-dried 100 mL flask was charged with $Pd_2(dba)_3$ (91.6 mg, 0.10 mmol, 0.02 equiv.), RuPhos (186.7 mg, 0.40 mmol, 0.08 equiv.) and a magnetic stir bar. DMA (23.5 mL, freshly distilled over CaH_2) was added via syringe, followed by 3-bromopyridine (790 mg, 5.0 mmol, 1.0 equiv.) and the zinc reagent (10 mL, 10 mmol, 2.0 equiv.). The reaction mixture was placed in a 70 °C oil bath and stirred overnight. The reaction mixture was quenched with 100 mL saturated NH_4Cl solution and extracted with diethyl ether (3x50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography provided the pure product.



2-Methyl-6-(4-methylpentyl)pyridine [11b] 2,6-lutidine (1.6 mL, 1.47 g, 13.75 mmol, 1.0 equiv.) was reacted with 1-bromo-3-methylbutane (1.9

mL, 2.33 g, 15.13 mmol, 1.1 equiv.) following method A. Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a light yellow oil (1.90 g, 10.7 mmol, 78% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

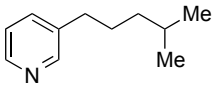
δ 7.46 (t, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 7.6, 4.0 Hz, 2H), 2.71 (t, *J* = 7.9 Hz, 2H), 2.52 (s, 3H), 1.72-1.64 (m, 2H), 1.56 (hept, *J* = 6.7 Hz, 1H), 1.27-1.21 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.07, 157.77, 136.56, 120.45, 119.54, 39.01, 38.92, 28.30, 28.10, 24.70, 22.74

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}N$ $[M+H]^+$: 178.1596, found 178.1601.



3-(4-Methylpentyl)pyridine [11c] Prepared from 3-bromopyridine (0.48 mL, 790 mg, 5.0 mmol, 1.0 equiv.) and 1-bromo-4-methylpentane (2.54 g, 15.39 mmol) following method B. Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a light yellow oil (662.8 mg, 4.1 mmol, 81% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

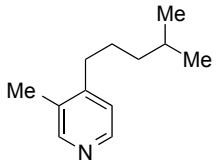
δ 8.46-8.40 (m, 2H), 7.48 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.20 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.66-1.50 (m, 3H), 1.26-1.17 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.09, 147.30, 138.11, 135.91, 123.36, 38.55, 33.40, 29.14, 27.97, 22.69

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}N$ $[M+H]^+$: 164.1439, found 164.1445.



3-Methyl-4-(4-methylpentyl)pyridine [11d] 3,4-lutidine (1.5 mL, 1.47 g, 13.75 mmol, 1.0 equiv.) was reacted with 1-bromo-3-methylbutane (1.9 mL, 2.33 g, 15.13 mmol, 1.1 equiv.) following method A. Purification by flash chromatography on silica eluting with 20→40% EtOAc/hexanes yielded the product as a yellow oil (1.80 g, 10.1 mmol, 74% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

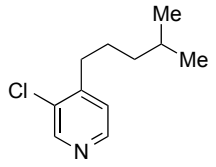
δ 8.34-8.28 (m, 2H), 7.02 (d, *J* = 5.0 Hz, 1H), 2.53 (t, *J* = 7.9 Hz, 2H), 2.25 (s, 3H), 1.63-1.49 (m, 3H), 1.29-1.19 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.66, 149.89, 147.55, 131.56, 123.46, 38.85, 32.78, 27.95, 27.07, 22.64, 16.16

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}N$ $[M+H]^+$: 178.1596, found 178.1601.



3-Chloro-4-(4-methylpentyl)pyridine [11e] Prepared following a modified version of general method A. In a flame-dried 100 mL round bottom flask was charged with diisopropylamine (2.3 mL, 1.61 g, 15.91 mmol, 1.16 equiv.), THF (6.3 mL) and a magnetic stir bar. The mixture was cooled down to -78 °C upon stirring, and *n*-butyllithium (1.6 M, 9.9 mL, 15.81 mmol, 1.15 equiv.) was added dropwise via syringe. The reaction mixture was stirred at -78 °C for 15 min and 0 °C for 5 min. The mixture was cooled back down to -78 °C, upon which 3-chloro-4-methylpyridine (1.5 mL, 1.75 g, 13.75 mmol, 1.0 equiv.) was added dropwise. The mixture was further stirred for 1 h, at which time 1-bromo-3-

methylbutane (1.9 mL, 2.33 g, 15.13 mmol, 1.1 equiv.) was added. The mixture was stirred for an additional 5 min at -78°C and was then allowed to warm up to ambient temperature, stirred overnight, and quenched with water (0.5 mL). Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a colorless oil (2.12 g, 10.7 mmol, 78% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

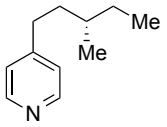
δ 8.50 (s, 1H), 8.36 (d, *J* = 4.9, 1H), 7.13 (d, *J* = 4.9 Hz, 1H), 2.69 (t, *J* = 7.7 Hz, 2H), 1.67-1.52 (m, 3H), 1.29-1.21 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.41, 149.22, 147.72, 132.21, 124.90, 38.64, 33.14, 27.91, 26.73, 22.64

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{17}NCl$ $[M+H]^+$: 198.1050, found 198.1051



(*S*)-4-(3-Methylpentyl)pyridine [11f] 4-picoline (1.4 mL, 1.28 g, 13.75 mmol, 1.0 equiv.) was reacted with (*S*)-1-bromo-2-methylbutane (1.9 mL, 2.29 g, 15.13 mmol, 1.1 equiv.) following method A. Purification by flash chromatography on silica eluting with 20→40% EtOAc/hexanes yielded the product as an orange oil (1.96 g, 12.0 mmol, 87% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

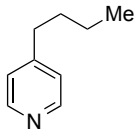
δ 8.45 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 2H), 2.57 (dddd, *J* = 41.3, 13.9, 10.4, 5.7 Hz, 2H), 1.67-1.56 (m, 1H), 1.46-1.30 (m, 3H), 1.18 (oct, *J* = 8.3 Hz, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 152.17, 149.75, 123.97, 37.38, 34.14, 32.96, 29.38, 19.14, 11.39

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}N$ $[M+H]^+$: 164.1439, found 164.1442.



4-Butylpyridine [11g] 4-picoline (1.4 mL, 1.28 g, 13.75 mmol, 1.0 equiv.) was reacted with 1-bromopropane (1.4 mL, 1.86 g, 15.13 mmol, 1.1 equiv.) following method A. Purification by flash chromatography on silica eluting with 20→40% EtOAc/hexanes yielded the product as a light yellow oil (953 mg, 7.05 mmol, 66% yield).

^{1}H NMR: (400 MHz, $CDCl_3$)

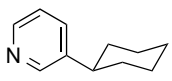
δ 8.48 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.11 (dd, *J* = 4.4, 1.5 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.66-1.59 (m, 2H), 1.36 (h, *J* = 7.3 Hz, 2H), 0.93 (d, *J* = 7.6 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.84, 149.75, 124.03, 35.08, 32.55, 22.40, 13.98

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_9H_{14}N$ $[M+H]^+$: 136.1126, found 136.1126.

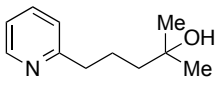


3-Cyclohexylpyridine [11h] Prepared from 3-bromopyridine (0.48 mL, 790 mg, 5.0 mmol, 1.0 equiv.) and bromocyclohexane (2.50 g, 15.39 mmol) following method B. Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a light yellow oil (803.5 mg, 5.0 mmol, quantitative yield). The spectral data matched those reported in the literature.[28]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.45 (d, *J* = 2.0 Hz, 1H), 8.40 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.48 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.18 (dd, *J* = 7.8, 4.8 Hz, 1H), 2.59-2.44 (m, 1H), 1.93-1.77 (m, 4H), 1.77-1.66 (m, 1H), 1.45-1.32 (m, 4H), 1.30-1.16 (m, 1H)

1.4.9 Experimental Procedures and Characterization for Figure 6



2-Methyl-5-(pyridin-2-yl)pentan-2-ol [12a] 2-(4-methylpentyl)pyridine **11a** (0.5 mmol, 81.6 mg) was reacted with (*S,S*)-Fe(PDP)(MeCN)$_2$(SbF$_6$)$_2$ **1** following the general procedure and the iterative oxidation protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a light yellow oil.

Run 1 (53.3 mg, 0.30 mmol, 59% yield; 23.8 mg, 0.15 mmol. 29% rsm)

Run 2 (53.3 mg, 0.30 mmol, 59% yield; 17.1 mg, 0.10 mmol, 21% rsm)

Average overall yield: 59% (25% rsm)

Oxidation with BF_3 protection under slow addition protocol:

Run 1 (32.4 mg, 0.18 mmol, 36% yield; 33.6 mg, 0.21 mmol. 41% rsm)

Run 2 (24.3 mg, 0.14 mmol, 27% yield; 39.0 mg, 0.24 mmol, 48% rsm)

Average overall yield: 32% (45% rsm)

^{1}H NMR: (400 MHz, $CDCl_3$)

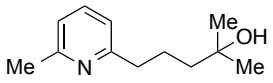
δ 8.51 (d, *J* = 4.1 Hz, 1H), 7.58 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 6.8, 5.3 Hz, 1H), 2.80 (t, *J* = 7.6 Hz, 2H), 1.94 (br s, 1H), 1.86-1.76 (m, 2H), 1.57-1.50 (m, 2H), 1.20 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.12, 149.22, 136.51, 122.98, 121.14, 70.97, 43.32, 38.55, 29.46, 24.71

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388, found 180.1394.



2-Methyl-5-(6-methylpyridin-2-yl)pentan-2-ol [15b] 2-methyl-6-(4-methylpentyl)pyridine **11b** (0.5 mmol, 88.6 mg) was reacted with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** following the general procedure and the iterative oxidation protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a light yellow oil.

Run 1 (57.0 mg, 0.29 mmol, 59% yield; 20.8 mg, 0.12 mmol, 23% rsm)

Run 2 (60.8 mg, 0.31 mmol, 63% yield; 19.4 mg, 0.11 mmol, 22% rsm)

Average overall yield: 61% (23% rsm)

Oxidation with BF_3 protection under slow addition protocol:

Run 1 (35.4 mg, 0.18 mmol, 37% yield; 35.7 mg, 0.20 mmol. 40% rsm)

Run 2 (30.7 mg, 0.16 mmol, 32% yield; 41.2 mg, 0.23 mmol, 47% rsm)

Average overall yield: 34% (43% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

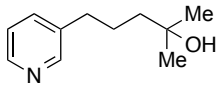
δ 7.46 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 7.6, 3.0 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.51 (s, 3H), 2.19 (br s, 1H), 1.82-1.73 (m, 2H), 1.56-1.49 (m, 2H), 1.19 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 161.45, 157.70, 136.73, 120.61, 119.78, 70.94, 43.17, 38.47, 29.45, 24.90, 24.54

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}NO$ $[M+H]^+$: 194.1545, found 194,1550.



2-Methyl-5-(pyridin-3-yl)pentan-2-ol [12c] 3-(4-methylpentyl)pyridine **11c** (0.5 mmol, 81.6 mg) was reacted with (*S,S*)-Fe(PDP)(MeCN)$_2$(SbF$_6$)$_2$ **1** following the general procedure and the iterative oxidation protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a light yellow oil.

Run 1 (44.1 mg, 0.25 mmol, 49% yield; 23.4 mg, 0.14 mmol, 29% rsm)

Run 2 (46.0 mg, 0.26 mmol, 51% yield; 25.2 mg, 0.15 mmol, 31% rsm)

Average overall yield: 50% (30% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

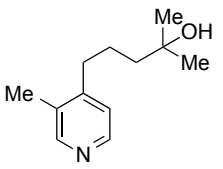
δ 8.43-8.36 (m, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.10 (br s, 1H), 1.73-1.64 (m, 2H), 1.51-1.45 (m, 2H), 1.18 (s, 6H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 149.91, 147.32, 137.75, 136.04, 123.47, 70.88, 43.34, 33.50, 29.44, 26.01

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388, found 180.1388



2-Methyl-5-(3-methylpyridin-4-yl)pentan-2-ol [12d] 3-methyl-4-(4-methylpentyl)pyridine **11d** (0.5 mmol, 88.6 mg) was reacted with (*S,S*)-Fe(PDP)(MeCN)$_2$(SbF$_6$)$_2$ **1** following the general procedure and the iterative oxidation protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil.

Run 1 (56.8 mg, 0.29 mmol, 59% yield; 23.3 mg, 0.13 mmol, 26% rsm)

Run 2 (54.0 mg, 0.28 mmol, 56% yield; 23.1 mg, 0.13 mmol, 26% rsm)

Average overall yield: 57% (26% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

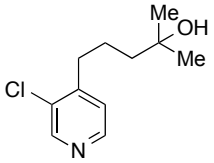
δ 8.29-8.24 (m, 2H), 7.01 (d, *J* = 5.0 Hz, 1H), 2.56 (t, *J* = 7.7 Hz, 2H), 2.36 (br s, 1H), 2.23 (s, 3H), 1.70-1.62 (m, 2H), 1.54-1.48 (m, 2H), 1.19 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.46, 149.66, 147.33, 131.65, 123.47, 70.54, 43.57, 32.84, 29.41, 23.92, 16.16

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}NO$ $[M+H]^+$: 194.1545, found 194.1552



5-(3-Chloropyridin-4-yl)-2-methylpentan-2-ol [12e] 3-chloro-4-(4-methylpentyl)pyridine **11e** (0.5 mmol, 98.8 mg) was reacted with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** following the general procedure and the iterative oxidation protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil.

Run 1 (33.8 mg, 0.16 mmol, 32% yield; 28.1 mg, 0.14 mmol, 28% rsm)

Run 2 (38.0 mg, 0.18 mmol, 36% yield; 28.8 mg, 0.15 mmol, 29% rsm)

Average overall yield: 34% (29% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

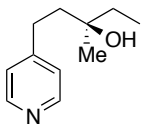
δ 8.49 (s, 1H), 8.34 (d, *J* = 4.9, 1H), 7.14 (d, *J* = 4.9 Hz, 1H), 2.72 (t, *J* = 7.7 Hz, 2H), 1.76-1.67 (m, 2H), 1.66 (br s, 1H), 1.56-1.50 (m, 2H), 1.21 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.33, 148.88, 147.66, 132.21, 124.90, 70.74, 43.32, 33.20, 29.44, 23.65

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{17}NOCl$ [M+H]+: 214.0999, found 214.1004



(*R*)-3-Methyl-1-(pyridin-4-yl)pentan-3-ol [12f] (*S*)-4-(3-methylpentyl)pyridine **11f** (0.5 mmol, 81.6 mg) was reacted with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ **1** following the general procedure and the iterative oxidation protocol. Purification by flash chromatography on silica (20 mL) eluting with 80% EtOAc/hexanes yielded the product as a colorless oil.

Run 1 (cycle 1: 26.6 mg, 0.15 mmol, 30% yield; 26.4 mg, 0.16 mmol, 32% rsm; cycle 2: 7.6 mg, 0.042 mmol, 26% yield; 5.9 mg, 0.036 mmol, 22% rsm; overall: 34.2 mg, 0.19 mmol, 38% yield; 5.9 mg, 0.036 mmol, 7% rsm)

Run 2 (cycle 1: 26.6 mg, 0.15 mmol, 30% yield; 27.1 mg, 0.17 mmol, 33% rsm; cycle 2: 6.7 mg, 0.038 mmol, 23% yield; 10.8 mg, 0.066 mmol, 40% rsm; overall: 33.3 mg, 0.19 mmol, 37% yield; 10.8 mg, 0.066 mmol, 13% rsm)

Average overall yield: 38% (10% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.46 (dd, *J* = 4.6, 1.4 Hz, 2H), 7.11 (d, *J* = 5.8 Hz, 2H), 2.68 (dd, *J* = 11.2, 5.7 Hz, 2H), 1.81 (br s, 1H), 1.73 (dd, *J* = 11.1, 5.3 Hz, 2H), 1.56 (q, *J* = 7.5 Hz, 2H), 1.22 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H)

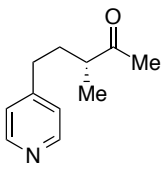
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 152.05, 149.69, 123.98, 72.55, 42.08, 34.65, 29.80, 26.42, 8.40

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388, found 180.1389

$[\alpha]_D^{25}$ = +4.3° (c=1.37, CH_2Cl_2)



(*R*)-3-methyl-5-(pyridin-4-yl)pentan-2-one [S7] Purification by flash chromatography on silica (20 mL) eluting with 80% EtOAc/hexanes yielded the product as a colorless oil.

Run 1 (cycle 1: 11% yield, 9.3 mg, 0.052 mmol; cycle 2: 10% yield, 2.9 mg, 0.016 mmol; overall: 14% yield, 12.2 mg, 0.069 mmol)

Run 2 (cycle 1: 12% yield, 10.8 mg, 0.061 mmol; cycle 2: 7% yield, 2.1 mg, 0.012 mmol; overall: 15% yield, 12.9 mg, 0.073 mmol)

Average overall yield: 14%

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.49 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.09 (d, *J* = 5.9 Hz, 2H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.52 (h, *J* = 7.0 Hz), 2.14 (s, 3H), 2.05-1.92 (m, 1H), 1.68-1.60 (m, 1H), 1.15 (d, *J* = 7.1 Hz, 3H)

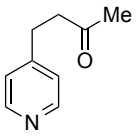
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 211.87, 150.85, 149.79, 123.90, 46.39, 33.05, 32.76, 28.32, 16.56

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1232, found 178.1237

$[\alpha]_D^{25}$ = -0.8° (c=1.38, CH_2Cl_2).



4-(Pyridin-4-yl)butan-2-one [12g] Following the general procedure, 4-butylpyridine **11g** (0.3 mmol, 40.6 mg) was reacted with (*R,R*)-Fe(CF_3PDP)$(MeCN)_2(SbF_6)_2$ **2** (101.7 mg, 0.125 mmol, 0.25 equiv.) and AcOH (86 µL, 90.2 mg, 1.5 mmol, 5.0 equiv.) in MeCN (3.0 mL, 0.50 M to AcOH), and H_2O_2 (153 µL, 2.7 mmol, 9.0 equiv., 50 wt. % in H_2O) in MeCN (3.6 mL, 0.75 M to H_2O_2) following the slow

addition protocol. Purification by flash chromatography on silica (50 mL) eluting with 80% EtOAc/hexanes yielded the product as a colorless oil. The spectral data matched those reported in the literature.[29]

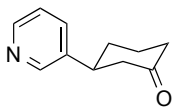
Run 1 (14.0 mg, 0.094 mmol, 31% yield; 10.1 mg, 0.075 mmol, 25% rsm);

Run 2 (14.4 mg, 0.097 mmol, 32% yield; 9.5 mg, 0.070 mmol, 23% rsm).

Average overall yield: 32% (24% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.47 (d, *J* = 5.4 Hz, 2H), 7.10 (d, *J* = 5.4 Hz, 2H), 2.87 (t, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.15 (s, 3H)



3-(Pyridin-3-yl)cyclohexan-1-one [12h] 3-cyclohexylpyridine **11h** (0.3 mmol, 48.4 mg) was protected according to the general procedure. According to the slow addition protocol, the resultant salt and AcOH (8.6 μL, 9.0 mg, 0.15 mmol, 0.5 equiv.) were dissolved in acetonitrile (0.45 mL, 0.67 M to 11h). (*R,R*)-Fe(CF_3PDP)(MeCN)$_2$(SbF_6)$_2$ **2** (101.7 mg, 0.125 mmol, 0.25 equiv.) was dissolved in MeCN (3.0 mL, 0.42 M) and loaded in a 1 mL syringe. Another 10 mL syringe was charged with H_2O_2 (86.5 μL, 1.5 mmol, 5.0 equiv., 50 wt. % in H_2O) in MeCN (3.6 mL, 0.42 M). Both syringes were fitted with 25G needles and were added simultaneously into the stirring reaction mixture via a syringe pump at 4 mL/h over approximately 1 h. Purification by MPLC on silica (12 g) eluting with 0→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil. The spectral data matched those reported in the literature.[30]

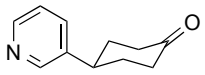
Run 1 (18.4 mg, 0.11 mmol, 35% yield; 2.3 mg, 0.014 mmol, 5% rsm)

Run 2 (15.2 mg, 0.087 mmol, 29% yield; 2.4 mg, 0.015 mmol, 5% rsm)

Average overall yield: 32% (5% rsm)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.51 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.53 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.26 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.04 (tq, *J* = 11.6, 3.7 Hz, 1H), 2.60 (ddt, *J* = 14.0, 4.2, 1.9 Hz, 1H), 2.56-2.51 (m, 1H), 2.51-2.45 (m, 1H), 2.39 (dt, *J* = 13.5, 6.3 Hz, 1H), 2.18 (ddt, *J* = 12.9, 6.6, 3.2 Hz, 1H), 2.10 (ddt, *J* = 11.3, 3.2, 1.7 Hz, 1H), 1.93-1.75 (m, 2H)



4-(Pyridin-3-yl)cyclohexan-1-one [S8] Purification by MPLC on silica (12 g) eluting with 0→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil. The spectral data matched those reported in the literature.[31]

Run 1 (4.8 mg, 0.027 mmol, 9% yield)

Run 2 (5.5 mg, 0.031 mmol, 10% yield)

Average overall yield: 10%

^{1}H NMR: (500 MHz, $CDCl_3$)

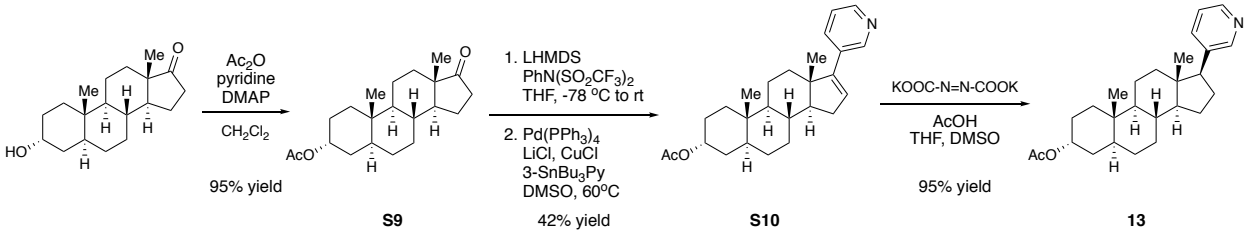
δ 8.55 (d, *J* = 2.0 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.55 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.26 (dd, *J* = 6.6, 6.0 Hz, 1H), 3.07 (tt, *J* = 12.2, 3.3 Hz, 1H), 2.54 (dd, *J* = 9.6, 5.0 Hz, 4H), 2.24 (ddt, *J* = 10.3, 5.2, 3.1 Hz, 2H), 1.96 (dq, *J* = 12.4, 8.6 Hz, 2H)

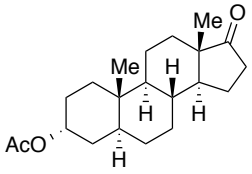
1.4.10 Synthesis of Substrate, Experimental Procedure, and Characterization for Figure 8

Table 4. Computational Data for Protonated Abiraterone Analogue (+)-**14**

Site (H_{eq} atom)	Electronic Parameter (E)	Local Sterics (L)	Through Space (TS)	Stereoele-ctronics (SE)	Steric/ Stereoelectronic Parameter (S)
C1	0.2013	H,H,Et,tBu	gauche	OAc	9.41
C6	0.2098	H,H,Et,iPr	-	Me	5.82
C7	0.2030	H,H,Et,iPr	gauche	-	6.90
C11	0.2147	H,H,Et,iPr	2gauche	2Me	7.44
C12	0.1957	H,H,Et,tBu	gauche	-	9.49
C15	0.2201	H,H,Et,iPr	gauche	Me	6.72
C17	0.2212	H,Et,Ph,tBu	-	-	12.59

Electron and steric parameters were assigned following procedures described by Gormisky and White.[5c] Due to the large steric hindrance of bridgehead axial hydrogens, no oxidation at these positions was ever observed. These hydrogens were therefore excluded from calculation. Sites directly attached to heteroatoms connecting to electron-withdrawing groups were excluded for the same reason. Aromatic rings were approximated as phenyl group when they are free to rotate and assigned the corresponding adjusted A value (4.0). Aromatic rings with ring-strained conformation were approximated as acyl group (K) and assigned the corresponding adjusted A value (2.25). For electron parameter, the purple lower limit is set as 105% of the lowest E, whereas the blue lower limit is set as 105% of the purple lower limit. For steric parameter, the purple limit is set as 140% of the lowest S, whereas the blue lower limit is set as 140% of the purple lower limit. Sites with one blue or two purple parameters were eliminated from site-selectivity calculation (Table 4).



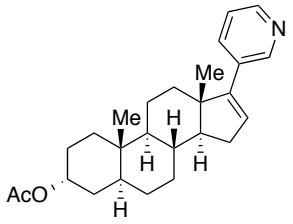


(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-Dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate [S9] In a flame-dried 100 mL round bottom flask equipped with a stir bar was charged (+)-androsterone (5.0 g, 17.2 mmol, 1.0 equiv.), pyridine (7.0 mL, 6.8 g, 86.1 mmol, 5.0 equiv.), 4-dimethylaminopyridine (DMAP) (210.1 mg, 1.72 mmol, 0.10 equiv.) and CH_2Cl_2 (34.4 mL). The reaction mixture was placed in ice bath upon stirring, and acetic anhydride (4.9 mL, 5.27 g, 51.6

mmol, 3.0 equiv.) was added dropwise via syringe. The reaction mixture was stirred at 0 °C for 5 min and was then allowed to warm to ambient temperature and stirred overnight. The reaction was washed with water (20 mL), 1 M HCl (4x20 mL) and brine (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica eluting with 10%→25% EtOAc/hexanes yielded the product as a white powder (5.57 g, 16.7 mmol, 97% yield).

^{1}H NMR: (500 MHz; $CDCl_3$)

δ 5.04-4.99 (m, 1H), 2.44 (dd, *J* = 19.2, 8.7 Hz, 1H), 2.14-2.00 (m, 4H), 1.94 (ddd, *J* = 12.6, 8.7, 5.9 Hz, 1H), 1.80 (dt, *J* = 11.8, 3.0 Hz, 2H), 1.76-1.69 (m, 1H), 1.69-1.59 (m, 2H), 1.59-1.54 (m, 1H), 1.54-1.51 (m, 1H), 1.54-1.43 (m, 4H), 1.35-1.18 (m, 6H), 1.01 (dq, *J* = 12.4, 4.7 Hz, 1H), 0.86 (s, 3H), 0.82 (s, 3H), 0.85-0.77 (m, 1H)



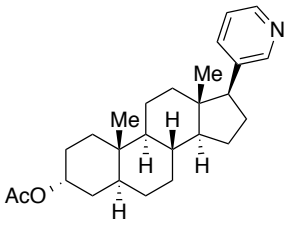
(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-Dimethyl-17-(pyridin-3-yl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate [S10] In a flame-dried 250 mL round bottom flask equipped with a stir bar was added **S9** (3.62 g, 10.89 mmol, 1.0 equiv.) and THF (72 mL). The reaction mixture was cooled down to -78 °C with stirring. LHMDS (2.00g, 11.98 mmol, 1.1 equiv.) was dissolved in THF (80 mL), and was slowly transferred via cannula into the reaction mixture. The reaction was stirred for 1 h. $PhN(SO_2CF_3)_2$ (4.28 g, 11.98 mmol, 1.1 equiv.) was then dissolved in THF (13.6 mL) and was added dropwise into the reaction mixture via syringe. The reaction was stirred for an additional 20 min and then allowed to warm up to ambient temperature and stirred for an additional hour. Water (10 mL) was then added to quench the reaction and THF was removed in vacuo. Diethyl

ether (50 mL) was added to extract the product, and the organic layer was washed with saturated NH_4Cl (20 mL) and brine (20 mL). The organic layer was then separated, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica eluting with 2→5% EtOAc/hexanes yielded the product as a white solid (2.75 g, 5.92 mmol, 54% yield) with minor $PhN(SO_2CF_3)_2$ as impurity, which was removed in the subsequent step.

The product (2.61 g, 5.62 mmol, 1.0 equiv.) was dissolved in DMSO (70 mL) at 60 °C and cannulated into a flame-dried 500 mL Schlenk flask charged with LiCl (1.43 g, 33.7 mmol, 6.0 equiv.), $Pd(PPh_3)_4$ (649.4 mg, 0.562 mmol, 0.10 equiv.), CuCl (2.78 g, 28.1 mmol, 5.0 equiv.), DMSO (150 mL) and a magnetic stir bar. 3-(tributylstannyl)pyridine (3.6 mL, 4.14 g, 11.2 mmol, 2.0 equiv.) was then added via syringe. The mixture was degassed through freeze-pump-thaw (-78 °C→0 °C) three times, and was stirred for 1 h at room temperature. The reaction flask was then placed into 60 °C oil bath and stirred vigorously for 20 h. The reaction was then quenched with the mixed solution of concentrated NH_4OH (5.5 mL) and brine (200 mL), extracted with diethyl ether (4x50 mL). The organic layers were then combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica eluting with 40% EtOAc/hexanes yielded the product as a white powder (1.69 g, 4.30 mmol, 77% yield, 42% overall yield).

^{1}H NMR: (500 MHz; $CDCl_3$)

δ 8.61 (s, 1H), 8.45 (d, *J* = 3.0 Hz, 1H), 7.63 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.21 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.97 (dd, *J* = 3.2, 1.6 Hz, 1H), 5.04-5.00 (m, 1H), 2.24 (ddd, *J* = 15.7, 6.4, 3.3 Hz, 1H), 2.05 (s, 3H), 2.04-1.98 (m, 1H), 1.81-1.69 (m, 3H), 1.69-1.63 (m, 3H), 1.58 (td, *J* = 11.3, 6.4 Hz, 1H), 1.54-1.46 (m, 4H), 1.46-1.32 (m, 2H), 1.30-1.20 (m, 3H), 1.11-1.02 (m, 1H), 1.00 (s, 3H), 0.94-0.86 (m, 1H), 0.84 (s, 3H)



(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-10,13-Dimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate [13] In a flame-dried 200 mL round bottom flask equipped with a stir bar was added (3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate **S10** (1.64 g, 4.17 mmol, 1.0 equiv.), THF (39 mL) and DMSO (39 mL). The mixture was cooled down to 0 °C upon stirring, and potassium azodicarboxylate (KOOC–N=N–COOK) (3x5.4 g, 83.3 mmol, 20 equiv.) was added in three equal portion over the course of 2 h, each followed by the addition of AcOH (3x3.2 mL, 3x3.33 g, 166.7 mmol, 40 equiv.). After adding the last portion of potassium azodicarboxylate, the reaction was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with brine (100 mL) and extracted with diethyl ether (3x50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica eluting with 20%→30%→40%→80% EtOAc/hexanes yielded the product as a white powder (1.55 g, 3.93 mmol, 94% yield).

^{1}H NMR: (500 MHz; $CDCl_3$)

δ 8.49-8.40 (m, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 7.1, 5.1 Hz, 1H), 5.03-4.98 (m, 1H), 2.65 (t, *J* = 9.8 Hz, 1H), 2.10-2.01 (m, 4H), 2.01-1.91 (m, 1H), 1.85-1.76 (m, 1H), 1.76-1.68 (m, 2H), 1.68-1.58 (m, 1H), 1.58-1.51 (m, 2H), 1.51-1.44 (m, 4H), 1.44-1.39 (m, 1H), 1.39-1.30 (m, 1H), 1.29-1.23 (m, 2H), 1.23-1.11 (m, 4H), 0.99 (dq, *J* = 12.5, 4.9 Hz, 1H), 0.86-0.79 (m, 1H), 0.78 (s, 3H), 0.46 (s, 3H)

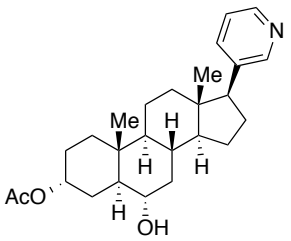
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.81, 150.52, 147.60, 136.60, 135.72, 122.86, 70.21, 56.47, 54.70, 54.51, 44.63, 40.25, 37.72, 36.05, 33.02, 32.11, 28.47, 26.23, 26.00, 24.54, 21.71, 20.53, 12.90, 11.51

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{26}H_{38}NO_2$ $[M+H]^+$: 396.2903, found 396.2894.

$[\alpha]_D^{25}$ = +17.9° (c = 1.03, CH_2Cl_2).



(3*R*,5*S*,6*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-6-Hydroxy-10,13-dimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate [15] (3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-10,13-dimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate **13** (0.3 mmol, 118.7 mg) was reacted with (*R,R*)-($FeCF_3PDP$)$(MeCN)_2(SbF_6)_2$ **2** following the general procedure and the iterative addition protocol. After oxidation MeCN was removed and the crude mixture was dissolved in CH_2Cl_2 (3 mL), saturated $NaHCO_3$ solution (10 mL) was then added and the mixture was stirred vigorously overnight. Purification by MPLC on silica (12 g) eluting with 0→70% EtOAc/hexanes yielded the product as a white crystalline solid. Recovered starting material was recycled twice.

Cycle 1 (21% yield, 25.9 mg, 0.063 mmol; 50% rsm, 59.4 mg, 0.15 mmol)

Cycle 2 (20% yield, 12.4 mg, 0.030 mmol; 50% rsm, 29.8 mg, 0.075 mmol)

Cycle 3 (20% yield, 6.1 mg, 0.015 mmol; 48% rsm, 14.4 mg, 0.036 mmol)

Overall Mass (44.4 mg, 0.11 mmol)

Overall yield: 36% (12% rsm)

Protection with excess HBF_4 (2.0 eq) was also attempted and similar yield was obtained (20% alcohol yield, 24.5 mg, 0.060 mmol; 4% ketone yield, 5.1 mg, 0.012 mmol; 46% rsm, 54.6 mg, 0.14 mmol).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.50-8.46 (m, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.17-5.13 (m, 1H), 3.49-3.41 (m, 1H), 2.72 (t, *J* = 9.8 Hz, 1H), 2.17-2.10 (m, 2H), 2.09 (s, 3H), 2.08-1.99 (m, 1H), 1.92-1.84 (m, 1H), 1.83-1.74 (m, 1H), 1.72-1.62 (m, 2H), 1.62-1.57 (m, 2H), 1.57-1.49 (m, 2H), 1.49-1.44 (m, 2H), 1.44-1.39 (m, 1H), 1.39-1.30 (m, 2H), 1.30-1.24 (m, 2H), 1.20 (dq, *J* = 13.4, 3.7 Hz, 1H), 1.04 (q, *J* = 11.9 Hz, 1H), 0.91 (dt, *J* = 11.9, 3.9 Hz, 1H), 0.84 (s, 3H), 0.51 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

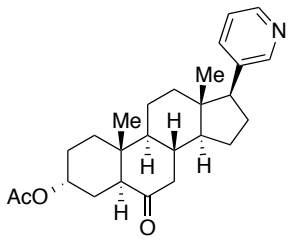
δ 170.75, 150.37, 147.56, 136.44, 135.82, 122.92, 69.67, 69.32, 56.13, 54.57, 53.93, 47.21, 44.59, 41.76, 37.49, 36.72, 34.80, 33.18, 27.43, 25.92, 25.86, 24.50, 21.70, 20.41, 12.87, 12.68

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{26}H_{38}NO_3$ $[M+H]^+$: 412.2852, found 412.2843

$[\alpha]_D^{25}$ = +17.4° (c = 0.78, CH_2Cl_2)

The site of oxidation was confirmed by oxidizing the product to **15-ketone** using DMP and matching the spectra reported below. The stereochemistry was assigned based on a combination of ^{1}H NMR, COSY, HSQC and NOESY 1D NMR methods.



(3*R*,5*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-Dimethyl-6-oxo-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate [15-Ketone] Purification by MPLC on silica (12 g) eluting with 0→70% EtOAc/hexanes followed by flash chromatography on silica (10 mL) eluting with 40% EtOAc/hexanes yielded the product as a white crystal.

Cycle 1 (3% yield, 4.3 mg, 0.010 mmol)

Cycle 2 (3% yield, 2.1 mg, 0.0051 mmol)

Cycle 3 (2% yield, 0.6 mg, 0.001 mmol)

Overall Mass (7.0 mg, 0.017 mmol)

Average overall yield: 6%

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.45 (s, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 7.6, 4.9 Hz, 1H), 5.15-5.09 (m, 1H), 2.72 (t, *J* = 9.8 Hz, 1H), 2.60 (dd, *J* = 12.1, 2.3 Hz, 1H), 2.39 (dd, *J* = 13.2, 4.3 Hz, 1H), 2.16-1.96 (m, 6H), 1.93-1.83 (m, 1H), 1.83-1.75 (m, 3H), 1.75-1.66 (m, 2H), 1.65-1.56 (m, 2H), 1.56-1.49 (m, 2H), 1.49-1.41 (m, 1H), 1.44-1.36 (m, 1H), 1.36-1.26 (m, 2H), 1.26-1.18 (m, 1H), 0.74 (s, 3H), 0.48 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

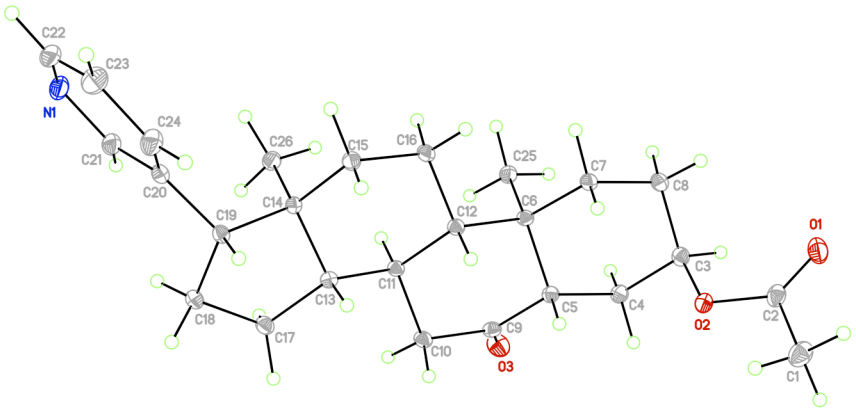
δ 211.62, 170.39, 150.50, 147.83, 136.01, 135.66, 122.95, 68.90, 56.64, 54.42, 54.02, 52.77, 46.84, 44.92, 41.39, 38.42, 37.18, 32.52, 25.80, 25.39, 25.16, 24.28, 21.58, 20.81, 12.86, 12.61

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{26}H_{36}NO_3$ $[M+H]^+$: 410.2695, found 410.2690

$[\alpha]_D^{25}$ = -19.8° (c = 0.51, CH_2Cl_2)

Site of oxidation was confirmed by X-ray crystallography.



Crystal data and structure refinement for cd66ssa (15-Ketone)

Identification code	cd66ssa	
Empirical formula	C26 H35 N O3	
Formula weight	409.55	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.4928(18) Å	a= 90°.
	b = 7.5529(13) Å	b= 98.217(4)°.
	c = 13.883(2) Å	g = 90°.
Volume	1089.0(3) $Å^3$	
Z	2	
Density (calculated)	1.249 Mg/m^3	
Absorption coefficient	0.633 mm^{-1}	
F(000)	444	
Crystal size	0.364 x 0.166 x 0.078 mm^3	

Theta range for data collection	3.216 to 72.014°.
Index ranges	-12<=h<=12, -8<=k<=9, -17<=l<=15
Reflections collected	14626
Independent reflections	4205 [R(int) = 0.0246]
Completeness to theta = 67.679°	99.9 %
Absorption correction Integration	
Max. and min. transmission	0.96348 and 0.87764
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4205 / 1 / 275
Goodness-of-fit on F2	1.137
Final R indices [I>2sigma(I)]	R1 = 0.0339, wR2 = 0.0847
R indices (all data)	R1 = 0.0342, wR2 = 0.0850
Absolute structure parameter	0.06(5)
Extinction coefficient	0.066(3)
Largest diff. peak and hole	0.320 and -0.333 e.$Å^{-3}$

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CHAPTER 2: MANGANESE-CATALYZED BENZYLIC C(sp^3)–H AMINATION FOR LATE-STAGE FUNCTIONALIZATION

Acknowledgements

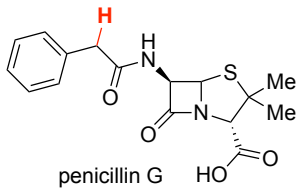
This chapter was adapted from the research article "Manganese-catalysed benzylic C(sp^3)–H amination for late-stage functionalization" (Clark, J. R.; Feng, K.; Sookezian, A.; White, M. C. *Nat. Chem.* **2018**, *10*, 583).

This work was a collaborative effort. The reaction optimization and the majority of the scope for substrates not containing basic nitrogen were established by Dr. Joseph R. Clark and Anasheh Sookezian; the mechanistic studies were carried out by Dr. Joseph R. Clark. These sections will not be described in this thesis.

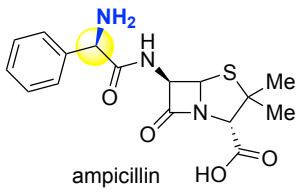
2.1 Introduction

In addition to hydroxylation, installation of nitrogen functionalities in natural products and bioactive molecules also has ability to effect unique changes in physical and biological activities, and has sparked continued interest in its methodological development.[32] For example, penicillin G is an antibiotic active against only Gram-positive bacteria. However, by introducing an amino group on its benzylic position, the resulting ampicillin becomes active also against Gram-negative bacteria (Figure 8).[33]

Figure 8. Installation of Amino Group Changes the Bioactivity of Penicillin G



Only active against Gram-positive bacteria.
Used to treat infections in 1942.

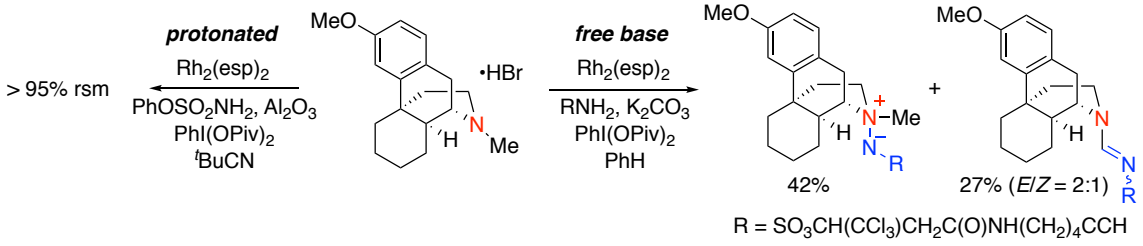


Broader spectrum of activity relative to penicillin G to include activity against Gram-negative bacteria (1961).

Indeed, benzylic amine motifs are prevalent in pharmaceuticals such as terbinafine, valsartan, meclizine, and sertraline, among others.[34] Unlike C–H oxidation, however, nature does not install nitrogen functionalities directly, but through oxidation and subsequent reductive amination.[35] Similarly, chemical methods that introduce nitrogen functionalities also heavily rely on the transformation of preexisting oxidized functionalities, often C=O or C–X (X = halogen).[36] In complex molecules, such strategy can be challenging and encounter issues of selectivity and functional group tolerance. A chemical method that directly installs nitrogen functionalities at late stages would effectively reduce the need for de novo synthesis and further facilitate discovery of bioactive small molecules.

The quest for direct, intermolecular amination was widely pursued in recent years and significant progress has been made. Most prominently, amination by rhodium catalysis was achieved preparatively across a wide range of C–H bonds via metallonitrene intermediates, allowing the ability to tune selectivity through ligand and oxidant modification.[37] Despite this advantage, however, the underlying problems for rhodium catalysis are that it lacks strong site- and chemoselectivity[38] and does not tolerate basic nitrogen.[39] Although the acid protection strategy was highly effective in Fe(PDP)-catalyzed C–H oxidation,[13] it was proven incompatible with rhodium-mediated amination, leading to only recovered starting material (Figure 9).[39a]

Figure 9. Attempts for Amination of Dextromethorphan by $Rh_2(esp)_2$

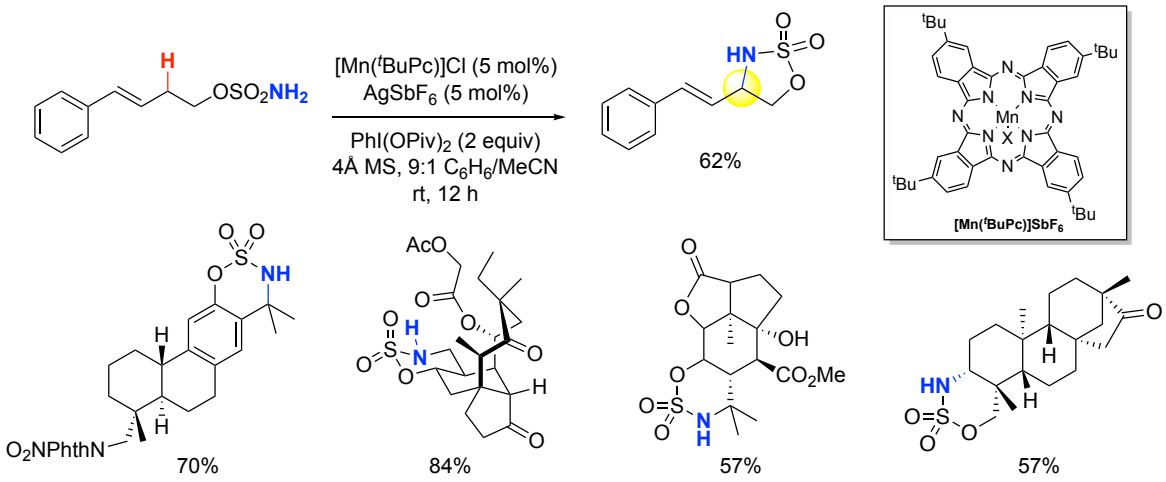


The inability of $Rh_2(esp)_2$ to aminate protonated nitrogen-containing substrates, such as dextromethorphan hydrobromide, can likely be attributed to its highly labile ligand that may

dissociate through proton exchange with the substrate. On the other hand, $Rh_2(esp)_2$ showed reactivity on dextromethorphan in lieu of an acid, but was only capable of aminating alpha to nitrogen and on nitrogen—two sites activated by hyperconjugation of the nitrogen lone-pair (Figure 10).[39b] To date, no amination by rhodium at sites remote from basic nitrogen has been demonstrated. Such limitations on reactivity and selectivity could significantly hinder its application in drug discovery where basic nitrogens motifs are prevalent.[7]

The high cost and toxicity of rhodium also calls for development of more sustainable base-metal amination catalysts. Compared with rhodium catalysis, reports of base-metal-catalyzed intermolecular amination were relatively scarce.[40] Among known methods prior to this work, iron- and cobalt-catalyzed amination has been demonstrated on a limited scope of simple substrates;[40a-d] furthermore, amination with cobalt requires a large excess of substrate.[40c-d] Copper-mediated amination was not chemoselective.[40e,f] Iron and manganese catalysts have also been shown to promote C–H azidation, but these reactions lack site-selectivity and scramble stereocenters, causing skeletal rearrangements.[41] Similar to rhodium catalysis, none of these strategies were able to tolerate basic amines, which could only be functionalized after irreversible nitrogen quaternization with methyl.[41b]

Figure 10. [Mn(^{t}BuPc)]-Catalyzed Intramolecular C–H Amination



Comparatively, base-metal-mediated intramolecular amination has seen more success.[42] Specifically, our group has previously developed two small-molecule, base-metal catalysts, [FePc] and [Mn(^{t}BuPc)], capable of promoting intramolecular amination on all types of C–H bonds (Figure 10).[42a,b] Since the metal center is connected to the phthalocyanine ligand through covalent bonds in these catalysts, I envisioned that they would be uniquely stable and compatible for the acid-protection strategy without degradation as seen in rhodium catalysis,[39a] thus enabling unprecedented remote amination of basic-nitrogen-containing substrates. These successes and hypotheses drove us to investigate and design base-metal phthalocyanine catalysts for intermolecular benzylic C–H amination.

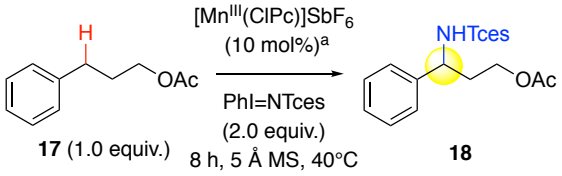
2.2 Results and Discussion

2.2.1 Reaction Development

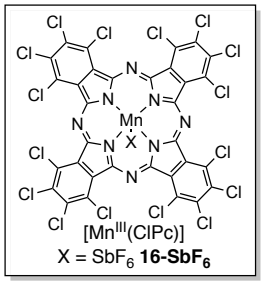
After extensive studies on the catalyst design and reaction conditions, we identified a manganese perchlorophthalocyanine complex, [Mn^{III}(ClPc)] **16**, as the optimal intermolecular benzylic amination catalyst.[43] The sixteen chlorine atoms on the phthalocyanine ring made the manganese nitrene intermediate highly electrophilic, and were crucial for the strong intermolecular reactivity of this catalyst. We eliminated a rate-limiting step in the catalysis by pre-forming the active iminoiodinane oxidant, PhI=NTces, instead of going through in situ formation as was in the intramolecular reactions.[42] This pre-formation allowed C–H cleavage to be the sole rate-limiting step. These modifications facilitated the reaction to produce synthetically useful yields in the amination of **17** (Table 5, entry 1). While benzene is an excellent solvent for substrates not containing basic nitrogen, solubility challenges would arise in the highly ionic protonated or complexed amine and pyridine substrates, and a polar solvent

compatible with these highly ionic substrates must be developed as an alternative. Considering the new solvent must not contain reactive functional groups (e.g., nitrile) or Lewis-basic functionalities that may cause proton/BF_3 exchange leading to in situ deprotection, I identified 1,2,dichloroethane (1,2-DCE) as an aprotic, non-coordinating solvent, which produced **18** in a comparable amination yield (entry 2).

Table 5. Reaction Development



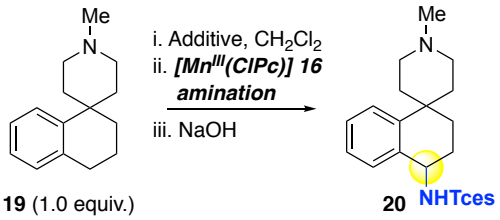
Entry	Solvent	% yield (% rsm)
1	C_6H_6	68 (32)
2[b]	1,2-DCE	60 (24)



[a]Reaction conditions: **17** (0.2 mmol, 1 equiv.), **16** (10 mol%), $AgSbF_6$ (10 mol%), PhI=NTces (2 equiv.), solvent (0.5 M), 5 Å molecular sieves (40 mg), 8 h. Yields are of isolated products. Recovered starting material (rsm) is reported based on ^{1}H NMR analysis of the crude reaction using 1,3,5-trimethylbenzene as an internal standard. [b]3 Å molecular sieves.

The discovery of 1,2-DCE as a suitable amination solvent allowed me to study the two nitrogen protecting strategies on a spirocyclic substrate **19**, a σ-receptor agonist containing a tertiary amine.[44] As expected, under no protection the desired amination product was not observed, and the decreased mass balance suggest deleterious side reactions may have occurred (Table 6, entry 1). However, under both HBF_4 and BF_3 protection, the desired product **20** was observed in synthetically useful yields, showing that both strategies are compatible with the manganese-catalyzed amination (entries 2 and 3). Consistent with what was seen in the remote C–H oxidation, protection with HBF_4 was more effective in producing higher yields and mass balances. However, the BF_3-amine complex of **19** was significantly more soluble in 1,2-DCE than the protonated amine, and in cases where low solubility of protonated amines results in low conversion, the use of BF_3 is more preferable (vide infra).

Table 6. Development of Nitrogen Protection Strategies



19 (1.0 equiv.) **20**

Entry	Additive	% yield (% rsm)
1	–	0 (47)
2	HBF_4•OEt_2	58 (10)
3	BF_3•OEt_2	51(2)

[a]Reaction conditions: **19** (0.3 mmol, 1 equiv.), additive (1.1 equiv.), CH_2Cl_2 (0.25 M); **16** (10 mol%), $AgSbF_6$ (10 mol%), PhI=NTces (2 equiv.), 1,2-DCE (0.5 M), 5 Å molecular sieves (40 mg), 15 h; 1 M NaOH workup. Yields are of isolated products. Recovered starting material (rsm) is reported based on ^{1}H NMR analysis of the crude reaction using 1,3,5-trimethylbenzene as an internal standard.

2.2.2 Reaction Scope

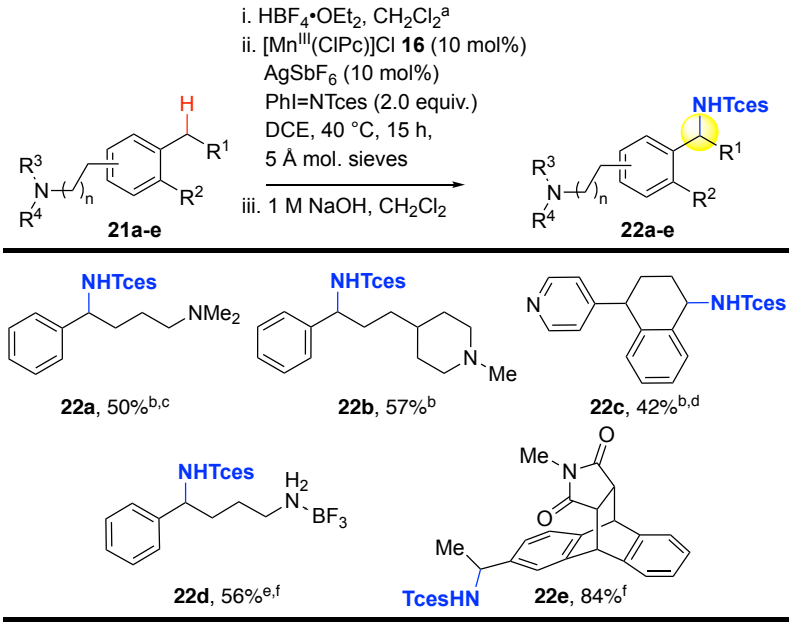
I first evaluated the optimized conditions on four simple molecules containing basic amines or a pyridine (Figure 11). Under the HBF_4 protection and subsequent [Mn^{III}(ClPc)] amination, substrates containing either a linear tertiary amine or an *N*-methylpyrrolidine motif were aminated in synthetically useful yields without demethylation (**22a**, **b**). These results represent the very first remote amination examples of tertiary amines. The less basic but medicinally prevalent pyridine was also well tolerated under the same amination conditions. Significantly, a tertiary benzylic site in pyridine-containing substrate **21c** was not functionalized despite its much lower bond dissociation energy, likely because of its steric bulk and deactivation via protonation.

Although primary amines can be remotely aminated as trifluoroacetamides,[43] BF_3 complexation offers an orthogonal choice of functionalizing these amines without the need for acylation: 4-phenylbutylamine **21d** was aminated as a stable amine-BF_3 complex in a good yield and the product was easily purified via silica column. Because BF_3 can be removed under mildly

basic or non-basic conditions,[13,43] protection with BF_3 would be especially useful in functionalizing amine substrates containing base-sensitive functional groups.

Additionally, as was observed in the remote C–H oxidation of imides,[13] imide nitrogens are deactivated by the two carbonyls it connects to and serve directly as electron-withdrawing groups, promoting remote amination in 84% yield in a single step with no need for acid protection (**22e**).

Figure 11. Amination of Simple Amines and Pyridine

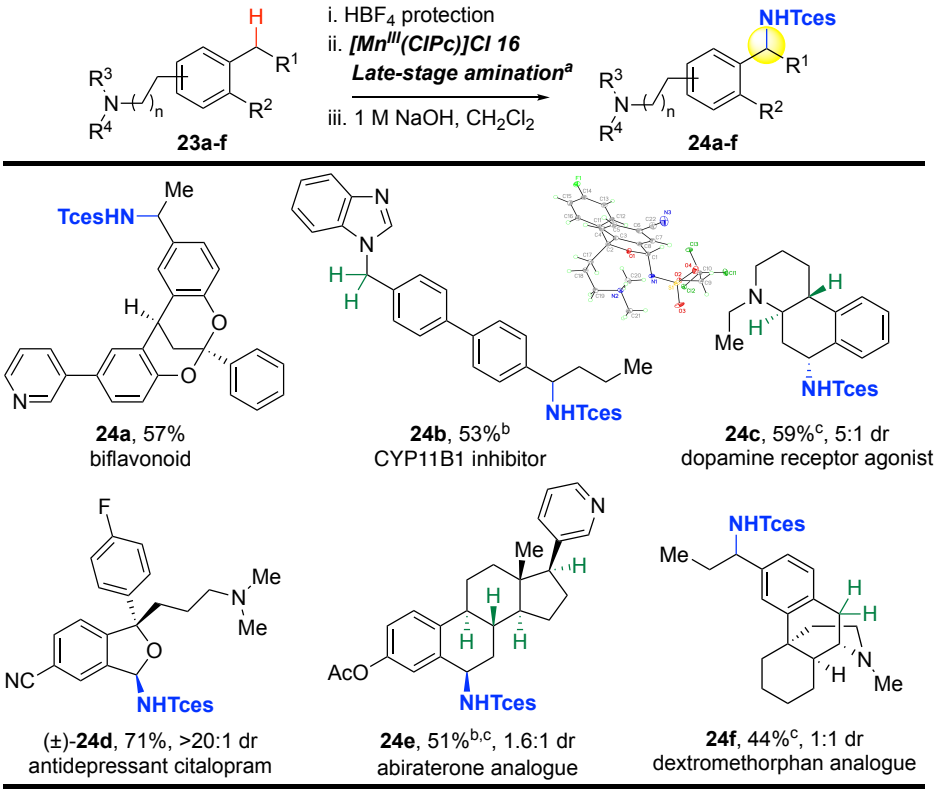


[a]Reaction conditions same as Table 5, substrate (0.2 mmol). [b]3 equiv. PhI=NTces. [c]15 mol% catalyst used. [d]3 Å molecular sieves. [e]Amine-BF_3 complex preformed and purified via column chromatography. [f]no HBF_4 protection or NaOH workup.

2.2.3 Application in Late-Stage Derivatization

The highly encouraging results from amination of simple amines and pyridine showed that the HBF_4 protonation/[Mn^{III}(ClPc)] amination strategy has great potential for late-stage derivatization of bioactive nitrogen-containing molecules. I identified six complex bioactive molecules, drugs, and natural product derivatives with multiple competitive sites and basic nitrogen heterocycles to investigate the amination efficiency of this strategy (Figure 12).

Figure 12. Late-Stage Amination of Natural Products, Bioactive Molecules, and Drugs



[a]Reaction conditions: **23** (0.2 mmol, 1 equiv.), additive (1.1 equiv.), CH_2Cl_2 (0.25 M); **16** (10 mol%), $AgSbF_6$ (10 mol%), PhI=NTces (2 equiv.), 1,2-DCE (0.5 M), 3 Å molecular sieves (40 mg), 15 h; 1 M NaOH workup. [b]BF_3•OEt_2 (1.1 equiv.) used for amine protection and decomplexed with TMEDA (5 equiv.) in CH_2Cl_2. [c]3 equiv. PhI=NTces.

The [Mn^{III}(ClPc)] **16** catalysis was proven highly chemoselective and site-selective because of its unique reactivity and bulky size, and only aminated the most electron rich and sterically accessible secondary benzylic site in all cases studied, despite them having more reactive tertiary aliphatic and benzylic sites. Biflavonoid natural products containing a 2,8-dioxabicyclo[3.3.1]nonane skeleton has shown interesting medicinal properties.[45] A bioflavonoid containing a pyridine motif, **23a**, was selectively aminated on the remote benzylic site while preserving the delicate structure and its bridgehead hydrogen. The acid-sensitive ketal skeleton was also tolerated by the HBF_4 protonation and [Mn^{III}(ClPc)] amination. A similar structure where bromine replaced the pyridyl group also produced the corresponding amination product in 73% yield in lieu of acid protection. Benzimidazole, another mildly basic heterocycle, was for

the first time tolerated in the amination of **23b**, a CYP11B1 inhibitor analogue,[46] in good yields. In this molecule, HBF_4 protonation rendered an insoluble salt and BF_3 protection was shown to be most effective. While the C–H bonds alpha to the benzimidazole ring were hyperconjugatively activated, the complexation rendered benzimidazole a strong electron-withdrawing group, promoting remote amination to produce **24b** as the only observed product.

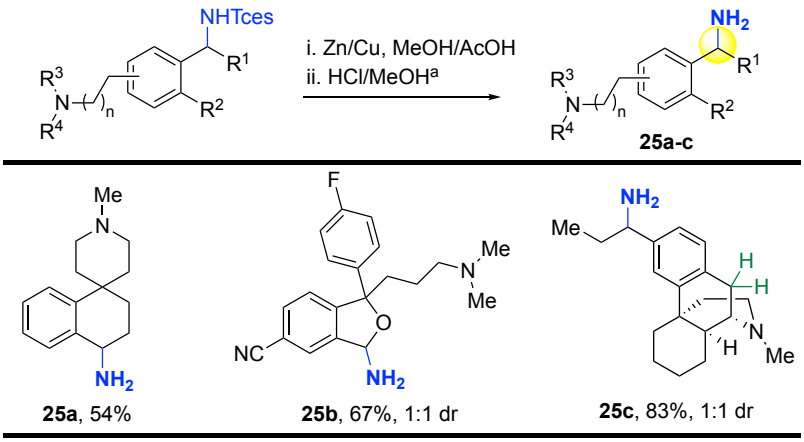
Likewise, in a dopamine receptor agonist analogue **23c** containing a tertiary amine and tertiary aliphatic and benzylic sites,[47] the steric bulk and inductive deactivation led to amination solely on the secondary benzylic site to produce **24c** in a good overall yield. X-ray crystallography showed that the pseudoaxial C–H was preferentially aminated in a 5:1 dr, possibly because of the pseudoaxial radical being stabilized by the phenyl ring. A similar diastereoselectivity was also observed in other substrates containing fused six-membered rings.

A widely used commercial antidepressant, citalopram, can be directly aminated after protonation by HBF_4. Due to the steric bulk of the fluorophenyl ring and the alkyl chain, the reaction proceeded in high diastereoselectivity to produce (±)-**24d** as a single diastereomer in 71% yield. An abiraterone analogue, having multiple tertiary aliphatic and benzylic sites, upon BF_3 complexation was selectively aminated on the less sterically encumbered C6 to give **24e** in a synthetically useful 51% yield. Significantly, previously reported examples of C–H azidation on the nitrogen-free, structurally similar estrone gave a mixture of tertiary benzylic amination, hydroxylation, and over-amination products,[41] showing the orthogonality of manganese-catalyzed amination in selectivity to the azidation strategies.

As mentioned previously, attempts to aminate dextromethorphan, an antitussive drug, under rhodium catalysis had been unsuccessful other than at positions alpha to nitrogen and on nitrogen.[39] However, the structurally rigidity of the $[Mn^{III}(ClPc)]$ **16** catalyst made it uniquely

suitable for the protonation strategy. Amination of an analogue of dextromethorphan having two secondary sites proceeded successfully to produce the remotely aminated **24f** in a synthetically useful 44% yield, while the secondary benzylic site proximal to nitrogen was inductively deactivated and preserved through the amination.

Figure 13. Tces Deprotection



[a]Reaction conditions: substrate (1 equiv.), Zn/Cu couple (10 equiv.), MeOH:AcOH (1:1). After filtration through a celite plug, the concentrated white solid was stirred in methanolic HCl at 40 °C for 12 h to yield the corresponding amine, purified via acid-base extraction.

The 2,2,2-trichloroethylsulfonyl (Tces) protecting group can be readily removed by treatment with Zn/Cu couple and subsequent stirring with HCl to generate the free amine.[38a] This deprotection can be done on both simple and complex amination products while preserving other functional groups (Figure 13). Together with the amination, this process allows chemists to install nitrogen functionalities as pre-protected, unreactive sulfonamides, carry on with other late-stage derivatizations, and finally deprotect to generate the active amine products.

2.3 Conclusion

Applying the HBF_4 protonation/BF_3 complexation strategies established for C–H hydroxylation, we have developed a manganese catalyst for unprecedented late-stage amination in substrates containing basic amines, as well as amination of pyridine and benzimidazole. This

catalytic system is highly chemoselective and site-selective, has shown orthogonal reactivity with noble metal catalysis, and has great potential to facilitate the drug discovery process by allowing rapid amine installation in current drugs and drug leads. Further development of this catalytic system would focus on expanding the substrate scope to functionalize less reactive sites, including allylic and aliphatic C–H bonds. Researchers have already started using [Mn^{III}(ClPc)] for amination at the final stage of synthesis,[48] and applications as such, especially in nitrogen-containing molecules, will likely become more prevalent both in time and as the catalyst's scope continues to broaden.

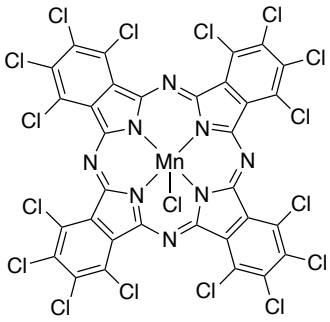
2.4 Experimental Section

2.4.1 General Methods

Experimental. The following commercially obtained reagents were used as received: Mn(II)Cl_2 (99.995%-Mn, Strem), tetrachlorophthalonitrile (≥96%, TCI), PhI$(OAc)_2$ (Sigma-Aldrich or Oakwood Chemicals), Mn$(OAc)_2$ (Sigma-Aldrich) and powdered 3 Å and 5 Å molecular sieves (Sigma-Aldrich). 2,2,2-trichloroethylsulfamate was synthesized according to a previously reported procedure[38a] and is also commercially available (Sigma-Aldrich). Anhydrous solvents were purified by passage through a bed of activated alumina immediately prior to use (Glass Countour, Laguna Beach, California). Chloroform-*d* was stored over 3 Å molecular sieves. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized with UV and Cerium-ammonium-molybdate and potassium permanganate stains. Flash chromatography was performed using American International ZEOprep 60 ECO silica gel (230-400 mesh).

Structural Analysis. ^{1}H-NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian VXR 500 (500 MHz), Varian Inova-500 (500 MHz), Varian Unity-500 (500 MHz) or Carver-Bruker 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, hept = septet, oct = octet, non = nonet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Unity-500 (125 MHz) or Carver-Bruker 500 (125MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). ^{19}F spectra were recorded on a Varian VXR 500 (470 MHz), Varian Unity-500 (470 MHz) or Carver-Bruker 500 (470 MHz) and are reported in ppm using $FCCl_3$ (0 ppm) as an external standard. Labeled solvent impurities were calculated out when reporting isolated yields. High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof μLtima spectrometer, and electron ionization (EI) and field desorption (FD) spectra were performed on a Micromass 70-VSE spectrometer. X-ray crystallographic analysis was carried out by Dr. Toby Woods and Dr. Danielle Gray at the University of Illinois George L. Clark X-Ray Facility.

2.4.2 Synthesis of Catalyst and Iminoiodinane



Manganese (III) perchlorophthalocyanine chloride [16] In a 200 mL flame-dried round bottom flask under argon containing a Teflon stir bar and equipped with a water cooled condenser was added consecutively tetrachlorophthalonitrile (3.99 g, 15.00 mmol, 4 equiv.), anhydrous manganese (II) chloride (472 mg, 3.75 mmol, 1

equiv.), freshly distilled 1-hexanol (45 mL, 0.33 M) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.24 mL, 15.00 mmol, 4 equiv.). The flask was placed in a 160 °C silicon oil bath and stirred for 8 h. Upon reaction completion, the flask was removed from the oil bath, allowed to cool to room temperature and cooled for 10 minutes in an ice bath. The contents were poured directly onto a glass fritted Buchner funnel and the solid washed consecutively and three times each with 5% HCl (3 x 20 mL), water (3 x 20 mL), and ethanol (3 x 40 mL). During the washes, the solid was broken up with a spatula to give a powdered turquoise solid after the last ethanol wash. The solid was collected and placed under vacuum at room temperature for 24 hours to remove any residual solvent to give a turquoise powdery solid (4.12 g, 95% yield) and transferred into the glove box for permanent storage.

UV-Vis: (1-Chloronaphthalene, λmax = nm, ε = $M^{-1}cm^{-1}$)

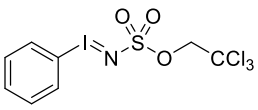
770 (ε = 84968), 691 (ε = 20629), 525 (ε = 10675), 400 (ε = 23658), 356 (ε = 25245)

IR: (ATR, cm-1)

3124, 2927, 2856, 1644, 1564, 1467, 1427, 1385, 1310, 1272, 1203, 1152, 1130, 1095, 1039, 954, 931, 763, 746, 734, 598, 572, 497

MS: (MALDI) (DHB Matrix)

m/z calculated for $C_{32}Cl_{16}MnN_8$ [M-Cl]+ : 1110.464, found 1110.507



2,2,2-Trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate [S11] In a flame-dried 100 mL round bottom flask under nitrogen was added 2,2,2-trichloroethyl sulfamate (2.0 g, 8.75 mmol, 1 equiv.), (diacetoxyiodo)benzene (2.82 g, 8.75 mmol, 1 equiv.) and anhydrous methanol (35 mL, 0.25 M). The contents were stirred to dissolve most of the (diacetoxyiodo)benzene and then cooled to 0 °C in an ice-water bath. Once cooled,

potassium hydroxide (1.23 g, 21.88 mmol, 2.5 equiv.) was added as pellets. The reaction was stirred for 30 minutes at 0 °C and then 7.5 hours at room temperature. Upon reaction completion, the contents were transferred to a separatory funnel containing 100 mL of water. Dichloromethane (100 mL) was added and the contents vigorously shaken to remove all excess potassium hydroxide (very important). The layers were separated and the aqueous layer was further extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with water (1 x 100 mL), shaking vigorously to remove any trace potassium hydroxide, and transferred directly to a 500 mL round bottom flask and the solvent removed by rotary evaporation at room temperature (do not exceed 30 °C as the iminoiodinane will not perform optimally) to give a slightly yellow solid. The contents were transferred to a 100 mL round bottom flask using 20 mL of methanol and the solvent was removed by rotary evaporation leaving a slightly yellow solid. The contents were azeotroped once with 20 mL of benzene and placed under vacuum for an additional 20 minutes to give a slightly yellow solid. The solid was triturated with diethyl ether (5 x 10 mL) while breaking up any solid chunks into a powdery solid. After vacuum drying for one hour an off-white powdery solid was obtained (1.78 g, 47% yield) and used as is. The contents were capped with a polyethylene cap and stored in the freezer. The iminoiodinane is stable for at least 3 months in the freezer. This procedure was adapted from a previously reported procedure[5] but deviates significantly in several steps and the above described procedure should be followed for best results.

^{1}H NMR: (499 MHz, Methanol-d_4)

δ 8.22 – 8.11 (d, J = 7.4 Hz, 0.6H), 8.10 – 7.96 (m, 1.4H), 7.68 (t, J = 7.5 Hz, 0.3H), 7.64 – 7.46 (m, 2.7H), 4.68 (s, 1.4H), 4.29 (s, 0.6H)

^{13}C NMR: (126 MHz, Methanol-d_4)

δ 136.3, 133.4, 133.3, 132.3, 132.2, 132.0, 122.6, 95.3, 79.0, 78.9

HRMS: (ESI-TOF MS ES-)

m/z calculated for $C_8H_7Cl_4NIO_3S$ $[M+Cl]^-$: 463.7945, found 463.7939

2.4.3 Experimental Procedures and Characterization for Table 5

General optimization procedure. In a 10 mL round bottom flask was added 5 Å powdered molecular sieves (40 mg) and a Teflon stir bar. The flask was sealed with a Suba Seal rubber septum, placed under vacuum, flame-dried for 45 seconds to activate the molecular sieves, cooled under a purged and completely air-free argon balloon and wrapped in foil to exclude light. Once cooled, solvent (0.40 mL, 0.5 M to substrate) and 3-phenylpropyl acetate **17** (35.6 mg, 0.20 mmol, 1 equiv., Sigma-Aldrich) were added and stirred for 10 minutes. $[Mn^{III}(ClPc)]$ **16** (0.020 mmol, 0.1 equiv.) and silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv.) were weighed in a foil wrapped 1 dram vial in the glove box and sealed with a Teflon cap. The vial was removed from the glove box and the contents added directly to the round bottom flask and stirred for 10 minutes while maintaining an argon atmosphere. In a 1 dram vial open to air, 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate **S11** (172.2 mg, 0.40 mmol, 2 equiv.) was weighed and added directly to the round bottom flask while maintaining an argon atmosphere. The Suba Seal rubber septum was replaced by a polyethylene cap, sealed tightly and stirred for 8 h at the given temperature. Upon reaction completion, the reaction was filtered through a 1-inch silica gel plug using diethyl ether as the eluent. The solvent was evaporated and a crude ^{1}H NMR in $CDCl_3$ was obtained using mesitylene (9.3 μL, 0.067 mmol, 0.33 equiv.) as an internal standard to obtain the ^{1}H NMR yield. The crude material was then concentrated and dry-loaded directly onto a silica gel column. Flash chromatography using gradient elution (500 mL of 100%

dichloromethane (removes excess $TcesNH_2$) then 300 mL of 2% diethyl ether in 98% dichloromethane followed by 300 mL of 5% diethyl ether in 95% dicholoromethane) gave the pure product as a white solid with slight discoloration.

Entry 1. According to the general procedure B for optimization studies, 5 Å powdered molecular sieves (40 mg), 3-phenylpropyl acetate **17** (35.6 mg, 0.20 mmol, 1 equiv.), C_6H_6 (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride **16** (23.1 mg, 0.020 mmol, 0.1 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.1 equiv.) and PhI=NTces **S11** (172.2 mg, 0.40 mmol, 2 equiv.) were combined in a 10 mL round-bottom flask and stirred for 8 h at 40 °C.

Run 1 (53 mg, 0.131 mmol, 66% isolated yield, 33% rsm by ^{1}H NMR)

Run 2 (54 mg, 0.133 mmol, 67% isolated yield, 33% rsm by ^{1}H NMR)

Run 3 (57 mg, 0.141 mmol, 71% isolated yield, 29% rsm by ^{1}H NMR)

Average yield: 68% (32% rsm)

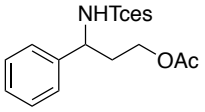
Entry 2. According to the general procedure B for optimization studies, 3 Å powdered molecular sieves (40 mg), 3-phenylpropyl acetate **17** (35.6 mg, 0.20 mmol, 1 equiv.), 1,2-dichloroethane (0.40 mL, 0.5 M), manganese (III) perchlorophthalocyanine chloride **16** (23.1 mg, 0.020 mmol, 0.1 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.1 equiv.) and PhI=NTces **S11** (172.2 mg, 0.40 mmol, 2 equiv.) were combined in a 10 mL round-bottom flask and stirred for 8 h at 40 °C.

Run 1 (61% ^{1}H NMR yield, 26% rsm by ^{1}H NMR)

Run 2 (59% ^{1}H NMR yield, 24% rsm by ^{1}H NMR)

Run 3 (49 mg, 0.121 mmol, **60% isolated yield**, 22% rsm by ^{1}H NMR)

3-Phenyl-3-(((2,2,2-trichloroethoxy)sulfonyl)amino)propyl acetate [18]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 3H), 5.73 (d, *J* = 7.7 Hz, 1H), 4.68 (q, *J* = 7.4 Hz, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.18-4.13(m, 1H), 4.05-4.00 (m, 1H), 2.32-2.25 (m, 1H), 2.18-2.11 (m, 1H), 2.04 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

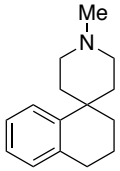
δ 171.2, 139.7, 129.2, 128.6, 126.7, 93.3, 78.1, 61.1, 56.9, 35.6, 21.0;

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{16}NO_5SCl_3Na$ $[M+Na]^+$: 425.9712, found 425.9706

2.4.4 Substrate Characterization for Table 6

1'-Methyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4'-piperidine] [19]



Synthesized using a previously reported synthesis and the spectral data matches the previously reported data.[49]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.49 (d, *J* = 7.9 Hz, 1H), 7.21-7.15 (m, 1H), 7.08 (td, *J* = 7.3, 1.2 Hz, 1H), 7.16-7.03 (m, 1H), 2.77 (t, *J* = 6.2 Hz, 2H), 2.76-2.70 (m, 2H), 2.35 (s, 3H), 2.26 (td, *J* = 11.8, 1.8 Hz, 2H), 2.16 (td, *J* = 13.8, 3.8 Hz, 2H), 1.87-1.80 (m, 2H), 1.78-1.70 (m, 2H), 1.65-1.57 (m, 2H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 145.16, 137.41, 129.06, 126.92, 126.03, 125.42, 51.84, 46.69, 38.56, 34.86, 30.99, 30.83, 19.02

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{15}H_{22}N$ $[M+H]^+$: 216.1752, found 216.1748

2.4.5 Experimental Procedures and Characterization for Table 6

General amination procedure for 3° amines and pyridines. To a 1 dram vial equipped with a stir bar were added the nitrogen-containing substrate (0.20 mmol, 1.0 equiv.) and methylene chloride (DCM) (0.8 mL). Tetrafluoroboric acid diethyl ether complex ($HBF_4{\cdot}OEt_2$) (30.2 μL, 35.6 mg, 0.22 mmol, 1.1 equiv.) was added dropwise while stirring. The reaction mixture was stirred for 1 h at room temperature. Upon reaction completion, the stir bar was removed, and the mixture was concentrated *in vacuo* and placed on vacuum overnight. In a 10 mL round-bottom flask equipped with a stir bar was added 40 mg of powdered 3 Å molecular sieves. The flask was then flame-dried under vacuum for 45 seconds, and refilled with argon using an thrice purged argon-filled balloon. In the 1-dram vial carrying the protonated substrate was added 0.2 mL of anhydrous 1,2-dichloroethane (DCE). The resulting solution or suspension was added into the round-bottom flask containing the 3 Å molecular sieves. This process is repeated 2x with 0.1 mL DCE each time to ensure complete transfer. The reaction flask was then wrapped in aluminum foil and stirred for 10 min, upon which time manganese (III) perchlorophthalocyanine chloride **16** (23.1 mg, 0.02 mmol, 0.10 equiv.) and silver hexafluoroantimonate ($AgSbF_6$) (6.9 mg, 0.02 mmol, 0.10 equiv.) were added while maintaining an argon atmosphere. The mixture was stirred for 10 min, and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (PhI=NTces) **S11** (172.2

mg, 0.40 mmol, 2.0 equiv.) was added while maintaining an argon atmosphere. The septum was replaced by a polyethylene yellow cap, and the flask was placed into 40 °C oil bath and stirred for 15 h. Upon completion, the flask was removed from the oil bath. Sodium hydroxide solution (1 M, 3 mL) and DCM (3 mL) were then added. The reaction mixture was vigorously stirred for 15 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The organic layers were combined, dried over anhydrous potassium carbonate, filtered and concentrated via rotary evaporation. The crude material was purified by flash chromatography to afford the aminated product. (***Note: Significant ketone byproduct formation and yield decrease were observed when an aged bottle of HBF_4·OEt_2 was used, possibly due to water absorption and/or decomposition.***)

Entry 1. Reaction without protection or base workup:

Run 1 (0 mg, 0 mmol, **0% yield**; 30.4 mg, 0.141 mmol, **47% rsm**)

Entry 2. Reaction with BF_3 protection (40.7 μL, 46.8 mg, 0.33 mmol, 1.1 equiv.) and base workup (1 M NaOH, 5 mL, 4 h):

Run 1 (64.8 mg, 0.147 mmol, 49% yield; 1.9 mg, 0.0090 mmol, 3% rsm)

Run 2 (70.3 mg, 0.159 mmol, 53% yield; 1.3 mg, 0.0060 mmol, 2% rsm)

Average overall yield: 51% (2% rsm)

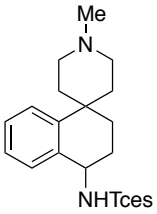
Entry 3. Reaction with HBF_4 protection (45.3 μL, 53.4 mg, 0.33 mmol, 1.1 equiv.) and base workup (1 M NaOH, 5 mL, 15 min):

Run 1 (78.9 mg, 0.18 mmol, 60% yield; 3.1 mg, 0.014 mmol, 5% rsm)

Run 2 (68.4 mg, 0.15 mmol, 52% yield; 9.6 mg, 0.045 mmol, 15% rsm)

Run 3 (81.0 mg, 0.18 mmol, 61% yield; 6.5 mg, 0.030 mmol, 10% rsm)

Average overall yield: 58% (10% rsm) ± 4.9



2,2,2-Trichloroethyl (1'-methyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4'-piperidin]-4-yl)sulfamate [20] According to the general amination procedure, 1'-methyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4'-piperidine] **19** (64.6 mg, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL) was protonated with $HBF_4{\cdot}OEt_2$ (45.3 μL, 53.4 mg, 0.33 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (34.6 mg, 0.030 mmol, 0.10 equiv.), $AgSbF_6$ (10.3 mg, 0.030 mmol, 0.10 equiv.), PhI=NTces (258.3 mg, 0.60 mmol, 2.0 equiv.), and 5 Å molecular sieves (60 mg) in DCE (0.6 mL) for 15 h. Following work-up, the crude material was purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, gradient elution 25% EtOAc/Hex (4 column volumes)→0%→1%→2%→3% MeOH/CH_2Cl_2 (2 column volumes each)), staining with $KMnO_4$ to afford the product as a green oil. To remove the minimal co-eluding manganese catalyst, the product was re-dissolved in CH_2Cl_2 (10 mL) and extracted with 3M HCl (2x10 mL) and water (2x10 mL). The aqueous layers were combined and basified with 50% NaOH, extracted with CH_2Cl_2 (3x10 mL). The organic layers were combined, dried over K_2CO_3, and concentrated via rotary evaporation to afford the pure product as a white solid. The remaining organic layer after the acid wash was also basified and extracted likewise to afford the product as a white solid with discoloration.

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.49 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 4.73 (t, *J* = 5.3 Hz, 1H), 4.69 (s, 2H), 2.69 (d, *J* = 11.4 Hz, 1H), 2.66 (d, *J* = 11.4 Hz, 1H), 2.31 (s, 3H), 2.27-2.17 (m, 2H), 2.17-1.94 (m, 4H), 1.90 (app t, *J* = 5.8 Hz, 2H), 1.51 (t, *J* = 12.9 Hz, 2H)

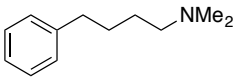
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 145.61, 134.79, 129.01, 128.81, 127.35, 126.66, 93.83, 78.10, 54.20, 51.57, 46.45, 38.26, 37.62, 34.82, 29.83, 26.24, 25.95

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{24}Cl_3N_2O_3S$ $[M+H]^+$: 441.0573, found 441.0565

2.4.6 Synthesis of Substrate and Characterization for Figure 11



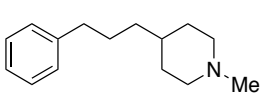
***N,N*-Dimethyl-4-phenylbutan-1-amine [21a]** In a 100 mL round-bottom flask were added 4-phenylbutan-1-amine (1.58 mL, 1.49 g, 10.0 mmol, 1.0 equiv.) and formaldehyde (37 wt%, 7.5 mL, 3.02 g, 100 mmol, 10.0 equiv.). Formic acid (3.8 mL, 4.60 g, 100 mmol, 10.0 equiv.) was then added dropwise. The mixture was then refluxed in a 100 °C oil bath for 4 h, then partitioned between water (50 mL) and CH_2Cl_2 (50 mL), upon which time a saturated potassium carbonate solution (10 mL) was added. The organic layer was isolated, and the aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated via rotary evaporation. The crude material was purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, 5% EtOAc/Hex (4 column volumes)) to afford the product as a light yellow oil (1.36 g, 7.65 mmol, 76% yield). The spectral data matched those reported in literature.[50]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.30-7.24 (m, 2H), 7.21-7.14 (m, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.21 (s, 6H), 1.64 (app p, *J* = 7.2 Hz, 2H), 1.55-1.46 (m, 2H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 142.60, 128.49, 128.34, 125.75, 59.82, 45.63, 35.97, 29.42, 27.52



1-Methyl-4-(3-phenylpropyl)piperidine [21b] In a 100 mL round-bottom flask equipped with a magnetic stir bar were added 1-methyl-4-(3-phenylpropyl)-1,2,3,6-tetrahydropyridine (717 mg, 3.33 mmol), palladium hydroxide on carbon (20 wt%, 112 mg) and toluene (0.3 M, 11.2 mL). The flask was placed into a metal pressure reactor and filled with hydrogen gas (60 psi). The reaction mixture was stirred for a week. Upon completion, the mixture was filtered and condensed via rotary evaporation. The crude material was purified by flash chromatography (50 mL silica, 25% EtOAc/Hex (4 column volumes)) to afford the product as a colorless oil (392.2 mg, 1.80 mmol, 54% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

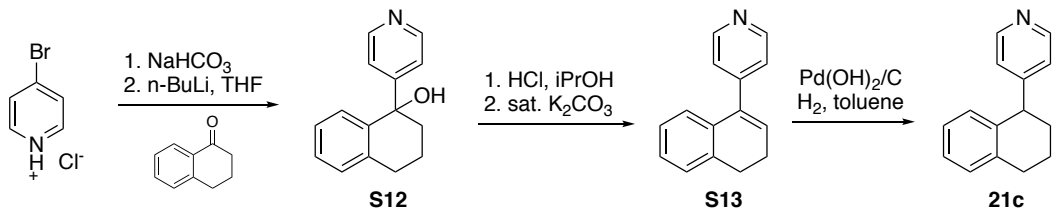
δ 7.30-7.25 (m, 2H), 7.20-7.15 (m, 3H), 2.82 (d, *J* = 11.5 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.24 (s, 3H), 1.86 (t, *J* = 11.1 Hz, 2H), 1.70-1.57 (m, 4H), 1.32-1.16 (m, 5H)

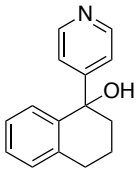
^{13}C NMR: (101 MHz, $CDCl_3$)

δ 142.83, 128.45, 128.33, 125.70, 56.18, 46.65, 36.36, 36.27, 35.20, 32.60, 28.89

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{15}H_{24}N$ $[M+H]^+$: 218.1909, found 218.1910

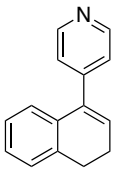




1-(Pyridin-4-yl)-1,2,3,4-tetrahydronaphthalen-1-ol [S12] To a 500 mL seperatory funnel was added 4-bromopyridine hydrochloride (3.12 g, 16.0 mmol) and diethyl ether (30 mL). Saturated sodium bicarbonate solution (30 mL) was then added. After the bubbles subsided, the substrate was partitioned between the two layers. The organic layer was isolated, and the aqueous layer was further extracted with Et_2O (2x30 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo in a 300 mL round-bottom flask. According to literature-reported method,[18] anhydrous Et_2O (60 mL) and tetrahydrofuran (THF) (40 mL) were then added, and the resulting solution was placed in a -78 °C cold bath. *n*-Butyllithium (1.6 M, 9.9 mL, 15.8 mmol) was quickly added, and the reaction mixture was stirred for 5 s. α-Tetralone (2.10 g, 14.4 mmol) in THF (40 mL) was then quickly added. The reaction was then taken out of the cold bath and stitrred overnight at room temperature. Saturated ammonium chloride (0.5 mL) was used to quench the reaction, and the resulting mixture was condensed in vacuo and directly loaded onto a flash column. Purification (150 mL silica, gradient elusion 2% (2 column columes)→5% MeOH/CH_2Cl_2 (4 column volumes)) afforded the product as an orange solid (1.53 g, 6.80 mmol, 47% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

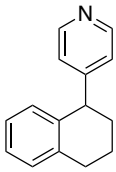
δ 8.54 (d, *J* = 5.0 Hz, 2H), 7.30 (d, *J* = 5.3 Hz, 2H), 7.24 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.19 (td, *J* = 7.6, 0.7 Hz, 1H), 7.13 (td, *J* = 7.5, 0.7 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 2.98-2.85 (m, 2H), 2.23 (s, 1H), 2.18-2.10 (m, 1H), 2.09-1.97 (m, 2H), 1.89-1.81 (m, 1H)



4-(3,4-Dihydronaphthalen-1-yl)pyridine [S13] To a 100 mL recovery flask carrying 1-(pyridin-4-yl)-1,2,3,4-tetrahydronaphthalen-1-ol **S12** (1.53 g, 6.80 mmol, 1.0 equiv.) were added isopropanol (30 mL) and concentrated hydrochloric acid (12 M, 11.3 mL, 136 mmol, 20 equiv.). The resulting solution was refluxed for 4 h. Upon completion, the solvent was removed in vacuo and the residue was redissolved in DCM (30 mL) and basified with saturated K_2CO_3. The aqueous layer was extracted with DCM (3x30 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (50 mL silica, 40% EtOAc/Hex (8 column volumes)) afforded the product as an orange oil (1.27 g, 6.13 mmol, 90% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.61 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.28 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.22 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.20 (td, *J* = 7.3, 1.3 Hz, 1H), 7.14 (td, *J* = 7.4, 1.8 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.20 (t, *J* = 4.7 Hz, 1H), 2.86 (t, *J* = 8.0 Hz, 2H), 2.46-2.41 (m, 2H)



4-(1,2,3,4-Tetrahydronaphthalen-1-yl)pyridine [21c] To a 100 mL round-bottom flask carrying 4-(3,4-dihydronaphthalen-1-yl)pyridine **S12** (1.27 g, 6.13 mmol) were added palladium hydroxide on carbon (20 wt%, 205 mg) and toluene (20.5 mL). The reaction was placed into a metal pressure reactor, sealed and purged with H_2 gas (3 x app. 100 psi). After purging the metal pressure reactor was pressurized with H_2 gas (app. 100 psi) and stirred for 2 days at room temperature. The resulting solution was filtered and concentrated in vacuo. Purification through flash chromatography (50 mL silica, gradient elution 20% (4 column volumes)→40% (8 column volumes)) afforded the product as a colorless viscous oil (1.24 g, 5.90 mmol, 96% yield), which was azeotroped once with anhydrous benzene (5 mL).

^{1}H NMR: (400 MHz, $CDCl_3$)

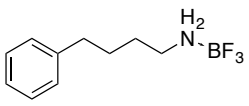
δ 8.49 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.16 (dd, *J* = 4.7, 0.8 Hz, 2H), 7.09-7.04 (m, 1H), 7.02 (dd, *J* = 4.7, 1.5 Hz, 2H), 6.79 (d, *J* = 7.6 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 1H), 2.97-2.80 (m, 2H), 2.23-2.13 (m, 1H), 1.90-1.70 (m, 3H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 157.06, 149.18, 137.76, 137.20, 130.11, 129.40, 126.65, 126.04, 124.43, 45.09, 32.68, 29.63, 20.61

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{15}H_{16}N$ $[M+H]^+$: 210.1283, found 210.1286



4-Phenylbutan-1-amine boron trifluoride complex [21d] In a flame-dried 100 mL round-bottom flask equipped with a stir bar were added 4-phenylbutan-1-amine (316 μL, 298.5 mg, 2.0 mmol, 1.0 equiv.) and CH_2Cl_2 (8 mL). The solution was placed in an ice bath, and boron trifluoride diethyl etherate (272 μL, 312.2 mg, 2.2 mmol, 1.1 equiv.) was added dropwise upon stirring. The reaction mixture was kept stirring in an ice bath for 30 min and then allowed to warm up to ambient temperature. The reaction mixture was then further stirred for 1 h, condensed through rotary evaporation and purified through flash chromatography (50 mL silica, 40% EtOAc/Hex (4 column volumes)) to afford the product as a white solid (296.0 mg, 1.36 mmol, 68% yield).

^{1}H NMR: (500 MHz, CD_3CN)

δ 7.33-7.26 (m, 2H), 7.24-7.16 (m, 3H), 4.56 (br s, 2H), 2.76 (p, *J* = 7.2 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.70-1.54 (m, 4H)

^{13}C NMR: (126 MHz, CD_3CN)

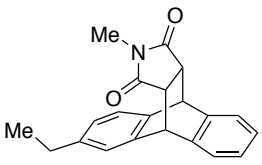
δ 143.08, 129.27, 129.24, 126.71, 41.58, 35.73, 29.10, 28.56

^{19}F NMR: (470 MHz, CD_3CN)

δ -151.98 (dd, J = 32.6, 15.9 Hz, 3F)

HRMS: (ESI-TOF MS ES-)

m/z calculated for $C_{10}H_{14}BF_3N$ $[M-H]^+$: 216.1171, found 216.1172



***rac*-(9*S*,10*R*,11*R*,15*S*)-2-ethyl-13-methyl-9,10-dihydro-9,10-[3,4]epipyrroloanthracene-12,14-dione [21e]** According to literature,[11] a 50 mL round-bottom flask equipped with a magnetic stir bar was charged with 2-ethylanthracene (936 mg, 4.54 mmol, 1.08 equiv.), *N*-methylmaleimide (467 mg, 4.20 mmol, 1.0 equiv.) and *m*-xylene (10 mL). The reaction mixture was heated at reflux for 7 h. Upon completion, the solvent was removed under reduced pressure through rotary evaporation. Purification by flash chromatography on silica (150 mL) eluting with 10% (5 column volumes)→20% EtOAc/hexanes (4 column volumes) yielded a light yellow solid as a mixture of diastereomers. The desired diastereomer was isolated through MPLC (40 g silica) four times eluting with 0%→20% EtOAc/hexanes (40 column volumes) as a white solid (297 mg, 0.937 mmol, 22% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.39-7.33 (m, 2H), 7.16 (m, 3H), 7.09 (s, 1H), 6.94 (d, J = 7.5 Hz, 1H), 4.74 (m, 2H), 3.21-3.16 (m, 2H), 2.55 (q, J = 7.5 Hz, 2H), 2.50 (s, 3H), 1.14 (t, J = 7.6 Hz, 3H)

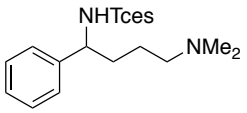
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 177.17, 143.36, 141.82, 141.69, 138.53, 135.82, 126.76, 126.73, 126.42, 124.79, 124.55, 124.30, 124.27, 47.22, 47.17, 45.76, 45.32, 28.75, 24.36, 15.94

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{21}H_{20}O_2N$ $[M+H]^+$: 318.1494, found 318.1495.

2.4.7 Experimental Procedures and Characterization for Figure 11



2,2,2-Trichloroethyl (4-(dimethylamino)-1-phenylbutyl)sulfamate [22a]

According to the general amination procedure, *N*,*N*-dimethyl-4-phenylbutan-1-amine **21a** (35.5 mg, 0.20 mmol, 1.0 equiv.) was protonated with $HBF_4{\cdot}OEt_2$ (30.2 μL, 35.6 mg, 0.22 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (34.6 mg, 0.030 mmol, 0.15 equiv.), $AgSbF_6$ (10.3 mg, 0.030 mmol, 0.15 equiv.), PhI=NTces (258.3 mg, 0.60 mmol, 3.0 equiv.), and 5 Å molecular sieves (40 mg) in DCE (0.4 mL). PhI=NTces was added in one portion. Following work-up, the crude material was purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, gradient elution 30% EtOAc/Hex (4 column volumes)→0%→1%→2%→3% MeOH/CH_2Cl_2 (2 column volumes each)), staining with $KMnO_4$. The resulting solid was redissolved in acetonitrile, and the undissolved green solid was removed. The solution was concentrated via rotary evaporation to afford the product as a light yellow oil.

Run 1 (40.5 mg, 0.10 mmol, 50% yield; 4.7 mg, 0.027 mmol, 13% rsm)

Run 2 (39.2 mg, 0.097 mmol, 49% yield; 3.8 mg, 0.021 mmol, 11% rsm)

Run 3 (41.0 mg, 0.10 mmol, 51% yield; 2.4 mg, 0.014 mmol, 7% rsm)

Average overall yield: 50% (10% rsm) ± 1.0

^{1}H NMR: (500 MHz, $CDCl_3$)

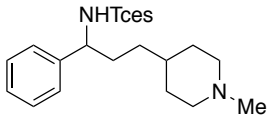
δ 7.39-7.30 (m, 4H), 7.24 (d, *J* = 6.9 Hz, 1H), 4.56 (t, *J* = 4.6 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 2.46 (dt, *J* = 11.4, 4.9 Hz, 1H), 2.34 (s, 6H), 2.34-2.27 (m, 1H), 2.10-2.00 (m, 2H), 1.58 (p, *J* = 4.8 Hz, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 141.99, 128.54, 127.33, 126.64, 94.16, 77.70, 59.66, 57.57, 44.63, 37.76, 23.03

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{14}H_{22}Cl_3N_2O_3S$ $[M+H]^+$: 403.0417, found 403.0409



2,2,2-Trichloroethyl (3-(1-methylpiperidin-4-yl)-1-phenylpropyl)sulfamate [22b] According to the general amination procedure, 1-methyl-4-(3-phenylpropyl)piperidine **21b** (43.5 mg, 0.20 mmol, 1.0 equiv.) was protonated with $HBF_4{\cdot}OEt_2$ (30.2 μL, 35.6 mg, 0.22 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 5 Å molecular sieves (40 mg) in DCE (0.4 mL). After 2 h of reaction, another batch of PhI=NTces (86.1 mg, 0.20 mmol, 1.0 equiv.) was quickly added to the reaction mixture. The reaction was further stirred for 13 h. Following work-up, the crude material was purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, gradient elution 30% EtOAc/Hex (4 column volumes)→0%→1%→2%→3% MeOH/CH_2Cl_2 (2 column volumes each)), staining with $KMnO_4$ to afford the product as a white solid with green discoloration.

Run 1 (53.9 mg, 0.12 mmol, 61% yield; 7.1 mg, 0.033 mmol, 16% rsm)

Run 2 (47.4 mg, 0.11 mmol, 53% yield; 7.6 mg, 0.035 mmol, 17% rsm)

Run 3 (51.0 mg, 0.11 mmol, 57% yield; 8.0 mg, 0.037 mmol, 18% rsm)

Average overall yield: 57% (17% rsm) ± 4.0

^{1}H NMR: (500 MHz, $CDCl_3$)

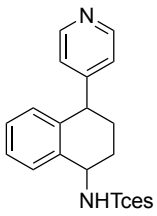
δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.33-7.27 (m, 3H), 4.46 (t, *J* = 7.4 Hz, 1H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.29 (d, *J* = 10.8 Hz, 1H), 2.81 (d, *J* = 11.4 Hz, 2H), 2.21 (s, 3H), 2.02-1.90 (m, 1H), 1.90-1.78 (m, 3H), 1.62 (d, *J* = 9.2 Hz, 2H), 1.40-1.28 (m, 1H), 1.28-1.14 (m, 4H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 140.75, 129.12, 128.39, 126.78, 93.47, 78.07, 59.91, 56.00, 46.53, 35.00, 34.25, 32.96, 32.38, 32.31

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{26}Cl_3N_2O_3S$ $[M+H]^+$: 443.0730, found 443.0727



2,2,2-Trichloroethyl (4-(pyridin-4-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)sulfamate [22c] According to the general amination procedure, 4-(1,2,3,4-tetrahydronaphthalen-1-yl)pyridine **21c** (41.9 mg, 0.20 mmol, 1.0 equiv.) was protonated with $HBF_4{\cdot}OEt_2$ (30.2 μL, 35.6 mg, 0.22 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 3 Å molecular sieves (40 mg) in DCE (0.4 mL). After 2 h of reaction, another batch of PhI=NTces (86.1 mg, 0.20 mmol, 1.0 equiv.) was quickly added to the reaction mixture. The reaction was further stirred for 13 h. Following work-up, the crude material was purified by flash chromatography (50 mL silica, gradient elution 20%→40%→60%→80% EtOAc/hexanes (2 column volumes each)) to afford the product as a white solid with green discoloration as a mixture of diastereomers.

Run 1 (38.4 mg, 0.088 mmol, 44% yield, 1:1 dr; 0.8 mg, 0.004 mmol, 2% rsm)

Run 2 (35.6 mg, 0.082 mmol, 41% yield, 1:1 dr; 6.7 mg, 0.032 mmol, 16% rsm)

Run 3 (35.6 mg, 0.082 mmol, 41% yield, 1:1 dr; 2.9 mg, 0.014 mmol, 7% rsm)

Average overall yield: 42% (8% rsm) ± 1.7, 1:1 dr

^{1}H NMR: (400 MHz, $CDCl_3$) (mixture of diastereomers)

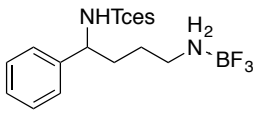
δ 8.34 (m, 2H), 7.63 (dd, *J* = 7.7, 3.9 Hz, 1H), 7.30 (td, *J* = 7.6, 3.5 Hz, 1H), 7.24-7.18 (m, 1H), 6.94 (m, 2H), 6.82 (m, 1H), 6.65 (d, *J* = 7.7 Hz, 0.5H), 6.02 (d, *J* = 7.8 Hz, 0.5H), 4.93-4.83 (m, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 4.16 (t, *J* = 6.1 Hz, 0.5H), 4.05 (d, *J* = 6.0 Hz, 0.5H), 2.39-2.28 (m, 0.5H), 2.24-2.07 (m, 2H), 2.07-1.94 (m, 1H), 1.88 (dt, *J* = 13.7, 7.0 Hz, 0.5H)

^{13}C NMR: (101 MHz, $CDCl_3$) (mixture of diastereomers)

δ 156.21, 155.88, 149.07, 148.85, 137.81, 137.51, 135.73, 135.55, 130.39, 130.10, 129.85, 129.36, 128.63, 127.86, 127.78, 124.44, 124.25, 93.81, 93.77, 78.07, 78.02, 60.57, 53.15, 44.79, 44.12, 28.41, 28.31, 28.04, 27.47

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{18}Cl_3N_2O_3S$ $[M+H]^+$: 435.0104, found 435.0104



2,2,2-Trichloroethyl (4-amino-1-phenylbutyl)sulfamate boron trifluoride complex [22d] Prepared according to the general optimization procedure. 4-phenylbutan-1-amine boron trifluoride complex **21d** (43.4 mg, 0.20 mmol, 1.0 equiv.) was reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 5 Å molecular sieves (40 mg) in DCE (0.4 mL) for 15 h. The crude material was purified by flash chromatography (50 mL silica, gradient elution CH_2Cl_2 (12

column volumes)→10%→20%→30%→40% EtOAc/Hex (4 column volumes each)), staining with ninhydrin to afford the product as a white solid with slight discoloration.

Run 1 (48.7 mg, 0.11 mmol, 55% yield; 11.4 mg, 0.053 mmol, 26% rsm)

Run 2 (54.4 mg, 0.12 mmol, 61% yield; 11.3 mg, 0.052 mmol, 26% rsm)

Run 3 (46.9 mg, 0.11 mmol, 53% yield; 12.8 mg, 0.059 mmol, 30% rsm)

Average overall yield: 56% (27% rsm) ± 4.1

^{1}H NMR: (500 MHz, CD_3CN)

δ 7.43-7.35 (m, 4H), 7.35-7.29 (m, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 4.57 (br s, 2H), 4.44 (q, *J* = 8.2 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.20 (d, *J* = 11.0 Hz, 1H), 2.76 (p, *J* = 7.1 Hz, 2H), 1.93-1.86 (m, 1H), 1.83-1.75 (m, 1H), 1.75-1.65 (m, 1H), 1.58-1.47 (m, 1H)

^{13}C NMR: (101 MHz, CD_3CN)

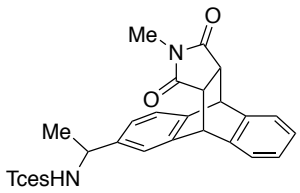
δ 142.19, 129.69, 128.86, 127.65, 94.22, 78.48, 59.76, 41.21, 34.61, 25.88

^{19}F NMR: (470 MHz, CD_3CN)

δ -151.91 (dd, *J* = 32.4, 15.9 Hz, 3F)

HRMS: (ESI-TOF MS ES-)

m/z calculated for $C_{12}H_{16}BCl_3F_3N_2O_3S$ $[M-H]^+$: 440.9992, found 440.9984



***rac*-2,2,2-trichloroethyl (1-((9*S*,10*R*,11*R*,15*S*)-13-methyl-12,14-dioxo-9,10-dihydro-9,10-[3,4]epipyrroloanthracen-2-yl)ethyl)sulfamate [22e].** Prepared according to the general optimization procedure. *rac*-(9*S*,10*R*,11*R*,15*S*)-2-ethyl-13-methyl-9,10-dihydro-9,10-[3,4]epipyrroloanthracene-12,14-dione **21e** (63.5 mg, 0.20 mmol, 1.0 equiv.) was reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$

(6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 5Å molecular sieves (40 mg) in benzene (0.4 mL) for 10 h. The crude reaction mixture was directly purified by flash chromatography (50 mL silica, 20%→30%→40%→50% EtOAc/Hex (2 column volumes each)) to afford the product as a white solid with slight discoloration as a mixture of diastereomers.

Run 1 (84.8 mg, 0.156 mmol, 78% yield, 1:1 dr)

Run 2 (95.8 mg, 0.176 mmol, 88% yield, 1:1 dr)

Run 3 (93.7 mg, 0.172 mmol, 86% yield, 1:1 dr)

Average overall yield: 84% yield ± 5.3, 1:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

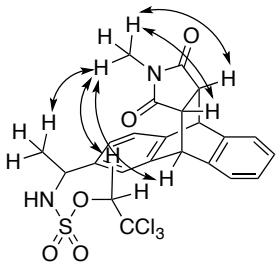
δ 7.39-7.33 (m, 2H), 7.30-7.23 (m, 2H), 7.18 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 5.15 (br s, 1H), 4.82-4.74 (m, 2H), 4.65 (app dq, *J* = 14.2, 7.0 Hz, 1H), 4.45-4.35 (m, 2H), 3.20 (app s, 2H), 2.50 (s, 3H), 1.54 (app t, *J* = 6.4 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

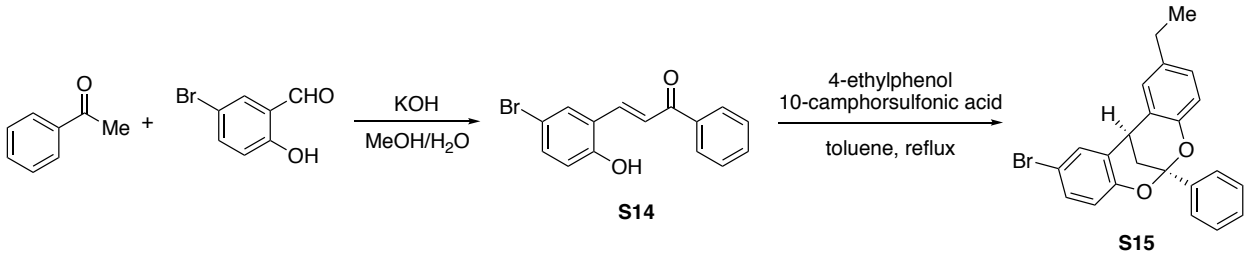
δ 177.16, 177.08, 176.99, 176.98, 141.13, 141.10, 141.08, 141.06, 140.83, 140.75, 139.46, 138.76, 138.64, 127.03, 127.02, 126.99, 126.98, 125.41, 125.37, 125.33, 124.85, 124.47, 124.44, 124.42, 123.25, 122.30, 93.39, 93.36, 78.11, 54.72, 54.69, 46.99, 46.95, 45.73, 45.65, 45.29, 24.46, 24.43, 23.43, 22.98

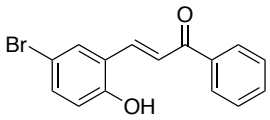
HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{23}H_{21}Cl_3N_2O_5SNa$ $[M+Na]^+$: 565.0134, found 565.0135.



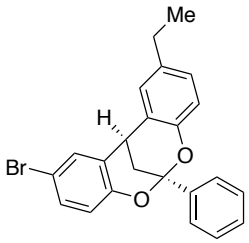
2.4.8 Synthesis of Substrate and Characterization for Figure 12





(*E*)-3-(5-Bromo-2-hydroxyphenyl)-1-phenylprop-2-en-1-one [S14]

Prepared according to literature-reported method.[51] In a 100 mL round-bottom flask equipped with a magnetic stir bar in ice bath were added potassium hydroxide (7.5 g, 134 mmol, 13.4 equiv.), water (1.3 mL), and methanol (6.3 mL). Acetophenone (1.2 mL, 1.20 g, 10 mmol, 1.0 equiv.) was added, and the reaction was stirred for 10 min. 5-Bromosalicylaldehyde (2.01 g, 10 mmol, 1.0 equiv.) was then added. The reaction mixture was then removed from ice bath and stirred overnight. Upon completion, the dark red mixture was acidified with 3M HCl until pH ~ 2. The resulting yellow mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica (150 mL) eluting with 20%→30%→40% (2 column volumes each)→100% EtOAc/hexanes (4 column volumes) yielded the product as a yellow powder (2.07 g, 6.83 mmol, 68% yield) with some minor impurities, which were removed in the subsequent step.



2-Bromo-10-ethyl-6-phenyl-cis-12H-6,12-methanodibenzo[d,g][1,3]dioxocine [(±)-S15] According to literature,[45] in a 250 mL round-bottom flask were added (*E*)-3-(5-bromo-2-hydroxyphenyl)-1-phenylprop-2-en-1-one **S14** (1.5 g, 5.0 mmol, 1.0 equiv.), 4-ethylphenol (733 mg, 6.0 mmol, 1.2 equiv.), DL-10-camphorsulfonic acid (174 mg, 0.75 mmol, 0.15 equiv.) and toluene (63 mL). The reaction was placed in 120 °C oil bath and refluxed for 43 h. The resulting dark green mixture was condensed via rotary evaporation. Purification by MPLC (40 g silica) eluting with 0%→10% EtOAc/hexanes (40 column volumes) yielded the product as a light yellow powder (772 mg, 1.90 mmol, 38% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

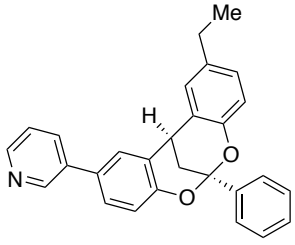
δ 7.75-7.69 (m, 2H), 7.49-7.40 (m, 3H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.24 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 4.02 (t, *J* = 2.9 Hz, 1H), 2.61 (qd, *J* = 7.5, 2.1 Hz, 2H), 2.39 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.34 (dd, *J* = 13.4, 3.0 Hz, 1H), 1.24 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.41, 149.86, 141.20, 137.74, 130.95, 129.94, 129.02, 128.70, 128.50, 127.91, 126.61, 125.84, 125.37, 118.72, 116.79, 113.44, 98.89, 34.29, 33.18, 28.17, 15.92

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{23}H_{20}O_2Br$ $[M+H]^+$: 407.0647, found 407.0630



3-(10-Ethyl-6-phenyl-cis-12*H*-6,12-methanodibenzo[*d*,*g*][1,3]dioxocin-2-yl)pyridine [(±)-23a] In a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar

were added 2-bromo-10-ethyl-6-phenyl-cis-12H-6,12-methanodibenzo[d,g][1,3]dioxocine (±)-**S15** (494 mg, 1.21 mmol, 1.0 equiv.), 3-pyridinylboronic acid (298 mg, 2.43 mmol, 2.0 equiv.), $Pd(dppf)Cl_2•CH_2Cl_2$ (99 mg, 0.121 mmol, 0.10 equiv.), and potassium carbonate (326 mg, 2.36 mmol, 2.0 equiv.) under N_2 atmosphere. Nitrogen-degassed water (0.5 mL) and 1,4-dioxane (2 mL) were added, and the septa was quickly replaced with a polyethylene yellow cap and secured with electric tape. The flask was then placed into 95 °C oil bath and stirred for 3 h. Upon completion, the reaction was quenched with water (10 mL), and extracted with EtOAc (3x10 mL). The organic layers were combined, dried over $MgSO_4$, and condensed through rotary evaporation. Purification by flash chromatography on silica (50 mL) eluting with 20% (6 column volumes)→30%→40% (4 column volumes each) EtOAc/hexanes yielded the product as a light yellow powder (291 mg, 0.718 mmol, 59% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

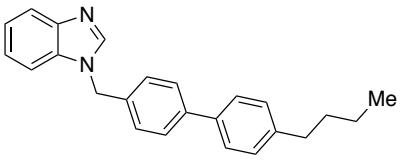
δ 8.82 (s, 1H), 8.57 (d, *J* = 4.2 Hz, 1H), 7.83 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.79-7.74 (m, 2H), 7.51-7.45 (m, 3H), 7.45-7.40 (m, 1H), 7.39-7.32 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 1.9 Hz, 1H), 7.01 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 4.15 (t, *J* = 2.8 Hz, 1H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.44 (d, *J* = 2.9 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 152.51, 149.91, 148.24, 148.19, 141.37, 137.69, 136.36, 134.14, 131.32, 128.99, 128.51, 127.81, 127.41, 127.04, 126.56, 126.08, 125.89, 125.82, 123.65, 117.65, 116.81, 99.01, 34.60, 33.48, 28.17, 15.94

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{28}H_{24}O_2N$ $[M+H]^+$: 406.1807, found 406.1804



1-((4'-Butyl-[1,1'-biphenyl]-4-yl)methyl)-1*H*-benzo[*d*]imidazole [23b] In a flame-dried 25 mL round-bottom flask under nitrogen with stirring was added K_2CO_3 (864 mg, 6.25 mmol, 5 equiv.), benzimidazole (297 mg, 2.51 mmol, 2 equiv.), 4-(bromomethyl)-4'-butyl-1,1'-biphenyl (380 mg, 1.25 mg, 1 equiv.) and DMF (3 mL). The reaction was stirred for 2 h at 120 °C. The reaction was brought to room temperature and poured into a separatory funnel where water (20 mL) was added and the mixture extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated using rotary evaporation. The product was purified using gradient silica gel flash chromatography (100% DCM to 95/5 DCM/MeOH) to give the pure product as a white solid (217 mg, 51% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

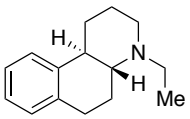
δ 7.98 (s, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.36-7.32 (m, 1H), 7.32-7.27 (m, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.39 (s, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 1.63 (p, *J* = 7.6 Hz, 2H), 1.38 (sxt, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.60, 141.37, 137.70, 134.18, 129.05, 127.67, 127.64, 127.00, 123.25, 122.44, 120.60, 110.20, 48.75, 35.42, 33.74, 22.52, 14.10

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{24}H_{25}N_2$ $[M+H]^+$: 341.2018, found 341.2012



Trans-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline [(±)-23c] To a 100 mL recovery flask equipped with a magnetic stir bar were added trans-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline[52] (209 mg, 1.10 mmol, 1.0 equiv.), acetic acid (0.22 mL, 1% v/v), and 1,2-dichloroethane (0.05 M, 22 mL). Acetaldehyde (0.31 mL, 242 mg, 5.50 mmol, 5.0 equiv.) was added dropwise as the solution turned orange. The mixture was stirred for 30 min, upon which sodium triacetoxyborohydride (350 mg, 1.65 mmol, 1.5 equiv.) was added in one portion and the reaction solution was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL). Dried over anhydrous $MgSO_4$, filtered and concentrated. The crude material was thrice purified by column chromatography (20 mL silica, gradient elution 2%→5%→10% MeOH/CH_2Cl_2 (5 column volumes each)) to afford the product as a white solid (109.7 mg, 0.509 mmol, 46% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

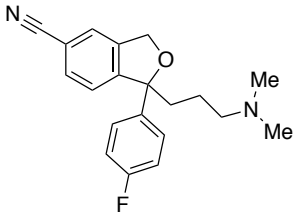
δ 7.29 (d, *J* = 7.6 Hz, 1H), 7.19-7.07 (m, 3H), 3.03 (app d, *J* = 11.3 Hz, 1H), 2.99-2.87 (m, 3H), 2.71 (dq, *J* = 13.9, 7.1 Hz, 1H), 2.67-2.60 (m, 1H), 2.53-2.46 (m, 1H), 2.34-2.25 (m, 2H), 2.16 (td, *J* = 10.5, 3.2 Hz, 1H), 1.89-1.77 (m, 2H), 1.69-1.58 (m, 1H), 1.32-1.22 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 138.83, 135.97, 128.51, 126.13, 126.08, 125.62, 63.31, 52.11, 46.62, 41.59, 29.26, 29.01, 26.11, 24.87, 9.28

HRMS: (ESI-TOF MS ES+)

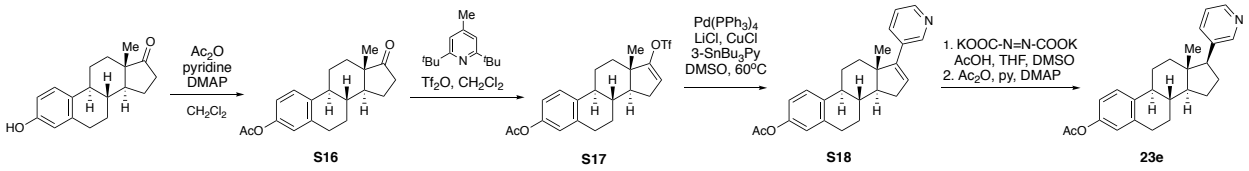
m/z calculated for $C_{15}H_{22}N$ $[M+H]^+$: 216.1752, found 216.1754

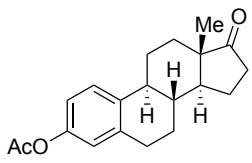


1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile [(±)-23d] To a 60 mL separatory funnel, commercial citalopram hydrobromide (203 mg, 0.5 mmol) was partitioned between CH_2Cl_2 (5 mL) and water (5 mL). Sodium hydroxide (50% wt, 5 mL) was then added, and the product was repartitioned between the layers. The aqueous layer was extracted with CH_2Cl_2 (3x5 mL) and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and condensed in vacuo. The product was obtained as a colorless gel (163 mg, 0.5 mmol, quantitative yield). The spectral data matched those reported in literature.[53]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.59 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.50 (s, 1H), 7.45-7.40 (m, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.04-6.97 (m, 2H), 5.20 (d, *J* = 12.9 Hz, 1H), 5.15 (d, *J* = 12.9 Hz, 1H), 2.26-2.19 (m, 2H), 2.17 (dd, *J* = 9.3, 5.0 Hz, 1H), 2.13 (s, 6H), 2.12-2.08 (m, 1H), 1.52-1.39 (m, 1H), 1.37-1.24 (m, 1H)



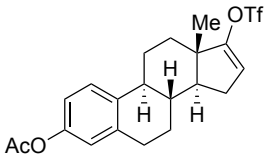


(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate [S16] In a flame-dried 100 mL round bottom flask equipped with a stir bar was charged (+)-estrone (2.70 g, 10.0 mmol, 1.0 equiv.), pyridine (4.0 mL, 3.96 g, 50.0 mmol, 5.0 equiv.), 4-dimethylaminopyridine (DMAP) (122.2 mg, 1.0 mmol, 0.10 equiv.) and CH_2Cl_2 (20 mL). The reaction mixture was placed in ice bath with stirring, and acetic anhydride (2.8 mL, 3.06 g, 30.0 mmol, 3.0 equiv.) was added dropwise via syringe. The reaction mixture was stirred at 0 °C for 5

min and then allowed to warm to ambient temperature and stirred overnight. The reaction was washed with water (20 mL), 1 M HCl (4x20 mL) and brine (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica (75 mL) eluting with 10%→25%→40% EtOAc/hexanes (2.5 column volumes each) yielded the product as a white powder (3.03 g, 9.70 mmol, 97% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

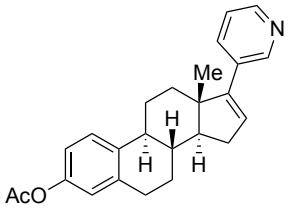
δ 7.29 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 2.90 (dd, *J* = 8.8, 4.1 Hz, 2H), 2.51 (dd, *J* = 19.0, 8.6 Hz, 1H), 2.41 (ddd, *J* = 12.4, 7.0, 3.7 Hz, 1H), 2.33-2.24 (m, 1H), 2.29 (s, 3H), 2.19-2.11 (m, 1H), 2.09-1.98 (m, 2H), 1.98-1.93 (m, 1H), 1.68-1.40 (m, 6H), 0.91 (s, 3H)



(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-(((trifluoromethyl)sulfonyl)oxy)-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate [S17] In a flame-dried 50 mL round bottom flask equipped with a stir bar was added **S16** (661 mg, 2.11 mmol, 1.0 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (448 mg, 2.18 mmol, 1.03 equiv.) and CH_2Cl_2 (5.8 mL). Trifluoromethanesulfonic anhydride (613 mg, 2.17 mmol, 1.03 equiv.) was added dropwise into the reaction mixture while stirring. The reaction was stirred for 6 h. Saturated $NaHCO_3$ (10 mL) was then added to quench the reaction and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layer was washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica (50 mL) eluting with 2% (4 column volumes)→5% EtOAc/hexanes (6 column volumes) yielded the product as a white solid (757 mg, 1.70 mmol, 81% yield).

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.25 (d, *J* = 8.0 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 5.62 (dd, *J* = 3.3, 1.7 Hz, 1H), 2.91 (dd, *J* = 9.8, 5.1 Hz, 2H), 2.44-2.37 (m, 1H), 2.33 (ddd, *J* = 14.9, 6.3, 3.5 Hz, 2H), 2.29 (s, 3H), 2.10 (ddd, *J* = 14.9, 11.2, 1.7 Hz, 1H), 1.96-1.87 (m, 2H), 1.79 (td, *J* = 11.3, 6.3 Hz, 1H), 1.71-1.57 (m, 3H), 1.51-1.37 (m, 1H), 1.00 (s, 3H)

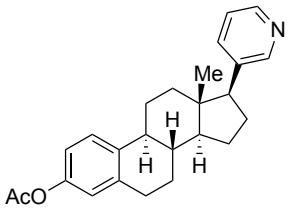


(8*S*,9*S*,13*S*,14*S*)-13-Methyl-17-(pyridin-3-yl)-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate [S18] In a flame-dried 300 mL round-bottom flask containing LiCl (1.05 g, 24.7 mmol, 6.0 equiv.) and equipped with a magnetic stir bar were added **S17** (1.83 g, 4.12 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (476 mg, 0.412 mmol, 0.10 equiv.), CuCl (2.04 g, 20.6 mmol, 5.0 equiv.), and DMSO (154 mL). 3-(tributylstannyl)pyridine (2.6 mL, 3.03 g, 8.24 mmol, 2.0 equiv.) was then added via syringe. The mixture was degassed through freeze-pump-thaw (-78 °C→0 °C) three times, and was stirred for 1 h at room temperature. The reaction flask was then placed into 60 °C oil bath and stirred vigorously for 13 h. Upon completion, the reaction was quenched with the mixed solution of concentrated NH_4OH (5.5 mL) and brine (200 mL), and extracted with diethyl ether (4x50 mL). The organic layers were then combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica (150 mL) eluting with 40% EtOAc/hexanes (7.5 column volumes) yielded the product as a white powder (1.31 g, 3.52 mmol, 85% yield).

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.65 (d, *J* = 2.1 Hz, 1H), 8.48 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.69 (app d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.27-7.23 (m, 1H), 6.85 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.81 (dd, *J* =

2.3 Hz, 1H), 6.03 (dd, *J* = 3.0, 1.6 Hz, 1H), 2.93 (dd, *J* = 11.3, 5.9 Hz, 2H), 2.44-2.32 (m, 3H), 2.29 (s, 3H), 2.20-2.11 (m, 2H), 2.02-1.93 (m, 1H), 1.82 (td, *J* = 11.4, 6.5 Hz, 1H), 1.75-1.64 (m, 3H), 1.56-1.44 (m, 1H), 1.04 (s, 3H)



(8*S*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-17-(pyridin-3-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate [23e] In a flame-dried 200 mL round bottom flask equipped with a stir bar was added **S18** (1.31 g, 3.52 mmol, 1.0 equiv.), THF (33 mL) and DMSO (33 mL). The mixture was cooled down to 0 °C upon stirring, and potassium azodicarboxylate (KOOC–N=N–COOK) (3x4.56 g, 70.5 mmol, 20 equiv.) was added in three equal portion over the course of 2 h, each followed by the addition of AcOH (3x2.7 mL, 3x2.82 g, 140.7 mmol, 40 equiv.). After adding the last portion of potassium azodicarboxylate, the reaction was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with brine (100 mL) and extracted with diethyl ether (3x50 mL). The organic layers were combined, dried over $MgSO_4$, condensed, transferred into a 100 mL round-bottom flask and concentrated *in vacuo*. Dichloromethane (7.0 mL), pyridine (1.4 mL, 1.39 g, 17.6 mmol, 5.0 equiv.), 4-dimethylaminopyridine (DMAP) (43 mg, 0.35 mmol, 0.10 equiv.), and acetic anhydride (1.0 mL, 1.08 g, 10.6 mmol, 3.0 equiv.) were added. The reaction was stirred overnight, and washed with water (5x5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by MPLC (40 g silica) eluting with 0%→70% EtOAc/hexanes (25 column volumes) yielded the product as a white powder (1.01 g, 2.69 mmol, 76% yield over 2 steps).

^{1}H NMR: (500 MHz, $CDCl_3$)

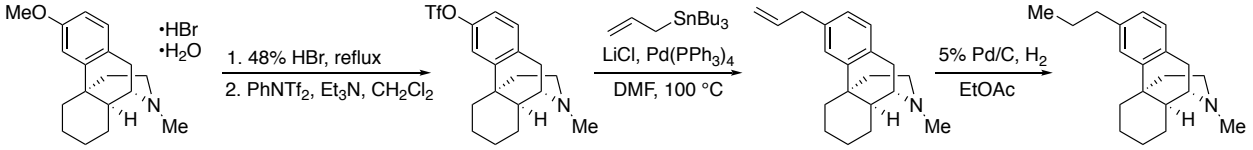
δ 8.49 (d, *J* = 1.9 Hz, 1H), 8.46 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.55 (app d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 7.22 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 2.92-2.85 (m, 2H), 2.78 (t, *J* = 9.8 Hz, 1H), 2.34-2.28 (m, 2H), 2.28 (s, 3H), 2.19-2.09 (m, 1H), 2.09-2.00 (m, 1H), 1.99-1.89 (m, 2H), 1.73-1.66 (m, 1H), 1.54-1.37 (m, 6H), 0.52 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

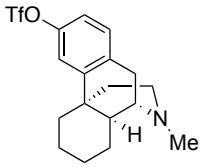
δ 169.99, 150.54, 148.52, 147.72, 138.36, 138.13, 136.38, 135.75, 126.50, 122.89, 121.63, 118.68, 55.37, 54.68, 44.79, 44.24, 38.94, 37.56, 29.72, 27.70, 26.20, 26.06, 24.30, 21.27, 12.85

HRMS: (EI+)

m/z calculated for $C_{25}H_{29}O_2N$ $[M]^+$: 375.2198, found 375.2199



S19 S20 23f

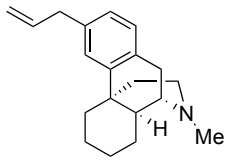


(4b*S*,8a*S*,9*S*)-11-Methyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-3-yl trifluoromethanesulfonate [S19] To a 100 mL round-bottom flask containing dextromethorphan hydrobromide monohydrate (4.99 g, 13.5 mmol, 1.0 equiv.) was added hydrobromic acid (48 wt%, 29.5 mL, 21.1 g, 261 mmol, 19 equiv.). The reaction was refluxed overnight, poured on ice, and basified with saturated potassium carbonate solution. The aqueous layer was extracted with chloroform (3x50 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and condensed through rotary evaporation to give the phenol intermediate as a white powder. In a 200 mL

round-bottom flask carrying the intermediate were added CH_2Cl_2 (90 mL) and triethylamine (37.6 mL, 27.3 g, 270 mmol, 20 equiv.). The mixture was cooled to 0 °C in ice bath, and *N*-Phenyl-bis(trifluoromethanesulfonimide) (7.22 g, 20.2 mmol, 1.5 equiv.) was added in one portion. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was then diluted with CH_2Cl_2, washed with sodium hydroxide (3x50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and condensed through rotary evaporation. Purification by flash chromatography on silica (250 mL) eluting with 2%→5%→10% (2 column volumes each) MeOH/CH_2Cl_2 doped with 2% NH_4OH yielded the product as an orange oil (4.49 g, 11.5 mmol, 86% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.18 (d, *J* = 8.5 Hz, 1H), 7.12 (s, 1H), 7.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.05 (d, *J* = 18.7 Hz, 1H), 2.86-2.80 (m, 1H), 2.62 (dd, *J* = 18.7, 5.7 Hz, 1H), 2.45 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.39 (s, 3H), 2.30 (d, *J* = 14.1 Hz, 1H), 1.99 (td, *J* = 12.3, 2.6 Hz, 1H), 1.86 (app d, *J* = 12.7 Hz, 1H), 1.78 (td, *J* = 12.8, 4.7 Hz, 1H), 1.66 (d, *J* = 12.8 Hz, 1H), 1.56 (d, *J* = 13.1 Hz, 1H), 1.48–1.34 (m, 3H), 1.30 (d, *J* = 13.2 Hz, 1H), 1.19 (q, *J* = 13.3 Hz, 1H), 1.04 (qd, *J* = 12.8, 3.4 Hz, 1H)

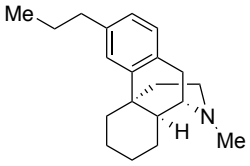


(4b*S*,8a*S*,9*S*)-3-Allyl-11-methyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene [S20] To a flame-dried 200 mL round-bottom flask were added (4b*S*,8a*S*,9*S*)-11-methyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-3-yl trifluoromethanesulfonate **S19** (2.33 g, 5.99 mmol, 1.0 equiv.), LiCl (1.02 g, 24.0 mmol, 4.0 equiv.), $Pd(PPh_3)_4$ (207.7 mg, 0.180 mmol, 0.030 equiv.), allyltributylstannane (2.1 mL, 2.18 g, 6.59 mmol, 1.1 equiv.), and DMF (24 mL, 0.25

M). The reaction was heated to 100 °C and stirred overnight. Upon cooling to room temperature, the reaction was washed with 10% ammonia solution (24 mL). The aqueous layer was extracted with ethyl acetate (3x30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and condensed via rotary evaporation. Purification by flash chromatography on silica (200 mL) eluting with 2% (1.5 column volumes)→5% (2.5 column volumes) MeOH/CH_2Cl_2 doped with 2% NH_4OH yielded the product as a yellow oil (1.41 g, 5.02 mmol, 84% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.05 (s, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 5.97 (ddt, *J* = 16.9, 1.0, 6.7 Hz, 1H), 5.10-5.01 (m, 2H), 3.35 (d, *J* = 6.6 Hz, 1H), 3.01 (d, *J* = 18.4 Hz, 1H), 2.84-2.78 (m, 1H), 2.62 (dd, *J* = 18.3, 5.6 Hz, 1H), 2.48-2.36 (m, 2H), 2.40 (s, 3H), 2.07 (td, *J* = 12.1, 2.6 Hz, 1H), 1.83 (app d, *J* = 12.5 Hz, 1H), 1.74 (td, *J* = 12.5, 4.6 Hz, 1H), 1.63 (d, *J* = 12.6 Hz, 1H), 1.51 (d, *J* = 12.4 Hz, 1H), 1.45–1.20 (m, 5H), 1.13 (qd, *J* = 12.4, 3.2 Hz, 1H)



(4b*S*,8a*S*,9*S*)-11-Methyl-3-propyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene [(+)-23f] To a 100 mL round-bottom flask were added (4b*S*,8a*S*,9*S*)-3-allyl-11-methyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene **S20** (1.41 g, 5.02 mmol, 1.0 equiv.), palladium on carbon (5% wt, 141 mg, 0.066 mmol, 0.013 equiv.), and ethyl acetate (20 mL). Hydrogen gas was allowed to pass through the reaction mixture, which was stirred overnight. The reaction progress was monitered by crude NMR. Upon completion, the palladium catalyst was removed via filtration, and the filtrate was condensed via rotary evapotation to give the product as a yellow gel (1.40 g, 4.94 mmol, 98% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.03 (d, *J* = 1.1 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.93 (dd, *J* = 7.7, 1.6 Hz, 1H), 3.00 (d, *J* = 18.3 Hz, 1H), 2.80 (dd, *J* = 5.4, 3.1 Hz, 1H), 2.60 (dd, *J* = 18.3, 5.7 Hz, 1H), 2.54 (dt, *J* = 8.2, 3.7 Hz, 2H), 2.46-2.38 (m, 2H), 2.39 (s, 3H), 2.07 (td, *J* = 12.2, 3.2 Hz, 1H), 1.82 (dt, *J* = 12.8, 3.0 Hz, 1H), 1.73 (td, *J* = 12.6, 4.8 Hz, 1H), 1.67-1.58 (m, 3H), 1.51 (app d, *J* = 12.0 Hz, 1H), 1.44–1.24 (m, 5H), 1.14 (qd, *J* = 12.1, 3.5 Hz, 1H), 0.93 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

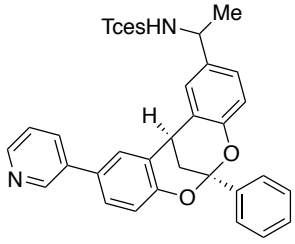
δ 140.61, 139.99, 134.66, 127.63, 125.66, 125.46, 58.30, 47.48, 45.49, 42.86, 42.15, 38.17, 37.03, 36.60, 26.83, 26.71, 24.95, 24.00, 22.28, 14.02

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{20}H_{30}N$ $[M+H]^+$: 284.2378, found 284.2372

$[\alpha]_D^{24}$ = +59.0º (c = 1.08, $CHCl_3$)

2.4.9 Experimental Procedures and Characterization for Figure 12



2,2,2-Trichloroethyl (1-(-6-phenyl-10-(pyridin-3-yl)-cis-12*H*-6,12-methanodibenzo[*d*,*g*][1,3]dioxocin-2-yl)ethyl)sulfamate [(±)-24a] According to the general amination procedure, 3-(10-ethyl-6-phenyl-cis-12*H*-6,12-methanodibenzo[*d*,*g*][1,3]dioxocin-2-yl)pyridine (±)-**23a** (81.0 mg, 0.20 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL) was protonated with $HBF_4{\cdot}OEt_2$ (30.2 µL, 35.6 mg, 0.22 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 3 Å molecular sieves (40 mg) in DCE (0.4 mL) for 15 h.

Following work-up, the crude material was purified by flash chromatography (50 mL silica, gradient elution 30%→40%→50% EtOAc/Hex (4 column volumes each)) to afford the product as a white solid with slight discoloration as a mixture of diastereomers.

Run 1 (66.0 mg, 0.104 mmol, 52% yield, 1:1 dr; 5.7 mg, 0.014 mmol, 7% rsm)

Run 2 (75.8 mg, 0.120 mmol, 60% yield, 1:1 dr; 4.1 mg, 0.010 mmol, 5% rsm)

Run 3 (76.1 mg, 0.120 mmol, 60% yield, 1:1 dr; 3.2 mg, 0.008 mmol, 4% rsm)

Average overall yield: 57% (5% rsm) ± 4.6, 1:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

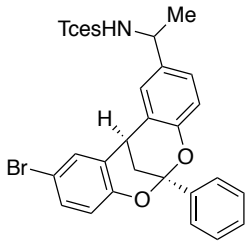
δ 8.59 (d, *J* = 1.0 Hz, 0.5H), 8.51 (d, *J* = 1.1 Hz, 0.5H), 8.16 (d, *J* = 4.0 Hz, 0.5H), 8.04 (d, *J* = 4.2 Hz, 0.5H), 7.81-7.70 (m, 2H), 7.69-7.62 (m, 1H), 7.57 (d, *J* = 6.0 Hz, 0.5H), 7.52-7.41 (m, 3.5H), 7.38 (d, *J* = 2.0 Hz, 0.5H), 7.37 (br s, 0.5H), 7.31 (dd, *J* = 4.3, 2.2 Hz, 1H), 7.26-7.19 (m, 1.5H), 7.17 (dd, *J* = 8.4, 2.2 Hz, 0.5H), 7.12 (dd, *J* = 7.8, 4.9 Hz, 0.5H), 7.10-7.04 (m, 2.5H), 4.80-4.74 (m, 0.5H), 4.74-4.68 (m, 0.5H), 4.47 (d, *J* = 10.8 Hz, 0.5H), 4.44 (d, *J* = 10.8 Hz, 0.5H), 4.41 (d, *J* = 10.8 Hz, 0.5H), 4.34 (d, *J* = 10.8 Hz, 0.5H), 4.17 (t, *J* = 3.1 Hz, 0.5H), 4.15 (t, *J* = 2.7 Hz, 0.5H), 2.47-2.36 (m, 2H), 1.67 (d, *J* = 6.9 Hz, 1.5H), 1.63 (d, *J* = 6.8 Hz, 1.5H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 152.25, 152.20, 151.85, 151.77, 147.22, 140.92, 140.88, 135.99, 135.84, 135.11, 134.32, 134.16, 130.95, 130.85, 129.13, 128.56, 127.06, 126.90, 126.86, 126.83, 126.73, 126.69, 126.15, 126.01, 125.83, 125.79, 125.77, 125.67, 123.72, 123.66, 117.75, 117.73, 117.29, 117.18, 99.15, 99.13, 93.68, 93.66, 77.98, 77.94, 54.30, 53.99, 34.39, 33.22, 33.19, 22.75, 22.61

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{30}H_{26}Cl_3N_2O_5S$ $[M+H]^+$: 631.0628, found 631.0612



2,2,2-trichloroethyl (1-(10-bromo-6-phenyl-cis-12*H*-6,12-methanodibenzo[*d*,*g*][1,3]dioxocin-2-yl)ethyl)sulfamate [(±)-S21]. Prepared according to the general amination procedure B. 2-bromo-10-ethyl-6-phenyl-cis-12H-6,12-methanodibenzo[d,g][1,3]dioxocine (±)-**S15** (81.5 mg, 0.20 mmol, 1.0 equiv.) was reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 5Å molecular sieves (40 mg) in benzene (0.4 mL) for 10 h. The crude reaction mixture was directly purified by flash chromatography (50 mL silica, 7.5% EtOAc/Hex (14 column volumes)) to afford the product as a white solid with slight discoloration as a mixture of diastereomers.

Run 1 (94.4 mg, 0.149 mmol, 75% yield, 1:1 dr)

Run 2 (96.9 mg, 0.153 mmol, 76% yield, 1:1 dr)

Run 3 (84.5 mg, 0.133 mmol, 67% yield, 1:1 dr)

Average overall yield: 73% yield ± 4.9, 1:1 dr

^{1}H NMR: (500 MHz, DMSO-d_6) (mixture of diastereomers)

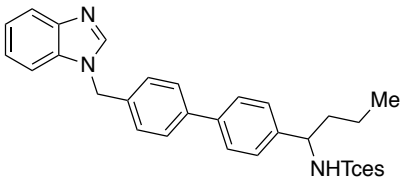
δ 8.89 (d, *J* = 8.1 Hz, 0.5H), 8.87 (d, *J* = 8.4 Hz, 0.5H), 7.73-7.66 (m, 3H), 7.55-7.42 (m, 4H), 7.30 (dt, *J* = 8.6, 2.8 Hz, 1H), 7.27-7.19 (m, 1H), 6.99 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 4.51 (dq, *J* = 12.4, 4.9 Hz, 1H), 4.46 (dd, *J* = 11.1, 7.6 Hz, 1H), 4.38 (dd, *J* = 11.1, 3.3 Hz, 0.5H), 4.34 (t, *J* = 2.6 Hz, 0.5H), 4.31 (t, *J* = 2.4 Hz, 0.5H), 4.23 (d, *J* = 11.2 Hz, 0.5H), 2.44-2.38 (m, 1.5H), 2.36 (dd, *J* = 13.6, 2.8 Hz, 0.5H), 1.47 (app t, *J* = 7.5 Hz, 3H)

^{13}C NMR: (126 MHz, DMSO-d_6) (mixture of diastereomers)

δ 150.78, 150.76, 150.60, 150.53, 140.59, 136.33, 136.19, 130.56, 130.03, 129.99, 129.21, 128.92, 128.34, 128.33, 126.34, 125.96, 125.89, 125.85, 125.77, 125.54, 125.51, 118.38, 116.29, 116.20, 112.73, 112.70, 98.65, 93.74, 93.69, 77.07, 77.04, 53.29, 53.20, 32.10, 32.08, 31.47, 31.38, 23.54, 22.83

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{25}H_{22}Cl_3BrNO_5S$ $[M+H]^+$: 631.9468, found 631.9452.



2,2,2-Trichloroethyl (1-(4'-((1*H*-benzo[*d*]imidazol-1-yl)methyl)-[1,1'-biphenyl]-4-yl)butyl)sulfamate [24b] To a 1 dram vial equipped with a stir bar were added 1-((4'-butyl-[1,1'-biphenyl]-4-yl)methyl)-1*H*-benzo[*d*]imidazole **24a** (68.1 mg, 0.20 mmol, 1.0 equiv.) and methylene chloride (DCM) (0.8 mL). Boron trifluoride diethyl ether complex ($BF_3{\cdot}OEt_2$) (27.2 μL, 31.2 mg, 0.22 mmol, 1.1 equiv.) was added dropwise while stirring. The reaction mixture was stirred for 1.5 h at room temperature. Upon reaction completion, the stir bar was removed, and the mixture was concentrated in vacuo and placed on vacuum overnight. The resulting white foamy solid was reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 3 Å molecular sieves (40 mg) in DCE (0.4 mL), according to the general amination procedure A. The reaction was stirred for 15 h in 40 °C oil bath. Upon completion, the flask was taken out of oil bath. Tetramethylethylenediamine (TMEDA) (150 μL, 116 mg, 1.0 mmol, 5.0 equiv.) was added, and DCM (1 mL) was used to wash off the solid remaining on the wall. The reaction mixture was further stirred for 4 h for complete removal of the BF_3 protection.

The resulting mixture was directly loaded onto a flash column and purified (50 mL silica, gradient elution 20%→30%→40% (4 column volumes each)→50%→60%→70% (2 column volumes each)→80% EtOAc/hexanes (6 column volumes)) to afford the product as a white solid with slight green discoloration.

Run 1 (57.9 mg, 0.102 mmol, 51% yield; 3.5 mg, 0.010 mmol, 5% rsm)

Run 2 (66.2 mg, 0.117 mmol, 58% yield; 5.4 mg, 0.016 mmol, 8% rsm)

Run 3 (57.2 mg, 0.101 mmol, 50% yield; 3.0 mg, 0.0088 mmol, 4% rsm)

Average overall yield: 53% (6% rsm) ± 4.4

^{1}H NMR: (500 MHz, $CDCl_3$)

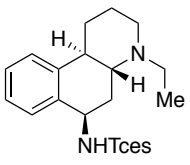
δ 8.00 (s, 1H), 7.85 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.53 (d, *J* = 6.5 Hz, 2H), 7.51 (d, *J* = 6.5 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.35-7.31 (m, 1H), 7.31-7.27 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.54 (d, *J* = 7.4 Hz, 1H), 5.41 (s, 2H), 4.57 (q, *J* = 7.4 Hz, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.34 (d, *J* = 10.8 Hz, 1H), 2.02-1.92 (m, 1H), 1.90-178 (m, 1H), 1.47-1.28 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 144.03, 143.38, 140.71, 140.35, 140.22, 134.84, 134.06, 127.82, 127.73, 127.70, 127.39, 123.35, 122.56, 120.60, 110.19, 93.45, 78.09, 59.18, 48.70, 39.13, 19.44, 13.76

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{26}H_{27}N_3O_3SCl_3$ $[M+H]^+$: 566.0839, found 566.0837



2,2,2-Trichloroethyl (trans-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolin-6-yl)sulfamate [(±)-24c] According to the general amination procedure, trans-4-ethyl-1,2,3,4,4a,5,6,10b-

octahydrobenzo[*f*]quinoline (±)-**23c** (43.1 mg, 0.20 mmol, 1.0 equiv.) was protonated with $HBF_4{\cdot}OEt_2$ (30.2 μL, 35.6 mg, 0.22 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 3 Å molecular sieves (40 mg) in DCE (0.4 mL). After 2 h of reacting, another batch of PhI=NTces (86.1 mg, 0.20 mmol, 1.0 equiv.) was quickly added to the reaction mixture. The reaction was further stirred for 13 h. Following work-up, the crude material was purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, gradient elution 30% EtOAc/Hex (4 column volumes)→0%→1%→2%→3% MeOH/CH_2Cl_2 (2 column volumes each)), staining with $KMnO_4$ to afford the product as a white solid with green discoloration as a mixture of diastereomers. The relative configuration was determined by NOESY and crystallography data.

Run 1 (53.6 mg, 0.121 mmol, 61% yield, 5:1 dr)

Run 2 (53.8 mg, 0.122 mmol, 61% yield, 6:1 dr)

Run 3 (49.3 mg, 0.112 mmol, 56% yield, 5:1 dr; 4.3 mg, 0.020 mmol, 10% rsm)

Average overall yield: 59% (3% rsm) ± 2.9, 5:1 dr

Data for major diastereomer (±)-**24c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

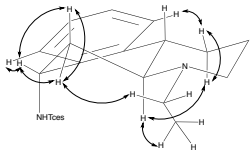
δ 7.48 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.31 (td, *J* = 7.7, 1.5 Hz, 1H), 7.26 (td, *J* = 7.3, 1.1 Hz, 1H), 4.98 (dd, *J* = 4.2, 2.7 Hz, 1H), 4.74 (d, *J* = 10.9 Hz, 1H), 4.72 (d, *J* = 10.9 Hz, 1H), 3.05 (dt, *J* = 11.4, 3.0 Hz, 1H), 2.95 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.75 (dt, *J* = 13.5, 2.3 Hz, 1H), 2.70 (dq *J* = 14.0, 6.7 Hz, 1H), 2.60-2.49 (m, 2H), 2.36-2.25 (m, 2H), 1.92-1.86 (m, 1H), 1.86-1.78 (m, 2H), 1.37 (qd, *J* = 12.7, 3.9 Hz, 1H), 1.08 (t, *J* = 7.2 Hz, 3H)

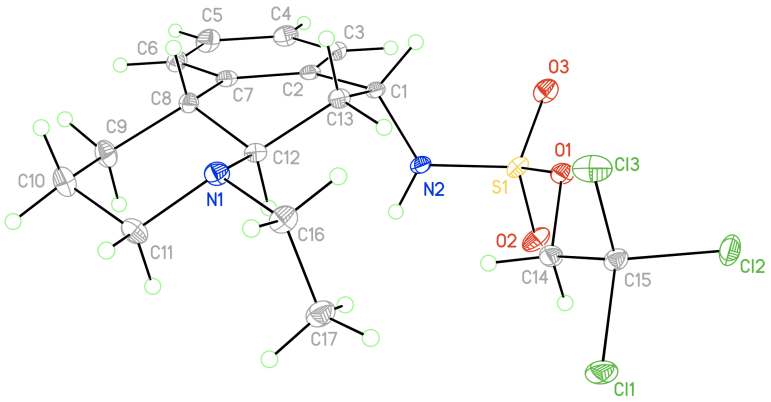
^{13}C NMR: (101 MHz, $CDCl_3$)

δ 139.92, 133.19, 129.69, 128.93, 127.08, 126.09, 93.72, 78.08, 57.90, 53.50, 52.36, 46.90, 42.47, 33.28, 29.18, 25.57, 9.64

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{24}Cl_3N_2O_3S$ $[M+H]^+$: 441.0573, found 441.0567





Crystal data and structure refinement for dd59bsa ((±)-24c)

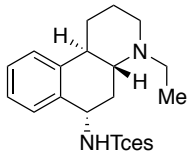
Identification code	dd59bsa
Empirical formula	C17 H25 Cl3 N2 O4 S
Formula weight	459.80
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 13.2896(3) Å a= 90°.

	b = 17.4119(5) Å b= 90°.
	c = 17.5827(5) Å g = 90°.
Volume	4068.59(19) $Å^3$
Z	8
Density (calculated)	1.501 Mg/m^3
Absorption coefficient	0.579 mm-1
F(000)	1920
Crystal size	0.474 x 0.22 x 0.084 mm^3
Theta range for data collection	2.317 to 28.347°.
Index ranges	-17<=h<=17, -22<=k<=23, -23<=l<=23
Reflections collected	46039
Independent reflections	5072 [R(int) = 0.0441]
Completeness to theta = 25.242°	99.9 %
Absorption correction Integration	
Max. and min. transmission	0.96329 and 0.82005
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5072 / 3 / 259
Goodness-of-fit on F2	1.255
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.0924
R indices (all data)	R1 = 0.0534, wR2 = 0.0944
Extinction coefficient	0.0044(2)
Largest diff. peak and hole	0.466 and -0.333 $e.Å^{-3}$

CCDC #1587015 ((±)-**24c**) contains the supplementary crystallographic data for this structure. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

One B-level alert: D-H Without Acceptor O4 -- >H4D is present. This is because there are no good acceptors for the second H atom on the water molecule, causing it to disorders over 2 sites.

Data for minor diastereomer (±)-**S22**:

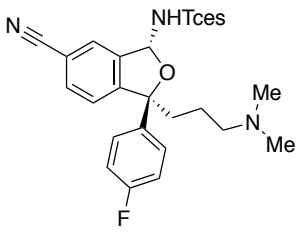


^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.61 (d, *J* = 6.9 Hz, 1H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.28 (d, *J* = 6.7 Hz, 1H), 7.27-7.24 (m, 1H), 4.92 (dd, *J* = 11.2, 6.1 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 10.8 Hz, 1H), 3.01 (d, *J* = 11.5 Hz, 1H), 2.99-2.95 (m, 1H), 2.92 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.68 (dq, *J* = 13.9, 7.3 Hz, 2H), 2.48 (dd, *J* = 12.6, 2.6 Hz, 1H), 2.30-2.19 (m, 2H), 1.89-1.76 (m, 2H), 1.63 (q, *J* = 11.7 Hz, 1H), 1.19 (qd, *J* = 12.7, 4.2 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H)

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{24}Cl_3N_2O_3S$ $[M+H]^+$: 441.0573, found 441.0566



Trans-2,2,2-trichloroethyl (6-cyano-3-(3-(dimethylamino)propyl)-3-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)sulfamate [(±)-24d]

According to the general amination procedure, 1-(3-

(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (±)-**23d** (64.9 mg, 0.20 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL) was protonated with $HBF_4{\cdot}OEt_2$ (30.2 µL, 35.6 mg, 0.22 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 3 Å molecular sieves (40 mg) in DCE (0.4 mL) for 15 h. Upon reaction completion, the reaction mixture was partitioned between 1M NaOH (3 mL) and CH_2Cl_2 (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, condensed *in vacuo*, and purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, gradient elution 30% EtOAc/Hex (4 column volumes)→0%→1%→2%→3% MeOH/CH_2Cl_2 (2 column volumes each)). The resulting solid was re-dissolved in acetonitrile, and the undissolved green solid was removed. The solution was concentrated via rotary evaporation. The resulting oil was re-dissolved in CH_2Cl_2 and concentrated via rotary evaporation to afford the product as a white solid with slight discoloration. The relative configuration was determined by NOESY and crystallography data.

Run 1 (77.7 mg, 0.141 mmol, 71% yield, >20:1 dr)

Run 2 (78.2 mg, 0.142 mmol, 71% yield, >20:1 dr)

Run 3 (77.2 mg, 0.140 mmol, 70% yield, >20:1 dr)

Average overall yield: 71% (0% rsm) ±0.6, >20:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 11.89 (br s, 1H), 8.00 (s, 1H), 7.56-7.47 (m, 3H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 8.6 Hz, 2H), 6.73 (s, 1H), 4.66 (d, *J* = 10.9 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 3.28 (dt, *J* = 11.4, 5.9 Hz, 1H), 2.71 (s, 6H), 2.65-2.59 (m, 1H), 2.48-2.39 (m, 1H), 2.38-2.29 (m, 1H), 1.85-1.66 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$)

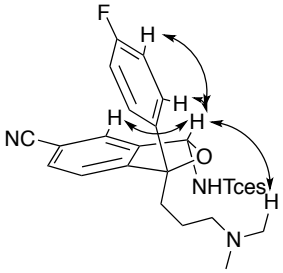
δ 162.40 (d, *J* = 247.4 Hz), 149.62, 142.09, 137.49, 132.63, 128.17, 126.99 (d, *J* = 8.1 Hz), 121.83, 118.56, 115.94 (d, *J* = 21.3 Hz), 112.48, 95.32, 90.96, 90.19, 77.78, 57.00, 42.88, 37.08, 20.67

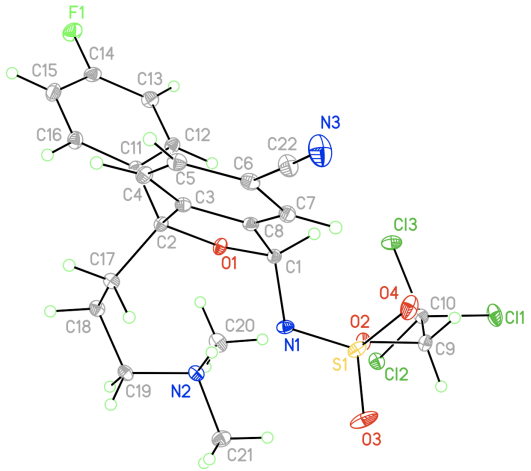
^{19}F NMR: (470 MHz, $CDCl_3$)

δ -114.82 (s, 1F)

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{22}H_{24}Cl_3N_3O_4FS$ $[M+H]^+$: 550.0537, found 550.0537





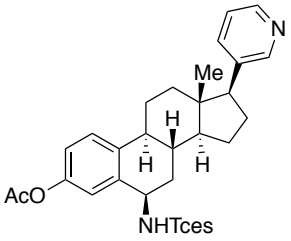
Crystal data and structure refinement for dm67bsa ((±)-24d)

Identification code	dm67bsa
Empirical formula	C22 H23 Cl3 F N3 O4 S

Formula weight	550.84	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.0968(2) Å	a= 103.2330(9)°.
	b = 10.1411(2) Å	b= 99.9696(10)°.
	c = 13.7748(3) Å	g = 95.6757(9)°.
Volume	1205.54(4) $Å^3$	
Z	2	
Density (calculated)	1.517 Mg/m^3	
Absorption coefficient	0.510 mm-1	
F(000)	568	
Crystal size	0.485 x 0.332 x 0.312 mm^3	
Theta range for data collection	2.297 to 28.349°.	
Index ranges	-12<=h<=12, -13<=k<=13, -18<=l<=18	
Reflections collected	26203	
Independent reflections	6018 [R(int) = 0.0235]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction Integration		
Max. and min. transmission	0.89495 and 0.86279	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6018 / 0 / 312	

Goodness-of-fit on F2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0256, wR2 = 0.0674
R indices (all data)	R1 = 0.0272, wR2 = 0.0685
Extinction coefficient	n/a
Largest diff. peak and hole	0.432 and -0.365 e.Å^{-3}

CCDC #1587014 ((±)-**24d**) contains the supplementary crystallographic data for this structure. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.



(8*S*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-17-(pyridin-3-yl)-6-(((2,2,2-trichloroethoxy)sulfonyl)amino)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate [24e] In a 1 dram vial equipped with a stir bar were added (8*S*,9*S*,13*S*,14*S*,17*S*)-13-methyl-17-(pyridin-3-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate **23e** (75.1 mg, 0.20 mmol, 1.0 equiv.) and methylene chloride (DCM) (0.8 mL). Boron trifluoride diethyl ether complex (BF_3•OEt_2) (27.2 μL, 31.2 mg, 0.22 mmol, 1.1 equiv.) was added dropwise while stirring. The reaction mixture was stirred for 1.5 h at room temperature. Upon reaction completion the stir bar was taken out, and mixture was concentrated *in vacuo* and placed on vacuum overnight. The resulting white foamy solid was reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 3 Å molecular sieves (40 mg) in DCE (0.4 mL), according to the general optimization procedure. After 2 h of reaction, another batch of PhI=NTces (86.1 mg, 0.20 mmol, 1.0 equiv.) was quickly

added to the reaction mixture. The reaction was further stirred for 13 h. Upon completion, the flask was taken out of oil bath. Tetramethylethylenediamine (TMEDA) (150 μL, 116 mg, 1.0 mmol, 5.0 equiv.) was added, and DCM (1 mL) was used to wash off the solid remaining on the wall. The reaction mixture was further stirred for 4 h for complete removal of the BF_3 protection. The resulting mixture was directly loaded onto a flash column and purified (50 mL silica, gradient elution 20%→30%→40%→50%→60%→70% EtOAc/hexanes (2 column volumes each)), staining with CAM to afford the product as a white solid with slight green discoloration as a mixture of diastereomers.

Run 1 (61.0 mg, 0.101 mmol, 51% yield, 1.8:1 dr)

Run 2 (62.7 mg, 0.104 mmol, 52% yield, 1.5:1 dr)

Run 3 (60.2 mg, 0.100 mmol, 50% yield, 1.4:1 dr)

Average overall yield: 51% (0% rsm) ± 1.0, 1.6:1 dr

Data for major diastereomer **24e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.34 (br s, 1H), 8.16 (br s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 2.6 Hz, 1H), 7.23 (dd, *J* = 8.5, 5.0 Hz, 1H), 7.01 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.94 (br s, 1H), 4.84 (t, *J* = 4.9 Hz, 1H), 4.71-4.66 (m, 2H), 2.72 (t, *J* = 9.8 Hz, 1H), 2.36-2.30 (m, 2H), 2.28 (s, 3H), 2.26-2.18 (m, 1H), 2.13-1.97 (m, 2H), 1.97-1.88 (m, 1H), 1.70 (td, *J* = 12.9, 4.7 Hz, 1H), 1.63-1.54 (m, 2H), 1.54-1.47 (m, 1H), 1.43 (td, *J* = 13.1, 4.0 Hz, 1H), 1.32 (qd, *J* = 14.0, 2.3 Hz, 1H), 0.37 (s, 3H)

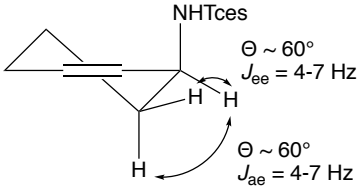
^{13}C NMR: (126 MHz, $CDCl_3$)

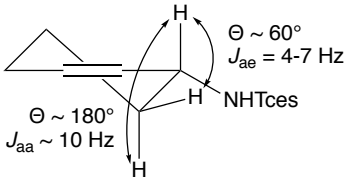
δ 169.79, 149.60, 149.27, 146.93, 138.44, 136.53, 136.31, 135.76, 126.94, 123.30, 123.17, 121.99, 93.90, 78.00, 54.43, 54.38, 52.83, 44.86, 44.02, 37.44, 35.05, 33.83, 25.99, 25.86, 24.22, 21.17, 12.76

HRMS: (ESI-TOF MS ES+)

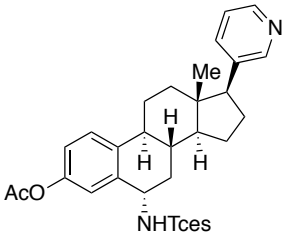
m/z calculated for $C_{27}H_{32}Cl_3N_2O_5S$ $[M+H]^+$: 601.1098, found 601.1110

Stereochemistry was assigned based on coupling constant and by analogy. See below for an explanation of coupling constants and representative coupling constants for the NHTces group in the axial and equatorial positions of the ring.





Data for minor diastereomer **S23**:



^{1}H NMR: (500 MHz, $CDCl_3$)

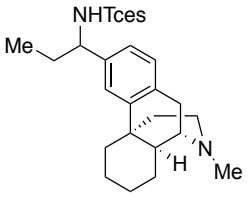
δ 8.45 (br s, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.28-7.24 (m, 1H), 6.97 (dd, *J* = 8.6, 2.5 Hz, 1H), 5.32 (d, *J* = 9.5 Hz, 1H), 4.90 (td, *J* = 10.2, 6.7 Hz, 1H), 4.76 (d, *J* = 10.7 Hz, 1H), 4.71 (d, *J* = 10.8 Hz, 1H), 2.78 (t, *J* = 9.8 Hz, 1H), 2.63 (ddd, *J* = 12.4, 6.5, 1.2 Hz, 1H), 2.40-2.33 (m, 1H), 2.33-2.30 (m, 1H), 2.28 (s, 3H), 2.29-2.26 (m, 1H), 2.20-1.99 (m, 2H), 1.95-1.86 (m, 1H), 1.73-1.67 (m, 1H), 1.66-1.57 (m, 1H), 1.57-1.38 (m, 4H), 0.51 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 169.90, 149.83, 149.35, 147.21, 138.56, 136.58, 136.47, 136.37, 127.03, 123.24, 121.56, 121.14, 93.80, 78.21, 55.07, 54.58, 54.54, 44.72, 44.28, 38.80, 37.35, 37.14, 26.14, 26.01, 24.23, 21.21, 12.79

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{27}H_{32}Cl_3N_2O_5S$ $[M+H]^+$: 601.1098, found 601.1086



2,2,2-Trichloroethyl(1-((4b*S*,8a*S*,9*S*)-11-methyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-3-yl)propyl)sulfamate [24f] According to the general amination procedure, (4b*S*,8a*S*,9*S*)-11-methyl-3-propyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthrene (+)-**23f** (56.7 mg, 0.20 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL) was protonated with HBF_4•OEt_2 (30.2 μL, 35.6 mg, 0.22 mmol, 1.1 equiv.), reacted with manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.10 equiv.), $AgSbF_6$ (6.9 mg, 0.020 mmol, 0.10 equiv.), PhI=NTces (172.2 mg, 0.40 mmol, 2.0 equiv.), and 3Å molecular sieves (40 mg) in DCE (0.4 mL). After 2 h of reaction, another batch of PhI=NTces (86.1 mg, 0.20 mmol, 1.0 equiv.) was quickly added to the reaction mixture. The reaction was further stirred for 13 h. Following work-up, the crude material was purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, gradient elution 40%→50% EtOAc/Hex (4 column volumes each)→0%→1%→2%→3% MeOH/CH_2Cl_2 (2 column volumes each)) to afford the product as a white solid with green discoloration as a mixture of diastereomers.

Run 1 (45.3 mg, 0.0888 mmol, 44% yield, 1:1 dr; 8.1 mg, 0.029 mmol, 14% rsm)

Run 2 (44.9 mg, 0.0880 mmol, 44% yield, 1.1 dr; 4.5 mg, 0.016 mmol, 8% rsm)

Run 3 (43.9 mg, 0.0861 mmol, 43% yield, 1:1 dr; 4.0 mg, 0.014 mmol, 7% rsm)

Average overall yield: 44% (10% rsm) ± 0.6, 1:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

δ 7.13 (s, 1H), 7.13-7.09 (m, 1H), 7.04 (app dt, *J* = 7.9, 1.7 Hz, 1H), 4.36 (q, *J* = 7.9 Hz, 1H), 4.27 (d, *J* = 10.9 Hz, 1H), 4.24 (app dd, *J* = 10.8, 1.4 Hz, 1H), 3.01 (d, *J* = 18.5 Hz, 1H), 2.82 (dd, *J* = 4.8, 3.1 Hz, 1H), 2.62 (dd, *J* = 18.5, 5.5 Hz, 1H), 2.46-2.37 (m, 2H), 2.39 (s, 3H), 2.05-1.92 (m, 2H), 1.88-1.72 (m, 3H), 1.62 (app d, *J* = 13.2 Hz, 1H), 1.53 (app d, *J* = 12.8 Hz, 1H), 1.45–1.25 (m, 5H), 1.24-1.14 (m, 1H), 1.12-1.00 (m, 2H), 0.90 (app td, *J* = 7.4, 2.4 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 141.14, 138.48, 138.37, 137.89, 128.57, 128.49, 124.14, 124.12, 123.63, 123.54, 93.56, 93.54, 78.25, 78.23, 61.26, 61.18, 57.98, 47.32, 45.28, 42.86, 42.83, 42.08, 37.28, 37.26, 36.57, 36.55, 30.37, 30.27, 26.79, 26.78, 26.64, 26.62, 24.25, 24.18, 22.34, 22.26, 10.85, 10.77

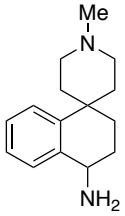
HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{22}H_{32}N_2O_3SCl_3$ $[M+H]^+$: 509.1199, found 509.1195

2.4.10 Experimental Procedures and Characterization for Figure 13

General procedure for Tces deprotection. According to a previously reported procedure,[38a] in a 50 mL round bottom flask under N_2 containing a Teflon stir bar was added the amination product (1 equiv.), Zn/Cu couple (10 equiv.), and 1:1 MeOH/AcOH. The reaction was vigorously stirred for 48 h then filtered through celite, using methanol to rinse the filter cake and concentrated. To the resulting solid was added methanolic HCl (prepared from mixing 1:13

acetyl chloride and MeOH) and the reaction heated to 40 °C for 12 h under N_2. Upon reaction completion, the solvent was removed in vacuo and the crude partitioned between 3 M HCl and CH_2Cl_2. The aqueous layer was washed with CH_2Cl_2 2x, and basified with 50% NaOH. The aqueous layer was then extracted with CH_2Cl_2 3x. The organic layers were combined and dried over K_2CO_3, filtered, and concentrated to produce the free amine. No further purification was necessary. *Note: this purification method is only effective for substrates that originally contain basic nitrogen functionalities. Amine products from substrates that do not contain basic nitrogen have poor solubility in 3 M HCl and should be purified via alternative methods such as reverse-phase chromatography.*

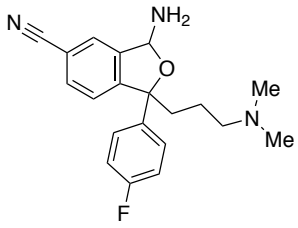


1'-Methyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4'-piperidin]-4-amine [25a]

According to the general Tces deprotection procedure, 2,2,2-trichloroethyl (1'-methyl-3,4-dihydro-2*H*-spiro[naphthalene-1,4'-piperidin]-4-yl)sulfamate **20** (18.7 mg, 0.0423 mmol, 1.0 equiv.) was reacted with Zn/Cu (27.7 mg, 0.423 mmol, 10 equiv.) in 1:1 MeOH/AcOH (2.6 mL), and then with AcCl (0.27 mL) in MeOH (3.3 mL) to produce the product as a colorless oil (5.3 mg, 0.023 mmol, **54% yield**).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.49 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.24 (td, *J* = 7.8, 1.8 Hz, 1H), 7.18 (t, *J* = 7.4, 1.5 Hz, 1H), 3.94 (dd, *J* = 5.5, 4.0 Hz, 1H), 2.75 (t, *J* = 11.5 Hz, 2H), 2.35 (s, 3H), 2.26 (p, *J* = 12.3 Hz, 3H), 2.18-2.04 (m, 2H), 2.04-1.91 (m, 2H), 1.81 (dd, *J* = 11.6, 8.4 Hz, 1H), 1.70-1.51 (m, 4H)



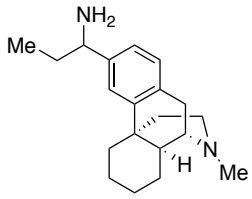
3-amino-1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile [25b] According to the general Tces deprotection procedure, trans-2,2,2-trichloroethyl (6-cyano-3-(3-(dimethylamino)propyl)-3-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)sulfamate (±)-**24d** (29.2 mg, 0.0530 mmol, 1.0 equiv.) was reacted with Zn/Cu (34.7 mg, 0.530 mmol, 10 equiv.) in 1:1 MeOH/AcOH (3.2 mL), and then with AcCl (0.34 mL) in MeOH (4.1 mL) to produce the product as a colorless oil (12.1 mg, 0.0357 mmol, **67% yield, 1:1 dr**).

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

δ 7.70-7.59 (m, 2H), 7.55-7.49 (m, 1H), 7.48-7.39 (m, 1.5H), 7.34 (d, *J* = 7.9 Hz, 0.5H), 7.07-6.95 (m, 2H), 6.14 (br t, *J* = 8.6 Hz, 0.5H), 6.02 (br s, 0.5 H), 2.34-2.16 (m, 4H), 2.14 (s, 3H), 2.13 (s, 3H), 1.54-1.36 (m, 1H), 1.36-1.16 (m, 1H)

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{20}H_{23}N_3OF$ $[M+H]^+$: 340.1825, found 340.1821



1-((4b*S*,8a*S*,9*S*)-11-methyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-3-yl)propan-1-amine [25c] According to the general Tces deprotection procedure, 2,2,2-trichloroethyl((4b*S*,8a*S*,9*S*)-11-methyl-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-3-yl)propyl)sulfamate **24f** (16.9 mg, 0.033 mmol, 1.0 equiv.) was reacted with Zn/Cu (21.7 mg, 0.033 mmol, 10 equiv.) in 1:1 MeOH/AcOH (2 mL), and then with AcCl (0.21 mL) in MeOH (2.6 mL) to produce the product as a colorless oil (8.2 mg, 0.027 mmol, **83% yield, 1:1 dr**).

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

δ 7.16 (s, 0.5H), 7.12 (s, 0.5H), 7.06 (s, 1H), 7.05-7.01 (m, 1H), 3.75 (app dt, *J* = 9.8, 6.9 Hz, 1H), 3.01 (d, *J* = 18.3 Hz, 1H), 2.80 (dd, *J* = 5.9, 3.1 Hz, 1H), 2.62 (dd, *J* = 18.3, 5.8 Hz, 1H), 2.47-2.39 (m, 2H), 2.39 (s, 3H), 2.06 (tt, *J* = 12.3, 3.3 Hz, 1H), 1.83 (dt, *J* = 12.9, 3.2 Hz, 1H), 1.74 (td, *J* = 13.2, 5.0 Hz, 1H), 1.70-1.59 (m, 3H), 1.55-1.46 (m, 2H), 1.43-1.36 (m, 2H), 1.36-1.29 (m, 2H), 1.29-1.19 (m, 2H), 1.12 (qd, *J* = 12.4, 3.9 Hz, 1H), 0.86 (app td, *J* = 7.4, 3.8 Hz, 3H)

2.5 References

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CHAPTER 3: LATE-STAGE OXIDATIVE C(sp^3)–H METHYLATION

Acknowledgements

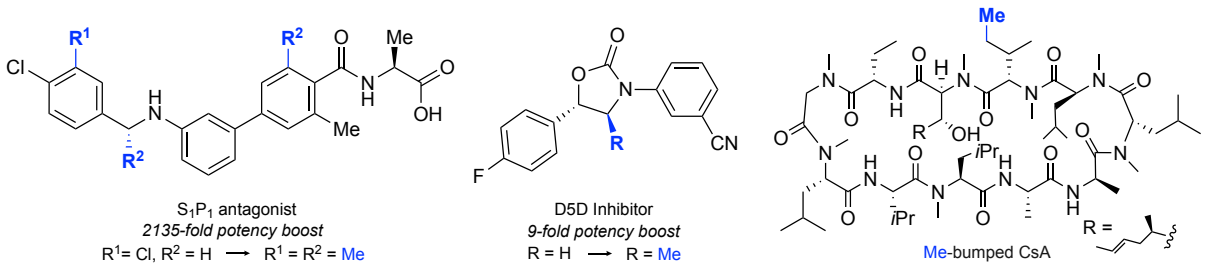
This chapter was adapted from the research article "Late-stage oxidative C(sp^3)–H methylation" (Feng, K.; Quevedo, R. E.; Kohrt, J. T.; Oderinde, M. S.; Reilly, U.; White, M. C. *Nature* **2020**, *580*, 621).

This work was a collaborative effort. The scope for simple piperidines, azepane, fused rings, and isochroman, and part of the late-stage examples were established by Raundi E. Quevedo. These sections will not be described in this thesis.

3.1 Introduction

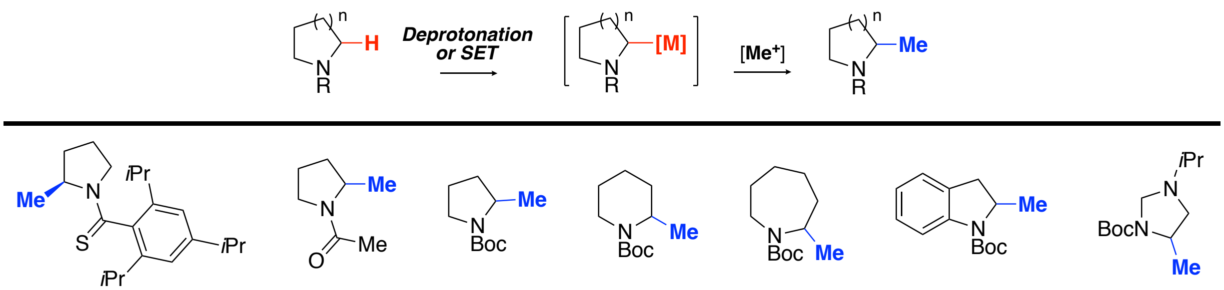
Among late-stage derivatizations, the installation of methyl groups is particularly attractive to medicinal chemists because of the unique improvements in biological properties it brings, often through comprehensive changes in binding affinity, solubility, and metabolism.[54] This phenomenon, commonly referred to as the "magic methyl" effect, is especially prevalent when methyl is installed alpha to heteroatoms such as nitrogen and oxygen, and has been shown to boost potency of potential drug candidates up to 2000 folds (Figure 14).[54e] The introduction of methyl groups also allows interrogation and manipulation of biological processes, such as through the bump-and-hole approach.[55]

Figure 14. Methylation Increases Potency and Enables Biological Process Interrogation



Despite these advantages of adding methyl groups, and its already ubiquity in small-molecule drugs,[54a] there had been no general methods that allow its late-stage installation in complex molecules. Traditional alkylation methods that have shown methylation examples rely on substrate-controlled metalation processes that involve lithiation, directing groups, or single-electron transfer (SET), which are limited in heterocycle scope.[56] Prior to this work to the best of our knowledge, only seven methylation examples on the simplest unfunctionalized azacycles were known (Figure 15).[56a-e]

Figure 15. All Known Methylation Examples Through Metalation

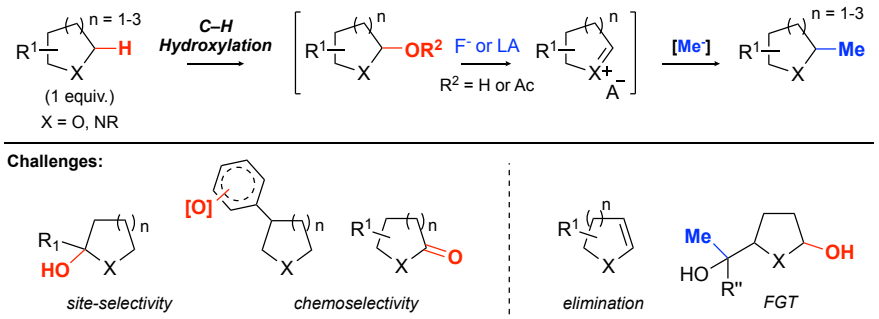


In order to enable methylation at late stages of synthesis, it is necessary to develop methods that tolerate epimerizable stereocenters, functional groups (e.g., ester, ketone, nitrile), remote basic nitrogen, and arenes. Such methods must also have good chemoselective and site-selectivity to distinguish competing sites in complex molecules.

We envisioned that this type of functionalization could be achieved in an oxidative fashion via hydroxylation. The resulting hemiaminal can then be activated to form an iminium and methylated with a methyl nucleophile (Figure 16). This approach will also provide a solution to an often overlooked, yet important issue for late-stage methylation: the small size and electron-neutrality of methyl group often mean no significant polarity change between the starting material and methylated product, resulting in inseparable mixtures in direct methylation examples.[56e] On the other hand, though its isolation is not necessary for sequential methylation,

the hemiaminal intermediate is distinctly more polar and offers the unique choice for facile removal of the starting material prior to methylation when product purification is difficult.

Figure 16. Oxidative Methylation



Challenges associated with this approach include site- and chemoselectivity between different oxidatively reactive sites and groups, as well as elimination and tolerance of electrophilic functional groups in methylation (Figure 16). Substrate-controlled alpha oxidations afford poor selectivity; in addition, the resulting alcohol intermediates are prone to overoxidation due to hyperconjugative activation of the installed oxygen atom, calling for reduction prior to or after oxidation.[57] Reports of alkylation of *N*-acylimminium are also of limited scope, as alkyl nucleophiles are strongly reactive and basic, thus promoting side reactions as listed above.[58]

3.2 Results and Discussion

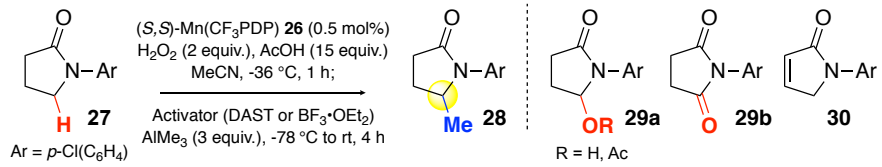
3.2.1 Reaction Development and Optimization

In order to achieve good selectivity, it is necessary to first tune the C–H hydroxylation step in a catalyst-controlled fashion. Prior to this work, our group developed a small-molecule manganese catalyst, Mn(CF_3PDP) **26**, that was able to hydroxylate strong methylene C–H bonds with good chemoselectivity and site-selectivity.[59] As a significant improvement to the previous iron catalysts,[5] electron-deficient arenes are tolerated under Mn(CF_3PDP) **26** catalysis. However, tolerance toward electron-neutral and electron-rich arenes and heteroarenes, as well as

overoxidation remained the main challenges for this catalytic system. For example, oxidation of lactam **27** with Mn(CF_3PDP) **26** under the reported standard conditions[59] gave predominantly overoxidized imide **29b** (Table 7A, entry 1).[60]

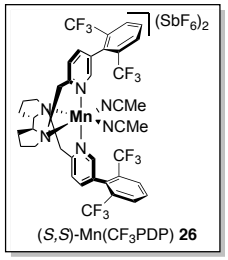
Table 7. Reaction Development and Optimization

A. Reaction Optimization

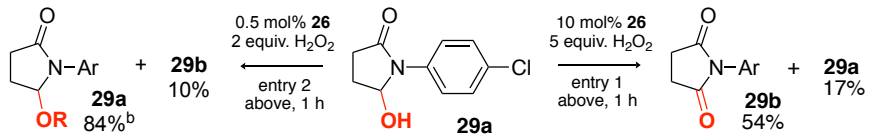


entry	deviation from above	**28** (%)	**29** (%)	**30** (%)
1	10 mol% **26**, 5 equiv. H_2O_2[a]	—	41 (**29b**)	—
2	No methylation step	—	82[b] (**29a**)	—
3	$MsCl/NEt_3$[c]	0	—	39
4	$BF_3•OEt_2$[d]	63	—	0
5	DAST[e]	64	—	0
6	Deoxo-Fluor[e]	61	—	0
7	TFAA/TMSOTf[f]	51	—	14
8	DAST/MeMgBr[g]	24	—	0

[C–H hydroxylation]
carbocycle
[Me^-]
N & O heterocycles
linear N



B. Chemoselectivity Study on Hydroxylation



For achiral substrates, (*R*,*R*)- and (*S*,*S*)-**26** can be used interchangeably. [a]No methylation step. [b]Mixture of hemiaminal (64%-71%) and hemiaminal acetate produced in situ from AcOH (13%-18%). [c]MsCl, 1 equiv.; NEt_3, 1 equiv.; $NaHCO_3$ wash; $AlMe_3$, 3 equiv., -78 °C, 2 h; rt, 1 h. [d]2 equiv. [e]1 equiv. [f]TFAA, 1 equiv.; TMSOTf, 1 equiv. [g]MeMgBr, 3 equiv., -78°C, 3 h.

Since these conditions (10 mol% **26**, 5 equiv. H_2O_2) were developed for unactivated secondary aliphatic C–H bonds, I reasoned that far less forcing conditions would suffice for hydroxylating the much more reactive α-C–H bonds. Lowering the catalyst and oxidant loading could effectively increase chemoselectivity by suppressing undesirable side-reactions. For instance, due to the bulky steric environment of the CF_3PDP ligand, the hydroxylation of **27** could be faster than that of the more hindered hemiaminal **29a**. Consistent with this hypothesis, when the catalyst loading was significantly lowered to 0.5 mol% and hydrogen peroxide to 2 equiv., an impressive 82% combined yield of hemiaminal and hemiaminal acetate, formed in situ from reaction with acetic acid, was obtained with minimum overoxidation (entry 2).

To directly probe this difference in oxidation rate, I subjected hemiaminal alcohol **29a** to these two different reaction conditions. Consistent with oxidation of **27**, only 10% of oxidation to imide was observed under the 0.5 mol% **26**, 2 equiv. H_2O_2 conditions with 84% recovered **29a**, while a majority of **29a** was oxidized when met with the more forcing 10 mol%, 5 equiv. H_2O_2 conditions, suggesting a slower alcohol oxidation rate (Table 7B). The enhanced chemoselectivity under the mild oxidation conditions also enabled tolerance of electron-neutral and electron-rich arenes, as the higher-energy aromatic oxidation pathways are likewise suppressed (vide infra). It is worth noting that this new condition represents one of the highest substrate to catalyst ratio (200:1), and enabled easy scale-up to gram scales without requiring large amounts of the precious catalyst. Comparatively, Fe(PDP) and Fe(CF_3PDP) led to predominantly aromatic oxidation.[5,61] Mn(PDP), having been shown to hydroxylate simple linear amides, was not reactive enough to produce a high hydroxylation yield, but can be beneficial in sterically hindered substrates where Mn(CF_3PDP) gives low yields.[62] A more thorough investigation on the effect of catalyst and oxidant loadings is described in the experimental section.

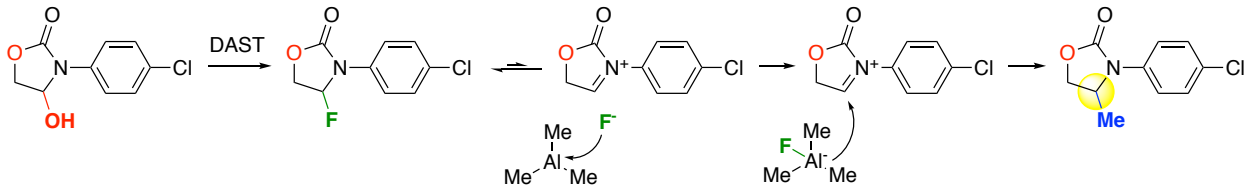
The next challenge rests on the conversion of the hemiaminal intermediates to the final methylated products. Common commercial alkylating reagents (e.g., organolithium, Grignard reagent) are highly nucleophilic and may prove detrimental to electrophilic functional groups. We selected trimethylaluminum as a mild nucleophile that has shown some functional group tolerance, such as for esters in a total synthesis.[63] While the most common way of converting hydroxyls is by first transforming them into good leaving groups such as mesylates, such tactics were unsuccessful at sites α to nitrogen, as the resulting hemiaminal mesylate was highly labile and was readily eliminated in the presence of a base necessary for mesylation to give enamine **30**

(Table 7A, entry 3). Mesylation, however, provides a viable path for methylation of carbocycles by activating secondary aliphatic alcohols, which will be described later in this chapter.

In order to promote iminium formation, it is necessary to activate the hemiaminal without using a base. The azaphilic Lewis acid BF_3•OEt_2 was previously shown to activate hemiaminals to form iminium ions for arylation.[61] Since trimethylaluminum is also mildly Lewis acidic and does not react with BF_3, I hypothesized their combination can be applied to achieve methylation. As expected, the desired methylation product **28** was obtained in 63% yield (entry 4). However, the binding between BF_3 and the hemiaminal hydroxyl is weak. In substrates containing other Lewis basic functional groups, such as aliphatic amides and nitriles, BF_3 may exchange onto and activate these groups toward nucleophilic attack, causing degradation of the substrate (vide infra). For these substrates, an alternative activation mode without the use of azaphilic Lewis acids is necessary.

The intrinsic weak Lewis acidity of trimethylaluminum is key to the discovery of this new activation mode. Although hydroxyl is a poor leaving group and cannot be taken off by trimethylaluminum directly,[63b] aluminum does have high affinity to fluorine that leads it to abstract fluorine atoms α to nitrogen for alkylation.[64] I imagined the hemiaminal hydroxyl can be in situ converted to fluoride and subsequently methylated (Figure 17).

Figure 17. Proposed Mechanism for Fluorine-Assisted Methylation



For in situ fluorination, I selected diethylaminosulfur trifluoride (DAST), a nucleophilic fluorinating reagent that does not require base for fluorination. Satisfyingly, the reaction proceeded with high efficiency and produced **28** in a comparable 64% yield, with methylation

done in one-pot with no workup or isolation of the fluorinated intermediate (Table 7A, entry 5). The hemiaminal acetate of **29a** also was fully converted to **28** under the fluorine-assisted methylation (see experimental section for conversion studies). The more thermally stable bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) can also be used in place of DAST for comparable results (entry 6). The use of Deoxo-Fluor is especially helpful when the methylated product is polar and co-eludes with *N*,*N*-diethylmethanesulfinamide, an similarly polar byproduct produced when using DAST.

A third way of activating the hemiaminal intermediates is by trifluoroacetic anhydride (TFAA) esterification and subsequent treatment with an oxophilic Lewis acid, trimethylsilyl triflate (TMSOTf).[63a] It is necessary to convert all hemiaminals into esters, as TMSOTf is not capable of directly activating hydroxyl like BF_3 for iminium formation, but rather produces silyl ethers. An in situ esterification with TFAA does not require the use of base like many other anhydrides, and is uniquely suitable for this reaction. Upon activating both hemiaminal trifluoroacetate from TFAA, and hemiaminal acetate originally produced in the hydroxylation with AcOH, methylation of **27** under these conditions gave **28** in 51% yield with partial enamine formation (entry 7). While this method is not as efficient as the previous two in simple molecules as elimination is more prone to occur, it may be advantageous to use when the hemiaminal acetate intermediate is found unreactive via DAST or BF_3 activation. This is often the case in oxazolidinone substrates (vide infra).

Other common commercial methyl nucleophiles are less Lewis acidic and therefore ineffective in this oxidative methylation strategy. For example, methylation of **27** with methylmagnesium bromide, run under cryogenic temperature to preserve the carbonyl, nonetheless only afforded **28** in 24% yield with byproducts (entry 8). The use of a Grignard

reagent was helpful, however, in less reactive intermediates such as imines, which were unreactive toward $AlMe_3$ (vide infra). Attempts of methylation with dimethylzinc afforded only side products.

3.2.2 Reaction Scope and Selectivity

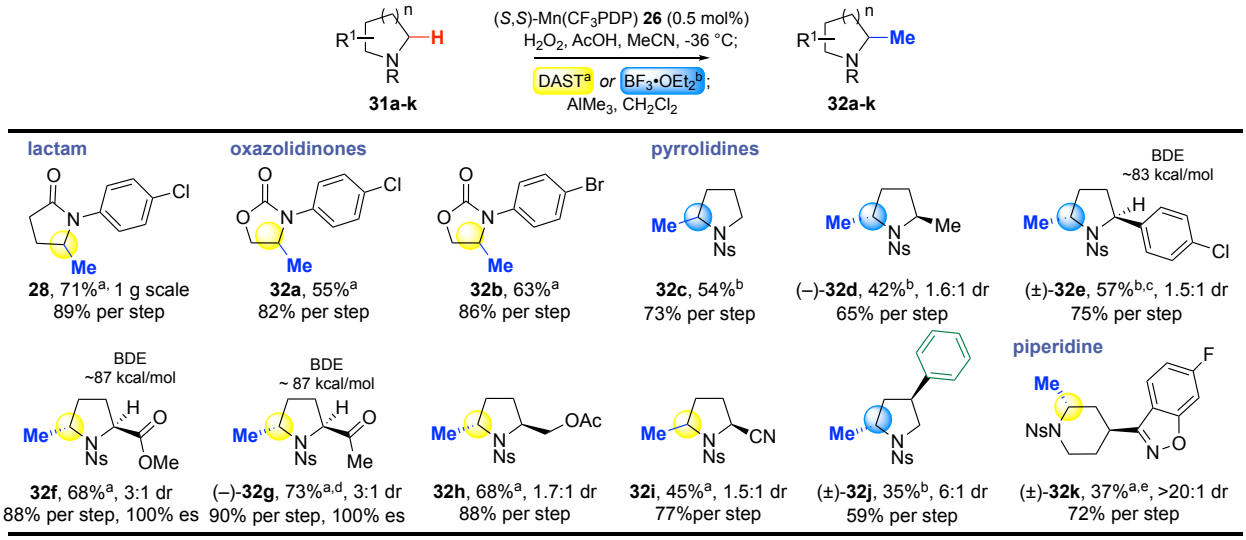
Having the choice of applying different activation modes allows researcher to tune the reaction to fit with the target substrate, thus expanding the scope of this method. In general, substrates with electrophilic functional groups should be activated with DAST, while those without these groups can be methylated with BF_3•OEt_2. The TFAA/TMSOTf activation is used when unreacted hemiaminal acetate is observed in large amount after DAST/BF_3-promoted methylation. One exception is the methylation of piperidines, where to curb enamine formation, both BF_3 and DAST should be attempted, as elimination is highly dependent on the substrate and the activation mode.[60]

The high substrate/catalyst ratio allows gram-scale reactions to be carried out without using a significant amount of catalyst. Lactam **27** was methylated in a 1 g scale in 71% yield via DAST activation, with only 34.6 mg of Mn(CF_3PDP) **26** (Figure 18).

Oxazolidinone **31a** was methylated via DAST activation in 55% yield. It is worth pointing out that BF_3 activation only produced 10% **32a**, likely due to its deleterious off-site activation of the more labile carbonyl. Although unreacted acetate was observed in this case, the TFAA/TMSOTf activation produced 20% enamine, bringing down the yield for **32a** to a lower 46%. In more complex oxazolidinone substrates with more hindered β-*N* positions, this elimination pathway was less favored and the TFAA/TMSOTf activation became highly

effective (vide infra). A 4-bromophenyl-containing oxazolidinone **31b** was also methylated via DAST activation in similar yields.

Figure 18. Methylation of Lactam, Oxazolidinones, Pyrrolidines, and Piperidine



Isolated yields are based on the average of three experiments. General oxidation: substrate (1 equiv.), (*S*,*S*)-**26** (0.5 mol%), AcOH in MeCN, -36 °C; H_2O_2 (2 or 5 equiv.) in MeCN syringe pump for 1 h. Mixture passed through silica plug, EtOAc flush, concentrated before isolation or methylation. For insoluble substrates, CH_2Cl_2 was added to MeCN and/or the temperature of the oxidation reaction was increased to 0 °C. [a]DAST activation: crude in CH_2Cl_2 (0.2 M), DAST (1 equiv.) added at –78 °C; room temperature (rt) for 1 h; cooled to -78 °C, AlMe3 added, stirred 2 h; rt for 1 h. [b]BF_3 activation: crude in CH_2Cl_2 (0.2 M), –78 °C, $AlMe_3$ (3 equiv.) and $BF_3{\cdot}OEt_2$ (2 equiv.) sequentially added, stirred 1 h; rt for 3 h. [c]2 mol% (*S*,*S*)-**26**. [d]$AlMe_3$ –78 °C, 3 h. [e]For facile purification, hemiaminal isolated before methylation. 10 mol% (*S*,*S*)-**26**, rt, starting material recycled once.

I then investigated the scope of methylation on substrates containing pyrrolidine, the fifth most common heterocycle in small-molecule drugs.[7] Although nosyl-protected simple pyrrolidine **31c** has very few steric elements and two identical sites for oxidation, at 0.5 mol% catalyst loading overoxidation was successfully curbed, and 54% of monomethylated **32c** was produced with only 15% demethylation and no significant imide formation. Likewise, the high site-selectivity along with low catalyst loading of (*S*,*S*)-**26** was successful in distinguishing a secondary alpha site from a tertiary alpha site, differentiated only by a methyl group, to produce **32d** in good yields. The strong regioselectivity of Mn(CF_3PDP) **26** was further demonstrated in the oxidative methylation of pyrrolidine substrates **31e-g**, where a benzylic of aliphatic tertiary alpha C–H has a significantly lower bond dissociation energy (BDE) than their secondary counterparts (BDE ~ 90 kcal/mol). Notably, full stereoretention was observed for chiral

substrates **31e** and **31f**, showing the regioselectivity was dictated by catalyst control on the C–H cleavage step.

While most methyl nucleophiles are not compatible with electrophilic functional groups, trimethylaluminum in the absence of another Lewis acid showed impressive tolerance toward these groups, including ester, ketone, and nitrile (**32f-i**). This broad functional group tolerance of these methylation methods is vital for its late-stage application, where these groups are prevalent in drugs and natural products. In addition, a phenyl group with no electron-withdrawing substituents was tolerated in methylation (**32j**), and the less sterically hindered site was preferentially methylated in 35% yield. Under the originally reported conditions, no aromatic rings with such electron density were tolerated.[59] This result further shows lowering catalyst loading brings dramatic increase in chemoselectivity, which is beneficial for late-stage methylation in drugs containing these electron-rich arenes.

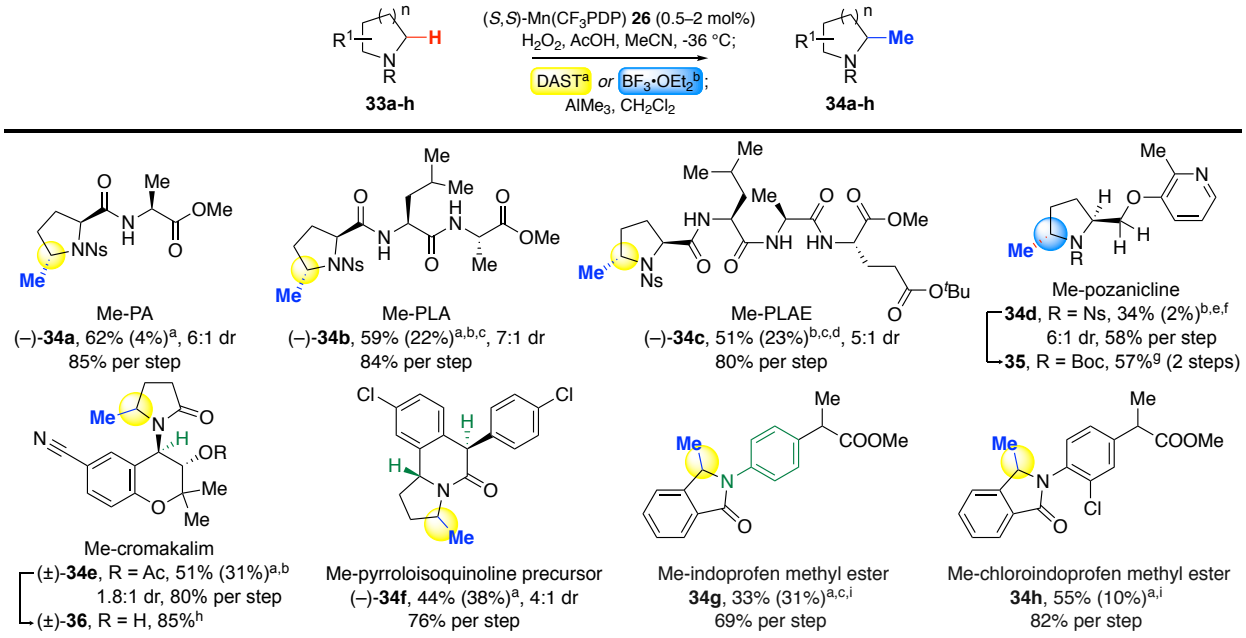
We have also explored methylation in other types of heterocycles, including piperidines, azepane, fused rings, and oxygen heterocycles.[60] For example, a piperidine substrate **31k** was successfully methylated in 37% yield without any protection of the benzisoxazole ring with only one diastereomer observed, likely because of the rigid half-chair conformation of the iminium intermediate.[65]

3.2.3 Application in Late-Stage Derivatization

The main objective for this method is to enable methylation at late stages of synthesis. Having seen its success on simple heterocycles, I next examined a series of bioactive molecules and natural products with multiple competing sites and functional groups with similar principles of selecting between the BF_3 and fluorine-assisted activation strategies.

Peptides are an important class of therapeutics and are of significant medicinal interest.[61] Their structural complexity provides an excellent opportunity to probe the versatility of this method. Despite having multiple mildly Lewis-basic amide motifs, late-stage methylation of peptides under the fluorine-assisted activation proceeded in excellent chemoselectivity and yields (Figure 19, **34a-c**). For example, the highly structural complex tetrapeptide **34c** was methylated exclusively at the secondary α-*N* site of the terminal proline in 51% yield and 74% mass balance. Notably, the use of Deoxo-Fluor in this case prevented the co-elusion of the methylation byproduct of DAST with similar polarity, and facilitated product purification. It is also worth noting that the BF_3 activation mode is not compatible with peptides, likely due to competition between the binding sites: an attempt to methylate tripeptide **33b** with BF_3 resulted in trace yield and a complex mixture of byproducts. This difference again highlights the importance of having multiple activation modes available for selection based on the nature of the substrate.

Figure 19. Late-Stage Methylation of Peptides, Drugs, and Drug Precursors



Generally, 0.5–2 mol% (*S*,*S*)-**26** and 2 or 5 equiv. H_2O_2 were used for oxidation. Higher catalyst and oxidant loadings were applied when conversions were low. Isolated yields are based on the average of three experiments. Explicit C–H bonds denote competing sites of oxidation. Green coloring denotes oxidatively labile aromatic groups. [a]DAST activation. [b]Oxidation intermediates isolated before methylation. [c]Starting material recycled once. In some cases, isolated yields are based on an average of two experiments. [d]Deoxo-Fluor used instead of DAST for activation. [e]BF_3 activation. [f]HBF_4 protection (see Chapter 1), 10 mol% (*S*,*S*)-**26**. [g]PhSH, Cs_2CO_3; Boc_2O. [h]1 M NaOH/MeOH. [i]For insoluble substrates, CH_2Cl_2 was added to MeCN and/or the temperature of the oxidation reaction was increased to 0 °C.

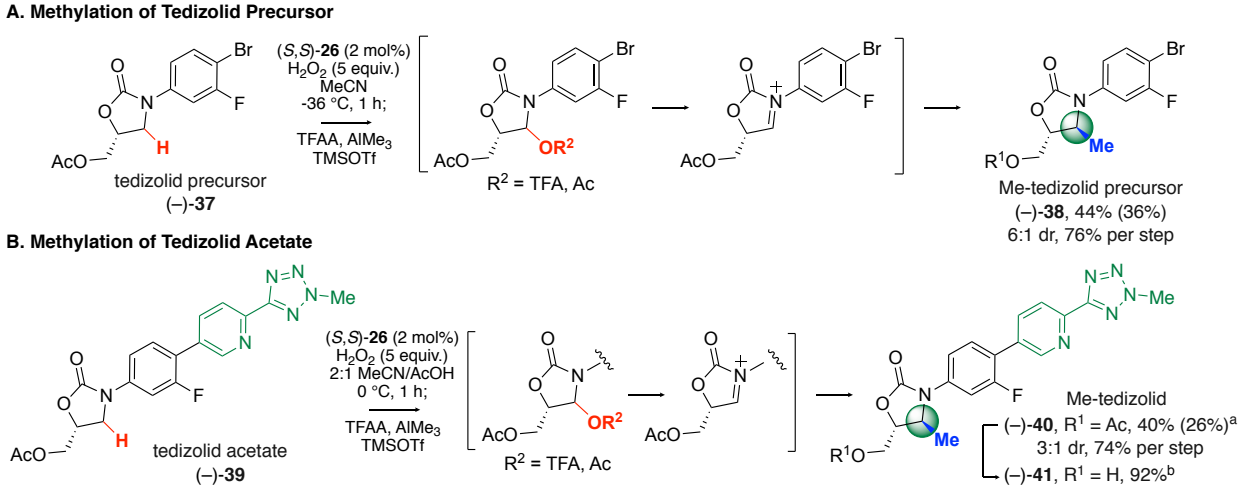
As developed and demonstrated in previous chapters, basic nitrogens can be tolerated in the oxidation step by protonation with HBF_4. Pozanicline, a neuroprotective drug with potential to treat attention deficit hyperactivity disorder (ADHD),[66] has a basic pyridine motif. In nosyl protected pozanicline **33d**, this pyridine was protected and deactivated with HBF_4, resulting in a 34% remotely methylated product **34d** in 6:1 dr under the BF_3 activation mode. Because of the strong inductive deactivation effect, sites alpha to oxygen were also deactivated to further effect a site-selective methylation. The fluorine-assisted activation can also be used for **33d** to give a similar yield but lower dr (3:1), likely caused by the differently sized counterions forming ion pair with the iminium intermediate at low temperatures. Notably, despite the weak Lewis acidity of trimethylaluminum, the methylation step proceeded unhindered without any protection on the basic pyridine nitrogen. For secondary amines, I chose nosyl group as a convenient chromophoric protecting group that does not generate complex rotational isomers upon protection, as well as its orthogonal deprotection compared with common acyl protecting groups. When necessary, the nosyl group can be easily removed using thiophenol to produce the free amine without requiring a strong base or acid, which may be detrimental for other delicate functional groups in the molecule. Subsequent protection with *tert*-butyloxycarbonyl (Boc) gave **35** in a combined 57% yield.

The high regioselectivity is further demonstrated in the methylation of acetylated cromakalim, a potassium channel activator with antihypertensive activities.[67] Cromakalim acetate **33e** contains a γ-lactam and both tertiary benzylic and secondary C–H bonds hyperconjugatively activated by nitrogen, was exclusively oxidized and methylated in 51% yield and 82% mass balance on the less sterically hindered secondary site. The acetate protecting group can be very easily unmasked using sodium hydroxide to produce methylated cromakalim

36 in high yields. Likewise, a precursor to pyrroloisoquinoline, a prevalent structure in compounds exhibiting neurotransmitter-uptake-inhibitory properties,[68] was methylated on the secondary site exclusively to produce **34f** in 44% yield and 82% mass balance.

The unprecedented mild oxidation conditions also enabled the methylation to occur in substrates containing electron-rich arenes. Indoprofen, a anti-inflammatory drug investigated for spinal muscular atrophies treatment, has an electron-rich aniline motif. Oxidation of its methyl ester derivative **33g** under the forcing conditions[59] resulted in predominantly aromatic oxidation such that the methylation attempt only produced **34g** in 7% yield with 16% rsm. In contrast, under the new oxidation conditions with substantially reduced catalyst loadings (2 mol%), a significant increase in both yield (33%) and mass balance (64%) was observed. This dramatic difference again showcased that lowering catalyst loadings effective suppressed deleterious aromatic oxidation pathways that require higher energy and increased chemoselectivity. Methylation of **33h**, a chlorinated analogue of indoprofen with lowered electron density on the aromatic ring, gave a further increased 55% yield.

Figure 20. Late-Stage Methylation of Tedizolid Precursor and Acetate



TFAA/TMSOTf activation: TFAA, rt, 1 h; cooled to –78 °C, $AlMe_3$ (3 equiv.) and TMSOTf (1 equiv.) sequentially added, 2 h; then rt, 1 h. [a]Oxidation intermediates isolated before methylation; 2 equiv. TMSOTf. [b]1M NaOH/MeOH.

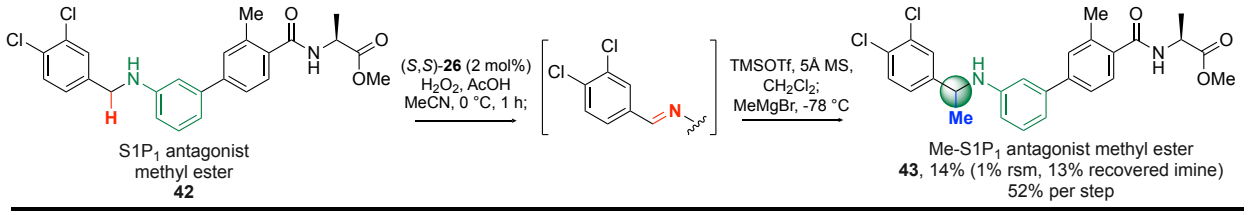
The unprecedented chemoselectivity of Mn(CF_3PDP) **26** under reduced catalyst loadings makes it uniquely effective methylating drugs with delicate structures. To further highlight its capability for late-stage methylation, I investigated the acetate of tedizolid, a commercial antibiotic for acute bacterial skin infections. Tedizolid contains pyridine, tetrazole, and *N*-methyl motifs all prone to oxidation. Methylation of an advanced intermediate to tedizolid **37** under DAST activation saw some unreacted acetate intermediate, but using TFAA/TMSOTf activation, all hydroxylated intermediates were activated and successfully converted to methylated **38** in 44% yield (Figure 20A). Comparing with **32a**, the more sterically hindered β position in this case likely prevented undesired elimination pathway. Methylation at this position in a D5D inhibitor with a similar oxazolidinone core had been demonstrated to result in a 9-fold boost in potency (vide supra, Figure 14),[54f] which makes this methylation especially interesting, as the bioactivity of methylated tedizolid had never been reported.

Lower solubility was observed for tedizolid acetate in acetonitrile. However, solubility significantly increased after doping the solvent with acetic acid. Impressively, with only minimal changes to the reaction conditions, oxidation with (*S*,*S*)-**26** rendered approximately 53% of hydroxylated intermediates without needing to protect the mildly basic pyridine nitrogen, and subsequent methylation gave an overall 40% yield and very similar mass balance as the tedizolid precursor **37** (Figure 20B). Subsequent treatment of sodium hydroxide easily unmasked the acetate to produce methylated tedizolid **41** in 92% yield. Comparatively, fluorination gave only 6% methylation with significant elimination, likely due to the basicity of pyridine, and BF_3 activation caused substrate decomposition. These examples again highlight the strong chemoselectivity of **26** and the advantage of having multiple activation modes for expanding the scope of methylation.

3.2.4 Expansion of the Methylation Scope

Although this method was mainly developed for methylation alpha to heteroatoms through iminium and oxonium intermediates, the substrate scope could be further expanded with minor tuning of reaction conditions. A sphingosine-1-phosphate receptor ($S1P_1$) agonist had seen a 2135-fold potency boost when three methyl groups were introduced on its benzylic position and on the aromatic ring (vide supra, Figure 14).[54e] With the lowered catalyst loading, the mild basicity and high electron density of aniline were tolerated by **26**. Oxidation of the $S1P_1$ antagonist methyl ester **42** gave approximately 30% of the imine intermediate without acid protection. However, imines are significantly less electrophilic than iminium and attempts to methylate with trimethylaluminum did not produce any desired product. Conversely, although methyl Grignard was ineffective in methylating hemiaminals, its strong nucleophilicity enabled addition to the imine activated by TMSOTf to give **43**, methylating at the same position where the "magic methyl" effect was observed (Figure 21).

Figure 21. Late-Stage Methylation of $S1P_1$ Antagonist **42**

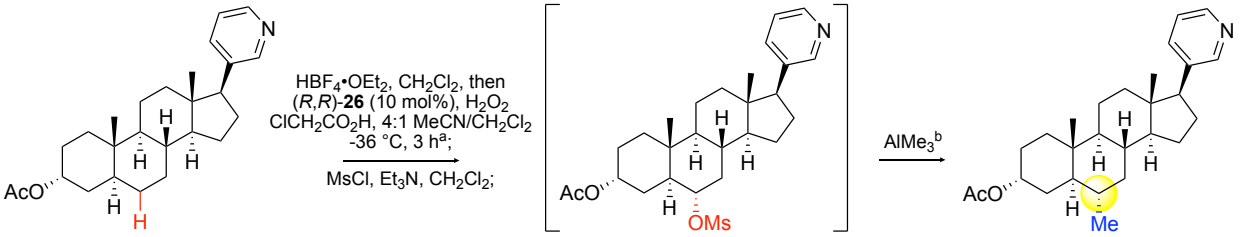


Oxidation intermediates isolated before methylation. TMSOTf (1.2 equiv.), 0 °C, 1 h, then MeMgBr (3.0 equiv.) –78 °C, 4 h, repeated once.

In addition to alpha oxidation, $Mn(CF_3PDP)$ **26** can effectively hydroxylate methylene C–H bonds at higher loadings.[59] For example, the abiraterone analogue **13** discussed in chapter 1 was selectively oxidized at C6 in approximately 32% yield (with 16% overoxidized ketone) in one step without the need to recycle the recovered starting material.[13] Although the ionization with BF_3 or nucleophilic displacement of a fluorine is difficult for the resulting aliphatic alcohols,

mesylates of such secondary alcohols are stable against elimination and can be activated by the Lewis acidic trimethylaluminum to effect methylation.[69]

Figure 22. Late-Stage Methylation of Abiraterone Analogue (+)-**13**



[a]Oxidation intermediates isolated before methylation. [b]MsCl and Et_3N added, rt, 1 h; $NaHCO_3$ wash, dried, condensed; redissolved in CH_2Cl_2, $AlMe_3$, –78 °C, stirred 2 h; then rt, 1 h.

By replacing fluorination with mesylation, abiraterone analogue **13** was successfully oxidized in its HBF_4 salt form and methylated at C6 in 15% yield to produce **44** as a single observed diastereomer (Figure 22). Consistent with literature reports,[69] the stereoretentive conversion from hydroxyl to methyl indicates the conversion likely went through a carbocation intermediate. To the best of our knowledge, this is the first example of remote C–H methylation at an unactivated C(sp^3)–H bond. This reaction further underscores the importance of developing catalysts that can control the oxidation to stop at the alcohol stage.

3.3 Conclusion

A highly site-selective and chemoselective C–H hydroxylation coupled to a set of Lewis acid/fluorine activation modes effecting methylation has enabled a general method for installing methyl groups directly into the hydrocarbon cores of complex, bioactive molecules. This transformation is of significant medicinal interest, and will likely facilitate the discovery of new medications by reducing time and cost in derivatizing lead compounds in search for higher potency and new biological activities.[70] We anticipate that the accelerated access to methylated

compounds made possible by this method will also empower a broader interrogation of the "magic methyl" effect on the biological activity of small molecules in pursuit of novel, affordable therapeutics.

3.4 Experimental Section

3.4.1 General Methods

Experimental. All C–H oxidations were run under air with no precautions taken to exclude moisture. All other reactions were run under nitrogen atmosphere with dry solvent in flame-dried glassware unless otherwise noted. Dry solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), dimethylsulfoxide (DMSO), and acetonitrile (MeCN) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, CA). Commercially available reagents that were used as received are noted in the individual reaction procedures. Trimethylaluminum ($AlMe_3$), DAST, TFAA, and BF_3•OEt_2 were purchased from Millipore-Sigma. TMSOTf was purchased from Oakwood Chemical. (*R,R*)- and (*S,S*)-Fe(PDP) **1**[5b], Fe(CF_3PDP) **2**[5c], Mn(CF_3PDP) **26**[59], Mn(PDP)[62b], and Mn(PDP)$(OTf)_2$[62a] were prepared according to literature procedures and stored in the fridge. Prior to use, catalysts were warmed to room temperature and weighed out in air. Thin-layer chromatography (TLC) was conducted with E. Merck TLC silica gel 60 F_{254} pre-coated plates (0.25 mm) or E. Merck TLC aluminum oxide 60 F_{254}, basic, pre-coated glass backed plates. Visualization was conducted with UV, CAM stain, and potassium permanganate ($KMnO_4$) stain. Flash chromatography was performed using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.) or basic aluminum oxide, Brockmann grade III (6% H_2O added to Brockmann grade I) prepared from Alfa Aesar aluminum oxide, activated, basic, Brockmann grade I, 58 angstroms,

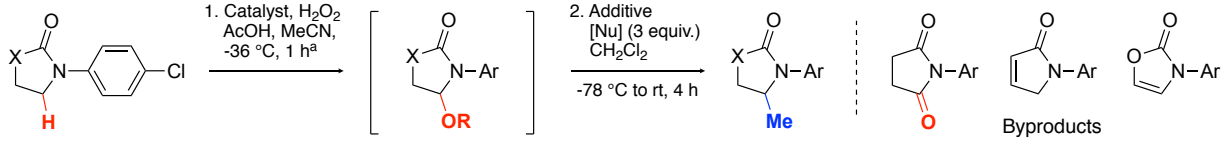
60 mesh power, S.A. 150m^2/g, CAS: 1344-28-1. Medium pressure liquid chromatography was performed on a Teledyne Isco CombiFlash Rf machine using pre-packed RediSep columns.

Structural analysis. ^{1}H-NMR spectra were recorded on a Varian Unity Inova 400 (400 MHz), Varian VXR 500 (500 MHz), Varian Unity 500 (500 MHz), or Carver-Bruker 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, hept = septet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Unity 500 (125 MHz) or Carver-Bruker 500 (125MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). ^{19}F spectra were recorded on a Varian Unity-500 (470 MHz), Varian Unity-500 (470 MHz) or Carver-Bruker 500 (470 MHz) and are reported in ppm using $FCCl_3$ (0 ppm) as an external standard. Labeled solvent impurities were calculated out when reporting isolated yields. High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof μLtima spectrometer.

3.4.2 Extended Reaction Optimization and Characterization

For better clarity, the reaction development and optimization were abbreviated as Table 7 in section 3.4.1. The complete optimization data are presented here as Table 8 (optimization of oxidation and methylation conditions), Table 7B (on rate of the oxidation), and Table 9 (study on methylation efficiency with a focus on the equivalence of activator and trimethylaluminum). The synthesis of starting materials and characterization of both starting materials and products are listed collectively at the end of this section.

Table 8. Development of Mn(CF_3PDP) **26**-Mediated Oxidative Methylation



27, X = CH_2; **31a**, X = O — **29a (OH)**, R = H; **29a (OAc)**, R = Ac, X = CH_2; **S24**, R = H; **S25**, R = Ac, X = O — **28**, X = CH_2; **32a**, X = O — **29b** — **30** — **S26**

Entry	Substrate	Catalyst	Loading (mol%)	Additive	[Nu]	**29a (OH)**/ **S24** (%)	**29a (OAc)**/ **S25** (%)	**28**/**32a** (%)	**29b** (%)	**30**/**S26** (%)	rsm (%)
1[b]	**27**	Fe(PDP) **1**	3x5	—	—	<5[j]	0	—	<5[j]	—	0
2[b]	**27**	Fe(CF_3PDP) **2**	3x5	—	—	8[j]	0	—	6[j]	—	0
3[c]	**27**	Mn(PDP)($OTf)_2$	1	—	—	12	0	—	0	—	75
4	**27**	Mn(PDP)($SbF_6)_2$	1	—	—	28	7	—	<5[j]	—	35
5[d]	**27**	Mn(CF_3PDP) **26**	10	—	—	13[j]	10	—	41	—	0
6	**27**	**26**	1	—	—	51	21	—	9	—	0
7	**27**	**26**	0.5	—	—	64	18	—	<5[j]	—	4
8[e]	**27**	**26**	0.5	BF_3•OEt_2	$AlMe_3$	<5[j]	0	63	<5[j]	0	11
9[e]	**31a**	**26**	0.5	BF_3•OEt_2	$AlMe_3$	11	5	10	—	4	27
10[f]	**31a**	**26**	0.5	DAST	$AlMe_3$	0	14[j]	55	—	0	16
11[f]	**27**	**26**	0.5	DAST	$AlMe_3$	0	0	64	<5[j]	0	12
12[f]	**27**	**26**	0.5	Deoxo-Fluor	$AlMe_3$	0	0	61	6	0	5
13[g]	**27**	**26**	0.5	TFAA/TMSOTf	$AlMe_3$	0	0	51	<5[j]	14	9
14[g]	**31a**	**26**	0.5	TFAA/TMSOTf	$AlMe_3$	0	0	46	—	20	13
15[h]	**27**	**26**	0.5	MsCl/Et_3N	$AlMe_3$	15	0	0	<5[j]	39	6
16[f]	**27**	**26**	0.5	DAST	$ZnMe_2$	17	9	0	11	0	14
17[f,i]	**27**	**26**	0.5	DAST	MeMgBr	24	<5[j]	24	<5[j]	0	9

[a]General oxidation (unless otherwise noted): **27** (0.3 mmol), catalyst (x mol%), (*R,R*) and (*S,S*) enantiomers used interchangeably), AcOH (15 equiv.), MeCN (0.5 M), -36 °C; H_2O_2 (2 equiv.) in MeCN (3.75 ml) syringe pump 1 h. Mixture passed through silica plug, EtOAc flush, concentrated before isolation or methylation. Isolated yields are based on the average of three experiments, unless otherwise noted. [b]Procedure from ref. 61. [c]Procedure from ref. 62a. [d]5 equiv. H_2O_2. [e]General BF_3-assisted alkylation: crude in CH_2Cl_2 (0.2 M), -78 °C, $AlMe_3$ (3 equiv.) and BF_3•OEt_2 (2 equiv.) sequentially added, stirred 1 h; room temperature (rt) for 3 h. [f]General fluorine-assisted alkylation: crude in CH_2Cl_2 (0.2 M), fluorine additive (1 equiv.) added at -78 °C; rt for 1 h; cooled to -78 °C, nucleophile (3 equiv.) added, stirred 2 h; rt for 1 h. [g]General TFAA/TMSOTf-assisted alkylation: crude in CH_2Cl_2 (0.2 M), TFAA (1 equiv.) added, stirred 1 h; cooled to -78 °C, $AlMe_3$ (3 equiv.) and TMSOTf (1 equiv.) sequentially added, stirred 2 h; rt for 1 h. [h]Crude in CH_2Cl_2 (0.2 M), MsCl (1 equiv.) and Et_3N (1 equiv.) added, stirred 1 h; washed $NaHCO_3$, dried, reduced; redissolved in CH_2Cl_2, $AlMe_3$ (3 equiv.) added at -78 °C, stirred 2 h; rt for 1 h. [i]MeMgBr (3 equiv.) added at -78 °C, stirred 3 h. [j]Yield determined by crude ^1H NMR.

Procedure A for reaction optimization studies (substrate oxidation). In a 40 mL vial the starting material (0.30 mmol, 1.0 equiv.) and the catalyst ((*R,R*)- and (*S,S*)-enantiomers were used interchangeably for achiral substrates) were dissolved in MeCN (0.6 mL, 0.50 M). AcOH (256 µL, 4.50 mmol, 15.0 equiv.) was then added. A 10 mL syringe was charged with a solution of H_2O_2 (34.3 µL, 0.60 mmol, 2.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.16 M), and fitted with a 25G needle. The vial was sealed with a screw cap fitted with a PTFE/Silicone septum and cooled to -36 °C with a 1,2-DCE/dry ice bath. The H_2O_2 solution was added into the stirring reaction mixture via a syringe pump at 3.75 mL/h. Upon completion, the reaction

mixture was added via syringe onto a 15 mL silica plug and allowed to sit for 5 min to ensure complete H_2O_2 consumption. EtOAc (150 mL) was then allowed to pass through the silica plug. The resulting solution was condensed under vacuum and purified by flash chromatography (50 mL silica, 20%→30%→40%→50%→75% EtOAc/Hex).

Procedure B for reaction optimization studies (BF_3-assisted methylation). The starting material was oxidized according to procedure A for reaction optimization studies. Upon passing through the silica plug, the resulting solution was condensed and transferred into a 25 mL recovery flask. The solvents were removed through rotary evaporation, and the residual acetic acid was removed under vacuum overnight. The crude was backfilled with nitrogen 3x, redissolved in CH_2Cl_2 (1.5 mL), and cooled to -78 °C with an acetone/dry ice bath. Trimethylaluminum (2 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was added dropwise, followed by boron trifluoride diethyl ether complex (74.1 μL, 0.60 mmol, 2.0 equiv.). The mixture was stirred at -78 °C for 1 h, then allowed to gradually warm up while further stirring for 3 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 and poured into a 60 mL separatory funnel with 5 mL 1 M NaOH. The aqueous layer was extracted with CH_2Cl_2 twice and the organic layers were combined, dried over $MgSO_4$, filtered, condensed, and purified by flash chromatography (50 mL silica, 10%→20%→30% EtOAc/Hex).

Procedure C for reaction optimization studies (fluorine-assisted methylation). The starting material was oxidized according to procedure A for reaction optimization studies. Upon passing through the silica plug, the resulting solution was condensed and transferred into a 25 mL recovery flask. The solvents were removed through rotary evaporation, and the residual acetic acid was removed under vacuum overnight. The crude was backfilled with nitrogen 3x, redissolved in CH_2Cl_2 (1.5 mL), and cooled to -78 °C with an acetone/dry ice bath. The

fluorinating reagent (0.30 mmol, 1.0 equiv.) was added, and the reaction was allowed to warm up to room temperature while stirring for 1 h. The flask was then again placed in -78 °C cold bath, and trimethylaluminum (2 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was added dropwise. The mixture was stirred at -78 °C for 2 h, then allowed to gradually warm up while further stirring for 1 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 and poured into a 60 mL separatory funnel with 5 mL 1 M NaOH. The aqueous layer was extracted with CH_2Cl_2 twice and the organic layers were combined, dried over $MgSO_4$, filtered, condensed, and purified by flash chromatography (50 mL silica, 10%→20%→30% EtOAc/Hex).

Entry 1. According to literature[61], **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) in a 40 mL vial was dissolved in MeCN (0.6 mL). The vial was placed into an ice bath and allowed to stir for 30 s, and AcOH (8.6 μL, 0.15 mmol, 0.5 equiv.) was added, followed by a solution of Fe(PDP) (14.0 mg, 0.015 mmol, 0.05 equiv.) in MeCN (0.3 mL). A solution of H_2O_2 (35.0 μL, 0.57 mmol, 1.9 equiv., 50 wt.% in H_2O) in MeCN (4.5 mL) at 0 °C was added dropwise via a pipet to the stirring solution over 2-3 minutes. After 10 min, a second portion of AcOH and Fe(PDP) were added to the reaction mixture, followed by the dropwise addition of a second portion of H_2O_2 solution in MeCN as described above. After an additional 10 minutes, a third portion of Fe(PDP) and AcOH dissolved in MeCN were added followed by the dropwise addition of a third portion of H_2O_2 solution in MeCN as described above. The reaction solution was stirred for 10 minutes after the last iterative addition, for a total reaction time of approximately 36 minutes. Upon completion, the reaction mixture was added via syringe onto a 15 mL silica plug and allowed to sit for 5 min to ensure complete H_2O_2 consumption. EtOAc (150 mL) was then allowed to pass through the silica plug. The resulting solution was condensed under vacuum.

Run 1 (trace **29a (OH)** by ^{1}H NMR; trace **29b** by ^{1}H NMR; 0% rsm)

Run 2 (trace **29a (OH)** by ^{1}H NMR; trace **29b** by ^{1}H NMR; 0% rsm)

Run 3 (trace **29a (OH)** by ^{1}H NMR; trace **29b** by ^{1}H NMR; 0% rsm)

Average overall yield: trace 29a (OH); trace 29b; 0% rsm

Entry 2. According to literature[61], **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) in a 40 mL vial was dissolved in MeCN (0.6 mL). The vial was placed into an ice bath and allowed to stir for 30 s, and AcOH (8.6 μL, 0.15 mmol, 0.5 equiv.) was added, followed by a solution of Fe(CF_3PDP) (20.3 mg, 0.015 mmol, 0.05 equiv.) in MeCN (0.3 mL). A solution of H_2O_2 (35.0 μL, 0.57 mmol, 1.9 equiv., 50 wt.% in H_2O) in MeCN (4.5 mL) at 0 °C was added dropwise via a pipet to the stirring solution over 2-3 minutes. After 10 min, a second portion of AcOH and Fe(CF_3PDP) were added to the reaction mixture, followed by the dropwise addition of a second portion of H_2O_2 solution in MeCN as described above. After an additional 10 minutes, a third portion of Fe(CF_3PDP) and AcOH dissolved in MeCN were added followed by the dropwise addition of a third portion of H_2O_2 solution in MeCN as described above. The reaction solution was stirred for 10 minutes after the last iterative addition, for a total reaction time of approximately 36 minutes. Upon completion, the reaction mixture was added via syringe onto a 15 mL silica plug and allowed to sit for 5 min to ensure complete H_2O_2 consumption. EtOAc (150 mL) was then allowed to pass through the silica plug. The resulting solution was condensed under vacuum.

Run 1 (8% **29a (OH)** by ^{1}H NMR; 6% **29b** by ^{1}H NMR; 0% rsm)

Run 2 (7% **29a (OH)** by ^{1}H NMR; 6% **29b** by ^{1}H NMR; 0% rsm)

Run 3 (10% **29a (OH)** by ^{1}H NMR; 6% **29b** by ^{1}H NMR; 0% rsm)

Average overall yield: 8% 29a (OH); 6% 29b; 0% rsm

Entry 3. According to literature[62a], **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) and $Mn(PDP)(OTf)_2$ (2.0 mg, 0.003 mmol, 0.01 equiv.) were dissolved in MeCN (1.2 mL, 0.25 M). AcOH (223 μL, 3.90 mmol, 13.0 equiv.) was then added. A 10 mL syringe was charged with a solution of H_2O_2 (60.1 μL, 1.05 mmol, 3.5 equiv., 30 wt.% in H_2O) in MeCN (0.7 mL, 1.5 M), and fitted with a 25G needle. The vial was sealed with a screw cap fitted with a PTFE/Silicone septum and cooled to -40 °C with an acetonitrile/dry ice bath. The H_2O_2 solution was added into the stirring reaction mixture via a syringe pump at 1.40 mL/h. Upon completion, the reaction mixture was added via syringe onto a 15 mL silica plug. EtOAc (150 mL) was then allowed to pass through the silica plug. The resulting solution was condensed under vacuum and purified by flash chromatography (50 mL silica, 10%→20%→30% EtOAc/Hex).

Run 1 (6.6 mg, 0.031 mmol, 10% **29a (OH)**; 41.6 mg, 0.213 mmol, 71% rsm)

Run 2 (9.4 mg, 0.044 mmol, 15% **29a (OH)**; 47.0 mg, 0.240 mmol, 80% rsm)

Run 3 (7.7 mg, 0.036 mmol, 12% **29a (OH)**; 44.3 mg, 0.227 mmol, 75% rsm)

Average overall yield: 12% 29a (OH); 75% rsm

Entry 4. According to procedure A for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(PDP)(MeCN)_2(SbF_6)_2$ (2.8 mg, 0.003 mmol, 0.01 equiv.).

Run 1 (20.2 mg, 0.0954 mmol, 32% **29a (OH)**; 2.5 mg, 0.0099 mmol, 3% **29a (OAc)**; trace **29b** by ^1H NMR; 17.7 mg, 0.0906 mmol, 30% rsm)

Run 2 (19.0 mg, 0.0817 mmol, 27% **29a (OH)**; 7.4 mg, 0.029 mmol, 10% **29a (OAc)**; trace **29b** by ^1H NMR; 19.1 mg, 0.0976 mmol, 33% rsm)

Run 3 (16.7 mg, 0.0787 mmol, 26% **29a (OH)**; 5.1 mg, 0.020 mmol, 7% **29a (OAc)**; trace **29b** by ^{1}H NMR; 25.0 mg, 0.128 mmol, 43% rsm)

Average overall yield: 28% 29a (OH); 7% 29a (OAc); trace 29b; 35% rsm

Entry 5. According to procedure A for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF6)_2$ (40.7 mg, 0.03 mmol, 0.1 equiv.) and H_2O_2 (85.8 μL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O).

Run 1 (16% **29a (OH)** by ^{1}H NMR; 7.9 mg, 0.031 mmol, 10% **29a (OAc)**; 23.7 mg, 0.118 mmol, 39% **29b**; 0% rsm)

Run 2 (10% **29a (OH)** by ^{1}H NMR; 7.7 mg, 0.030 mmol, 10% **29a (OAc)**; 26.6 mg, 0.127 mmol, 42% **29b**; 0% rsm)

Average overall yield: 13% 29a (OH); 10% 29a (OAc); 41% 29b; 0% rsm

Entry 6. According to procedure A for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF_6)_2$ (4.1 mg, 0.003 mmol, 0.01 equiv.).

Run 1 (31.9 mg, 0.151 mmol, 50% **29a (OH)**; 14.3 mg, 0.0564 mmol, 19% **29a (OAc)**; 9.7 mg, 0.038 mmol, 13% **29b**; 0% rsm)

Run 2 (33.9 mg, 0.160 mmol, 53% **29a (OH)**; 19.2 mg, 0.0755 mmol, 25% **29a (OAc)**; 5.7 mg, 0.0272 mmol, 9% **29b**; 0% rsm)

Run 3 (31.3 mg, 0.148 mmol, 49% **29a (OH)**; 14.6 mg, 0.0574 mmol, 19% **29a (OAc)**; 3.2 mg, 0.015 mmol, 5% **29b**; 0% rsm)

Average overall yield: 51% 29a (OH); 21% 29a (OAc); 9% 29b; 0% rsm

Entry 7. According to procedure A for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF_6)_2$ (2.0 mg, 0.0015 mmol, 0.005 equiv.).

Run 1 (39.0 mg, 0.184 mmol, 61% **29a (OH)**; 17.2 mg, 0.0681 mmol, 23% **29a (OAc)**; trace **29b** by ^{1}H NMR; 2.7 mg, 0.014 mmol, 5% rsm)

Run 2 (42.2 mg, 0.199 mmol, 66% **29a (OH)**; 13.0 mg, 0.0513 mmol, 17% **29a (OAc)**; trace **29b** by ^{1}H NMR; 4.7 mg, 0.024 mmol, 8% rsm)

Run 3 (41.5 mg, 0.196 mmol, 66% **29a (OH)**; 11.5 mg, 0.0543 mmol, 15% **29a (OAc)**; trace **29b** by ^{1}H NMR; 0% rsm)

Average overall yield: 64% 29a (OH); 18% 29a (OAc); trace 29b; 4% rsm

Entry 8. According to procedure B for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was methylated using BF_3•OEt_2 and $AlMe_3$ as described.

Run 1 (trace **29a (OH)** by ^{1}H NMR; 37.2 mg, 0.177 mmol, 59% **28**; trace **29b** by ^{1}H NMR; 9.9 mg, 0.051 mmol, 17% rsm)

Run 2 (41.8 mg, 0.199 mmol, 66% **28**; trace **29b** by ^{1}H NMR; 4.1 mg, 0.021 mmol, 7% rsm)

Run 3 (41.2 mg, 0.196 mmol, 65% **28**; trace **29b** by ^{1}H NMR; 5.3 mg, 0.027 mmol, 9% rsm)

Average overall yield: trace 29a (OH); 63% of 28; trace 29b; 11% rsm

Entry 9. According to procedure B for optimization studies, **31a** (59.3 mg, 0.30 mmol, 1.0 equiv.) was methylated using BF_3•OEt_2 and $AlMe_3$ as described.

Run 1 (3.5 mg, 0.015 mmol, 5% **S24**; 6.6 mg, 0.026 mmol, 9% **S25**; 6.2 mg, 0.029 mmol, 10% **32a**; 3.3 mg, 0.017 mmol, 6% **S26**; 14.0 mg, 0.0708 mmol, 24% rsm)

Run 2 (10.9 mg, 0.0510 mmol, 17% **S24**; 0.8 mg, 0.003 mmol, 1% **S25**; 6.1 mg, 0.029 mmol, 10% **32a**; 1.7 mg, 0.0087 mmol, 3% **S26**; 18.3 mg, 0.0925 mmol, 31% rsm)

Run 3 (6.3 mg, 0.029 mmol, 10% **S24**; 3.8 mg, 0.015 mmol, 5% **S25**; 7.2 mg, 0.034 mmol, 11% **32a**; 1.6 mg, 0.0082 mmol, 3% **S26**; 15.3 mg, 0.0774 mmol, 26% rsm)

Average overall yield: 11% S24; 5% S25; 10% 32a, 4% S26; 27% rsm

Entry 10. According to procedure C for optimization studies, **31a** (59.3 mg, 0.30 mmol, 1.0 equiv.) was methylated using DAST (39.6 μL, 0.30 mmol, 1.0 equiv.) and $AlMe_3$ as described.

Run 1 (14% **S25** by ^1H NMR; 35.9 mg, 0.170 mmol, 57% **32a**; 6.0 mg, 0.030 mmol, 10% rsm)

Run 2 (17% **S25** by ^1H NMR; 35.3 mg, 0.167 mmol, 56% **32a**; 6.6 mg, 0.033 mmol, 11% rsm)

Run 3 (10% **S25** by ^1H NMR; 33.2 mg, 0.157 mmol, 52% **32a**; 15.8 mg, 0.0800 mmol, 27% rsm)

Average overall yield: 14% S25; 55% 32a; 16% rsm

Entry 11. According to procedure C for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was methylated using DAST (39.6 μL, 0.30 mmol, 1.0 equiv.) and $AlMe_3$ as described.

Run 1 (38.3 mg, 0.183 mmol, 61% **28**; trace **29b** by ^1H NMR; 7.2 mg, 0.037 mmol, 12% rsm)

Run 2 (42.1 mg, 0.201 mmol, 67% **28**; trace **29b** by ^1H NMR; 4.1 mg, 0.021 mmol, 7% rsm)

Run 3 (39.9 mg, 0.190 mmol, 63% **28**; trace **29b** by ^1H NMR; 10.0 mg, 0.0511 mmol, 17% rsm)

Average overall yield: 64% of 28; trace 29b; 12% rsm

Entry 12. According to procedure C for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was methylated using Deoxo-Fluor (55.3 μL, 0.30 mmol, 1.0 equiv.) and $AlMe_3$ as described.

Run 1 (38.2 mg, 0.182 mmol, 61% **28**; 7.6 mg, 0.036 mmol, 12% **29b** by ^{1}H NMR; 0% rsm)

Run 2 (38.7 mg, 0.185 mmol, 62% **28**; 1.8 mg, 0.0086 mmol, 3% **29b**; 2.8 mg, 0.014 mmol, 5% rsm)

Run 3 (38.6 mg, 0.184 mmol, 61% **28**; 1.3 mg, 0.0060 mmol, 2% **29b**; 5.3 mg, 0.027 mmol, 9% rsm)

Average overall yield: 61% of 3, 6% 29b, 5% rsm

Entry 13. According to a modified procedure C for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF_6)_2$ (2.0 mg, 0.0015 mmol, 0.005 equiv.) and worked up as described. The crude was backfilled with nitrogen 3x and redissolved in CH_2Cl_2 (1.5 mL). Trifluoroacetic anhydride (41.7 μL, 0.3 mmol, 1.0 equiv.) was added at room temperature, and the reaction was stirred for 1 h. The reaction flask was then placed in a -78 °C acetone/dry ice bath, and trimethylaluminum (2 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was added dropwise, followed by TMSOTf (54.3 μL, 0.30 mmol, 1.0 equiv.). The mixture was stirred at -78 °C for 2 h, then allowed to gradually warm up while further stirring for 1 h before quenching as described.

Run 1 (32.0 mg, 0.153 mmol, 51% **28**; trace **29b** by ^{1}H NMR; 9.5 mg, 0.049 mmol, 16% **30**; 4.3 mg, 0.022 mmol, 7% rsm)

Run 2 (34.2 mg, 0.163 mmol, 54% **28**; trace **29b** by ^{1}H NMR; 7.6 mg, 0.039 mmol, 13% **30**; 7.1 mg, 0.036 mmol, 11% rsm)

Run 3 (31.0 mg, 0.148 mmol, 49% **28**; trace **29b** by ^{1}H NMR; 7.0 mg, 0.036 mmol, 12% **30**; 4.7 mg, 0.024 mmol, 8% rsm)

Average overall yield: 51% of 28; trace 29b; 14% 30; 9% rsm

Entry 14. According to a modified procedure C for optimization studies, **31a** (59.3 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF_6)_2$ (2.0 mg, 0.0015 mmol, 0.005 equiv.) and worked up as described. The crude was backfilled with nitrogen 3x and redissolved in CH_2Cl_2 (1.5 mL). Trifluoroacetic anhydride (41.7 μL, 0.3 mmol, 1.0 equiv.) was added at room temperature, and the reaction was stirred for 1 h. The reaction flask was then placed in a -78 °C acetone/dry ice bath, and trimethylaluminum (2 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was added dropwise, followed by TMSOTf (54.3 μL, 0.30 mmol, 1.0 equiv.). The mixture was stirred at -78 °C for 2 h, then allowed to gradually warm up while further stirring for 1 h before quenching as described.

Run 1 (26.8 mg, 0.127 mmol, 42% **32a**; 9.7 mg, 0.050 mmol, 17% **S26**; 9.6 mg, 0.049 mmol, 16% rsm)

Run 2 (28.1 mg, 0.133 mmol, 44% **32a**; 11.5 mg, 0.0588 mmol, 20% **S26**; 5.4 mg, 0.027 mmol, 9% rsm)

Run 3 (33.1 mg, 0.156 mmol, 52% **32a**; 14.2 mg, 0.0726 mmol, 24% **S26**; 7.3 mg, 0.044 mmol, 15% rsm)

Average overall yield: 46% of 32a; 20% S26; 13% rsm

Entry 15. According to a modified procedure C for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF6)_2$ (2.0 mg, 0.0015 mmol, 0.005 equiv.) and worked up as described. The crude was backfilled with nitrogen 3x and redissolved in CH_2Cl_2 (1.5 mL). MsCl (23.2 μL, 0.3 mmol, 1.0 equiv.) and Et_3N (41.8 μL, 0.3 mmol, 1.0 equiv.) were added at room temperature, and the reaction was stirred for 1 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, and poured into a 60 mL separatory

funnel containing 5 mL $NaHCO_3$. The aqueous layer was extracted with 5 mL CH_2Cl_2 2x, and the organic layers were combined, dried over MgSO4, condensed under vacuum, and transferred back into the 25 mL recovery flask. The crude was backfilled with N2 3x and 1.5 mL CH_2Cl_2 was added. The reaction flask was then placed in a -78 °C acetone/dry ice bath, and trimethylaluminum (2 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was added dropwise. The mixture was stirred at -78 °C for 2 h, then allowed to gradually warm up while further stirring for 1 h before quenching as described.

Run 1 (11.4 mg, 0.0539 mmol, 18% **29a (OH)**; trace **29b** by ^{1}H NMR; 19.7 mg, 0.102 mmol, 34% **30**; 1.6 mg, 0.0082 mmol, 3% rsm)

Run 2 (12.1 mg, 0.0575 mmol, 19% **29a (OH)**; trace **29b** by ^{1}H NMR; 23.4 mg, 0.121 mmol, 40% **30**; 2.5 mg, 0.013 mmol, 4% rsm)

Run 3 (4.5 mg, 0.021 mmol, 7% **29a (OH)**; trace **29b** by ^{1}H NMR; 24.6 mg, 0.127 mmol, 42% **30**; 7.1 mg, 0.036 mmol, 12% rsm)

Average overall yield: 15% 29a (OH); trace 29b; 39% 30; 6% rsm

Entry 16. According to a modified procedure C for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF_6)_2$ (2.0 mg, 0.0015 mmol, 0.005 equiv.) and worked up as described. The crude was backfilled with nitrogen 3x, redissolved in CH_2Cl_2 (1.5 mL), and cooled to -78 °C with an acetone/dry ice bath. DAST (39.6 μL, 0.30 mmol, 1.0 equiv.) was added, and the reaction was allowed to warm up to room temperature while stirring for 1 h. The flask was then again placed in -78 °C cold bath, and dimethylzinc (2 M in toluene, 450 μL, 0.90 mmol, 3.0 equiv.) was added dropwise. The mixture

was stirred at -78 °C for 2 h, then allowed to gradually warm up while further stirring for 1 h before quenching as described.

Run 1 (5.6 mg, 0.026 mmol, 9% **29a (OH)**; 3.0 mg, 0.0018 mmol, 4% **29a (OAc)**; trace **29b** by ^{1}H NMR; 14.6 mg, 0.0745 mmol, 25% rsm)

Run 2 (15.3 mg, 0.0725 mmol, 24% **29a (OH)**; 6.9 mg, 0.027 mmol, 9% **29a (OAc)**; 10.8 mg, 0.0513 mmol, 17% **29b**; 0% rsm)

Run 3 (10.9 mg, 0.0513 mmol, 17% **29a (OH)**; 10.0 mg, 0.0393 mmol, 13% **29a (OAc)**; trace **3** by ^{1}H NMR; 10.8 mg, 0.0513 mmol, 17% **29b**; 10.6 mg, 0.0542 mmol, 18% rsm)

Average overall yield: 17% 29a (OH); 9% 29a (OAc); 11% 29b; 14% rsm

Entry 17. According to a modified procedure C for optimization studies, **27** (58.7 mg, 0.30 mmol, 1.0 equiv.) was oxidized using $Mn(CF_3PDP)(MeCN)_2(SbF_6)_2$ (2.0 mg, 0.0015 mmol, 0.005 equiv.) and worked up as described. The crude was backfilled with nitrogen 3x, redissolved in CH_2Cl_2 (1.5 mL), and cooled to -78 °C with an acetone/dry ice bath. DAST (39.6 μL, 0.30 mmol, 1.0 equiv.) was added, and the reaction was allowed to warm up to room temperature while stirring for 1 h. The flask was then again placed in -78 °C cold bath, and MeMgBr (3 M in THF, 300 μL, 0.90 mmol, 3.0 equiv.) was added dropwise. The mixture was stirred at -78 °C for 3 h, then directly quenched with 1 M HCl (3 mL) without warming up.

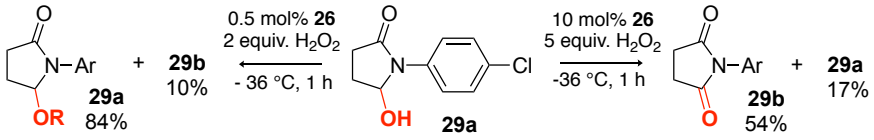
Run 1 (17.8 mg, 0.0841 mmol, 28% **29a (OH)**; trace **29a (OAc)** by ^{1}H NMR; 14.9 mg, 0.0709 mmol, 24% **28;** trace **29b** by ^{1}H NMR; 1.8 mg, 0.0092 mmol, 3% rsm)

Run 2 (22.0 mg, 0.104 mmol, 35% **29a (OH)**; trace **29a (OAc)** by ^{1}H NMR; 16.3 mg, 0.0776 mmol, 26% **28;** trace **29b** by ^{1}H NMR; 7.6 mg, 0.039 mmol, 13% rsm)

Run 3 (5.4 mg, 0.026 mmol, 9% **29a (OH)**; 4.5 mg, 0.018 mmol, 6% **29a (OAc)**; 13.9 mg, 0.0664 mmol, 22% **28;** trace **29b** by ^{1}H NMR; 10.0 mg, 0.0511 mmol, 10% rsm)

Average overall yield: 24% 29a (OH); trace 29a (OAc); 24% of 28; trace 29b; 9% rsm

On the conversion of hemiaminal acetate: the hemiaminal acetate of lactam **29** and other heterocyclic cores have been observed to react with BF_3 and DAST to furnish methylated products; however, with carbamate substrates like **31a**, hemiaminal acetates do not react effectively (Table 8, entry 10, 14% **S25**).



Oxidation of **29a (OH)** (42.3 mg, 0.20 mmol, 1.0 equiv.) with 0.5 mol% **26** and 2 equiv. H_2O_2:

Run 1 (4.8 mg, 0.023 mmol, 11% **29b**; 5.5 mg, 0.022 mmol, 11% **29a (OAc)**; 29.7 mg, 0.140 mmol, 70% rsm **29a (OH)**)

Run 2 (3.8 mg, 0.018 mmol, 9% **29b**; 7.6 mg, 0.030 mmol, 15% **29a (OAc)**; 30.3 mg, 0.143 mmol, 72% rsm **29a (OH)**)

Average yield: 10% imide 29b; 71% hemiaminal 29a (OH); 13% hemiaminal acetate 29a (OAc)

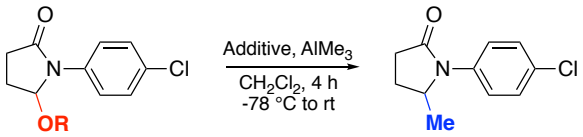
Oxidation of **29a (OH)** (42.3 mg, 0.20 mmol, 1.0 equiv.) with 10 mol% **26** and 5 equiv. H_2O_2:

Run 1 (21.4 mg, 0.102 mmol, 51% **29b**; 2.1 mg, 0.0082 mmol, 4% **29a (OAc)**; 13% rsm **29a (OH)** by ^{1}H NMR)

Run 2 (23.3 mg, 0.111 mmol, 56% **29b**; 4.2 mg, 0.017 mmol, 8% **29a (OAc)**; 9% rsm **29a (OH)** by ^{1}H NMR)

Average yield: 54% imide 29b; 11% hemiaminal 29a (OH); 6% hemiaminal acetate 29a (OAc)

Table 9. Methylation Efficiency Study



29a (OH), R = H
29a (OAc), R = Ac

28

Entry	Substrate	Additive (equiv.)	$AlMe_3$	**28** (%)	rsm (%)
1	**29a (OH)**	BF_3•OEt_2 (2)	3 equiv.	60	15
2	**29a (OH)**	BF_3•OEt_2 (3.3)	5 equiv.	64	11
3	**29a (OAc)**	BF_3•OEt_2 (2)	3 equiv.	86	0
4	**29a (OAc)**	BF_3•OEt_2 (3.3)	5 equiv.	92	0
5	**29a (OH)**	DAST (1)	3 equiv.	81	0
6	**29a (OH)**	DAST (1.7)	5 equiv.	87	0
7	**29a (OAc)**	DAST (1)	3 equiv.	78	0
8	**29a (OAc)**	DAST (1.7)	5 equiv.	85	0

Entry 1. According to general procedure B for optimization studies, **29a (OH)** (21.2 mg, 0.10 mmol, 1.0 equiv.) was methylated using BF_3• OEt_2 (24.7 µL, 0.20 mmol, 2.0 equiv.) and $AlMe_3$ (2 M, 150 µL, 0.30 mmol, 3.0 equiv.) as described. Starting material did not fully dissolve and likely contributed to lower conversion.

Run 1 (12.6 mg, 0.0601 mmol, 60% 3; 3.1 mg, 0.0146 mmol, 15% rsm)

Entry 2. According to general procedure B for optimization studies, assuming a 60% oxidation yield to mimic reagent equivalences for a one-pot procedure, **29a (OH)** (21.2 mg, 0.10 mmol, 1.0 equiv.) was methylated using BF_3•OEt_2 (40.7 µL, 0.33 mmol, 3.3 equiv.) and $AlMe_3$ (2 M, 250 µL, 0.50 mmol, 5.0 equiv.) in 0.5 mL CH_2Cl_2 as described. Starting material did not fully dissolve and likely contributed to lower conversion.

Run 1 (13.5 mg, 0.0644 mmol, 64% 3; 2.3 mg, 0.0108 mmol, 11% rsm)

Entry 3. According to general procedure B for optimization studies, **29a (OAc)** (25.4 mg, 0.10 mmol, 1.0 equiv.) was methylated using BF_3• OEt_2 (24.7 μL, 0.20 mmol, 2.0 equiv.) and $AlMe_3$ (2 M, 150 μL, 0.30 mmol, 3.0 equiv.) as described.

Run 1 (18.0 mg, 0.0858 mmol, 86% 3; 0% rsm)

Entry 4. According to general procedure B for optimization studies, assuming a 60% oxidation yield to mimic reagent equivalences for a one-pot procedure, **29a (OAc)** (25.4 mg, 0.10 mmol, 1.0 equiv.) was methylated using BF_3•OEt_2 (40.7 μL, 0.33 mmol, 3.3 equiv.) and $AlMe_3$ (2 M, 250 μL, 0.50 mmol, 5.0 equiv.) in 0.5 mL CH_2Cl_2 as described.

Run 1 (19.4 mg, 0.0924 mmol, 92% **3**; 0% rsm)

Entry 5. According to general procedure C for optimization studies, **29a (OH)** (21.2 mg, 0.10 mmol, 1.0 equiv.) was methylated using DAST (13.2 μL, 0.10 mmol, 1.0 equiv.) and $AlMe_3$ (2 M, 150 μL, 0.30 mmol, 3.0 equiv.) as described.

Run 1 (17.0 mg, 0.0811 mmol, 81% **3**; 0% rsm)

Entry 6. According to general procedure C for optimization studies, assuming a 60% oxidation yield to mimic reagent equivalences for a one-pot procedure, **29a (OH)** (21.2 mg, 0.10 mmol, 1.0 equiv.) was methylated using DAST (22.4 μL, 0.17 mmol, 1.7 equiv.) and $AlMe_3$ (2 M, 250 μL, 0.50 mmol, 5.0 equiv.) in 0.5 mL CH_2Cl_2 as described.

Run 1 (18.2 mg, 0.0868 mmol, 87% **3**; 0% rsm)

Entry 7. According to general procedure C for optimization studies, **29a (OAc)** (25.4 mg, 0.10 mmol, 1.0 equiv.) was methylated using DAST (13.2 μL, 0.10 mmol, 1.0 equiv.) and $AlMe_3$ (2 M, 150 μL, 0.30 mmol, 3.0 equiv.) as described.

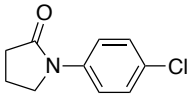
Run 1 (16.4 mg, 0.0782 mmol, 78% **3**; 0% rsm)

Entry 8. According to general procedure C for optimization studies, assuming a 60% oxidation yield to mimic reagent equivalences for a one-pot procedure, **29a (OAc)** (25.4 mg, 0.10 mmol, 1.0 equiv.) was methylated using DAST (22.4 μL, 0.17 mmol, 1.7 equiv.) and $AlMe_3$ (2 M, 250 μL, 0.50 mmol, 5.0 equiv.) in 0.5 mL CH_2Cl_2 as described.

Run 1 (17.9 mg, 0.0854 mmol, 85% **3**; 0% rsm)

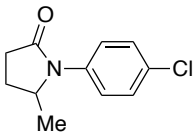
All entries suggest mostly similar yields and conversions between stoichiometric and one-pot equivalences of activators and trimethylaluminum. However, the one-pot equivalences produce slightly higher yields and are recommended for carrying out the methylation.

1-(4-Chlorophenyl)pyrrolidin-2-one [27]



Prepared according to literature procedures and the NMR data matched those reported.[71]

1-(4-Chlorophenyl)-5-methylpyrrolidin-2-one [28]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.37-7.29 (m, 4H), 4.27 (sxt, *J* = 6.1 Hz, 1H), 2.63 (ddd, *J* = 17.2, 9.5, 6.2 Hz, 1H), 2.52 (ddd, *J* = 17.0, 9.5, 7.1 Hz, 1H), 2.36 (ddt, *J* = 13.5, 9.5, 7.2 Hz, 1H), 1.79-1.69 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H)

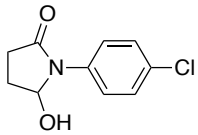
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.29, 136.27, 130.98, 129.16, 125.02, 55.53, 31.36, 26.72, 20.12

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{13}NOCl$ $[M+H]^+$: 210.0686, found 210.0686

1-(4-Chlorophenyl)-5-hydroxypyrrolidin-2-one [29a (OH)]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.48 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 5.63 (br s, 1H), 3.18 (br s, 1H), 2.83-2.69 (m, 1H), 2.53-2.38 (m, 2H), 2.09-2.00 (m, 1H)

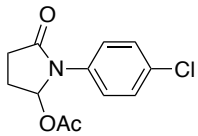
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.35, 135.86, 131.67, 129.33, 124.50, 85.21, 29.75, 28.38

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{10}H_{11}NO_2Cl$ $[M+H]^+$: 212.0478, found 212.0482

1-(4-Chlorophenyl)-5-oxopyrrolidin-2-yl acetate [29a (OAc)]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.38 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 9.2 Hz, 2H), 6.60 (d, *J* = 5.8 Hz, 1H), 2.87-2.70 (m, 1H), 2.61-2.42 (m, 2H), 2.19-2.10 (m, 1H), 2.05 (s, 3H)

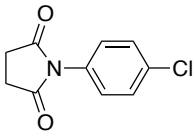
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.82, 170.36, 135.45, 132.05, 129.41, 124.43, 86.04, 29.41, 26.46, 21.24

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{10}H_9NOCl$ $[M\text{-}Ac]^+$: 194.0373, found 194.0364

1-(4-Chlorophenyl)pyrrolidine-2,5-dione [29b]

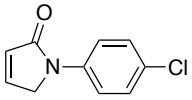


^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.44 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 2.89 (s, 4H)

These data matched those reported in the literature.[72]

1-(4-Chlorophenyl)-1,5-dihydro-2*H*-pyrrol-2-one [30]



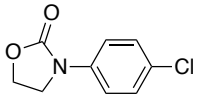
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.68 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.19 (dt, *J* = 6.1, 2.0 Hz, 1H), 6.28 (dt, *J* = 6.1, 2.0 Hz, 1H), 4.43 (t, *J* = 2.0 Hz, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.21, 142.35, 137.86, 129.40, 129.27, 129.22 120.01, 53.24

These data matched those reported in the literature.[73]



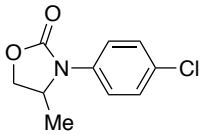
3-(4-Chlorophenyl)oxazolidin-2-one [31a] In a 100 mL recovery flask were added 2-oxazolidinone (523 mg, 6.0 mmol, 1.2 equiv.), 1-chloro-4-iodobenzene (1.19 g, 5.0 mmol, 1.0 equiv.), $Pd_2(dba)_3$ (45.8 mg, 0.05 mmol, 0.01 equiv.), XantPhos (86.8 mg, 0.15 mmol, 0.03 equiv.), and potassium phosphate (1.49 g, 7.0 mmol, 1.4 equiv.). A reflux condenser was placed on the flask, and the system was refilled with argon 3x. 1,4-dioxane (30 mL) was then added, and the mixture was refluxed in 100 °C oil bath overnight under nitrogen atmosphere. Upon completion, the reaction was diluted with CH_2Cl_2 and passed through a Celite plug. The resulting solution was condensed in vacuo and purification via flash chromatography yielded the product as a pale yellow powder (818 mg, 4.14 mmol, 83% yield).

^{1}H NMR: (400 MHz, $CHCl_3$)

δ 7.50 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 9.1 Hz, 2H), 4.50 (dd, *J* = 8.7, 7.2 Hz, 2H), 4.04 (dd, *J* = 8.8, 7.2 Hz, 2H)

These data matched those reported in the literature.[74]

3-(4-Chlorophenyl)-4-methyloxazolidin-2-one [32a]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.36 (AB q, *J* = 9.0 Hz, 4H), 4.57 (t, *J* = 8.3 Hz, 1H), 4.53-4.44 (m, 1H), 4.02 (dd, *J* = 8.2, 5.7 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 3H)

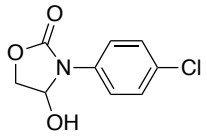
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 155.55, 135.30, 130.56, 129.36, 123.01, 68.75, 52.33, 18.45

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{10}H_{11}NO_2Cl$ $[M+H]^+$: 212.0478, found 212.0473.

3-(4-Chlorophenyl)-4-hydroxyoxazolidin-2-one [S24]



^{1}H NMR: (400 MHz, CD_3CN)

δ 7.59 (d, *J* = 9.1 Hz, 2H), 7.41 (d, *J* = 9.1 Hz, 2H), 5.79-5.72 (m, 1H), 4.75 (d, *J* = 8.1 Hz, 1H), 4.51 (dd, *J* = 9.9, 6.2 Hz, 1H), 4.15 (dd, *J* = 9.9, 1.8 Hz, 1H)

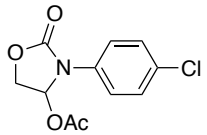
^{13}C NMR: (126 MHz, CD_3CN)

δ 155.71, 136.87, 130.81, 129.81, 124.04, 81.20, 71.31

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_9H_9NO_3Cl$ $[M+H]^+$: 214.0271, found 214.0278

3-(4-Chlorophenyl)-2-oxooxazolidin-4-yl acetate [S25]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.44 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 5.5 Hz, 1H), 4.64 (dd, *J* = 10.8, 5.7 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 2.10 (s, 3H)

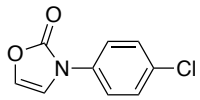
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.45, 154.70, 134.21, 132.04, 129.61, 123.23, 81.54, 68.58, 21.04

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{10}NO_4ClNa$ $[M+Na]^+$: 278.0196, found 278.0198

3-(4-Chlorophenyl)oxazol-2(3*H*)-one [S26]



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.53 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.92 (d, *J* = 2.2, 1H)

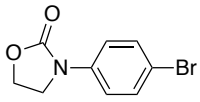
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.19, 134.16, 132.33, 129.77, 128.96, 122.26, 114.80

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_9H_7NO_2Cl$ $[M+H]^+$: 196.0165, found 196.0170

3.4.3 Synthesis of Substrates and Characterization for Figure 18



3-(4-Bromophenyl)oxazolidin-2-one [31b] In a 100 mL recovery flask were added 2-oxazolidinone (523 mg, 6.0 mmol, 1.2 equiv.), 1-bromo-4-iodobenzene (1.41 g, 5.0 mmol, 1.0 equiv.), $Pd_2(dba)_3$ (45.8 mg, 0.05 mmol, 0.01 equiv.), XantPhos (86.8 mg, 0.15 mmol, 0.03 equiv.), and potassium phosphate (1.49 g, 7.0 mmol, 1.4 equiv.). A reflux condenser was placed on the flask, and the system was refilled with argon 3x. 1,4-dioxane (30 mL) was then added, and the mixture was refluxed in 100 °C oil bath overnight under nitrogen atmosphere. Upon completion, the reaction was diluted with CH_2Cl_2 and passed through a Celite plug. The resulting solution was condensed in vacuo and purification via flash

chromatography yielded the product as a pale yellow crystalline solid, which was triturated with diethyl ether (3x5 mL) (1.03 g, 4.24 mmol, 85% yield).

^{1}H NMR: (500 MHz, $CHCl_3$)

δ 7.48 (d, *J* = 9.1 Hz, 2H), 7.43 (d, *J* = 9.1 Hz, 2H), 4.48 (dd, *J* = 8.7, 7.2 Hz, 2H), 4.03 (dd, *J* = 8.7, 7.3 Hz, 2H)

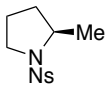
These data matched those reported in the literature.[74]

General procedure for nosyl protection. In a 100 mL recovery flask at room temperature was added the amine (1.0 equiv.), 4-dimethylaminopyridine (DMAP) (0.1 equiv.), and methylene chloride (0.2 M). Triethylamine (Et_3N) (1.1 equiv.) was then added, followed by 4-nitrobenzenesulfonyl chloride (NsCl) (1.1 equiv.). The reaction was allowed to stir overnight, then quenched with saturated sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted twice with methylene chloride. The combined organic layer was dried over anhydrous magnesium sulfate, filtered, condensed in vacuo, and purified through flash chromatography.

1-((4-Nitrophenyl)sulfonyl)pyrrolidine [31c] According to the general procedure for nosyl protection, pyrrolidine (285 mg, 4.0 mmol, 1.0 equiv.) was reacted with DMAP (48.9 mg, 0.4 mmol, 0.1 equiv.), Et_3N (614 μL, 445 mg, 4.4 mmol, 1.1 equiv.), and NsCl (975 mg, 4.4 mmol, 1.1 equiv.) in CH_2Cl_2 (20 mL). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 20%→40%→60% EtOAc/Hex) to afford the product as a light yellow powder (1.00 g, 3.91 mmol, 98% yield). The NMR data matched those reported in the literature.[75]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.38 (d, *J* = 8.9 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 3.29 (ddd, *J* = 6.8, 4.4, 2.8 Hz, 4H), 1.86-1.76 (m, 4H)

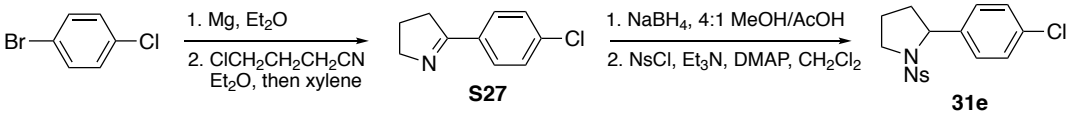


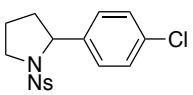
(*R*)-2-Methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine [31d] According to the general procedure for nosyl protection, (*R*)-2-methylpyrrolidine (250 mg, 2.94 mmol, 1.0 equiv.) was reacted with DMAP (35.7 mg, 0.294 mmol, 0.1 equiv.), Et_3N (451 μL, 327 mg, 3.23 mmol, 1.1 equiv.), and NsCl (717 mg, 3.23 mmol, 1.1 equiv.) in CH_2Cl_2 (14.7 mL). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 10%→400 mL 20% EtOAc/Hex) to afford the product as a light yellow powder (653 mg, 2.41 mmol, 89% yield). The spectra data match with **32c** (vide infra).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 3.78 (pd, *J* = 6.5, 4.2 Hz, 1H), 3.49 (ddd, *J* = 10.4, 7.1, 4.8 Hz, 1H), 3.19 (dt, *J* = 10.3, 7.4 Hz, 1H), 1.97-1.84 (m, 1H), 1.81-1.70 (m, 1H), 1.67-1.51 (m, 2H), 1.33 (d, *J* = 6.4 Hz, 3H)

$[\alpha]_D^{24}$ = -70.4º (c = 1.00, CH_2Cl_2)





2-(4-Chlorophenyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine [31e] In a flame-dried 25-mL recovery flask equipped with a magnetic stir bar were added magnesium (304 mg, 12.5 mmol, 1 equiv.) and small piece of iodine. Diethyl ether (1 mL) was then added to afford a brown solution. 1-Chloro-4-iodobenzene (2.4 g, 12.5 mmol, 1 equiv.)

dissolved in Et_2O (1 mL) was then added dropwise. The reaction was allowed to stir at room temperature for 30 min. 4-chlorobutanenitrile (1.2 mL, 1.3 g, 12.5 mmol, 1 equiv.) was dissolved in Et_2O (1.2 mL) and added to the freshly prepared Grignard reagent. The resulting mixture was refluxed for 1 h; upon which diethyl ether was removed through distillation while xylene (12.5 mL) was added to the flask. The resulting mixture was then refluxed overnight. Upon completion, the reaction mixture was partitioned between ethyl acetate and NH_4Cl solution, and the aqueous layer extracted with EtOAc (2x10 mL). The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. Purification by flash chromatography afforded 5-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrrole **S27** as a yellow powder (922 mg, 5.13 mmol, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 4.06 (dd, J = 7.5, 2.0 Hz, 2H), 2.97-2.87 (m, 2H), 2.10-2.00 (m, 2H).

In a 100-mL recovery flask was added **S27** (922 mg, 5.13 mmol, 1 equiv.), MeOH (6.1 mL), and AcOH (1.5 mL). The reaction mixture was cooled to -36 °C, and sodium borohydride (433 mg, 11.4 mmol, 2.23 equiv.) was added slowly in one portion. The solution was then allowed to warm up to room temperature and stirred for 2 h. The solvents were removed in vacuo and water was added. The mixture was partitioned between 1 M NaOH and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The organic layers were combined, dried over K_2CO_3, and condensed in vacuo. According to the general procedure for nosyl protection, the crude was directly reacted with DMAP (62.7 mg, 0.513 mmol, 0.1 equiv.), Et_3N (787 µL, 571 mg, 5.64 mmol, 1.1 equiv.), and NsCl (1.25 g, 5.64 mmol, 1.1 equiv.) in CH_2Cl_2 (25 mL). Following workup, the crude material was purified by flash chromatography (75 mL silica, gradient elution 100 mL 0%→ 200 mL 10%→400 mL 50% EtOAc/Hex) to afford the product as a light yellow powder (787 mg, 2.15 mmol, 42% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.31 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.81 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.65 (ddd, *J* = 9.7, 6.9, 5.0 Hz, 1H), 3.53 (dt, *J* = 9.9, 7.0 Hz, 1H), 2.18-2.05 (m, 1H), 2.02-1.89 (m, 1H), 1.89-1.74 (m, 2H)

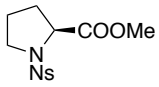
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.10, 144.34, 140.70, 133.49, 128.76, 128.54, 127.79, 124.33, 63.25, 49.64, 36.08, 24.28

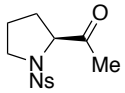
HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{16}H_{16}ClN_2O_4S$ $[M+H]^+$: 367.0519, found 367.0524

Methyl ((4-nitrophenyl)sulfonyl)-*L*-prolinate [31f]



Synthesized using a previously reported synthesis and the NMR data matched those reported.[61]



(*S*)-1-(1-((4-Nitrophenyl)sulfonyl)pyrrolidin-2-yl)ethan-1-one [31g] In a 100-mL recovery flask containing *tert*-butyl (*S*)-2-acetylpyrrolidine-1-carboxylate[76] (1.05 g, 4.93 mmol, 1 equiv.) were added CH_2Cl_2 (10 mL) and trifluoroacetic acid (1.9 mL, 24.7 mmol, 5 equiv.). The mixture was stirred overnight, concentrated, redissolved in CH_2Cl_2 (10 mL), and washed with NaOH (1M, 5 mL). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. According to the general procedure for nosyl protection, the crude was directly reacted with DMAP (60.2 mg, 0.493 mmol, 0.1 equiv.), Et_3N (756 μL, 548 mg, 5.42 mmol, 1.1 equiv.), and NsCl (1.20 g, 5.42 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL). Following workup, the crude material was purified thrice

by flash chromatography (50 mL silica, 400 mL 40% EtOAc/Hex) to afford the product as a light yellow powder (203 mg, 0.68 mmol, 14% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 4.20 (dd, *J* = 8.7, 4.7 Hz, 1H), 3.48 (dt, *J* = 9.6, 6.5 Hz, 1H), 3.34 (dt, *J* = 9.7, 6.8 Hz, 1H), 2.26 (s, 3H), 2.06-1.95 (m, 1H), 1.95-1.79 (m, 2H), 1.78-1.64 (m, 1H)

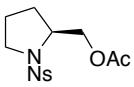
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 206.69, 150.39, 143.66, 128.96, 124.48, 67.65, 49.06, 29.82, 26.48, 24.90

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{17}N_2O_6S$ $[M+H]^+$: 329.0807, found 329.0804

$[\alpha]_D^{24}$ = -71.4º (c = 0.72, CH_2Cl_2)



(*S*)-(1-((4-Nitrophenyl)sulfonyl)pyrrolidin-2-yl)methyl acetate [31h] According to the general procedure for nosyl protection, L-prolinol (425 mg, 4.20 mmol, 1 equiv.) was reacted with DMAP (51.3 mg, 0.420 mmol, 0.1 equiv.), Et_3N (644 μL, 467 mg, 4.62 mmol, 1.1 equiv.), and NsCl (1.02 g, 4.62 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elusion 300 mL 30%→50% EtOAc/Hex) to afford (*S*)-(1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methanol as a mixture with byproducts (roughly 1.01 g, 3.53 mmol). The crude was transferred to a 100-mL recovery flask, where DMAP (43.1 mg, 0.353 mmol, 0.1 equiv.), CH_2Cl_2 (7 mL), Et_3N (1.48 mL, 1.07 g, 10.6 mmol, 3 equiv.), and Ac_2O (1.67 mL, 1.80 g, 17.7 mmol, 5 equiv.) were added in order. The mixture was stirred overnight, and partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The

organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. Purification by flash chromatography (50 mL silica, gradient elusion 200 mL 20%→30%→40% EtOAc/Hex) afforded the product as a white powder (1.14 g, 3.48 mmol, 83% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.38 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 4.21 (dd, *J* = 11.2, 4.9 Hz, 1H), 4.13 (dd, *J* = 11.1, 6.9 Hz, 1H), 3.97-3.90 (m, 1H), 3.50 (ddd, *J* = 10.5, 7.2, 4.0 Hz, 1H), 3.24-3.17 (m, 1H), 2.07 (s, 3H), 1.98-1.86 (m, 1H), 1.82-1.74 (m, 1H), 1.72-1.62 (m, 2H)

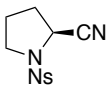
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.79, 150.33, 143.57, 128.80, 124.54, 65.89, 58.37, 49.44, 28.86, 24.18, 21.01

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{17}N_2O_6S$ $[M+H]^+$: 329.0807, found 329.0804

$[\alpha]_D^{24}$ = -87.5º (c = 0.99, CH_2Cl_2)



(*S*)-1-((4-Nitrophenyl)sulfonyl)pyrrolidine-2-carbonitrile [31i] According to literature[77], in a 250-mL round-bottom flask were added ((4-nitrophenyl)sulfonyl)-*L*-proline (4.53 g, 15.1 mmol, 1 equiv.), THF (20 mL), Et_3N (2.1 mL, 1.53 g, 15.1 mmol, 1 equiv.), and ethyl carbonochloridate (1.44 mL, 1.64 g, 15.1 mmol, 1 equiv.). The reaction mixture was stirred for 20 min, upon which NH_4OH (30 wt%, 1 mL, 17.6 mmol, 1.17 equiv.) was added. The reaction was then stirred overnight. Upon completion, the solvent was removed in vacuo and the crude redissolved in CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ and isolated, dried over $MgSO_4$, and condensed in vacuo. THF (80 mL) and Et_3N (6.3 mL, 4.58 g, 45.3 mmol, 3 equiv.) were then added, followed by TFAA (3.2 mL, 4.76 g, 22.7 mmol, 1.5 equiv.). The reaction mixture was stirred for 3 h, and then quenched with water. The solvent was removed in

vacuo and the residue redissolved in CH_2Cl_2, washed with 10% citric acid, brine, and sat. $NaHCO_3$. Purification by flash chromatography (50 mL silica, gradient elusion 200 mL 20%→40%→60%→80%→100% EtOAc/Hex) and recrystallization (80 mL methanol, 45 mL hexanes) afforded the product as a yellow crystalline solid (2.50 g, 8.89 mmol, 59% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.41 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 2H), 4.74 (dd, *J* = 6.2, 4.3 Hz, 1H), 3.56 (dd, *J* = 9.1, 7.7 Hz, 1H), 3.35 (ddd, *J* = 9.3, 6.9, 5.0 Hz, 1H), 2.35-2.23 (m, 2H), 2.19-2.07 (m, 2H)

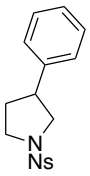
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.65, 143.56, 128.89, 124.69, 117.38, 48.80, 47.64, 32.04, 24.90

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{12}N_3O_4S$ $[M+H]^+$: 282.0549, found 282.0556

$[\alpha]_D^{24}$ = -93.5º (c = 1.11, CH_2Cl_2)



1-((4-nitrophenyl)sulfonyl)-3-phenylpyrrolidine [31j] According to the general procedure for nosyl protection, 3-phenylpyrrolidine (294 mg, 2.00 mmol, 1.0 equiv.) was reacted with Et_3N (307 µL, 223 mg, 2.20 mmol, 1.1 equiv.), and NsCl (488 mg, 2.20 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL). Following workup, the crude material was purified by flash chromatography (50 mL silica, 200 mL 20% EtOAc/Hex) to afford the product as a yellow powder (613 mg, 1.84 mmol, 92% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.39 (d, *J* = 8.6 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.34-7.19 (m, 3H), 7.10 (d, *J* = 7.2 Hz, 2H), 3.78 (dt, *J* = 6.8, 2.0 Hz, 1H), 3.58 (ddd, *J* = 9.8, 8.8, 3.3 Hz, 1H), 3.46-3.38 (m,

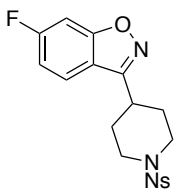
1H), 3.35-3.27 (m, 1H), 3.26 (t, *J* = 7.7 Hz, 1H), 2.27 (ddd, *J* = 13.1, 6.7, 3.2 Hz, 1H), 1.96 (dq, *J* = 12.6, 9.1 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.26, 143.25, 139.97, 128.92, 128.62, 127.38, 126.98, 124.54, 54.35, 48.07, 44.02, 32.86

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{16}H_{17}N_2O_4S$ $[M+H]^+$: 333.0909, found 333.0898



6-Fluoro-3-(1-((4-nitrophenyl)sulfonyl)piperidin-4-yl)benzo[*d*]isoxazole [31k]

6-Fluoro-3-(4-piperidinyl)benzisoxazole hydrochloride (2.05 g, 8.00 mmol, 1 equiv.) was dissolved in DCM (15 mL, 0.5 M). DMAP (90 mg, 0.80 mmol, 0.1 equiv.), triethylamine (3.3 mL, 24 mmol, 3 equiv.) and nosyl chloride (3.5 g, 16 mmol, 2 equiv.) were added respectively. The solution was stirred for 12 hours before being diluted with 1 M NaOH (10 mL). The aqueous layer was extracted with DCM (3x15 mL), and the combined organics were dried with Na_2SO_3 and concentrated *in vacuo*. The resulting brown oil was purified by flash chromatography (200 mL silica, DCM loaded, gradient elution 200 mL 0% → 300 mL 15% → 20% → 30% → 40% EtOAc/Hex → 1.6 L EtOAc) to afford the desired product as a yellow powder in 77% yield (2.50 g, 6.17 mmol).

^{1}H NMR: (500 MHz, $CHCl_3$)

δ 8.41 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.57 (dd, *J* = 8.7, 5.0 Hz, 1H), 7.25 (dd, *J* = 5.2, 1.6 Hz 1H), 7.07 (td, *J* = 8.8, 2.2 Hz, 1H), 3.88 (dt, *J* = 11.9, 3.8 Hz, 2H), 3.12 (tt, *J* = 9.8, 5.1 Hz, 1H), 2.73 (ddd, *J* = 12.1, 9.6, 4.2 Hz, 2H), 2.34 – 2.07 (m, 4H)

^{13}C NMR: (126 MHz, $CHCl_3$)

δ 164.36 (d, *J* = 251.7 Hz), 164.10 (d, *J* = 13.6 Hz), 159.71, 150.40, 142.65, 128.91, 124.58, 122.13 (d, *J* = 11.1 Hz), 116.98, 112.94 (d, *J* = 25.1 Hz), 97.81 (d, *J* = 26.8 Hz), 45.86, 33.22, 29.68

^{19}F NMR: (471 MHz, $CHCl_3$)

δ -108.69 (td, *J* = 8.6, 5.1 Hz)

HRMS: (ESI TOF MS ES+)

m/z calculated for $C_{18}H_{17}FN_3O_5S$ $[M+H]^+$: 406.0873; found 406.0870

3.4.4 Experimental Procedures and Characterization for Figure 18

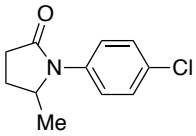
General procedure for C–H oxidation. To a 40 mL vial equipped with a stir bar were added the substrate (0.30 mmol, 1.0 equiv.,), (*S*,*S*)-Mn(CF_3PDP) **26** (2.0 mg, 0.0015 mmol, 0.005 equiv.), MeCN (0.6 mL, 0.5 M), and AcOH (257 μL, 4.50 mmol, 15.0 equiv.). For achiral or racemic substrates, (*R*,*R*)- and (*S*,*S*)-**26** can be used interchangeably. The reaction mixture was then placed into a -36 °C dry ice/1,2-dichloroethane bath. A 10 mL syringe was charged with a solution of H_2O_2 (85.2 μL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). The syringe was then fitted with a 25G needle and the solution was slowly added into the stirring reaction mixture via a syringe pump at 3.75 mL/h. Upon completion, the vial was taken from the cold bath, and the reaction mixture was immediately loaded onto a 15 mL silica plug. Ethyl acetate was used to rinse the vial (2x1 mL), and the resulting washes were also loaded onto the silica plug. The plug was allowed to sit for five minutes in order to decompose any remaining hydrogen peroxide as well as absorbing the reaction mixture. Ethyl acetate (150 mL) was then allowed to pass through the plug, and the eluent was concentrated in vacuo, transferred into a 25

mL recovery flask, condensed and placed on vacuum overnight to remove the residual acetic acid.

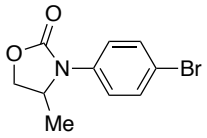
General procedure for BF_3-promoted methylation. The crude from oxidation was dissolved in CH_2Cl_2 (1.5 mL, 0.2 M), backfilled with nitrogen 3x, and placed into a -78 °C dry ice/acetone bath. Trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was then added dropwise, followed by boron trifluoride diethyl etherate (74.0 μL, 0.60 mmol, 2.0 equiv.). The reaction mixture was stirred at -78 °C for 1 h, then allowed to warm to room temperature while stirring for 3 h. Upon completion, the reaction was diluted with CH_2Cl_2 (5 mL) and poured into a 60 mL separatory funnel containing 3 mL 1 M NaOH for quenching. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and condensed in vacuo before subjecting to purification via flash or medium pressure chromatography.

General procedure for DAST-promoted methylation. The crude from oxidation was dissolved in CH_2Cl_2 (1.5 mL, 0.2 M), backfilled with nitrogen 3x, and placed into a -78 °C dry ice/acetone bath. Diethylaminosulfur trifluoride (39.6 μL, 48.3 mg, 0.30 mmol, 1.0 equiv.) or Deoxo-Fluor (55.3 μL, 66.4 mg, 0.30 mmol, 1.0 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 1 h. The reaction was then placed back into -78 °C cold bath, where trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was then added dropwise. The reaction mixture was stirred at -78 °C for 2 h, then allowed to warm to room temperature while stirring for 1 h. Upon completion, the reaction was diluted with CH_2Cl_2 (5 mL) and poured into a 60 mL separatory funnel containing 3 mL 1 M NaOH for quenching. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The organic layers were combined, dried

over anhydrous $MgSO_4$, filtered, and condensed in vacuo before subjecting to purification via flash or medium pressure chromatography.



1-(4-Chlorophenyl)-5-methylpyrrolidin-2-one [28] Gram scale: Following the general oxidation and DAST-promoted procedures, 1-(4-chlorophenyl)pyrrolidin-2-one **27** (1.0 g, 5.11 mmol, 1.0 equiv.) in MeCN (10.2 mL) in a 100 mL round-bottom flask was oxidized with (*S*,*S*)-Mn(CF_3PDP) (34.6 mg, 0.0256 mmol, 0.005 equiv.), acetic acid (4.38 mL, 76.7 mmol, 15.0 equiv.), and H_2O_2 (581 µL, 10.2 mmol, 2.0 equiv., 50 wt.% in H_2O) in MeCN (60 mL, in 50 mL HSW syringe). Following oxidation, the solution was passed through 100 mL silica and flushed with 1 L of EtOAc. The solution was concentrated *in vacuo* and transferred to a 100 mL round bottom flask and left on a high vacuum pump overnight. The crude was then dissolved in 25.6 mL of CH_2Cl_2 under nitrogen and placed in a dry ice/acetone cold bath. DAST (675 µL, 5.11 mmol, 1.0 equiv.) was added and the solution was stirred for an hour. $AlMe_3$ (7.67 mL, 15.3 mmol, 3.0 equiv.) was then added slowly. The reaction was stirred at -78°C for two hours before removing the dry ice bath and stirring at rt for an additional hour. A 3 M solution of sodium hydroxide (100 mL) was cooled to 0 °C at the end of the reaction and transferred to a 250 mL separatory funnel. The reaction mixture was cooled to 0 °C and slowly transferred to the separatory funnel. The organic layer was carefully extracted, and the aqueous layer was washed with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried with $MgSO_4$, concentrated *in vacuo*, and purified via MPLC (40 g silica, 80 column volumes 0%→30% EtOAC/Hex) to afford the desired product as a light orange gel (764.6 mg, 3.647 mmol, 71% yield; 112.3 mg, 0.574 mmol, 11% rsm). See section 3.4.2 for product characterization.



3-(4-Bromophenyl)-4-methyloxazolidin-2-one [32b] According to a modified general oxidation and DAST-promoted methylation procedures, 3-(4-bromophenyl)oxazolidin-2-one **31b** (72.6 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.8 mL, 0.375 M) was placed in ice bath and oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 μL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (34.6 μL, 0.60 mmol, 2.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Following oxidation, the crude was methylated with DAST (39.6 μL, 48.3 mg, 0.30 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 10%→200 mL 20%→400 mL 30% EtOAc/Hex) to afford the product as a white powder.

Run 1 (48.6 mg, 0.190 mmol, 63% yield)

Run 2 (49.6 mg, 0.194 mmol, 65% yield)

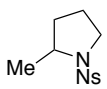
Run 3 (46.2 mg, 0.180 mmol, 60% yield)

Average overall yield: 63% (0% rsm) ± 2.5

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.50 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 4.57 (t, *J* = 8.3 Hz, 1H), 4.53-4.44 (m, 1H), 4.02 (dd, *J* = 8.3, 5.5 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 3H)

The spectral data match with those reported in the literature.[78]



2-Methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine [32c] According to the general oxidation and BF_3-promoted methylation procedures, 1-((4-nitrophenyl)sulfonyl)pyrrolidine **31c** (76.9 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 μL,

4.50 mmol, 15.0 equiv.), and H_2O_2 (34.6 μL, 0.60 mmol, 2.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Following oxidation, the crude was methylated with trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) and BF_3•OEt_2 (74.0 μL, 0.60 mmol, 2.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 10%→400 mL 20% EtOAc/Hex) to afford the product as a white solid.

Run 1 (39.9 mg, 0.147 mmol, 49% yield; 4.6 mg, 0.018 mmol, 6% rsm; 20% 2,5-dimethylation by ^{1}H NMR, 1.4:1 dr)

Run 2 (43.9 mg, 0.162 mmol, 54% yield, 6.0 mg, 0.023 mmol, 8% rsm; 10% 2,5-dimethylation by ^{1}H NMR, 1.3:1 dr)

Run 3 (48.5 mg, 0.179 mmol, 60% yield, 9.6 mg, 0.037 mmol, 12% rsm; 14% 2,5-dimethylation by ^{1}H NMR, 1.3:1 dr)

Average overall yield: 54% (9% rsm) ± 5.5; 15% 2,5-dimethylation, 1.3:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

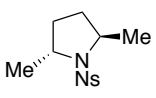
δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 3.76 (pd, *J* = 6.5, 3.8 Hz, 1H), 3.49 (ddd, *J* = 10.0, 7.0, 4.8 Hz, 1H), 3.17 (dt, *J* = 10.0, 7.2 Hz, 1H), 1.96-1.82 (m, 1H), 1.81-1.67 (m, 1H), 1.67-1.50 (m, 2H), 1.32 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.09, 144.14, 128.58, 124.40, 56.71, 49.19, 33.64, 24.06, 22.75

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{15}N_2O_4S$ $[M+H]^+$: 271.0753, found 271.0751



(2*R*,5*R*)-2,5-Dimethyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine [32d] According to the general oxidation and BF_3-promoted methylation procedures, (*R*)-2-methyl-

1-((4-nitrophenyl)sulfonyl)pyrrolidine **31d** (81.1 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 µL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (34.6 µL, 0.60 mmol, 2.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Following oxidation, the crude was methylated with trimethylaluminum (2.0 M in hexanes, 450 µL, 0.90 mmol, 3.0 equiv.) and BF_3•OEt_2 (74.0 µL, 0.60 mmol, 2.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 5%→600 mL 20% EtOAc/Hex) to afford the product as a white solid as a mixture of diastereomers. The stereochemistry was determined by analogy to compounds **32g** and **34a**. The ^{1}H NMR data matched those synthesized via an alternate route as reported by literature.[79]

Run 1 (39.1 mg, 0.138 mmol, 46% yield, 1.4:1 dr; 11.0 mg, 0.041 mmol, 14% rsm)

Run 2 (35.0 mg, 0.123 mmol, 41% yield, 2:1 dr; 13.5 mg, 0.050 mmol, 17% rsm)

Run 3 (33.5 mg, 0.118 mmol, 39% yield, 1.4:1 dr; 10.7 mg, 0.040 mmol, 13% rsm)

Average overall yield: 42% (15% rsm) ± 3.6, 1.6:1 dr

Characterization of major diastereomer **32d**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.33 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 4.08 (app p, *J* = 6.5 Hz, 2H), 2.21-2.08 (m, 2H), 1.63-1.52 (m, 2H), 1.21 (d, *J* = 6.4 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

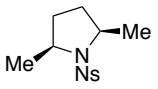
δ 149.76, 148.69, 128.17, 124.33, 56.99, 31.30, 21.57

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{17}N_2O_4S$ $[M+H]^+$: 285.0909, found 285.0911

$[\alpha]_D^{24}$ = -21.6º (c = 0.21, CH_2Cl_2)

Characterization of minor diastereomer **S28**:



^{1}H NMR: (400 MHz, $CDCl_3$)

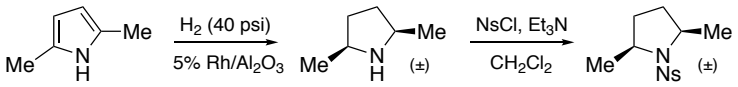
δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 3.80-3.58 (m, 2H), 1.70-1.52 (m, 4H), 1.37 (d, *J* = 6.3 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.10, 144.34, 128.69, 124.37, 58.15, 32.30, 23.74

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{17}N_2O_4S$ $[M+H]^+$: 285.0909, found 285.0916

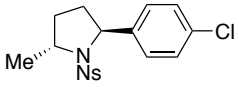


Synthesis of the reference compound: According to literature[79], in a 25 mL recovery flask equipped with a magnetic stir bar were added 2,5-dimethylpyrrole (200 mg, 2.1 mmol, 1.0 equiv.), 5% rhodium on alumina (14.3 mg), and acetic acid (714 μL). The flask was placed into a bomb, backfilled with hydrogen 3x, and pressurized with hydrogen to 40 psi. The reaction was stirred for 3 d. Upon completion, the reaction mixture as diluted with CH_2Cl_2, and rhodium was removed via filtration. The filtrate was basified with 3 M NaOH and extracted with CH_2Cl_2 3x. The combined organic layer was dried over K_2CO_3, filtered, and carefully condensed in vacuo. Crude NMR of the resulting free amine shows a 3:1 syn/anti diastereomeric ratio. The ^{1}H NMR data of the anti-isomer matched those reported in the literature.[80] The crude was dissolved in CH_2Cl_2 (20 mL), where NsCl (512 mg, 2.31 mmol, 1.1 equiv.) and Et_3N (322 μL, 2.31 mmol, 1.1 equiv.) were added and the reaction was stirred overnight. Upon completion, the reaction

mixture was washed with sat. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 2x. The combined organic layer was dried over $MgSO_4$, filtered, and condensed in vacuo. Purification by medium-pressure liquid chromatography (12 g silica, 100 column volumes 0% → 25% EtOAc/Hex) afforded nosyl 2,5-dimethylpyrrolidine as a mixture of diastereomers (193 mg, 0.680 mmol, 32% yield, 3:1 dr).

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.36 (d, *J* = 8.8 Hz, 1.54H), 8.32 (d, *J* = 8.8 Hz, 0.46H), 8.08-7.96 (m, 2H), 4.07 (p, *J* = 6.4 Hz, 0.46H), 3.78-3.62 (m, 1.54H), 2.21-2.07 (m, 0.46H), 1.70-1.49 (m, 3.54H), 1.36 (d, *J* = 6.4 Hz, 2.31H), 1.20 (d, *J* = 6.4 Hz, 0.69H)



Trans-2-(4-chlorophenyl)-5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine [(±)-32e] According to the general oxidation and BF_3-promoted methylation procedures, 2-(4-chlorophenyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine **31e** (73.4 mg, 0.20 mmol, 1.0 equiv.) in MeCN (0.4 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (5.4 mg, 0.006 mmol, 0.02 equiv.), AcOH (172 μL, 3.00 mmol, 15.0 equiv.), and H_2O_2 (57.7 μL, 1.00 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (2.50 mL, 0.4 M). Following oxidation, the crude was methylated with trimethylaluminum (2.0 M in hexanes, 300 μL, 0.60 mmol, 3.0 equiv.) and BF_3•OEt_2 (49.3 μL, 0.40 mmol, 2.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 5%→10%→20% EtOAc/Hex) to afford the product as a white powder as a mixture of diastereomers. The stereochemistry was determined by analogy to compounds **32g** and **34a**.

Run 1 (40.2 mg, 0.106 mmol, 53% yield, 1.3:1 dr; 8% rsm by ^{1}H NMR)

Run 2 (45.8 mg, 0.120 mmol, 60% yield, 1.4:1 dr; 6% rsm by ^{1}H NMR)

Run 3 (43.1 mg, 0.113 mmol, 57% yield, 1.7:1 dr; 6% rsm by ^{1}H NMR)

Average overall yield: 57% (7% rsm) ± 3.5, 1.5:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

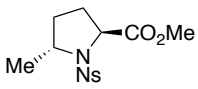
δ 8.31 (d, *J* = 8.8 Hz, 0.74H), 8.12 (d, *J* = 8.8 Hz, 1.26H), 7.90 (d, *J* = 8.8 Hz, 0.74H), 7.62 (d, *J* = 8.9 Hz, 1.26H), 7.27 (d, *J* = 9.1 Hz, 0.74H), 7.24 (d, *J* = 8.6 Hz, 0.74H), 7.08 (d, *J* = 8.4 Hz, 1.26H), 6.93 (d, *J* = 8.5 Hz, 1.26H), 4.97 (d, *J* = 8.4 Hz, 0.63H), 4.72 (t, *J* = 6.7 Hz, 0.37H), 4.34 (p, *J* = 6.5 Hz, 0.63H), 4.03 (sxt, *J* = 6.4 Hz, 0.37H), 2.53 (tdd, *J* = 12.9, 8.9, 7.1 Hz, 0.63H), 2.29 (tt, *J* = 12.8, 7.5 Hz, 0.63H), 2.03-1.96 (m, 0.37H), 1.93-1.85 (m, 0.37H), 1.85-1.74 (m, 1H), 1.70 (ddt, *J* = 12.7, 7.1, 1.3 Hz, 0.63H), 1.59 (dd, *J* = 11.8, 5.9 Hz, 0.37 H), 1.48 (d, *J* = 6.4 Hz, 1.11H), 1.43 (d, *J* = 6.4 Hz, 1.89H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.12, 149.52, 147.47, 144.37, 140.39, 140.27, 133.35, 133.43, 128.78, 128.77, 128.50, 128.34, 128.10, 127.91, 124.30, 123.82, 64.91, 63.27, 58.37, 58.34, 34.67, 33.16, 32.28, 31.85, 22.75, 22.12

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{18}N_2O_4SCl$ $[M+H]^+$: 381.0676, found 381.0683



Methyl (2*S*,5*R*)-5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate [32f] According to the general oxidation and DAST-promoted methylation procedures, methyl ((4-nitrophenyl)sulfonyl)-*L*-prolinate **31f** (94.2 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 μL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (85.2 μL, 1.50 mmol,

5.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Following oxidation, the crude was methylated with DAST (39.6 μL, 48.3 mg, 0.30 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 10%→400 mL 20% EtOAc/Hex) to afford the product as a white solid or gel as a mixture of diastereomers. The stereochemistry was determined by analogy to compounds **32g** and **34a** and by converting the product to methyl 1-((4-fluorophenyl)sulfonyl)-5-methylpyrrolidine-2-carboxylate and comparing the ^{1}H NMR spectra to those reported in the literature.[81]

Run 1 (71.9 mg, 0.219 mmol, 73% yield; 3:1 dr; 19% rsm by ^{1}H NMR)

Run 2 (61.1 mg, 0.186 mmol, 62% yield, 2:1 dr; 16% rsm by ^{1}H NMR)

Run 3 (68.2 mg, 0.208 mmol, 69% yield, 3:1 dr; 13% rsm by ^{1}H NMR)

Average overall yield: 68% (16% rsm) ± 5.6, 3:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

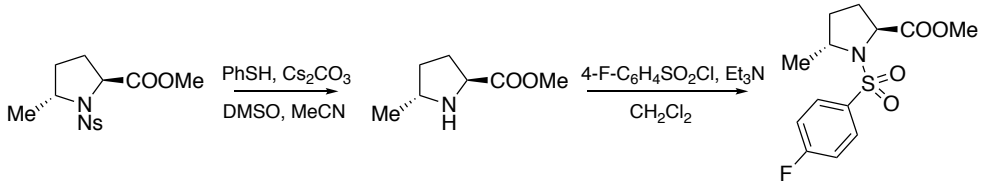
δ 8.36 (d, *J* = 9.1 Hz, 0.5H), 8.33 (d, *J* = 8.8 Hz, 1.5H), 8.10 (d, *J* = 8.7 Hz, 0.5H), 8.04 (d, *J* = 9.0 Hz, 1.5H), 4.51 (dd, *J* = 8.6, 1.3 Hz, 0.75H), 4.39 (dd, *J* = 8.0, 5.5 Hz, 0.25H), 4.08 (pd, *J* = 6.3, 1.7 Hz, 0.75H), 3.94 (sxt, *J* = 6.4 Hz, 0.25H), 3.74 (s, 0.75H), 3.67 (s, 2.25 H), 2.37-2.17 (m, 1.5H), 2.10-2.00 (m, 0.5H), 1.97 (ddt, *J* = 12.6, 6.3, 1.4 Hz, 0.75H), 1.94-1.86 (m, 0.25H), 1.69-1.58 (m, 1H), 1.30 (d, *J* = 6.4 Hz, 0.75H), 1.26 (d, *J* = 6.5 Hz, 2.25H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 172.43, 172.39, 150.19, 149.99, 146.46, 145.17, 128.86, 128.79, 124.34, 124.10, 61.92, 61.68, 58.04, 56.63, 52.73, 52.53, 33.03, 32.14, 29.55, 28.69, 21.75, 21.60

HRMS: (ESI-TOF MS ES+) (mixture of diastereomers)

m/z calculated for $C_{13}H_{17}N_2O_6S$ $[M+H]^+$: 329.0807, found 329.0800

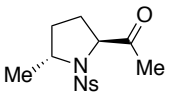


Synthesis of the reference compound: In a 25 mL recovery flask equipped with a magnetic stir bar were added methyl 5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate **32f** (75.7 mg, 2.6:1 anti/syn, 0.23 mmol, 1.0 equiv.), cesium carbonate (300 mg, 0.92 mmol, 4.0 equiv.), MeCN (8.5 mL). The flask was backfilled with nitrogen 3x, and DMSO (171 μL) and thiophenol (83 μL, 0.81 mmol, 3.5 equiv.) were added. The reaction was stirred in 45 °C oil bath for 2 d. Upon completion, the reaction mixture as diluted with CH_2Cl_2, and washed with sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 3x. The combined organic layer was dried over K_2CO_3, filtered, and carefully condensed in vacuo at 0 °C. Purification by flash chromatography (50 mL silica, 200 mL 50% EtOAc/Hex→10% MeOH/CH_2Cl_2) followed by condensation in vacuo at 0 °C produced the free amine as a mixture with water and CH_2Cl_2. The water was removed using a separatory funnel and the aqueous layer extracted with CH_2Cl_2 1x. The combined organic layer was dried over K_2CO_3, filtered, and 4-fluorosulfonyl chloride (224 mg, 1.15 mmol, 5.0 equiv.) and triethylamine (160 μL, 1.15 mmol, 5.0 equiv.) were added directed, and the reaction was stirred overnight. Upon completion, the reaction mixture was washed with sat. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 2x. The combined organic layer was dried over $MgSO_4$, filtered, and condensed in vacuo. Purification by medium-pressure liquid chromatography (12 g silica, 100 column volumes 0%→40% EtOAc/Hex) afforded methyl 1-((4-fluorophenyl)sulfonyl)-5-methylpyrrolidine-2-carboxylate as a mixture of diastereomers

(30.4 mg, 0.101 mmol, 44% yield, 2:1 anti/syn). The ^{1}H NMR data of the syn product matched those reported in the literature.[81]

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.96-7.86 (m, 2H), 7.23-7.12 (m, 2H), 4.49-4.43 (m, 0.67H), 4.30 (dd, *J* = 8.1, 5.5 Hz, 0.33H), 4.10-4.01 (m, 0.67H), 3.85 (sxt, *J* = 6.4 Hz, 0.33H), 3.74 (s, 1H), 3.66 (s, 2H), 2.36-2.18 (m, 1.34H), 2.08-1.90 (m, 1.33H), 1.90-1.78 (m, 0.33H), 1.69-1.52 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 1H), 1.22 (d, *J* = 6.5 Hz, 2H)



1-((2*S*,5*R*)-5-Methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)ethan-1-one [32g] According to the general oxidation procedure, (*S*)-1-(1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)ethan-1-one **31f** (59.7 mg, 0.20 mmol, 1.0 equiv.) in MeCN (0.4 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (1.4 mg, 0.0010 mmol, 0.005 equiv.), AcOH (172 μL, 3.00 mmol, 15.0 equiv.), and H_2O_2 (56.8 μL, 1.00 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (2.50 mL, 0.4 M). Following oxidation, the crude was dissolved in CH_2Cl_2 (1.0 mL, 0.2 M), backfilled with nitrogen 3x, and placed into a -78 °C dry ice/acetone bath. DAST (26.4 μL, 32.2 mg, 0.20 mmol, 1.0 equiv.) was added, and the reaction was allowed to warm to room temperature while stirring for 1 h. The reaction was then placed back into -78 °C cold bath, where trimethylaluminum (2.0 M in hexanes, 300 μL, 0.60 mmol, 3.0 equiv.) was then added dropwise. The reaction mixture was stirred at -78 °C for 3 h, and then directly quenched with 1 M NaOH. Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 10%→400 mL 20%→200 mL 30% EtOAc/Hex) to afford the product as a white solid. The stereochemistry was determined based on ^{1}H NMR, COSY, NOESY 1D, and NOESY 2D NMR methods.

Run 1 (44.3 mg, 0.142 mmol, 71% yield; 3:1 dr; 3% rsm by ^{1}H NMR)

Run 2 (46.0 mg, 0.147 mmol, 74% yield, 3:1 dr; 3% rsm by ^{1}H NMR)

Run 3 (45.8 mg, 0.147 mmol, 73% yield, 3:1 dr)

Average overall yield: 73% (2% rsm) ± 1.5, 3:1 dr

Characterization of major diastereomer **32g**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 4.64 (dd, *J* = 9.4, 1.7 Hz, 1H), 4.02 (p, *J* = 6.6 Hz, 1H), 2.37-2.25 (m, 1H), 2.22 (s, 3H), 2.06 (tt, *J* = 12.5, 7.2 Hz, 1H), 1.85 (ddt, *J* = 13.2, 7.0, 1.8 Hz, 1H), 1.63-1.56 (m, 1H), 1.25 (d, *J* = 6.3 Hz, 3H)

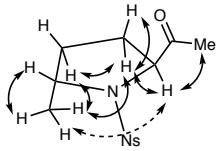
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 206.07, 150.02, 146.39, 128.94, 124.09, 67.95, 56.56, 31.96, 27.04, 26.81, 21.26

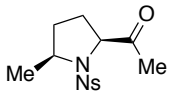
HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{17}N_2O_5S$ $[M+H]^+$: 313.0858, found 313.0862

$[\alpha]_D^{24}$ = -35.5º (c = 0.81, CH_2Cl_2)



Characterization of minor diastereomer **S29**:



^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.39 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 2H), 4.09 (t, *J* = 7.4 Hz, 1H), 3.85 (td, *J* = 6.8, 4.6 Hz, 1H), 2.37 (s, 3H), 2.05-1.95 (m, 1H), 1.86 (dq, *J* = 13.0, 6.9 Hz, 1H), 1.77-1.67 (m, 1H), 1.61-1.52 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H)

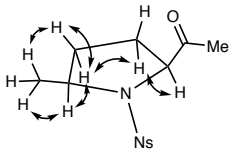
^{13}C NMR: (126 MHz, $CDCl_3$)

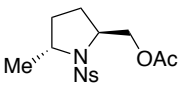
δ 207.09, 150.46, 143.49, 129.06, 124.53, 69.30, 58.34, 32.66, 27.98, 25.94, 22.53

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{17}N_2O_5S$ $[M+H]^+$: 313.0858, found 313.0869

$[\alpha]_D^{24}$ = -69.6º (c = 0.57, CH_2Cl_2)





((2*S*,5*R*)-5-Methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methyl acetate [32h] According to the general oxidation and DAST-promoted methylation procedures, (*S*)-(1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methyl acetate **31h** (98.5 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 µL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (34.6 µL, 0.60 mmol, 2.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Following oxidation, the crude was methylated with DAST (39.6 µL, 48.3 mg, 0.30 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 450 µL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 10%→400 mL 20% EtOAc/Hex) to afford the product as a light yellow solid as a mixture of diastereomers. The stereochemistry was determined by analogy to compounds **32g** and **34a**, and by reducing **32f** with $LiAlH_4$ and acetylating the resulting alcohol to form **32h** (3:1 dr anti/syn) as a reference.

The ^{1}H NMR data of the reduction/acetylation product matched those obtained via oxidative methylation.

Run 1 (69.2 mg, 0.202 mmol, 67% yield; 1.7:1 dr; 4.0 mg, 0.012 mmol, 4% rsm)

Run 2 (70.7 mg, 0.207 mmol, 69% yield, 1.7:1 dr; 10.4 mg, 0.0316 mmol, 11% rsm)

Run 3 (68.4 mg, 0.200 mmol, 67% yield, 1.7:1 dr; 13.1 mg, 0.0400 mmol, 13% rsm)

Average overall yield: 68% (9% rsm) ± 1.2, 1.7:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

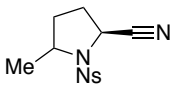
δ 8.36 (d, *J* = 8.4 Hz, 0.76H), 8.33 (d, *J* = 8.7 Hz, 1.24H), 8.09-8.00 (m, 2H), 4.37-4.28 (m, 0.62H), 4.20 (dd, *J* = 11.1, 4.8 Hz, 0.38H), 4.16-4.09 (m, 1H), 4.10-3.98 (m, 1.24H), 3.90 (td, *J* = 7.1, 3.6 Hz, 0.38H), 3.70 (sxt, *J* = 6.3 Hz, 0.38H), 2.21-2.01 (m, 1.52H), 2.07 (s, 1.14H), 1.96 (s, 1.86H), 1.86 (dd, *J* = 12.2, 6.1 Hz, 0.62H), 1.78-1.68 (m, 0.62H), 1.57 (dq, *J* = 9.8, 5.1 Hz, 1.24H), 1.36 (d, *J* = 6.3 Hz, 1.14H), 1.20 (d, *J* = 6.4 Hz, 1.86H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.77, 170.49, 150.29, 149.22, 147.69, 143.76, 128.84, 128.28, 124.49, 124.40, 66.26, 64.83, 59.85, 58.43, 58.30, 57.71, 32.32, 31.45, 27.46, 27.04, 23.00, 21.11, 20.99, 20.87

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{14}H_{19}N_2O_6S$ $[M+H]^+$: 343.0964, found 343.0960



(2*S*)-5-Methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carbonitrile [32i] To a 40 mL vial equipped with a stir bar were added (*S*)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carbonitrile **31i** (84.4 mg, 0.30 mmol, 1.0 equiv.), MeCN (0.6 mL, 0.5 M), and AcOH (257 μL, 4.50 mmol, 15.0 equiv.). The vial was then placed into ice bath while stirring. A 1 mL syringe was charged with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol,

0.005 equiv.) in MeCN (0.375 mL, 0.004 M to catalyst). Likewise, a 10 mL syringe was charged with H_2O_2 (85.2 µL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Both syringes were fitted with 25G needles and solutions were added simutaneously using the same syringe pump over 1 h at 0 °C. The reaction mixture was then worked up according to the general oxidation procedure. Following work up, the crude was methylated with DAST (39.6 µL, 48.3 mg, 0.30 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 450 µL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 10%→600 mL 20% EtOAc/Hex) to afford the product as a white gel as a mixture of diastereomers.

Run 1 (42.8 mg, 0.145 mmol, 48% yield; 1.5:1 dr; 26% rsm by ^{1}H NMR)

Run 2 (38.2 mg, 0.129 mmol, 43% yield, 1.5:1 dr; 28% rsm by ^{1}H NMR)

Run 3 (38.3 mg, 0.130 mmol, 43% yield, 1.5:1 dr; 32% rsm by ^{1}H NMR)

Average overall yield: 45% (29% rsm) ± 2.9, 1.5:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

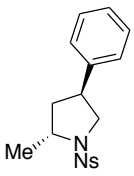
δ 8.40 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.6 Hz, 1.2H), 8.11 (d, *J* = 8.6 Hz, 0.8H), 4.76 (d, *J* = 7.5 Hz, 0.6H), 4.73 (dd, *J* = 8.2, 3.8 Hz, 0.4H), 4.04 (sxt, *J* = 6.5 Hz, 0.4H), 3.86 (p, *J* = 6.7 Hz, 0.6H), 2.44-2.31 (m, 0.6H), 2.30-2.09 (m, 2.4H), 1.91-1.77 (m, 1H), 1.40 (d, *J* = 6.4 Hz, 1.8H), 1.31 (d, *J* = 6.3 Hz, 1.2H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 150.56, 150.47, 145.13, 143.62, 129.31, 128.64, 124.73, 124.44, 118.45, 116.93, 58.21, 56.20, 50.12, 49.62, 33.43, 32.72, 30.88, 29.41, 22.44, 21.60

HRMS: (ESI-TOF MS ES+) (mixture of diastereomers)

m/z calculated for $C_{11}H_{13}N_2O_4S$ $[M\text{-}CN]^+$: 269.0596, found 269.0589



Trans-2-methyl-1-((4-nitrophenyl)sulfonyl)-4-phenylpyrrolidine [(±)-32j]

According to a modified general oxidation procedure and the BF_3-promoted methylation procedure, 1-((4-nitrophenyl)sulfonyl)-3-phenylpyrrolidine **31j** (99.7 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 µL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (34.6 µL, 0.60 mmol, 2.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M) at 0 °C in ice bath. Following oxidation, the crude was methylated with trimethylaluminum (2.0 M in hexanes, 450 µL, 0.90 mmol, 3.0 equiv.) and BF_3•OEt_2 (74.0 µL, 0.60 mmol, 2.0 equiv.). Following workup, the crude material was purified by medium-pressure liquid chromatography (24 g silica, 70 column volumes 0%→20% EtOAc/Hex) to afford the product as a light yellow solid as a mixture of diastereomers. The stereochemistry was determined by ^{1}H NMR, NOESY 2D, and COSY methods.

Run 1 (36.5 mg, 0.105 mmol, 35% yield, 6:1 dr; 31.6 mg, 0.0951 mmol, 32% rsm)

Run 2 (38.5 mg, 0.123 mmol, 37% yield, 6:1 dr; 26.4 mg, 0.0794 mmol, 26% rsm)

Run 3 (35.3 mg, 0.102 mmol, 34% yield, 7:1 dr; 21.1 mg, 0.0635 mmol, 21% rsm)

Average overall yield: 35% (26% rsm) ± 1.5, 6:1 dr

Characterization of major diastereomer (±)-**32j**:

^{1}H NMR: (500 MHz, $CDCl_3$)

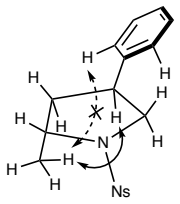
δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.28-7.18 (m, 3H), 7.06-7.03 (m, 2H), 3.99 (qd, *J* = 6.4, 4.3 Hz, 1H), 3.91 (dd, *J* = 9.4, 7.2 Hz, 1H), 3.56 (p, *J* = 8.8 Hz, 1H), 3.06 (t, *J* = 9.7 Hz, 1H), 1.97-1.90 (m, 2H), 1.44 (d, *J* = 6.4 Hz, 3H)

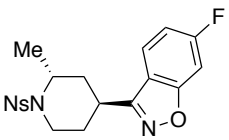
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.19, 143.60, 139.42, 128.87, 128.65, 127.36, 126.96, 124.44, 56.64, 55.48, 41.67, 39.81, 23.44

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{19}N_2O_4S$ $[M+H]^+$: 347.1066, found 347.1059





6-fluoro-3-(trans-2-methyl-1-((4-nitrophenyl)sulfonyl)piperidin-4-yl)benzo[*d*]isoxazole [(±)-32k] According to modified general oxidation and DAST-promoted methylation procedures, in a 40-mL vial were added 6-fluoro-3-(1-((4-nitrophenyl)sulfonyl)piperidin-4-yl)benzo[*d*]isoxazole **31k** (121.6 mg, 0.30 mmol, 1.0 equiv.), 1:1.7 MeCN/CH_2Cl_2 (2.7 mL, 0.11 M), and AcOH (257 μL, 4.50 mmol, 15.0 equiv.). H_2O_2 (85.2 μL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in 4:1 MeCN/CH_2Cl_2 (3.75 mL) and (*S*,*S*)-Mn(CF_3PDP) (40.7 mg, 0.03 mmol, 0.10 equiv.) in 4:1 MeCN/CH_2Cl_2 (0.37 mL) were transferred to 10 mL and 1 mL synringes and added concurrently via a syringe pump into the vial in 1 h at room temperature. Following oxidation and workup, the oxidation products were isolated from the starting material through flash chromatography (50 mL silica, 200 mL 2% MeOH/CH_2Cl_2), and methylated with DAST (39.6 μL, 48.3 mg, 0.30 mmol, 1.0 equiv.) (florination at -78 °C for 10 min, then room temperature for 50 min) and trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, 300 mL 20% EtOAc/Hex) to afford the product

as a white solid. The starting material was resubjected to the reaction conditions 1x. The stereochemistry was determined based on ^{1}H NMR, COSY, and NOESY 2D NMR methods.

Run 1 (1st cycle: 37.7 mg, 0.0898 mmol, 30% yield, >20:1 dr; 42.2 mg, 0.104 mmol, 35% rsm. 2nd cycle: 10.0 mg, 0.0238 mmol, 23% yield, >20:1 dr; 17.7 mg, 0.0438 mmol, 42% rsm. Overall: 47.7 mg, 0.114 mmol, 38% yield, >20:1 dr; 17.7 mg, 0.0438 mmol, 15% rsm)

Run 2 (1st cycle: 34.8 mg, 0.0830 mmol, 28% yield, >20:1 dr; 33.0 mg, 0.0814 mmol, 27% rsm. 2nd cycle: 11.9 mg, 0.0283 mmol, 35% yield, >20:1 dr; 11.4 mg, 0.0281 mmol, 35% rsm. Overall: 46.7 mg, 0.111 mmol, 37% yield, >20:1 dr; 11.4 mg, 0.0281 mmol, 9% rsm)

Run 3 (1st cycle: 37.7 mg, 0.0898 mmol, 30% yield, >20:1 dr; 35.6 mg, 0.0878 mmol. 29% rsm. 2nd cycle: 6.3 mg, 0.015 mmol, 17% yield, >20:1 dr; 17.2 mg, 0.0424 mmol, 48% rsm. Overall: 44.0 mg, 0.105 mmol, 35% yield, >20:1 dr; 17.2 mg, 0.0424 mmol, 14% rsm)

Average overall yield: 37% (13% rsm) ± 1.5, >20:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.38 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.52 (dd, *J* = 8.7, 5.0 Hz, 1H), 7.26-7.22 (m, 1H), 7.06 (td, *J* = 8.8, 2.1 Hz, 1H), 4.53 (p, *J* = 6.3 Hz, 1H), 4.05-3.96 (m, 1H), 3.45 (tt, *J* = 12.4, 3.5 Hz, 1H), 3.27 (td, *J* = 13.4, 2.7 Hz, 1H), 2.16-2.05 (m, 2H), 1.99-1.91 (m, 1H), 1.88 (qd, *J* = 13.0, 4.6 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

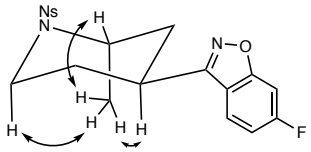
δ 164.27 (d, *J* = 251.3 Hz), 164.19 (d, *J* = 14.0 Hz), 160.06, 150.11, 147.01, 128.28, 124.69, 122.13 (d, *J* = 11.1 Hz), 116.85, 112.90 (d, *J* = 25.3 Hz), 97.88 (d, *J* = 26.9 Hz), 48.81, 40.13, 35.32, 30.25, 28.85

^{19}F NMR: (470 MHz, $CDCl_3$)

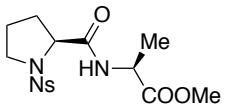
δ -108.67 (td, *J* = 8.6, 5.1 Hz)

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{19}H_{19}N_3O_5SF$ $[M+H]^+$: 420.1029, found 420.1041



3.4.5 Synthesis of Substrates and Characterization for Figure 19



Methyl ((4-nitrophenyl)sulfonyl)-*L*-prolyl-*L*-alaninate [33a] In a 500-mL round-bottom flask were added ((4-nitrophenyl)sulfonyl)-*L*-proline[61] (4.53 g, 15.1 mmol, 1 equiv.), *L*-alanine methyl ester hydrochloride (2.11 g, 15.1 mmol, 1 equiv.), and CH_2Cl_2 (160 mL). The mixture was cooled to 0 °C, and DIPEA (2.63 mL, 1.95 g, 15.1 mmol, 1 equiv.) was added dropwise, followed by HOBt (80 wt%, 2.81 g, 16.6 mmol, 1.1 equiv.) and EDC (2.34 g, 15.1 mmol, 1 equiv.). The mixture was then taken out of the ice bath and stirred overnight, and washed with 10% citric acid, brine, and sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$ and condensed in vacuo. Purification by medium-pressure liquid chromatography (40 g silica, 15 column volumes 0%→5%→10 column volumes 5% MeOH/CH_2Cl_2) afforded the product as a pale yellow powder (2.62 g, 6.81 mmol, 45% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.40 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 4.55 (p, *J* = 7.2 Hz, 1H), 4.19 (dd, *J* = 8.5, 2.9 Hz, 1H), 3.78 (s, 3H), 3.58 (ddd, *J* = 10.8, 7.4, 3.4 Hz, 1H), 3.27 (td, *J* = 9.4, 6.6 Hz, 1H), 2.27-2.19 (m, 1H), 1.94-1.81 (m, 1H), 1.81-1.67 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

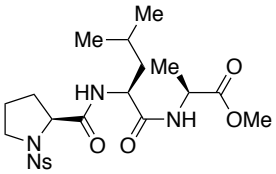
δ 172.94, 170.23, 150.63, 142.53, 129.21, 124.66, 62.47, 52.76, 49.86, 48.56, 30.37, 24.71, 18.48

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{15}H_{20}N_3O_7S$ $[M+H]^+$: 386.1022, found 386.1020

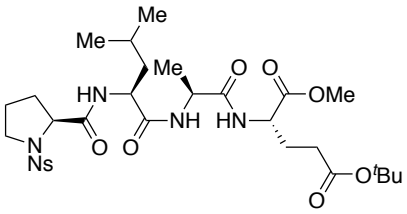
$[\alpha]_D^{24}$ = -120.9º (c = 1.15, CH_2Cl_2)

Methyl ((4-nitrophenyl)sulfonyl)-*L*-prolyl-*L*-leucyl-*L*-alaninate [33b]



Prepared according to the general procedure for peptide couplings as reported in literature and the NMR data matched those reported.[61]

5-(*tert*-Butyl) 1-methyl ((4-nitrophenyl)sulfonyl)-*L*-prolyl-*L*-leucyl-*L*-alanyl-*L*-glutamate [33c]



Prepared according to the general procedure for peptide couplings as reported in literature.[61]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.47 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 4.58 – 4.50 (m, 2H), 4.46 (ddd, *J* = 9.9, 7.7, 4.4 Hz, 1H), 4.06 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.75 (s, 3H), 3.72 (ddd, *J* = 10.5, 6.7, 4.2 Hz, 1H),

3.19 (ddd, *J* = 10.0, 8.4, 6.6 Hz, 1H), 2.42 – 2.26 (m, 2H), 2.21 – 1.79 (m, 5H), 1.76 – 1.60 (m, 4H), 1.44 (s, 9H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H)

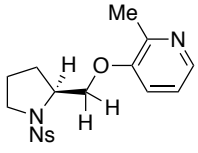
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.31, 172.07, 172.05, 171.44, 171.40, 150.97, 140.45, 129.63, 124.99, 80.94, 62.80, 52.88, 52.60, 51.99, 50.37, 48.97, 40.37, 31.85, 31.22, 28.23, 27.51, 25.50, 24.81, 23.25, 21.56, 17.47

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{30}H_{46}N_5O_{11}S$ $[M+H]^+$: 684.2915, found 684.2917.

$[\alpha]_D^{24}$ = -99.8º (c = 1.22, CH_2Cl_2)



(*S*)-2-Methyl-3-((1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methoxy)pyridine [33d] According to the general procedure for nosyl protection, L-prolinol (425 mg, 4.20 mmol, 1 equiv.) was reacted with DMAP (51.3 mg, 0.420 mmol, 0.1 equiv.), Et_3N (644 μL, 467 mg, 4.62 mmol, 1.1 equiv.), and NsCl (1.02 g, 4.62 mmol, 1.1 equiv.) in CH_2Cl_2 (10 mL). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elusion 200 mL 2%→5% MeOH/CH_2Cl_2) to afford (*S*)-(1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methanol with minor byproducts (roughly 970 mg, 3.39 mmol, 81% yield). In a separate 100-mL recovery flask triphenylphosphine (1.34 g, 5.09 mmol, 1.5 equiv.) and THF (13 mL) were added. The reaction was cooled to 0 °C, where DEAD (799 μL, 886 mg, 5.09 mmol, 1.5 equiv.) was added dropwise, and the reaction was stirred for 30 min. (*S*)-(1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methanol and 2-methylpyridin-3-ol (555 mg, 5.09 mmol, 1.5 equiv.) in THF (5 mL) were then both added

to the reaction mixture, and the reaction was stirred overnight at room temperature. The solvent was removed in vacuo, and the brown crude was repeatedly washed with hexanes and then CH_2Cl_2. The CH_2Cl_2 wash was recrystallized by slowly evaporating CH_2Cl_2 in the fume hood, and the resulting crystals were washed with EtOAc 3x to afford the product as off-white crystals (434 mg, 1.15 mmol, 23% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.11 (dd, *J* = 4.5, 1.7 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.21-7.06 (m, *J* = 2H), 4.30 – 4.20 (m, 1H), 4.06 – 3.96 (m, 2H), 3.59 (ddd, *J* = 10.7, 7.1, 4.0 Hz, 1H), 3.26 – 3.17 (m, 1H), 2.43 (s, 3H), 2.14 – 1.98 (m, 2H), 1.85 – 1.67 (m, 2H).

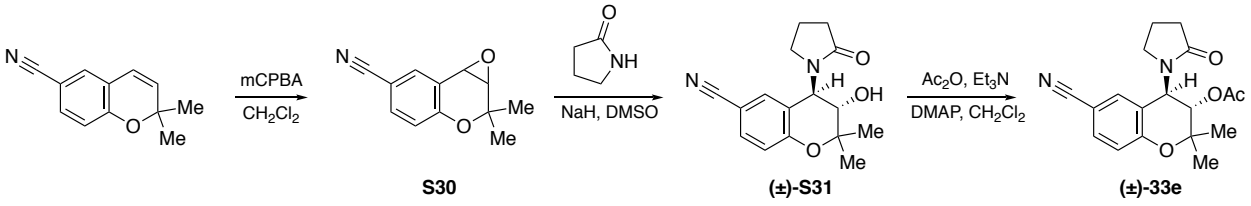
^{13}C NMR: (126 MHz, $CDCl_3$)

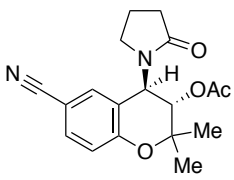
δ 152.64, 150.33, 148.68, 143.27, 141.06, 128.70, 124.58, 121.96, 117.50, 69.69, 58.87, 49.65, 29.13, 24.28, 19.62

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{20}N_3O_5S$ $[M+H]^+$: 378.1124, found 378.1116

$[\alpha]_D^{24}$ = -149.7º (c = 1.00, CH_2Cl_2)





Trans-6-cyano-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)chroman-3-yl acetate [(±)-33e] In a 100-mL round-bottom flask were added 2,2-dimethyl-4a,8a-dihydro-2*H*-chromene-6-carbonitrile (878 mg, 4.74 mmol, 1.0 equiv.) and CH_2Cl_2 (18 mL). The solution was placed into an ice bath, and mCPBA (70 wt%, 1.4 g, 5.69

mmol, 1.2 equiv.) was added in one portion. The reaction was stirred overnight and quenched with sat. $Na_2S_2O_3$ and then sat. $NaHCO_3$. Purification by flash column chromatography (50 mL silica, 200 mL 20%→30% EtOAc/Hex) afforded 2,2-dimethyl-1a,7b-dihydro-2*H*-oxireno[2,3-*c*]chromene-6-carbonitrile **S30** as a pale-white oil (954 mg, 4.74 mmol, quantitative yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 3.91 (d, *J* = 4.4 Hz, 1H), 3.54 (d, *J* = 4.3 Hz, 1H), 1.60 (s, 3H), 1.30 (s, 3H). In a 100-mL round-bottom flask carrying **S30** was added 2-pyrrolidinone (403 mg, 4.74 mmol, 1.0 equiv.) and DMSO (28 mL). NaH (60 wt%, 190 mg, 4.74 mmol, 1.0 equiv.) was then added upon stirring. The reaction was stirred for 6 h, quenched with water, and extracted with EtOAc 3x. The organic layer was washed with water 2x and brine 1x, and dried over $MgSO_4$. Purification by medium-pressure liquid chromatography (40 g silica, 50 column volumes 40%→100% EtOAc/Hex→10 column volumes EtOAc) afforded trans-3-hydroxy-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)chromane-6-carbonitrile (±)-**S31** as a white powder (755 mg, 2.64 mmol, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.44 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.23 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.11 (d, *J* = 6.8 Hz, 1H), 3.74 (dd, *J* = 10.4, 6.6 Hz, 1H), 3.37 (dt, *J* = 9.5, 7.6 Hz, 1H), 3.04 (td, *J* = 8.9, 4.4 Hz, 1H), 2.62 – 2.51 (m, 2H), 2.21 – 2.01 (m, 2H), 1.53 (s, 3H), 1.27 (s, 3H). In a 100-mL round-bottom flask carrying **S31** (385 mg, 1.34 mmol, 1.0 equiv.) was added DMAP (16.4 mg, 0.134 mmol, 0.1 equiv.), CH_2Cl_2 (10 mL), Et_3N (934 μL, 678 mg, 6.70 mmol, 5.0 equiv.), and Ac_2O (380 μL, 410 mg, 4.02 mmol, 3.0 equiv.). The reaction was stirred overnight, and then quenched with sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 2x and the organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. Purification by flash chromatography (50 mL silica, 300 mL 40%→60% EtOAc/Hex) afforded the product as a white powder (326 mg, 0.99 mmol, 74% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

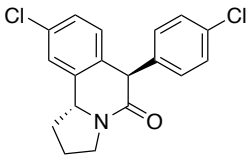
δ 7.48 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.26 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.46 (d, *J* = 10.1 Hz, 1H), 5.15 (d, *J* = 10.1 Hz, 1H), 3.37 (dt, *J* = 9.3, 7.3 Hz, 1H), 2.93 (dt, *J* = 9.2, 6.7 Hz, 1H), 2.53 (dt, *J* = 17.1, 7.6 Hz, 1H), 2.41 (dt, *J* = 17.0, 8.4 Hz, 1H), 2.11 (s, 3H), 2.01 (p, *J* = 7.5 Hz, 2H), 1.43 (s, 3H), 1.35 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 176.97, 170.40, 157.15, 133.40, 132.02, 120.56, 119.14, 118.88, 105.02, 78.66, 69.80, 49.72, 42.60, 31.20, 26.39, 21.02, 19.63, 18.32

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{18}H_{21}N_2O_4$ $[M+H]^+$: 329.1501, found 329.1511



rel-(6*R*,10b*R*)-9-Chloro-6-(4-chlorophenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one [33f] According to literature[82], in a 100-mL round-bottom flask were added 2-(3-chlorophenyl)pyrrolidine (910 mg, 5.01 mmol, 1.0 equiv.), 4-chloromandelic acid (934 mg, 5.01 mmol, 1.0 equiv.), and xylene (15 mL). A Dean-Stark trap and reflux condenser were placed on top of the flask. The reaction was refluxed for 40 h, and the solvent was removed in vacuo. PPA (7.5 mL) was then added to the flask, and the flask was placed into a 100 °C oil bath and heated for 1.5 h. Upon completion, water (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 3x. The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. Purification by flask chromatography (75 mL silica, 300 mL 30% EtOAc/Hex) followed by medium-pressure liquid chromatography (40 g silica, 60 column volumes 0%→40% EtOAc/Hex)

afforded the product as a light yellow foam (170 mg, 0.51 mmol, 10% yield). Stereochemistry was assigned by ^{1}H NMR, COSY, and NOESY 1D methods.

^{1}H NMR: (500 MHz, $CDCl_3$)

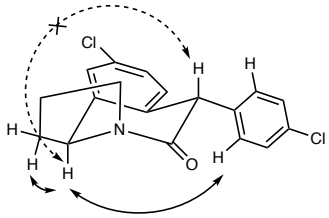
δ 7.34 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.28 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 4.84 (s, 1H), 4.47 (dd, *J* = 10.1, 5.8 Hz, 1H), 3.65 – 3.50 (m, 2H), 2.63-2.57 (m, 1H), 2.19 – 2.09 (m, 1H), 2.00 – 1.86 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$)

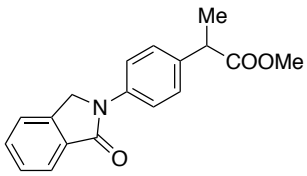
δ 167.85, 138.84, 136.06, 133.95, 133.64, 133.43, 130.00, 128.97, 128.74, 128.60, 125.01, 58.77, 53.24, 45.49, 31.71, 23.06

HRMS: (ESI-TOF MS ES+)

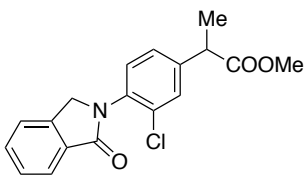
m/z calculated for $C_{18}H_{16}NOCl_2$ $[M+H]^+$: 332.0609, found 332.0604



Methyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate [33g]



Prepared according to literature and the NMR data matched those reported.[83]



Methyl 2-(3-chloro-4-(1-oxoisoindolin-2-yl)phenyl)propanoate [33h]

In a 50-mL recovery flask was added methyl 2-(4-(1-oxoisoindolin-2-

yl)phenyl)propanoate **33g** (713 mg, 2.41 mmol, 1.0 equiv.), toluene (12 mL), trifluoroacetic acid (92 μL, 137 mg, 1.21 mmol, 0.5 equiv.), and *N*-chlorosuccinimide (484 mg, 3.62 mmol, 1.5 equiv.). The reaction was stirred at room temperature overnight, quenched with $NaHCO_3$, and extracted with CH_2Cl_2 3x. The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. Purification by medium-pressure liquid chromatography (40 g silica, 55 column volumes 0%→50% EtOAc/Hex) afforded the product as a white powder (544 mg, 1.65 mmol, 68% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.96 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.62 (td, *J* = 7.5, 1.2 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.31 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.80 (s, 2H), 3.75 (q, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 1.53 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.26, 168.29, 142.12, 141.77, 134.90, 132.81, 132.16, 132.04, 130.19, 129.85, 128.41, 127.25, 124.62, 123.01, 52.46, 52.35, 45.04, 18.60

IR: (cm^{-1})

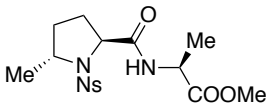
2955, 1733, 1683, 1500, 1469, 1447, 1433, 1399, 1336, 1302, 1255, 1212, 1197, 1168, 1100, 1078, 1046, 1016, 972, 921, 895, 867, 838, 800, 784, 758, 735, 682, 609, 578, 510, 484, 455

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{18}H_{17}NO_3Cl$ $[M+H]^+$: 330.0897, found 330.0897

3.4.6 Experimental Procedures and Characterization for Figure 19

General procedures. In Figure 19 the same general procedures for C–H oxidation, BF_3-promoted methylation, and DAST-promoted methylation were followed for all substrates unless otherwise specified.



Methyl ((2*S*,5*R*)-5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carbonyl)-*L*-alaninate [34a] According to the general oxidation and DAST-promoted methylation procedures, methyl ((4-nitrophenyl)sulfonyl)-*L*-prolyl-*L*-alaninate **33a** (115.6 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 μL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (85.2 μL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Following oxidation, the crude was methylated with DAST (39.6 μL, 48.3 mg, 0.30 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 20%→400 mL 30% EtOAc/Hex) to afford the product as a white solid or gel. The stereochemistry was determined based on ^{1}H NMR, COSY, and NOESY 1D NMR methods.

Run 1 (75.7 mg, 0.189 mmol, 63% yield; 6:1 dr; 3% rsm by ^{1}H NMR)

Run 2 (75.5 mg, 0.189 mmol, 63% yield, 6:1 dr; 2% rsm by ^{1}H NMR)

Run 3 (73.5 mg, 0.184 mmol, 61% yield, 6:1 dr; 6% rsm by ^{1}H NMR)

Average overall yield: 62% (4% rsm) ± 1.2, 6:1 dr

A similar yield (69.0 mg, 0.173 mmol, 58% yield; 5:1 dr; 14% rsm by ^{1}H NMR) was obtained when substituting DAST for Deoxo-Fluor (55.3 μL, 66.4 mg, 0.30 mmol, 1.0 equiv.).

Characterization for major diastereomer **34a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.33 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 6.38 (d, *J* = 7.2 Hz, 1H), 4.45 (p, *J* = 7.2 Hz, 1H), 4.40-4.36 (m, 1H), 4.07-4.00 (m, 1H), 3.75 (s, 3H), 2.32-2.20 (m, 2H), 2.11-2.00 (m, 1H), 1.66-1.58 (m, 1H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H)

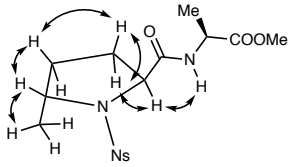
^{13}C NMR: (126 MHz, $CDCl_3$)

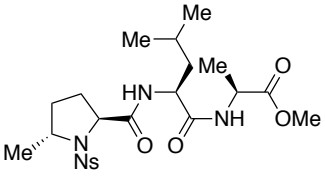
δ 173.13, 170.79, 150.10, 146.04, 129.02, 124.13, 63.10, 57.21, 52.77, 48.42, 32.46, 29.09, 21.42, 18.42

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{16}H_{22}N_3O_7S$ $[M+H]^+$: 400.1178, found 400.1180

$[\alpha]_D^{24}$ = -102.0º (c = 0.10, CH_2Cl_2)





Methyl ((2*S*,5*R*)-5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carbonyl)-*L*-leucyl-*L*-alaninate [34b] According to the general oxidation and DAST-promoted methylation procedures, methyl ((4-nitrophenyl)sulfonyl)-*L*-prolyl-*L*-leucyl-*L*-alaninate **33b** (149.6 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 μL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (85.2 μL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). For facile product isolation, the oxidized products were isolated following oxidation by flash chromatography (dry loading, 50 mL silica, gradient elution 200 mL 20%→30%→40%→100% EtOAc/$CHCl_3$). The starting material was resubjected 1x to the oxidation conditions, and the oxidized products were combined. The combined hemiaminal was then methylated with DAST (39.6 μL, 48.3 mg, 0.30 mmol, 1.0 equiv.) and

trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 500 mL 50%→200 mL 75% EtOAc/Hex) to afford the product as a white solid as a mixture of diastereomers. The stereochemistry was determined by analogy to compounds **32g** and **34a**.

Run 1 (93.4 mg, 0.182 mmol, 61% yield, 6:1 dr; 31.3 mg, 0.0628 mmol, 21% rsm)

Run 2 (86.8 mg, 0.169 mmol, 56% yield, 8:1 dr; 33.9 mg, 0.0680 mmol, 23% rsm)

Average overall yield: 59% (22% rsm) ± 3.5, 7:1 dr

Methylation with BF_3•OEt_2: trace yield, 18% rsm by ^{1}H NMR.

Characterization for major diastereomer **34b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 4.54 (p, *J* = 7.3 Hz, 1H), 4.47 (td, *J* = 9.4, 4.8 Hz, 1H), 4.32 (d, *J* = 8.6 Hz, 1H), 4.24 (p, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 2.26 (tdd, *J* = 12.0, 8.7, 6.1 Hz, 1H), 2.17 (dq, *J* = 12.0, 5.6, 4.8 Hz, 1H), 2.13-2.06 (m, 1H), 1.82 (ddd, *J* = 13.8, 8.8, 4.8 Hz, 1H), 1.68-1.54 (m, 3H), 1.37 (d, *J* = 7.3 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H)

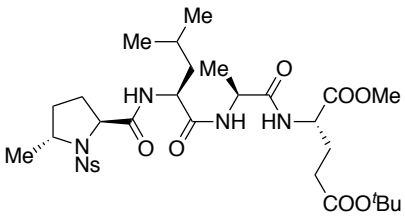
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 173.20, 171.25, 171.20, 150.31, 145.31, 129.19, 124.40, 62.96, 57.99, 52.55, 52.12, 48.22, 41.01, 32.18, 29.55, 25.18, 23.26, 21.74, 20.46, 18.16

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{22}H_{33}N_4O_8S$ $[M+H]^+$: 513.2019, found 513.2025

$[\alpha]_D^{24}$ = -101.9º (c = 0.87, CH_2Cl_2)



5-(*tert*-Butyl) 1-methyl ((2*S*,5*R*)-5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carbonyl)-*L*-leucyl-*L*-alanyl-*L*-glutamate [34c] According to the general oxidation and fluorination-promoted methylation procedures, 5-(*tert*-butyl) 1-methyl ((4-nitrophenyl)sulfonyl)-*L*-prolyl-*L*-leucyl-*L*-alanyl-*L*-glutamate **33c** (205.1 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.005 equiv.), AcOH (257 μL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (85.2 μL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). For facile product isolation, the oxidized products were isolated following oxidation by flash chromatography (dry loading, 50 mL silica, gradient elution 200 mL 50%→60%→400 mL 70% EtOAc/Hex), and methylated with Deoxo-Fluor (55.3 μL, 66.4 mg, 0.30 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, gradient elution 200 mL 20%→400 mL 30% EtOAc/Hex) to afford the product as a white solid. The starting material was then resubjected once to the oxidation and methylation conditions. The stereochemistry was determined by analogy to compounds **32g** and **34a**.

Run 1 (1st cycle: 81.3 mg, 0.117 mmol, 39% yield, 6:1 dr; 75.2 mg, 0.110 mmol, 37% rsm. 2nd cycle: 26.8 mg, 0.0384 mmol, 35% yield, 4:1 dr; 37.1 mg, 0.0543 mmol, 49% rsm. Overall: 108.1 mg, 0.155 mmol, 52% yield, 5:1 dr; 37.1 mg, 0.0543 mmol, 18% rsm)

Run 2 (1st cycle: 71.4 mg, 0.102 mmol, 34% yield, 5:1 dr; 97.7 mg, 0.143 mmol, 48% rsm. 2nd cycle: 31.8 mg, 0.0456 mmol, 32% yield, 5:1 dr; 52.6 mg, 0.0769 mmol, 54% rsm. Overall: 103.2 mg, 0.148 mmol, 49% yield, 5:1 dr; 52.6 mg, 0.0769 mmol, 26% rsm)

Run 3 (1st cycle: 80.6 mg, 0.115 mmol, 38% yield, 6:1 dr; 113.2 mg, 0.166 mmol, 55% rsm. 2nd cycle: 27.2 mg, 0.0390 mmol, 29% yield, 4:1 dr; 49.6 mg, 0.0725 mmol, 55% rsm. Overall: 107.8 mg, 0.154 mmol, 51% yield, 5:1 dr; 49.6 mg, 0.0725 mmol, 24% rsm)

Average overall yield: 51% (23% rsm) ± 1.5, 5:1 dr

Characterization for major diastereomer **34c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.41 (d, *J* = 8.3 Hz, 2H), 8.15 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.43 (d, *J* = 7.5 Hz, 1H), 4.52 (app p, *J* = 7.4 Hz, 2H), 4.45-4.36 (m, 2H), 4.33 (p, *J* = 6.6 Hz, 1H), 3.74 (s, 3H), 2.42-2.23 (m, 3H), 2.21-2.07 (m, 3H), 2.07-1.96 (m, 1H), 1.91-1.80 (m, 1H), 1.73-1.59 (m, 3H), 1.45 (s, 9H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.95 (d, *J* = 6.1 Hz, 3H)

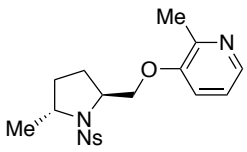
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.37, 172.10, 172.07, 171.43, 150.49, 145.47, 129.21, 124.70, 80.97, 63.07, 58.07, 53.02, 52.59, 51.98, 48.93, 40.52, 32.23, 31.92, 29.55, 28.25, 27.50, 25.47, 23.30, 21.51, 19.95, 17.56

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{31}H_{48}N_5O_{11}S$ $[M+H]^+$: 698.3071, found 698.3071

$[\alpha]_D^{24}$ = -73.0º (c = 0.38, CH_2Cl_2)



2-Methyl-3-(((2*S*,5*R*)-5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methoxy)pyridine [34d] According to a modified general oxidation procedure and the BF_3-promoted methylation procedure, in a 40-mL vial was added (*S*)-2-methyl-3-((1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methoxy)pyridine **33d**

(75.5 mg, 0.20 mmol, 1.0 equiv.), CH_2Cl_2 (0.8 mL), and HBF_4•OEt_2 (29.9 μL, 0.22 mmol, 1.1 equiv.). The reaction mixture was stirred for 1 h, and the solvent was removed in vacuo. The crude was placed on high vacuum overnight to remove the residual acid. The crude was then redissolved in MeCN (0.4 mL, 0.5 M) and oxidized with (*S*,*S*)-Mn(CF_3PDP) (27.1 mg, 0.020 mmol, 0.10 equiv.), AcOH (172 μL, 3.00 mmol, 15.0 equiv.), and H_2O_2 (56.8 μL, 1.00 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (2.50 mL, 0.4 M). Following oxidation, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and poured into a 60-mL separatory funnel containing 1.5 M K_2CO_3 (5 mL), and the mixture was shaken vigorously for deprotonation. The layers were seperated and the aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. For facile isolation, the oxidaion products were isolated by flash chromatography (50 ml silica dry loading, 200 mL 2%→5% MeOH/CH_2Cl_2), and then methylated with trimethylaluminum (2.0 M in hexanes, 300 μL, 0.60 mmol, 3.0 equiv.) and BF_3•OEt_2 (74.1 μL, 85.2 mg, 0.60 mmol, 3.0 equiv.). Following workup, the crude material was purified by medium-pressure liquid chromatography (12 g silica, 50 column volumes 0%→5% MeOH/CH_2Cl_2) to afford the product as a white solid as a mixture of diastereomers. The stereochemistry was determined by analogy to compounds **32g** and **34a**.

Run 1 (28.2 mg, 0.0720 mmol, 36% yield; 6:1 dr; 2% rsm by ^{1}H NMR)

Run 2 (26.6 mg, 0.0680 mmol, 34% yield, 5:1 dr; 2% rsm by ^{1}H NMR)

Run 3 (25.9 mg, 0.0662 mmol, 33% yield, 6:1 dr; 2% rsm by ^{1}H NMR)

Average overall yield: 34% (2% rsm) ± 1.5, 6:1 dr

Lower mass balance was likely caused by overoxidation resulting from high catalyst loading (ca. 51% hemiaminal produced from oxidation with the rest of the material being a complex mixture). Methylation with DAST: 28% yield, 3:1 dr by ^{1}H NMR.

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

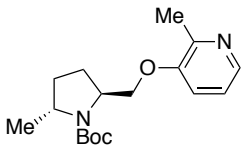
δ 8.38 (d, *J* = 8.7 Hz, 0.32H), 8.15 (d, *J* = 8.9 Hz, 1.68H), 8.11 (d, *J* = 4.5 Hz, 0.16H), 8.09-8.02 (m, 1.16H), 7.96 (d, *J* = 8.8 Hz, 1.68H), 7.18 (d, *J* = 8.0 Hz, 0.16H), 7.12 (dd, *J* = 8.2, 4.8 Hz, 0.16H), 7.05 (dd, *J* = 8.1, 4.8 Hz, 0.84H), 6.95 (d, *J* = 8.1 Hz, 0.84H), 4.33-4.18 (m, 1.84H), 4.13 (dd, *J* = 9.8, 2.6 Hz, 0.84H), 4.05 (dd, *J* = 9.8, 6.0 Hz, 0.84H), 4.02-3.93 (m, 0.32H), 3.72 (sxt, *J* = 6.3 Hz, 0.16H), 2.46 (s, 0.48H), 2.41-2.31 (m, 0.84H), 2.29 (s, 2.52H), 2.28-2.20 (m, 0.84H), 2.11 (dd, *J* = 12.9, 7.1 Hz, 0.84H), 2.08-1.99 (m, 0.16H), 1.80-1.71 (m, 0.48H), 1.65 (dd, *J* = 12.1, 6.8 Hz, 0.84H), 1.42 (d, *J* = 6.3 Hz, 0.48H), 1.29 (d, *J* = 6.4 Hz, 2.52H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 152.69, 152.26, 150.35, 149.64, 148.77, 148.32, 147.70, 143.35, 141.16, 141.11, 128.83, 127.91, 124.57, 124.22, 121.93, 121.78, 117.55, 116.83, 70.15, 68.34, 60.45, 59.21, 58.43, 58.03, 32.26, 31.95, 27.58, 27.51, 22.94, 21.67, 19.82, 19.72

HRMS: (ESI-TOF MS ES+) (mixture of diastereomers)

m/z calculated for $C_{18}H_{22}N_3O_5S$ $[M+H]^+$: 392.1280, found 392.1272



***tert*-Butyl (2*R*,5*S*)-2-methyl-5-(((2-methylpyridin-3-yl)oxy)methyl)pyrrolidine-1-carboxylate [35]** According to literature[5], in a 25-mL recovery flask was added 2-methyl-3-(((2*S*,5*R*)-5-methyl-1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methoxy)pyridine **34d** as a mixture of diastereomers (15.8 mg, 0.0404 mmol, 1.0 equiv.), MeCN (1.5 mL), and cesium carbonate (52.7 mg, 0.162 mmol, 4.0 equiv.). The flask was backfilled with nitrogen 3x, and DMSO (30 μL) and thiophenol (14.5 μL, 15.6 mg, 0.141 mmol, 3.5 equiv.) were added. The flask was placed in 45 °C oil bath and

stirred vigorously overnight. Upon completion, the crude was partitioned between CH_2Cl_2 and sat. $NaHCO_3$ (5 mL each), and the aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over K_2CO_3, condensed in vacuo, and purified through flask chromatography (20 mL alumina Brockman III, 150 mL 25% EtOAc/Hex→100 mL 5% MeOH/CH_2Cl_2) to generate the free amine as a mixture with some side products. The product was redissolved in CH_2Cl_2 (1 mL), and Boc_2O (9.7 mg, 0.0444 mmol, 1.1 equiv.) was added. The reaction was stirred overnight, and directly purified through medium-pressure liquid chromatography (12 g silica, 50 column volumes 0%→5% MeOH/CH_2Cl_2) to afford the product as a colorless oil as a mixture of diastereomers and rotamers (7.0 mg, 0.023 mmol, 57% yield, 5:1 dr).

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

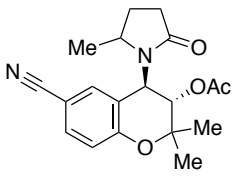
δ 8.13-8.02 (br s, 1H), 7.25-7.10 (m, 1H), 7.10-7.03 (m, 1H), 4.26-3.74 (m, 4H), 2.49 (s, 0.5H), 2.47 (s, 2.5H), 2.28-1.95 (m, 3H), 1.61-1.53 (m, 1H), 1.47 (s, 9H), 1.25 (d, J = 6.3 Hz, 0.5H), 1.23-1.15 (br s, 2.5H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 154.39, 153.66, 153.25, 153.14, 149.11, 148.76, 140.76, 140.41, 121.96, 121.73, 117.81, 117.49, 79.85, 79.59, 68.09, 67.23, 56.01, 55.98, 53.85, 53.77, 30.85, 29.76, 28.75, 28.69, 26.50, 25.66, 20.48, 19.85, 19.70, 19.52

HRMS: (ESI-TOF MS ES+) (mixture of diastereomers)

m/z calculated for $C_{17}H_{27}N_2O_3$ $[M+H]^+$: 307.2022, found 307.2022



***rel*-(3*S*,4*R*)-6-Cyano-2,2-dimethyl-4-(2-methyl-5-oxopyrrolidin-1-yl)chroman-3-yl acetate [(±)-34e]** According to the general oxidation and

DAST-promoted methylation procedures, *rel*-(3*S*,4*R*)-6-cyano-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)chroman-3-yl acetate (±)-**33e** (65.7 mg, 0.20 mmol, 1.0 equiv.) in MeCN (0.4 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.0 mg, 0.0015 mmol, 0.0075 equiv.), AcOH (172 μL, 3.00 mmol, 15.0 equiv.), and H_2O_2 (57.7 μL, 1.00 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (2.50 mL, 0.4 M). For facile product isolation, the oxidized products were isolated following oxidation by flash chromatography (dry loading, 50 mL silica, gradient elution 200 mL 20%→30%→50% EtOAc/$CHCl_3$), and methylated with DAST (26.4 μL, 32.2 mg, 0.20 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 300 μL, 0.60 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, 300 mL 60% EtOAc/Hex) to afford the product as a white solid as a mixture of diastereomers.

Run 1 (34.9 mg, 0.102 mmol, 51% yield, 1.6:1 dr; 18.0 mg, 0.0548 mmol, 27% rsm)

Run 2 (36.6 mg, 0.107 mmol, 53% yield, 2:1 dr; 21.7 mg, 0.0661 mmol, 33% rsm)

Run 3 (25.9 mg, 0.0756 mmol, 50% yield, 1.7:1 dr; 16.7 mg, 0.0508 mmol, 34% rsm) [0.15 mmol scale]

Average overall yield: 51% (31% rsm) ± 1.5, 1.8:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

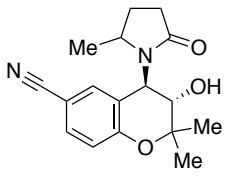
δ 7.50-7.40 (m, 1.36H), 7.23 (s, 0.64H), 6.94 (d, *J* = 8.5 Hz, 0.64H), 6.88 (d, *J* = 9.0 Hz, 0.36H), 5.70-5.16 (br m, 2H), 3.94 (sxt, *J* = 6.5 Hz, 0.36H), 3.56 (sxt, *J* = 6.5 Hz, 0.64H), 2.56 (ddd, *J* = 17.1, 10.0, 5.0 Hz, 0.36H), 2.51-2.39 (m, 1.28H), 2.34 (ddd, *J* = 17.3, 9.6, 8.2 Hz, 0.36H), 2.22-2.13 (m, 1H), 2.11 (s, 1.92H), 2.09 (s, 1.08H), 1.68-1.52 (m, 1H), 1.42 (s, 1.08H), 1.40 (s, 1.92H), 1.29 (m, 3H), 1.18 (br s, 1.92H), 0.73 (br d, *J* = 4.8 Hz, 1.08H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 177.10, 176.55, 170.34, 170.10, 157.06, 156.20, 133.10, 132.07, 123.98, 120.93, 119.27, 118.95, 118.87, 118.71, 104.73, 104.72, 79.10, 78.84, 72.38, 69.24, 53.56, 53.03, 50.24, 49.32, 30.38, 30.30, 27.92, 27.74, 26.48, 26.44, 21.93, 21.06, 21.02, 20.60, 19.35, 19.26

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{19}H_{23}N_2O_4$ $[M+H]^+$: 343.1658, found 343.1666



***rel*-(3*S*,4*R*)-3-Hydroxy-2,2-dimethyl-4-(2-methyl-5-oxopyrrolidin-1-yl)chromane-6-carbonitrile [(±)-36]** In a 25-mL round-bottom flask containing *rel*-(3*S*,4*R*)-6-cyano-2,2-dimethyl-4-(2-methyl-5-oxopyrrolidin-1-yl)chroman-3-yl acetate (±)-**34e** (38.1 mg, 0.102 mmol, 1.0 equiv.) was added 1 M NaOH in methanol (1 mL, 1 mmol, 10 equiv.). The reaction mixture was stirred for 1 h at room temperature and partitioned between water and CH_2Cl_2 (5 mL each). The aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The organic layers were combined, dried over $MgSO_4$, condensed in vacuo, and purified by flash chromatography (20 mL silica, 200 mL 80% EtOAc/Hex) to afford the product as a white solid as a mixture of diastereomers (26.1 mg, 0.0869 mmol, 85% yield, 1.5:1 dr).

Characterization of major diastereomer (±)-**36**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.47 (d, *J* = 8.5 Hz, 1H), 7.26 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 5.52-5.14 (br s, 1H), 3.99-3.80 (br s, 1H), 3.80-3.63 (br s, 1H), 3.63-3.40 (br s, 1H), 2.70-2.40 (br m, 2H), 2.31 (dq, *J* = 15.6, 7.7 Hz, 1H), 1.74 (td, *J* = 13.0, 5.8 Hz), 1.51 (s, 3H), 1.25 (s, 3H), 1.13 (br s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 178.79, 157.69, 133.18, 131.96, 120.44, 119.26, 119.10, 104.22, 80.93, 74.62, 53.10, 30.27, 27.87, 26.67, 21.56, 18.11

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{21}N_2O_3S$ $[M+H]^+$: 301.1552, found 301.1554

Characterization of minor diastereomer (±)-**S32**:

^{1}H NMR: (500 MHz, $CDCl_3$)

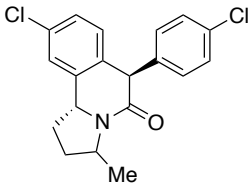
δ 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.39 (t, *J* = 1.5 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.17 (d, *J* = 10.6 Hz, 1H), 3.98 (m, 2H), 3.23 (br s, 1H), 2.61 (ddd, *J* = 17.2, 9.6, 4.7 Hz, 1H), 2.47 (ddd, *J* = 17.3, 9.8, 8.2 Hz, 1H), 2.31 (dddd, *J* = 12.5, 9.8, 7.4, 4.8 Hz, 1H), 1.73-1.65 (m, 1H), 1.56 (s, 3H), 1.25 (s, 3H), 0.85 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 177.95, 156.55, 132.94, 132.58, 123.94, 119.22, 118.64, 104.07, 80.48, 69.21, 53.41, 51.78, 30.56, 27.51, 26.85, 22.25, 18.50

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{21}N_2O_3$ $[M+H]^+$: 301.1552, found 301.1555



***rel*-(6*R*,10b*R*)-9-chloro-6-(4-chlorophenyl)-3-methyl-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one [(±)-34f]** According to the general oxidation and DAST-promoted methylation procedures, *rel*-(6*R*,10b*R*)-9-chloro-6-(4-chlorophenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one (±)-**33f** (33.2 mg, 0.10 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.17 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (2.7 mg, 0.002 mmol, 0.02 equiv.), AcOH (86 μL, 1.50 mmol, 15.0 equiv.),

and H_2O_2 (28.4 μL, 0.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (1.25 mL, 0.4 M), and methylated with DAST (13.2 μL, 16.1 mg, 0.10 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 150 μL, 0.30 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, 200 mL 20%→30%→50% EtOAc/Hex) to afford the product as a colorless oil as a mixture of diastereomers.

Run 1 (14.1 mg, 0.0407 mmol, 41% yield, 4:1 dr; 11.4 mg, 0.0343 mmol, 34% rsm)

Run 2 (14.2 mg, 0.0410 mmol, 41% yield, 4:1 dr; 14.5 mg, 0.0436 mmol, 44% rsm)

Run 3 (16.8 mg, 0.0485 mmol, 49% yield, 4:1 dr; 12.2 mg, 0.0367 mmol, 37% rsm)

Average overall yield: 44% (38% rsm) ± 4.6, 4:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$)

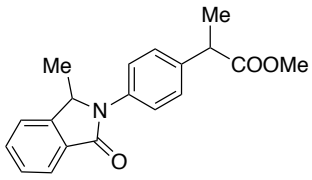
δ 7.36 (d, *J* = 8.0 Hz, 0.8H), 7.32 (d, *J* = 8.0 Hz, 0.2H), 7.28-7.26 (m, 0.8H), 7.26-7.24 (m, 0.2H), 7.24-7.20 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 0.8H), 7.15 (d, *J* = 8.0 Hz, 0.2H), 7.03 (d, *J* =8.6 Hz, 2H), 4.84 (s, 0.8H), 4.76 (s, 0.2H), 4.53 (dd, *J* = 10.7, 5.9 Hz, 0.2H), 4.38 (dd, *J* = 11.0, 5.9 Hz, 0.8H), 4.26-4.14 (m, 1H), 2.53 (dd, *J* = 12.2, 6.2 Hz, 0.2H), 2.48-2.38 (m, 0.8H), 2.30 (dt, *J* = 13.7, 7.3 Hz, 0.2H), 2.18-2.03 (m, 1.6H), 1.89-1.71 (m, 1H), 1.63-1.54 (m, 0.2H), 1.31 (d, *J* = 6.2 Hz, 0.6H), 1.23 (d, *J* = 6.3 Hz, 2.4H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 168.02, 167.54, 139.75, 138.45, 136.98, 135.13, 134.70, 133.65, 133.55, 133.40, 133.28, 129.33, 129.89, 128.98, 128.91, 128.77, 128.57, 128.45, 125.21, 124.43, 59.13, 58.70, 53.95, 53.77, 53.40, 53.21, 32.01, 31.62, 31.14, 28.28, 19.99, 19.62

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{19}H_{18}NOCl_2$ $[M+H]^+$: 346.0765, found 346.0751



Methyl 2-(4-(1-methyl-3-oxoisoindolin-2-yl)phenyl)propanoate [34g] According to the general oxidation and DAST-promoted methylation procedures, methyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate **33g** (59.0 mg, 0.20 mmol, 1.0 equiv.) in 4:1 MeCN/CH_2Cl_2 (0.4 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (5.4 mg, 0.004 mmol, 0.02 equiv.), AcOH (172 μL, 3.00 mmol, 15.0 equiv.), and H_2O_2 (57.7 μL, 1.00 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (2.50 mL, 0.4 M), and methylated with DAST (26.4 μL, 32.2 mg, 0.20 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 300 μL, 0.60 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, 300 mL 60% EtOAc/Hex) to afford the product as a white solid as a mixture of diastereomers. The starting material was resubjected once to the oxidation and methylation conditions and the products were combined.

Run 1 (1st cycle: 14.2 mg, 0.0459 mmol, 23% yield, 1:1 dr; 28.3 mg, 0.0958 mmol, 48% rsm. 2nd cycle: 6.4 mg, 0.0207 mmol, 22% yield, 1:1 dr; 16.3 mg, 0.0552 mmol, 58% rsm. Overall: 20.6 mg, 0.0666 mmol, 33% yield, 1:1 dr; 16.3 mg, 0.0552 mmol, 28% rsm)

Run 2 (1st cycle: 13.0 mg, 0.0420 mmol, 21% yield, 1:1 dr; 37.3 mg, 0.126 mmol, 63% rsm. 2nd cycle: 8.2 mg, 0.0265 mmol, 21% yield, 1:1 dr; 19.2 mg, 0.0650 mmol, 51% rsm. Overall: 21.2 mg, 0.0685 mmol, 34% yield, 1:1 dr; 19.2 mg, 0.0650 mmol, 33% rsm)

Run 3 (1st cycle: 10.3 mg, 0.0333 mmol, 17% yield, 1:1 dr; 39.7 mg, 0.134 mmol, 67% rsm. 2nd cycle: 8.9 mg, 0.0288 mmol, 22% yield, 1:1 dr; 19.5 mg, 0.0660 mmol, 49% rsm. Overall: 18.9 mg, 0.0611 mmol, 31% yield, 1:1 dr; 19.5 mg, 0.0660 mmol, 33% rsm)

Average overall yield: 33% (31% rsm) ± 1.5, 1:1 dr

Oxidative methylation with (*S*,*S*)-Mn(CF_3PDP) (0.10 equiv.): 7% yield, 16% rsm by ^{1}H NMR.

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

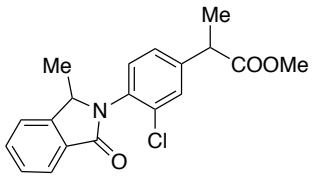
δ 7.92 (d, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 5.19 (q, *J* = 6.7 Hz, 1H), 3.75 (app qd, *J* = 7.1, 2.6 Hz, 1H), 3.68 (app d, *J* = 2.7 Hz, 3H), 1.52 (app dd, *J* = 7.2, 4.8 Hz, 3H), 1.46 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 175.04, 167.05, 146.38, 137.59, 137.54, 136.19, 132.23, 131.86, 128.55, 128.38, 128.35, 124.29, 123.55, 122.10, 57.00, 52.24, 45.10, 45.08, 18.96, 18.71

HRMS: (ESI-TOF MS ES+) (mixture of diastereomers)

m/z calculated for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1443, found 310.1446



Methyl 2-(3-chloro-4-(1-methyl-3-oxoisoindolin-2-yl)phenyl)propanoate [34h] According to the general oxidation and DAST-promoted methylation procedures, methyl 2-(3-chloro-4-(1-oxoisoindolin-2-yl)phenyl)propanoate **33h** (66.0 mg, 0.20 mmol, 1.0 equiv.) in 4:1 MeCN/CH_2Cl_2 (0.4 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (5.4 mg, 0.004 mmol, 0.02 equiv.), AcOH (172 μL, 3.00 mmol, 15.0 equiv.), and H_2O_2 (57.7 μL, 1.00 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (2.50 mL, 0.4 M), and methylated with DAST (26.4 μL, 32.2 mg, 0.20 mmol, 1.0 equiv.) and trimethylaluminum (2.0 M in hexanes, 300 μL, 0.60 mmol, 3.0 equiv.). Following workup, the crude material was purified by flash chromatography (50 mL silica, 300 mL 60% EtOAc/Hex) to afford the product as a white solid as a mixture of diastereomers.

Run 1 (35.5 mg, 0.103 mmol, 52% yield, 1:1 dr; 5.0 mg, 0.015 mmol, 8% rsm)

Run 2 (39.4 mg, 0.115 mmol, 57% yield, 1:1 dr; 6.6 mg, 0.020 mmol, 10% rsm)

Run 3 (38.3 mg, 0.112 mmol, 56% yield, 1:1 dr; 8.3 mg, 0.025 mmol, 13% rsm)

Average overall yield: 55% (10% rsm) ± 2.7, 1:1 dr

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

δ 7.94 (d, *J* = 7.6 Hz, 1H), 7.62 (td, *J* = 7.5, 1.2 Hz, 1H), 7.55-7.45 (m, 3H), 7.30 (d, *J* = 2.8 Hz, 2H), 5.16-5.07 (m, 1H), 3.75 (app qd, *J* = 7.4, 2.3 Hz, 1H), 3.71 (s, 1.5H), 3.71 (s, 1.5H), 1.53 (app dd, *J* = 7.2, 2.4 Hz, 3H), 1.40 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 174.27, 167.65, 147.36, 142.08, 142.05, 133.47, 132.25, 131.30, 129.92, 129.83, 128.44, 127.13, 127.06, 124.51, 122.25, 58.36, 52.46, 45.04, 18.80, 18.63

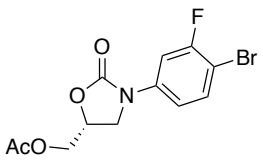
IR: (cm^{-1}) (mixture of diastereomers)

2978, 2951, 1735, 1699, 1563, 1500, 1469, 1434, 1408, 1378, 1334, 1297, 1250, 1210, 1164, 1116, 1095, 1058, 1014, 972, 888, 862, 825, 793, 758, 718, 692, 610, 538

HRMS: (ESI-TOF MS ES+) (mixture of diastereomers)

m/z calculated for $C_{19}H_{19}NO_3Cl$ $[M+H]^+$: 344.1053, found 344.1048

3.4.7 Synthesis of Substrates, Experimental Procedures, and Characterization for Figure 20



(*R*)-(3-(4-Bromo-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl acetate [37] In a 100-mL recovery flask were added (*R*)-3-(4-bromo-3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one (Aldrich, 1.00 g, 3.45 mmol, 1.0 equiv.), DMAP (42 mg, 0.345 mmol, 0.1 equiv.), CH_2Cl_2 (20 mL), Et_3N (2.4 mL, 1.74 g, 17.2 mmol, 5 equiv.), and Ac_2O (978 μL, 1.06 g, 10.4 mmol, 3.0 equiv.). The reaction was stirred overnight, and partitioned between sat. $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 3x. The organic layers were combined, dried over $MgSO_4$, and condensed

in vacuo. Purification by flask chromatography (55 mL silica, 300 mL 50% EtOAc/Hex) afforded the product as a white solid (1.10 g, 3.33 mmol, 97% yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.56 – 7.53 (m, 1H), 7.53-7.50 (m, 1H), 7.16 (ddt, *J* = 8.9, 2.3, 1.1 Hz, 1H), 4.89 (dddd, *J* = 8.8, 6.2, 4.9, 3.9 Hz, 1H), 4.38 (dd, *J* = 12.3, 3.9 Hz, 1H), 4.31 (dd, *J* = 12.3, 4.9 Hz, 1H), 4.10 (t, *J* = 9.0 Hz, 1H), 3.80 (dd, *J* = 8.9, 6.3 Hz, 1H), 2.10 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.62, 159.35 (d, *J* = 246.6 Hz), 153.79, 138.80 (d, *J* = 9.7 Hz), 133.73 (d, *J* = 1.8 Hz), 114.46 (d, *J* = 3.4 Hz), 106.86 (d, *J* = 27.9 Hz), 103.64 (d, *J* = 21.1 Hz), 70.16, 64.02, 47.00, 20.78

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -104.51 (dd, *J* = 10.9, 7.4 Hz)

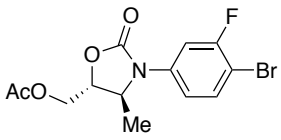
HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{12}NO_4FBr$ $[M+H]^+$: 331.9934, found 331.9943

$[\alpha]_D^{24}$ = -48.2º (c = 0.91, CH_2Cl_2)

General procedure for TFAA-promoted methylation. The crude from oxidation was dissolved in CH_2Cl_2 (1.5 mL, 0.2 M), backfilled with nitrogen 3x, and trifluoroacetic anhydride (41.7 µL, 63.0 mg, 0.30 mmol, 1.0 equiv.) was added. The reaction was stirred at room temperature for 1 h, and then placed into a -78 °C dry ice/acetone bath. Trimethylaluminum (2.0 M in hexanes, 450 µL, 0.90 mmol, 3.0 equiv.) and trimethylsilyl triflate (TMSOTf) (54.5 µL, 66.7 mg, 0.30 mmol, 1.0 equiv.) were then added dropwise. The reaction mixture was stirred at -78 °C for 2 h, then allowed to warm to room temperature while stirring for 1 h. Upon completion,

the reaction was diluted with CH_2Cl_2 (5 mL) and poured into a 60 mL separatory funnel containing 3 mL 1 M NaOH for quenching. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and condensed in vacuo before subjecting to purification via flash or medium pressure chromatography.



((4*S*,5*R*)-3-(4-Bromo-3-fluorophenyl)-4-methyl-2-oxooxazolidin-5-yl)methyl acetate [38] According to the general oxidation and TFAA-promoted methylation procedures, (*R*)-(3-(4-bromo-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl acetate **37** (99.6 mg, 0.30 mmol, 1.0 equiv.) in MeCN (0.6 mL, 0.5 M) was oxidized with (*S*,*S*)-Mn(CF_3PDP) (8.1 mg, 0.0060 mmol, 0.02 equiv.), AcOH (257 μL, 4.50 mmol, 15.0 equiv.), and H_2O_2 (85.2 μL, 1.50 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). Following oxidation, the crude was methylated with TFAA (41.7 μL, 63.0 mg, 0.30 mmol, 1.0 equiv.), trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.), and TMSOTf (54.5 μL, 66.7 mg, 0.30 mmol, 1.0 equiv.). Following workup, the crude material was purified by medium-pressure liquid chromatography (12 g silica, 50 column volumes 0%→50% EtOAc/Hex) to afford the product as a white solid as a mixture of diastereomers. The stereochemistry was determined by ^{1}H NMR and NOESY 1D methods.

Run 1 (46.8 mg, 0.135 mmol, 45% yield; 6:1 dr; 38.9 mg, 0.117 mmol, 39% rsm)

Run 2 (45.0 mg, 0.130 mmol, 43% yield, 7:1 dr; 36.9 mg, 0.111 mmol, 37% rsm)

Run 3 (46.0 mg, 0.133 mmol, 44% yield, 5:1 dr; 33.1 mg, 0.100 mmol, 33% rsm)

Average overall yield: 44% (36% rsm) ± 1.0, 6:1 dr

Methylation with DAST:

Run 1 (31.7 mg, 0.0916 mmol, 31% yield, 11:1 dr; 7.6 mg, 0.020 mmol, 6% hemiaminal acetate; 41.1 mg, 0.124 mmol, 41% rsm)

Run 2 (32.2 mg, 0.0930 mmol, 31% yield, 12:1 dr; 10.0 mg, 0.0256 mmol, 9% hemiaminal acetate; 42.5 mg, 0.128 mmol, 43% rsm)

Average overall yield: 31% (42% rsm) ± 0.0, 12:1 dr; 8% hemiaminal acetate

Characterization of major diastereomer **38**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 10.4, 2.5 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.39 (q, *J* = 4.7 Hz, 1H), 4.36-4.27 (m, 2H), 4.24 (p, *J* = 6.0 Hz, 1H), 2.08 (s, 3H), 1.40 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.62, 159.37 (d, *J* = 247.1 Hz), 154.01, 137.30 (d, *J* = 9.3 Hz), 133.78 (d, *J* = 1.5 Hz), 117.43 (d, *J* = 3.4 Hz), 109.71 (d, *J* = 26.8 Hz), 104.67 (d, *J* = 21.1 Hz), 77.64, 63.57, 54.19, 20.74, 18.60

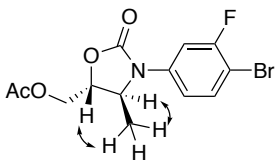
^{19}F NMR: (470 MHz, $CDCl_3$)

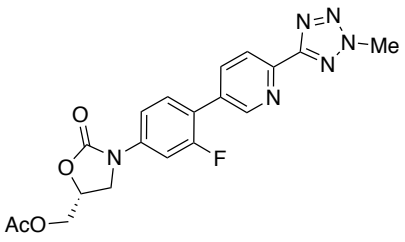
δ -104.50 (dd, *J* = 10.3, 7.8 Hz)

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{14}NO_4FBr$ $[M+H]^+$: 346.0090, found 346.0088

$[\alpha]_D^{24}$ = -44.3º (c = 1.10, CH_2Cl_2)





(*R*)-(3-(3-Fluoro-4-(6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl)phenyl)-2-oxooxazolidin-5-yl)methyl acetate [39] In a 50-mL recovery flask were added (*R*)-3-(4-bromo-3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one (Aldrich, 500 mg, 1.72 mmol, 1.0 equiv.), B_2Pin_2 (875 mg, 3.45 mmol, 2.0 equiv.), Pd(dppf)Cl_2•CH_2Cl_2 (70.2 mg, 0.086 mmol, 0.05 equiv.), and KOAc (677 mg, 6.90 mmol, 4.0 equiv.). The flask was backfilled with nitrogen 3x, and DMSO (5 mL) was added. The septum was quickly replaced by a yellow polyethylene cap, and the joint was secured with parafilm. The reaction was placed in 80 °C oil bath and stirred overnight. Upon completion, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc 2x, and the organic layers were combined, washed with brine 3x, dried over $MgSO_4$, and condensed in vacuo. 5-(4-bromophenyl)-2-methyl-2*H*-tetrazole (413 mg, 1.72 mmol, 1.0 equiv.), Pd(dppf)Cl_2•CH_2Cl_2 (28.1 mg, 0.034 mmol, 0.02 equiv.), and cesium carbonate (1.68 g, 5.16 mmol, 3.0 equiv.) were added to the crude, and the flask was backfilled with nitrogen 3x. Water (2.6 mL) and dioxane (5.2 mL) were added, and the septum was quickly replaced by a polyethylene yellow cap. The reaction mixture was heated at 70 °C while stirring overnight. Upon completion, the reaction mixture was partitioned between EtOAc and water. A large amount of off-white precipitate formed and was collected through filtration. The aqueous layer was extracted with EtOAc 2x, and the organic layers were combined with the solid, and condensed in vacuo. The resulting crude was triturated 3x with EtOAc, and the remaining solid was mixed with CH_2Cl_2 (10.3 mL), DMAP (21.0 mg, 0.172 mmol, 0.1 equiv.), Et_3N (1.2 mL, 870 mg, 8.60 mmol, 5.0 equiv.), and Ac_2O (488 μL, 527 mg, 5.16 mmol, 3.0 equiv.) were added. The reaction was stirred overnight, and partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2

3x, and the organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. Purification by flash chromatography (50 mL silica, gradient elution 300 mL 80%→600 mL 100% EtOAc/Hex) followed by twice trituration of the resulting solid with 25% EtOAc/Hex afforded the product as a pale pink powder (383 mg, 0.923 mmol, 54% overall yield).

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.94 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.62 (dd, *J* = 12.7, 2.0 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.93 (dq, *J* = 9.7, 5.2 Hz, 1H), 4.47 (s, 3H), 4.42 (dd, *J* = 12.3, 3.8 Hz, 1H), 4.34 (dd, *J* = 12.3, 4.8 Hz, 1H), 4.18 (t, *J* = 8.9 Hz, 1H), 3.88 (dd, *J* = 8.9, 6.2 Hz, 1H), 2.12 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.65, 164.87, 160.27 (d, *J* = 249.1 Hz), 153.87, 150.04 (d, *J* = 3.0 Hz), 145.72, 139.91 (d, *J* = 10.7 Hz), 137.22 (d, *J* = 3.1 Hz), 132.28, 130.82 (d, *J* = 4.6 Hz), 122.15, 120.61 (d, *J* = 13.7 Hz), 113.93 (d, *J* = 3.2 Hz), 106.54 (d, *J* = 28.4 Hz), 70.26, 64.08, 47.05, 39.90, 20.81

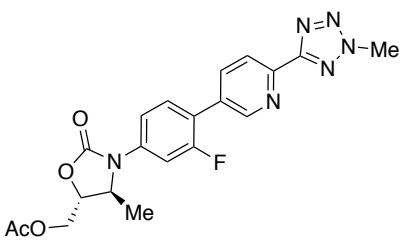
^{19}F NMR: (470 MHz, $CDCl_3$)

δ -114.34 (dd, *J* = 12.8, 8.3 Hz)

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{19}H_{18}N_6O_4F$ $[M+H]^+$: 413.1374, found 413.1381

$[\alpha]_D^{24}$ = -49.4º (c = 0.68, CH_2Cl_2)



((4*S*,5*R*)-3-(3-Fluoro-4-(6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl)phenyl)-4-methyl-2-oxooxazolidin-5-yl)methyl acetate [40] According to a modified general

oxidation procedure and the TFAA-promoted methylation procedure, (*R*)-(3-(3-fluoro-4-(6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl)phenyl)-2-oxooxazolidin-5-yl)methyl acetate **39** (82.5 mg, 0.20 mmol, 1.0 equiv.) and (*S*,*S*)-Mn(CF_3PDP) (5.4 mg, 0.0040 mmol, 0.02 equiv.) in a 40-mL vial were dissolved in 2:1 MeCN/AcOH (3.0 mL, 0.067 M). The reaction mixture was then placed into an ice bath at 0°C. A 10 mL syringe was charged with a solution of H_2O_2 (56.8 μL, 1.00 mmol, 5.0 equiv., 50 wt.% in H_2O) in MeCN (2.50 mL, 0.4 M). The syringe was then fitted with a 25G needle and the solution was slowly added into the stirring reaction mixture via a syringe pump at 2.50 mL/h. Upon completion, the vial was taken from the cold bath, and the reaction mixture was immediately loaded onto a 15 mL silica plug. Ethyl acetate was used to rinse the vial (2x1 mL), and the resulting washes were also loaded onto the silica plug. The plug was allowed to sit for five minutes in order to decompose any remaining hydrogen peroxide as well as absorbing the reaction mixture. Ethyl acetate (150 mL) was then allowed to pass through the plug and the eluent condensed. For facile isolation, the oxidation products were isolated from the crude by medium-pressure liquid chromatography (24 g silica, 50 column volumes 0%→10% MeOH/CH_2Cl_2). The crude from oxidation was dissolved in CH_2Cl_2 (1.0 mL, 0.2 M), backfilled with nitrogen 3x, and trifluoroacetic anhydride (27.8 μL, 42.0 mg, 0.20 mmol, 1.0 equiv.) was added. The reaction was stirred at room temperature for 1 h, and then placed into a -78 °C dry ice/acetone bath. Trimethylaluminum (2.0 M in hexanes, 300 μL, 0.90 mmol, 3.0 equiv.) and TMSOTf (72.7 μL, 88.9 mg, 0.40 mmol, 2.0 equiv.) were then added dropwise. The reaction mixture was stirred at -78 °C for 2 h, then allowed to warm to room temperature while stirring for 1 h. Upon completion, the reaction was diluted with CH_2Cl_2 (5 mL) and poured into a 60 mL separatory funnel containing 3 mL 1 M NaOH for quenching. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over anhydrous

$MgSO_4$, filtered, and condensed in vacuo. Flash chromatography (20 mL silica, 200 mL EtOAc) afforded the product as a white solid as a mixture of diastereomers. The stereochemistry was determined by analogy to **41**.

Run 1 (33.4 mg, 0.0783 mmol, 39% yield, 3:1 dr; 25.0 mg, 0.0606 mmol, 30% rsm)

Run 2 (33.0 mg, 0.0773 mmol, 39% yield, 3:1 dr; 22.5 mg, 0.0546 mmol, 27% rsm)

Run 3 (35.3 mg, 0.0829 mmol, 41% yield, 3:1 dr; 17.6 mg, 0.0427 mmol, 21% rsm)

Average overall yield: 40% (26% rsm) ± 1.2, 3:1 dr

Methylation with Deoxo-Fluor: 4.9 mg, 0.012 mmol, 6% yield, 5:1 dr; 10.6 mg, 0.0261 mmol, 13% hemiaminal acetate; 14.7 mg, 0.0358 mmol, 18% enamine; 16.5 mg, 0.0400 mmol, 20% rsm

Methylation of isolated hemiaminal acetate intermediate [0.026 mmol scale] with BF_3: 0% yield, 5% rsm by ^{1}H NMR

Characterization of major diastereomer **40**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.94 (s, 1H), 8.32 (dd, *J* = 8.1, 0.9 Hz, 1H), 8.06 (dt, *J* = 8.2, 1.8 Hz, 1H), 7.52 (t, *J* = 8.5 Hz, 1H), 7.46 (dd, *J* = 12.4, 2.2 Hz, 1H), 7.34 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.48 (s, 3H), 4.46-4.41 (m, 1H), 4.38-4.30 (m, 3H), 1.45 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.67, 164.82, 160.27 (d, *J* = 249.5 Hz), 154.09, 150.00 (d, *J* = 3.4 Hz), 145.78, 138.51 (d, *J* = 10.9 Hz), 137.33 (d, *J* = 3.8 Hz), 132.26 (d, *J* = 1.8 Hz), 130.86 (d, *J* = 4.6 Hz), 122.17, 121.44 (d, *J* = 13.8 Hz), 116.74 (d, *J* = 3.4 Hz), 109.28 (d, *J* = 27.3 Hz), 77.71, 63.66, 54.21, 39.91, 20.81, 18.79

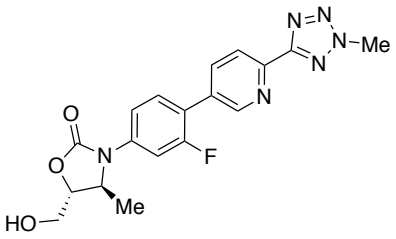
^{19}F NMR: (470 MHz, $CDCl_3$)

δ -114.90 (app t, *J* = 9.2 Hz)

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{20}H_{20}N_6O_4F$ $[M+H]^+$: 427.1530, found 427.1532

$[\alpha]_D^{24}$ = -52.9º (c = 0.67, CH_2Cl_2)



(4*S*,5*R*)-3-(3-Fluoro-4-(6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl)phenyl)-5-(hydroxymethyl)-4-methyloxazolidin-2-one [41] In a 10-mL round-bottom flask containing ((4*S*,5*R*)-3-(3-fluoro-4-(6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl)phenyl)-4-methyl-2-oxooxazolidin-5-yl)methyl acetate **40** (major diastereomer) (10.7 mg, 0.025 mmol, 1.0 equiv.) was added 1 M NaOH in methanol (0.25 mL, 0.25 mmol, 10 equiv.). The reaction mixture was stirred for 1 h at room temperature and directly loaded onto column and purified by flash chromatography (20 mL silica, 200 mL 0%→100 mL 5% EtOAc/MeOH) to afford the product as a white foam (8.8 mg, 0.023 mmol, 92% yield). The stereochemistry was determined by ^{1}H NMR, COSY, and NOESY 1D methods.

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.92 (s, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 8.04 (dt, *J* = 8.2, 1.8 Hz, 1H), 7.52 (t, *J* = 8.5 Hz, 1H), 7.49 (dd, *J* = 12.4, 2.1 Hz, 1H), 7.34 (dd, *J* = 8.9, 2.1 Hz, 1H), 4.52-4.47 (m, 1H), 4.47 (s, 3H), 4.31 (dt, *J* = 5.6, 3.7 Hz, 1H), 4.01 (d, *J* = 12.7, 3.3 Hz, 1H), 3.81 (d, *J* = 11.4 Hz, 1H), 2.26 (br s, 1H), 1.45 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 164.85, 160.20 (d, *J* = 249.5 Hz), 154.69, 150.02 (d, *J* = 3.0 Hz), 145.73, 138.64 (d, *J* = 10.6 Hz), 137.25 (d, *J* = 3.8 Hz), 132.31, 130.73 (d, *J* = 4.4 Hz), 122.15, 121.37 (d, *J* =

13.3 Hz), 117.07 (d, J = 3.4 Hz), 109.55 (d, J = 27.0 Hz), 80.65, 62.34, 53.21, 39.89, 18.68

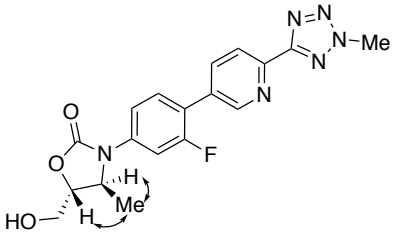
^{19}F NMR: (470 MHz, $CDCl_3$)

δ -114.67 (dd, J = 12.3, 8.7 Hz)

HRMS: (ESI-TOF MS ES+)

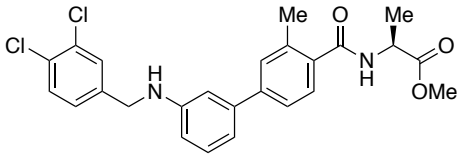
m/z calculated for $C_{18}H_{18}N_6O_3F$ $[M+H]^+$: 385.1424, found 385.1413

$[\alpha]_D^{24}$ = -49.2º (c = 0.44, CH_2Cl_2)

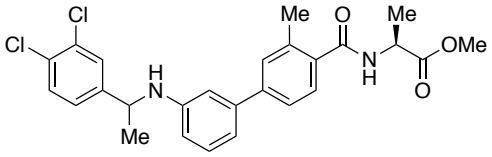


3.4.8 Synthesis of Substrate, Experimental Procedure, and Characterization for Figure 21

Methyl (3'-((3,4-dichlorobenzyl)amino)-3-methyl-[1,1'-biphenyl]-4-carbonyl)-*L*-alaninate [42]



Prepared according to literature procedures and the NMR data matched those reported.[54e]



Methyl (3'-((1-(3,4-dichlorophenyl)ethyl)amino)-3-methyl-[1,1'-biphenyl]-4-carbonyl)-*L*-alaninate [43]

To a 40 mL vial equipped with a stir bar were added methyl (3'-((3,4-dichlorobenzyl)amino)-3-methyl-[1,1'-biphenyl]-4-carbonyl)-*L*-alaninate **42**

(141.4 mg, 0.30 mmol, 1.0 equiv,), (*S*,*S*)-Mn(CF_3PDP) (8.1 mg, 0.0060 mmol, 0.02 equiv.), MeCN (1.8 mL, 0.17 M), and AcOH (257 μL, 4.50 mmol, 15.0 equiv.). The reaction mixture was heated on 70 °C hot plate until fully dissolved, then placed into an ice bath at 0°C. A 10 mL syringe was charged with a solution of H_2O_2 (85.2 μL, 1.50 mmol, 5.0 equiv, 50 wt.% in H_2O) in MeCN (3.75 mL, 0.4 M). The syringe was then fitted with a 25G needle and the solution was slowly added into the stirring reaction mixture via a syringe pump at 3.75 mL/h. Upon completion, the vial was taken from the cold bath, and the reaction mixture was immediately loaded onto a 15 mL silica plug. Ethyl acetate was used to rinse the vial (2x1 mL), and the resulting washes were also loaded onto the silica plug. The plug was allowed to sit for five minutes in order to decompose any remaining hydrogen peroxide as well as absorbing the reaction mixture. Ethyl acetate (150 mL) was then allowed to pass through the plug, and the eluent was concentrated in vacuo. The recovered starting material was isolated by flash chromatography (dry loading, 50 mL silica, gradient elution 400 mL 30%→500 mL 40% EtOAc/Hex). All other fractions were combined, condensed in vacuo, transferred into a 25 mL recovery flask, condensed, and placed on vacuum overnight. To the same recovery flask was then added CH_2Cl_2 (1.5 mL) and flame-dried 5 Å powdered molecular sieves (40 mg). The flask was again placed in ice bath, backfilled with N_2 3x, and TMSOTf (1.2 equiv. to crude imine) was added dropwise. The reaction was allowed to stir at 0 °C for 1 h, then placed into a -78 °C cold bath. Methylmagnesium bromide (3 M, 3.0 equiv. to crude imine) was then added, and the reaction was stirred at -78 °C for 4 h. Water (100 μL) was added to quench the reaction, which was then warmed to room temperature in a water bath. The crude was transferred to a 20 mL Erlenmeyer flask, dried over $MgSO_4$, and condensed in vacuo. It was observed by crude ^{1}H NMR that there was unreacted imine. The crude was transferred into a 25 mL recovery flask,

placed on vacuum overnight, and resubjected 1x to same amounts of TMSOTf and MeMgBr. Following workup, the crude material was purified by medium-pressure liquid chromatography (12 g silica, 50 column volumes gradient elution 0%→50% EtOAc/Hex) to afford the product as a white foam.

Run 1 (18.6 mg, 0.0383 mmol, 13% yield; 16.4 mg, 0.0349 mmol, 12% recovered imine)

Run 2 (22.3 mg, 0.0459 mmol, 15% yield; 20.0 mg, 0.0426 mmol, 14% recovered imine; 1.5 mg, 0.0032 mmol, 1% rsm)

Run 3 (20.8 mg, 0.0428 mmol, 14% yield; 19.0 mg, 0.0405 mmol, 13% recovered imine; 1.5 mg, 0.0032 mmol, 1% rsm)

Average overall yield: 14% (1% rsm) ± 1.0; 13% recovered imine

Lower mass balance resulted from aromatic oxidation and hydrolysis of the imine intermediate during oxidation, which formed aldehyde product that was subsequently oxidized to carboxylic acid.

^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of diastereomers)

δ 7.50 (d, *J* = 2.1 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.33-7.28 (m, 2H), 7.24 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.69 (s, 1H), 6.45 (d, *J* = 8.0, 2.3 Hz, 1H), 6.36 (d, *J* = 7.6 Hz, 1H), 4.81 (p, *J* = 7.2 Hz, 1H), 4.48 (q, *J* = 6.7 Hz, 1H), 4.14 (br s, 1H), 3.80 (s, 3H), 2.50 (s, 3H), 1.53 (d, *J* = 7.4 Hz, 6H)

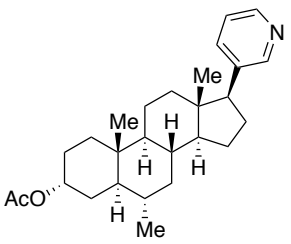
^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of diastereomers)

δ 173.65, 169.37, 147.18, 145.82, 143.45, 141.47, 136.90, 134.48, 132.93, 130.92, 130.88, 130.00, 129.81, 128.08, 127.52, 125.43, 124.53, 117.03, 112.76, 112.46, 53.08, 52.70, 48.48, 25.10, 20.18, 18.75

HRMS: (ESI-TOF MS ES+) (mixture of diastereomers)

m/z calculated for $C_{26}H_{27}N_2O_3Cl_2$ $[M+H]^+$: 485.1399, found 485.1393

3.4.9 Experimental Procedures and Characterization for Figure 22



(3*R*,5*R*,6*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-6,10,13-Trimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate [(+)-44]

According to a modified general oxidation procedure, in a 40-mL vial was added (3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-10,13-dimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (+)-**13** (118.7 mg, 0.30 mmol, 1.0 equiv.), CH_2Cl_2 (1.2 mL), and HBF_4•OEt_2 (44.9 µL, 0.33 mmol, 1.1 equiv.). The reaction mixture was stirred for 1 h, and the solvent was removed in vacuo. The crude was placed on high vacuum overnight to remove the residual acid. (*R*,*R*)-Mn(CF_3PDP) (40.7 mg, 0.030 mmol, 0.10 equiv.) and $ClCH_2COOH$ (425 mg, 4.50 mmol, 15.0 equiv.) were added to the crude, and the mixture was dissolved in 4:1 MeCN/CH_2Cl_2 (1 mL, 0.3 M) and placed in a -36 °C dry ice/1,2-DCE bath. A 10 mL syringe was charged with a solution of H_2O_2 (85.2 µL, 1.50 mmol, 5.0 equiv, 50 wt.% in H_2O) in 4:1 MeCN/CH_2Cl_2 (3.75 mL, 0.4 M). The syringe was then fitted with a 25G needle and the solution was slowly added into the stirring reaction mixture over 3 h via a syringe pump at 1.25 mL/h. Following oxidation, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and cooled to 0 °C. 3 M NaOH (5 mL) was added, and the mixture was stirred vigorously for 5 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. For facile isolation, the alcohol product (+)-**15** was isolated by medium-pressure liquid chromatography (12 g silica, 100 column volumes 0%→70% EtOAc/Hex), and redissolved in CH_2Cl_2 (1 mL). MsCl (23.2 µL,

34.4 mg, 0.30 mmol, 1.0 equiv.) was added, followed by Et_3N (41.8 μL, 30.4 mg, 0.30 mmol, 1.0 equiv.). The reaction was stirred at room temperature for 1 h, and then partitioned between sat. $NaHCO_3$ and CH_2Cl_2. The layers were separated and the aqueous layer was extracted wit CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo, then redissolved in CH_2Cl_2 (1 mL) and cooled to -78 °C. Trimethylaluminum (2.0 M in hexanes, 450 μL, 0.90 mmol, 3.0 equiv.) was then added, and the reaction was stirred at -78 °C for 2 h and room temperature for 1 h. Upon completion, the mixture was diluted the CH_2Cl_2 and quenched with 1 M NaOH (5 mL). The layers were separated and the aqueous layer was extracted wit CH_2Cl_2 (2x5 mL). The organic layers were combined, dried over $MgSO_4$, and condensed in vacuo. The crude material was purified by flash chromatography (20 mL silica, 200 mL 20% EtOAc/Hex) to afford the product as a white solid. Stereochemistry was assigned by ^1H NMR, COSY, and 1D NOESY methods on the product's deacetylated derivative **S33**.

Run 1 (16.7 mg, 0.0408 mmol, 14% yield, >20:1 dr; 11.8 mg, 0.0298 mmol, 10% rsm; 24.2 mg, 0.059 mmol, 20% **15-Ketone**)

Run 2 (19.0 mg, 0.0464 mmol, 15% yield, >20:1 dr; 24.9 mg, 0.0629 mmol, 21% rsm; 15.6 mg, 0.038 mmol, 13% **15-Ketone**)

Run 3 (21.5 mg, 0.0525 mmol, 17% yield, >20:1 dr; 23.5 mg, 0.0594 mmol, 20% rsm; 17.2 mg, 0.042 mmol, 14% **15-Ketone**)

Average overall yield: 15% (17% rsm) ± 1.5, >20:1 dr; 16% 15-Ketone

An average of 32% desired alcohol intermediate (+)-**15** was produced in the oxidation. Lower mass balance partially resulted from the more challenging methylation procedure: approximately 80% yield in mesylation of the alcohol, and approximately 68% yield in methylation of the mesylate.

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.49-8.41 (m, 2H), 7.54 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.05 (p, *J* = 2.9 Hz, 1H), 2.67 (t, *J* = 9.9 Hz, 1H), 2.11-1.92 (m, 2H), 2.06 (s, 3H), 1.87-1.77 (m, 2H), 1.74-1.66 (m, 2H), 1.66-1.43 (m, 5H), 1.42-1.05 (m, 8H), 0.86-0.80 (m, 1H), 0.79 (s, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.71 (q, *J* = 12.2 Hz, 1H), 0.47 (s, 3H)

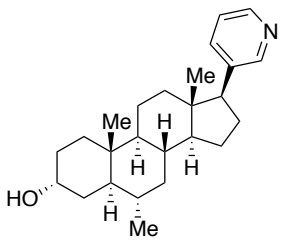
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.84, 150.42, 147.50, 136.66, 135.85, 122.90, 70.05, 56.42, 54.67, 54.51, 46.52, 44.58, 41.93, 37.74, 36.15, 35.59, 33.20, 30.93, 28.93, 26.03, 25.93, 24.51, 21.73, 20.55, 20.38, 12.92, 12.51

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{27}H_{40}NO_2$ $[M+H]^+$: 410.3059, found 410.3052

$[\alpha]_D^{24}$ = +13.3º (c = 0.95, CH_2Cl_2)



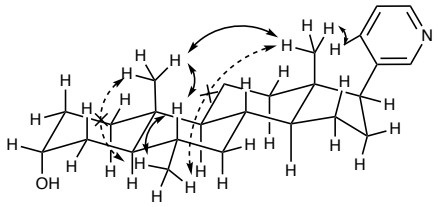
(3*R*,5*R*,6*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-6,10,13-Trimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol [S33] Prepared by reacting (+)-**44** (7.5 mg, 0.018 mmol, 1.0 equiv.) with 1 M NaOH/MeOH (1 mL, 6 h at room temperature), the reaction mixture was partitioned between water and CH_2Cl_2, the aqueous layer was extracted with CH_2Cl_2 2x. The organic layers were combined, dried over $MgSO_4$, filtered, and condensed in vacuo to afford **S33** as a white solid (5.4 mg, 0.015 mmol, 83% yield). The stereochemistry was determined by ^{1}H NMR, COSY, and 1D NOESY methods.

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.55-8.30 (br s, 2H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 7.1, 4.9 Hz, 1H), 4.07 (br s, 1H), 2.67 (t, *J* = 9.8 Hz, 1H), 2.07 (dtd, *J* = 14.5, 11.1, 3.7 Hz, 1H), 2.01-1.92 (m, 1H), 1.86-1.79 (m, 1H), 1.77 (dq, *J* = 14.3, 3.0 Hz, 1H), 1.73-1.66 (m, 2H), 1.65-1.56 (m, 3H), 1.54 (dt, *J* = 11.5, 3.1 Hz, 1H), 1.51-1.42 (m, 2H), 1.40-1.25 (m, 5H), 1.24-1.10 (m, 3H), 0.88-0.82 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.78 (s, 3H), 0.71 (q, *J* = 12.2 Hz, 1H), 0.47 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.47, 147.51, 135.84, 122.47, 66.54, 56.42, 54.66, 54.64, 45.64, 44.58, 42.01, 37.76, 36.46, 35.63, 32.49, 31.81, 31.00, 28.81, 26.04, 24.52, 20.54, 20.40, 12.93, 12.35



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