MANGANESE-CATALYZED INTERMOLECULAR BENZYLIC C–H AMINATION

BY

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THESIS

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ABSTRACT

Reactions that directly install nitrogen into C—H bonds of complex molecules are significant due to their ability to immediately change the chemical and biological properties of a given molecule. While selective intramolecular C—H amination reactions are known, intermolecular C—H amination reactions with high reactivity and selectivity are scarce. Achieving high levels of reactivity while maintaining excellent site-selectivity and functional group tolerance remains an important challenge for intermolecular C—H amination. We report a novel manganese perchlorophthalocyanine catalyst [Mn(ClPc)] for a highly site-selective intermolecular benzylic C—H amination of bioactive molecules and natural products. [Mn(ClPc)] is selective for benzylic C—H bonds over other C—H bond types and selects among multiple benzylic C—H bonds based on their electronic and steric properties.

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CHAPTER 1: INTRODUCTION

Introduction of nitrogen into organic frameworks has the potential to drastically change the physical and biological properties of a given molecule. For example, ampicillin, the first broad spectrum penicillin derivative, differs from penicillin G by the presence of a benzylic amine (Figure 1).[1] It is estimated that 5/6 pharmaceuticals contain at least one nitrogen atom,[2] and more specifically, the importance of nitrogen in the benzylic position of pharmacophores can be gleaned by its appearance in top selling FDA approved drugs such as

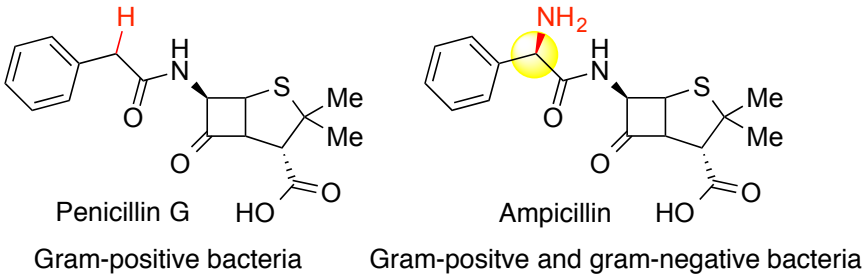


Figure 1. *Introduction of benzylic amine results in new biological activity.*

imatinib, meclizine, clopidogrel, sertraline, rivastigmine, donepezil, and many others.[3] In nature, such nitrogen functionality is installed through oxygenated intermediates.[4] For example, in the biosynthesis of *(S)-p*-hydroxyphenylglycine, a crucial component of several peptidic natural products, the benzylic amine is installed from the benzylic ketone.[5] Analogously, standard synthetic methods for nitrogen installation include N-alkylation, reductive amination, and hydroamination. These methods, while useful, rely on functional group manipulations and require preoxidized starting materials, oftentimes leading to lengthy synthetic sequences. A more rapid approach includes the direct insertion of nitrogen functionality into inert C–H bonds. This C(sp^3)–H functionalization method would allow for the rapid construction and diversification of natural products and pharmaceuticals.

Some of the inherent challenges in developing such a method stem from the ubiquitous, yet inert nature of C–H bonds. An effective reagent must be reactive enough to cleave strong C–H bonds while maintaining high levels of chemoselectivity and functional group tolerance. This system must also be able to discriminate between different types of C–H bonds in order to avoid highly complex mixtures resulting from functionalization at multiple sites. One class of oxidants traditionally used for amination reactions are nitrenes, electron-deficient nitrogen analogs of carbenes that exhibit similar reactivity. These species have traditionally been prepared from the photolytic or thermal decomposition of azides.[6] While highly reactive, methods utilizing these nitrenes suffer from a lack of chemoselectivity, making them difficult to use in complex molecule settings. However, controlled reactivity can be obtained by employing transition metal catalysis. As such, many of the advances in this field have been developed utilizing noble metals such as rhodium.[7-11] These dirhodium catalysts are postulated to go through metallonitrene intermediates, affording greater levels of selectivity and tunability. Several powerful catalysts have been developed capable of inserting into a variety of bond types, both intramolecularly (e.g. aliphatic 3° and 2°, **Figure 2a**) and intermolecularly (e.g. benzylic and aliphatic 3°, **Figure 2b,c**).[12]

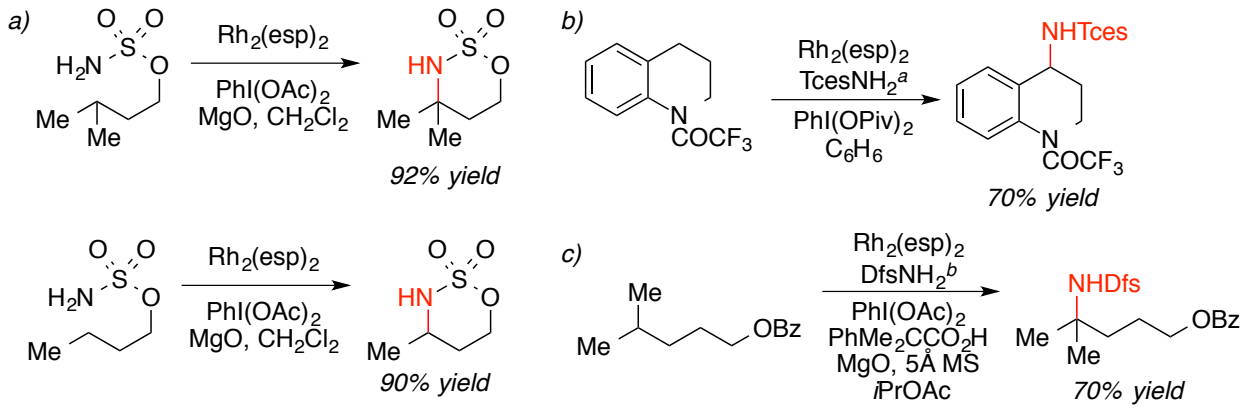


Figure 2. *Rhodium catalyzed Aminations. a. TcesNH$_2$ = 2,2,2-trichloroethoxysulfonamide; b. Dfs = 2,6- difluorophenoxysulfonamide.*

Owing to the high reactivity of these catalysts, the most common of which is $Rh_2(esp)_2$, these rhodium-catalyzed aminations suffer from a number of limitations. One of the biggest limitations is site-selectivity. As shown in **Figure 3a**, in a molecule containing both a benzylic site and a tertiary site, standard conditions lead to an 8:1 mixture of products stemming from amination at both sites. Moreover, in a tetralin derivative containing more than one benzylic site, $Rh_2(esp)_2$ targets both benzylic positions and results in a 7:1 mixture of isomers as well as 15% diamination product (**3b**).[12]

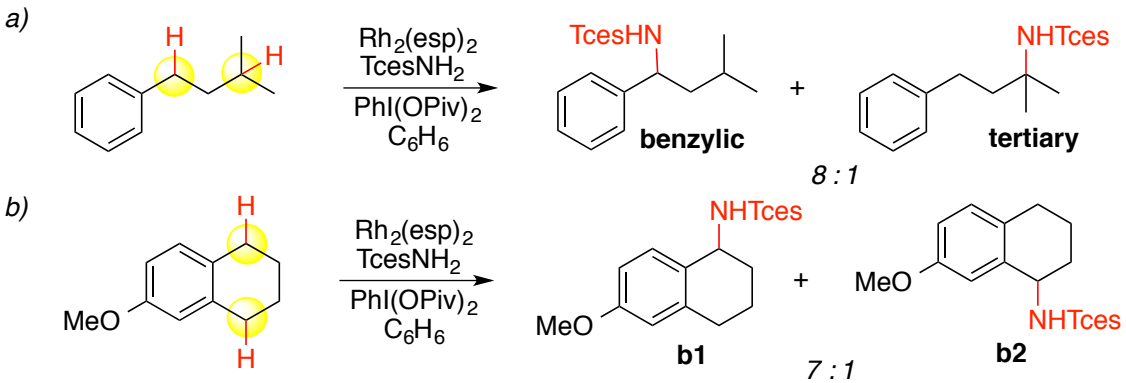


Figure 3. *Site selectivity of $Rh_2(esp)_2$.*

Other methods of nitrogen introduction have been developed using first row metals, including iron and manganese.[13,14] The first of these methods is an iron-catalyzed azidation reaction utilizing $Fe(OAc)_2$ and a hypervalent iodide as the azide source, some examples shown in **Figure 4**. This system is able to react with benzylic as well as tertiary C–H bonds. For example, a hydrocarbon bearing two electronically differentiated tertiary sites is oxidized to give a 45% overall yield of product with a 5:1 site-selectivity, favoring the distal tertiary site (Figure 4a). Similarly, an estrone derivative containing two benzylic sites is oxidized in 44% yield at the more reactive tertiary, benzylic site in addition to 24% yield of diazidation (Figure 4b).

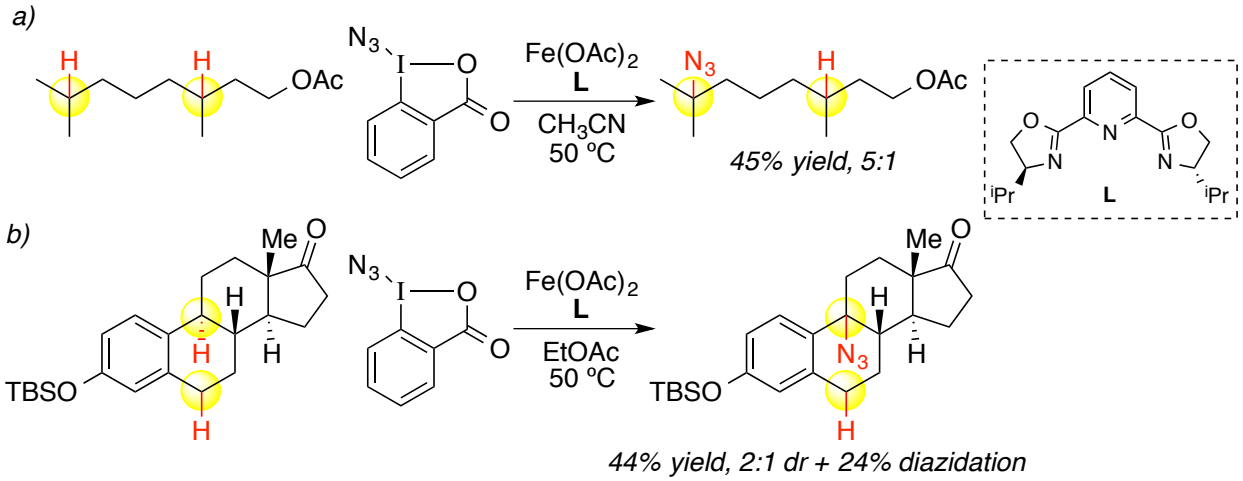


Figure 4. *Fe-catalyzed azidation.*

The second first-row metal catalyzed method is a manganese-catalyzed azidation utilizing either Mn(TMP)Cl or Mn(salen)Cl with NaN_3 as the azide source and iodosylbenzene as the oxidant.[15] The scope of this reaction includes benzylic, tertiary, secondary, as well as a-aminal C–H bonds. Due to the various types of C–H bonds that can be oxidized using this method, selective oxidation of complex molecules becomes a challenge. As shown in **Figure 5**, an estrone derivative is oxidized to give a modest 38% yield of azidation at the tertiary benzylic site as well as 18% diazidation of the tertiary as well as the secondary benzylic sites. Additionally, these reactions suffer from oxygenated side products due to the presence of a manganese oxo species during the catalytic cycle.

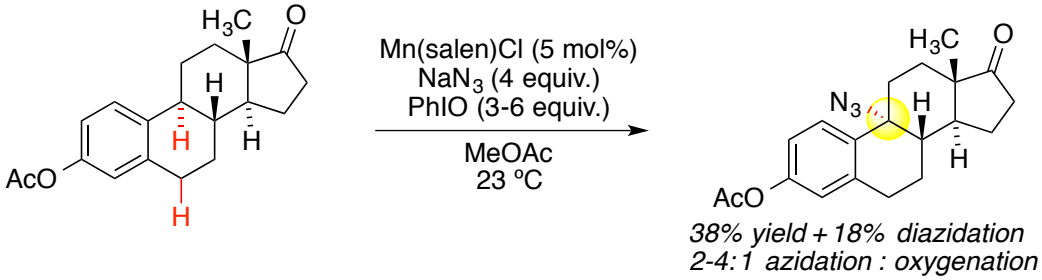


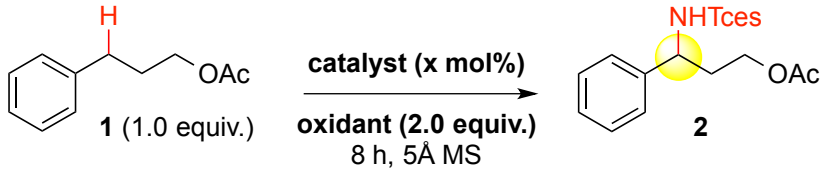
Figure 5. *Mn-catalyzed azidation.*

These first-row metal catalyzed reactions offer orthogonal reactivity to the rhodium systems due to the nature of their mechanisms. Both of these systems are thought to proceed through a step-

wise, radical mechanism, where functionalization occurs through an azide radical. Moreover, it is thought that in both of these methods, at least one of the steps involved in functionalization is not directly controlled by the same metal species. Conversely, in the case of the rhodium catalyzed aminations, the metallonitrene generated is directly involved in the functionalization, offering higher levels of control over the reactivity of the system.[8] We postulated that if we could find a system utilizing a first-row metal catalyst that proceeds through a metallonitrene intermediate, we could bridge the gap between these two modes of reactivity. We envisioned a catalytic system where the reactive metallonitrene proceeds through a rapid rebound, step-wise mechanism, which could offer orthogonal reactivity to the concerted mechanism of rhodium.

CHAPTER 2: REACTION DEVELOPMENT

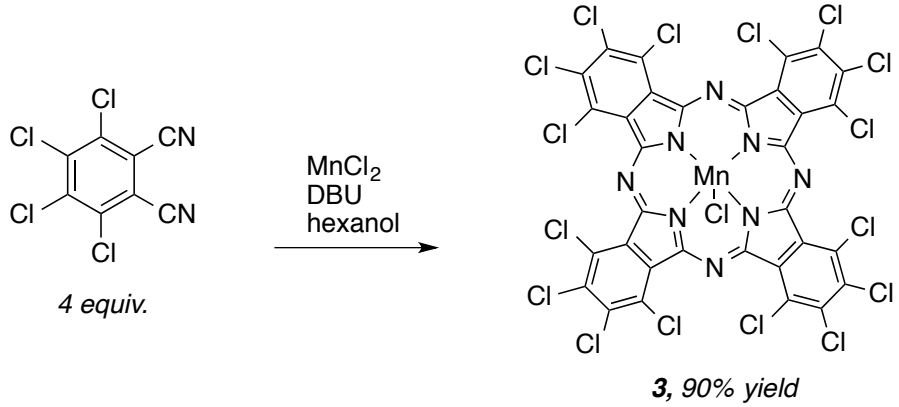
Reaction development began by examining iron and manganese phthalocyanine catalysts previously demonstrated in our group to be highly effective in intramolecular C—H amination via metallonitrene intermediates.[16,17] Currently, two main strategies exist for the formation of the active iminoiodinane for nitrene reactions, one is in-situ formation of the oxidant during the reaction and the other is a preformation and isolation of the oxidant that is then added directly



Entry	Sulfamate Ester	Oxidant	Catalyst (mol%)	Solvent	Temp	Yield (%) (RSM)
1	NH_2Tces	$PhI(OPiv)_2$	$[Fe(Pc)]SbF_6$ (10)	C_6H_6	23 °C	0% (100%)
2	NH_2Tces	$PhI(OPiv)_2$	$[Mn(Pc)]SbF_6$ (10)	C_6H_6	23 °C	trace (96%)
3[a]	NH_2Tces	$PhI(OPiv)_2$	$[Mn(Pc)]SbF_6$ (10)	C_6H_6	23 °C	trace (95%)
4	NH_2Tces	$PhI(OPiv)_2$	$[Mn(^tBuPc)]SbF_6$ (10)	C_6H_6	23 °C	trace (94%)
5		PhI=NTces	$[Fe(Pc)]SbF_6$ (10)	C_6H_6	23 °C	9%* (85%)
6		PhI=NTces	$[Mn(^tBuPc)]SbF_6$ (10)	C_6H_6	23 °C	12%* (88%)
7		PhI=NTces	$[Mn(Pc)]SbF_6$ (10)	C_6H_6	23 °C	17%* (83%)
8		PhI=NTces	$[Mn(Cl_{16}Pc)]SbF_6$ (10)	C_6H_6	23 °C	53%* (41%)
9		PhI=NTces	$[Mn(Cl_{16}Pc)]SbF_6$ (10)	C_6H_6	40 °C	68%* (32%)
10		PhI=NTces	$[Mn(Cl_{16}Pc)]SbF_6$ (5)	C_6H_6	40 °C	47%* (49%)
11		PhI=NTces(1 eq)	$[Mn(Cl_{16}Pc)]SbF_6$ (10)	C_6H_6	40 °C	42%* (58%)
12[b]		PhI=NTces	$[Mn(Cl_{16}Pc)]SbF_6$ (10)	1,2 DCE	40 °C	60%* (24%)
13		PhI=NTces	$[Mn(Cl_{16}Pc)]Cl$ (10)	C_6H_6	40 °C	50%* (43%)
14		PhI=NTces	$AgSbF_6$ (10)	C_6H_6	40 °C	0% (100%)
15	NH_2Tces	$PhI(OPiv)_2$	$[Mn(ClPc)]SbF_6$ (10)	C_6H_6	23 °C	trace (97%)

***Table 1**. Reaction development and optimization. a. 2.2 equiv of MgO used as an additive. b. 3Å molecular sieves used. *isolated yield.*

into the reaction. The combination of 2,2,2-trichloroethyl sulfamate ($TcesNH_2$) and $PhI(OPiv)_2$ oxidant (*in situ strategy*) in the presence of iron phthalocyanine gave no product whereas manganese phthalocyanines gave trace product (Table 1, entries 1-4). Previous mechanistic studies for C—H amination processes suggested that *in situ* formation of iminoiodinane, an equilibrium process that favors the sulfamate ester, may be rate-determining.[12,17] Examining if elimination of this step could enhance reactivity by using preformed iminoiodinane (PhI=NTces) gave improved yields of benzylic amination across all the phthalocyanine catalysts examined, with [MnPc]Cl giving the best results (entries 5-7). We further hypothesized that electron withdrawing ligand modifications may promote formation of an electrophilic metallonitrene that is more reactive towards intermolecular C—H amination. Gratifyingly, a novel perchlorinated manganese phthalocyanine catalyst $[Mn(ClPc)]\cdot SbF_6$ significantly improved the yield of desired amination to 53% (entry 8, Table 1).[18] The addition of 5Å MS is necessary to remove trace water from the reaction and eliminate the formation of an undesirable benzylic ketone side product. Additionally, increasing the reaction temperature from 23 °C to 40 °C further increased the yield of product to 68% (entry 9). Lowering the catalyst loading or cutting the PhI=NTces to 1.0 equivalent led to a 47% and 42% yield, respectively (entries 10-11). Replacing the benzene



3, *90% yield*

Figure 6. *Synthesis of* $[MnCl_{16}Pc]Cl$.

solvent with 1,2-dichloroethane, a polar aprotic solvent compatible with polar substrates and complex molecules (*vide infra*), gave a synthetically useful 60% yield (entry 12). In the absence of $AgSbF_6$, a synthetically useful 50% yield is still obtained (entry 13), whereas elimination of [Mn(ClPc)]Cl resulted in no product formation (entry 14). Re-examination of the *in situ* iminoiodinane formation under optimized [Mn(ClPc)] conditions did not lead to a productive reaction (entry 15), which suggests that preformation of the oxidant is crucial for this reaction when utilizing a phthalocyanine catalyst. It is important to note that this novel phthalocyanine catalyst **3** can be easily synthesized in one step from commercially available starting materials, as shown in figure 6 (See appendix).

CHAPTER 3: REACTION SCOPE

With these new conditions, we began to look at the substrate scope of this transformation. We began by looking at the electronic effects of the aryl ring on the reactivity of the benzylic position.

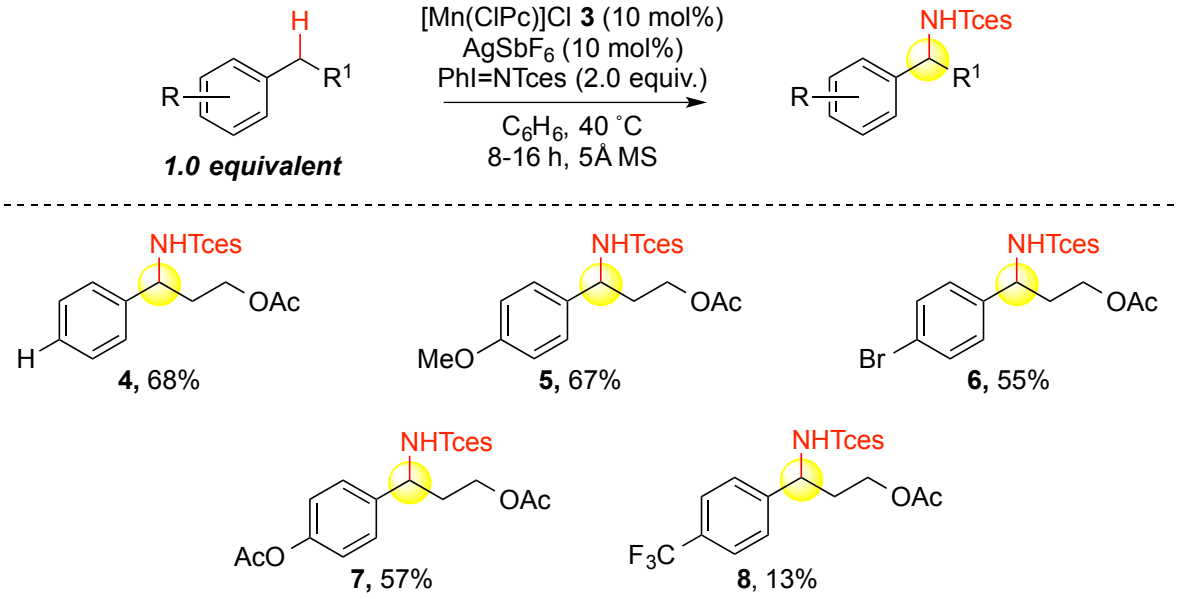


Figure 7. *Electronic effects of aromatic ring on benzylic reactivity.*

As shown in **Figure 7**, substrates with electron-neutral or electron-rich phenyl rings work well in this reaction. Products **4** and **5** are synthesized in the same yield from their respective starting materials. Generally, amination reactions work better on more electron-rich systems, and so initially we were puzzled by the equal yields achieved in these reactions. However, upon further inspection, we observed no recovered starting material in the reaction to produce **5**. Therefore, we hypothesize that in very electron-rich systems, some of the substrate is being consumed in an unidentified, but destructive pathway, leading to an overall comparable yield to more neutral systems where starting material is present at the end of the reaction. Additionally, this system works well for moderately electron-poor substrates to furnish products **6** and **7** bearing *p*-Br and *p*-OAc functionality. However, once more electron-poor groups are substituted on the ring, we

observe a big drop in yield, as demonstrated in product **8** bearing a *p*-CF_3 group. We then looked at nitrogen-containing substrates. Primary amines work well in this reaction when protected as trifluoroacetamides (**9** and **10**). Substrate **10** shows that substitution b to the reaction site is well-tolerated in this reaction.

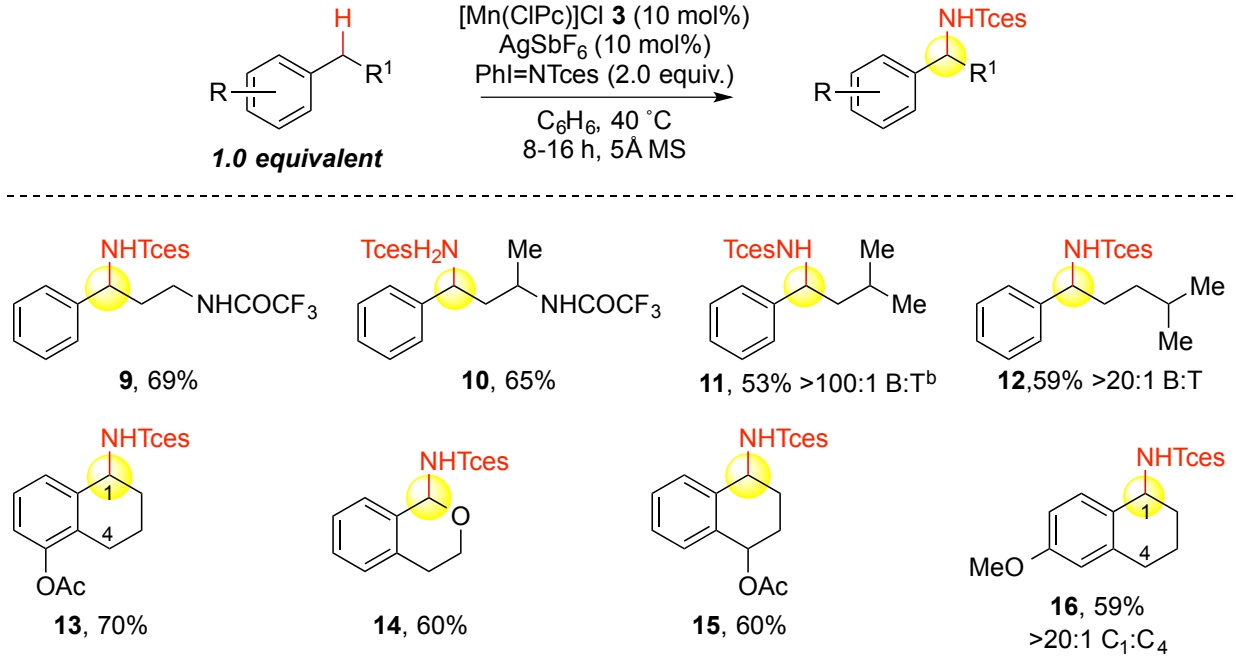


Figure 8. *Substrate scope, primary amines and site-selectivity.*

We then began to explore the selectivity of this system for benzylic amination over amination of other bond types. Isopentylbenzene works well in this reaction furnishing product **11** in 53% yield. We were excited to find that we observe no tertiary amination product by LC/MS or NMR. In comparison, the same substrate under rhodium catalysis gives an 8:1 mixture of inseparable isomers. Similarly, isohexylbenzene also works well in this reaction, furnishing product **12** in good yield with no tertiary amination observed by NMR. In substrates containing more than one benzylic site, we observe great selectivity for the more sterically and electronically activated site on the molecule. For example, 5-acetoxytetralin bearing two methylene benzylic sites (C_1 and C_4) revealed preferential amination at the C_1 site over the C_4

site, likely because of the 1,3 strain present at C_4 (**13**, 70%). Oxygen substitution in cyclic ethers activates adjacent C—H bonds towards amination via hyperconjugation (**14**, 60% yield). In contrast, oxygen with an electron withdrawing substituent like acyl deactivates the proximal C—H bond toward amination (**15**, 60% yield). Additionally, electronic substitution on the aromatic ring can have substantial effects on site-selectivity and reactivity in this protocol. For example, 6-methoxytetralin contains two potential sites for oxidation, differentiated by the electron-donating para-methoxy group on the phenyl ring. We isolate amination product at C_1 (**16**, 59%), the more electronically favored site, with only trace diaminated product detected in the crude reaction mixture (determined by LC/MS). In contrast, under rhodium catalysis an inseparable 7:1 mixture of C_1:C_4 amination products is reported alongside a 15% yield of diamination product.[8] The methoxy substitution on 7-methoxytetralone provides electronic activation to the benzylic methylene C—H bonds to achieve a synthetically useful 51% yield of aminated tetralone (Figure 9, **17**). It is significant to note that an unsubstituted α-tetralone affords only trace amounts of aminated product.

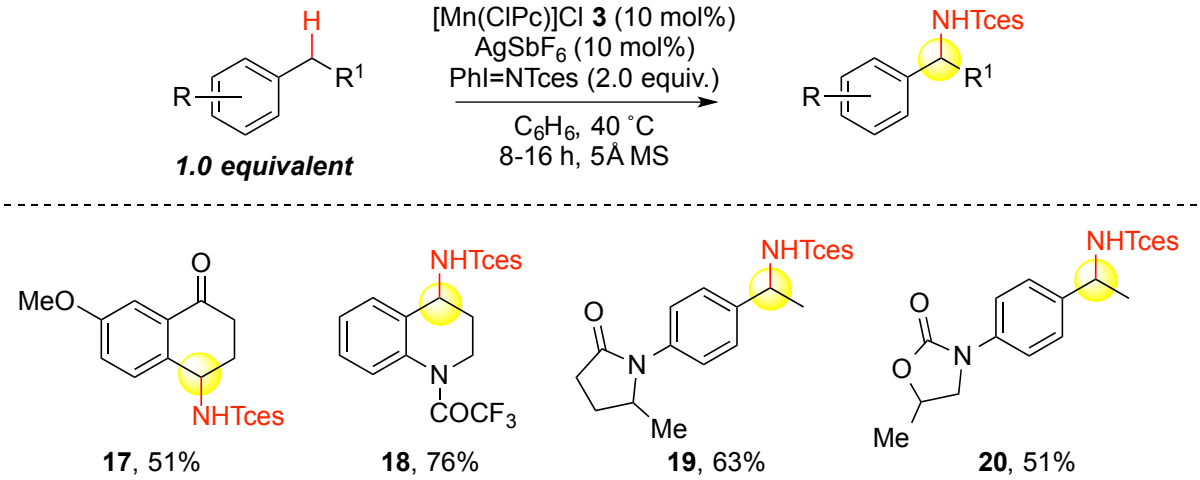


Figure 9. *Substrate scope, heterocycles.*

Nitrogen-containing heterocycles are also well tolerated in this reaction. Tetrahydroquinoline works well in this reaction when the amine is protected as a trifluoroacetamide (**18**, 76%). Moderately basic amide-containing heterocycles were also examined under [Mn(ClPc)] catalysis: An *N*-aryl lactam derived substrate underwent benzylic C—H amination in good yield (**19**, 63% yield) and *N*-aryl oxizolidinone, a structural motif found in pharmaceuticals like linazolid, was aminated to form **20** in 51% yield. Notably, we do not observe any α-aminal oxidation or N-oxide formation in either of these reactions.

Site-selective intermolecular C—H functionalization processes constitute powerful methods because of their capacity to make atomistic changes that may profoundly impact a

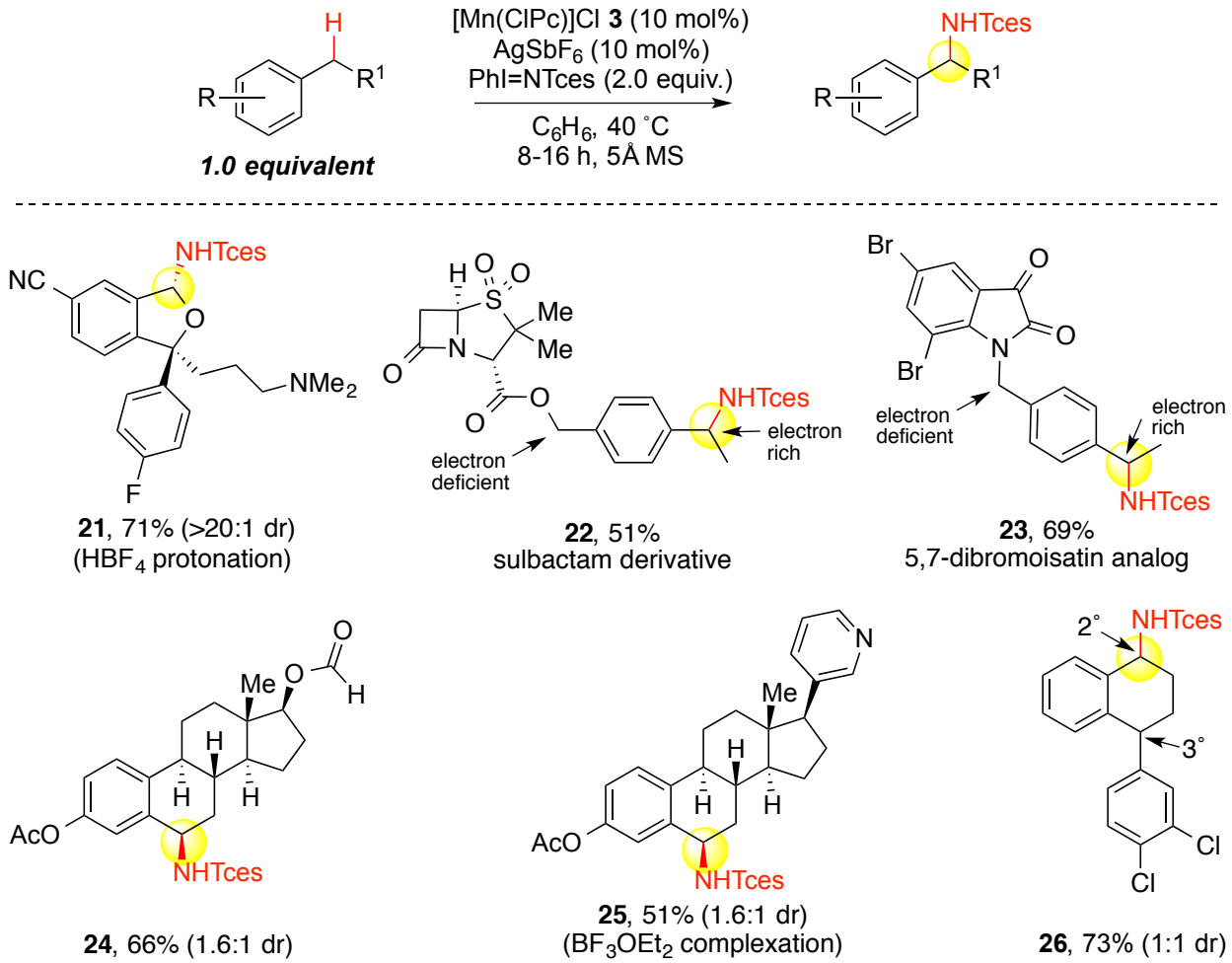


Figure 10. *Bioactive molecules and natural products.*

molecule's biological and physical properties.[19,20] We sought to evaluate the [Mn(ClPc)]-catalyzed benzylic C—H amination in such pharmaceutical settings where late-stage amination may be beneficial (Figure 10). Citalopram, a commonly prescribed antidepressant, works well in this reaction to furnish compound **21** in great yield and a single disastereomer. In substrates containing two possible sites of functionalization differentiated by electronic factors, we observe a preference for the more electronically activated site. For example, in an alkylated derivative of the antiobiotic sulbactam bearing two electronically differentiated benzylic sites, a 50% yield of aminated product **22** was isolated at the benzylic site distal from the electron-poor ester linkage. Similarly, a 5,7-dibromoisatin derivative containing two benzylic sites is oxidized in 69% yield at the more electron-rich site, with no amination at the more electron-poor site isolated (**23**).

In substrates containing more than one benzylic position differentiated by steric factors, we observe preference for the more sterically accessible site, even if the more congested site is tertiary, and therefore, more reactive. This is demonstrated in an estradiol derivative where we isolated a 66% yield of product at only the more sterically exposed site (**24**). It is notable that the formyl group on this substrate, usually an oxidatively unstable moiety, is tolerated in this reaction. Similarly, we are able to substitute the formyl group with a pyridyl group and maintain good levels of reactivity (**25**). Finally, we were able to isolate a 73% yield of desired oxidation

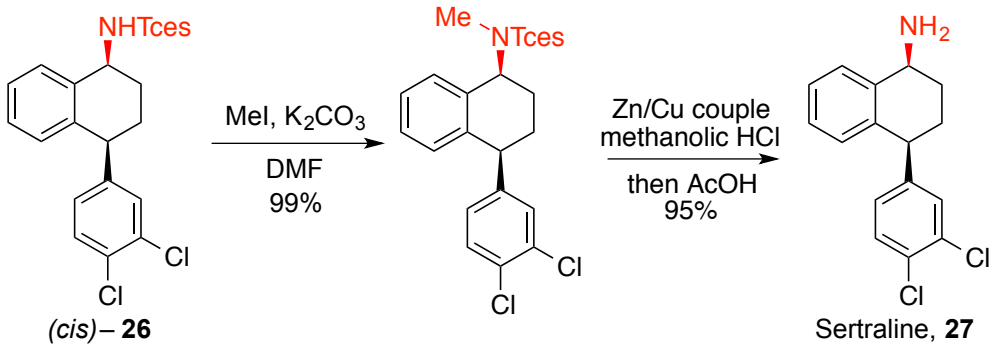


Figure 11. *Synthesis of Sertraline.*

product **26** from its hydrocarbon precursor. Again, we do not observe any functionalization at the more sterically congested, tertiary site. The *cis* diastereomer of product **26** was then easily derivatized to furnish antidepressant Sertraline (**27**) in two steps, providing an overall 4 step synthetic sequence from commercial starting materials (Figure 11).

CHAPTER 4: UNSUCCESSFUL SUBSTRATES

During the course of reaction and scope development, we found many substrates that did not work well for this system.

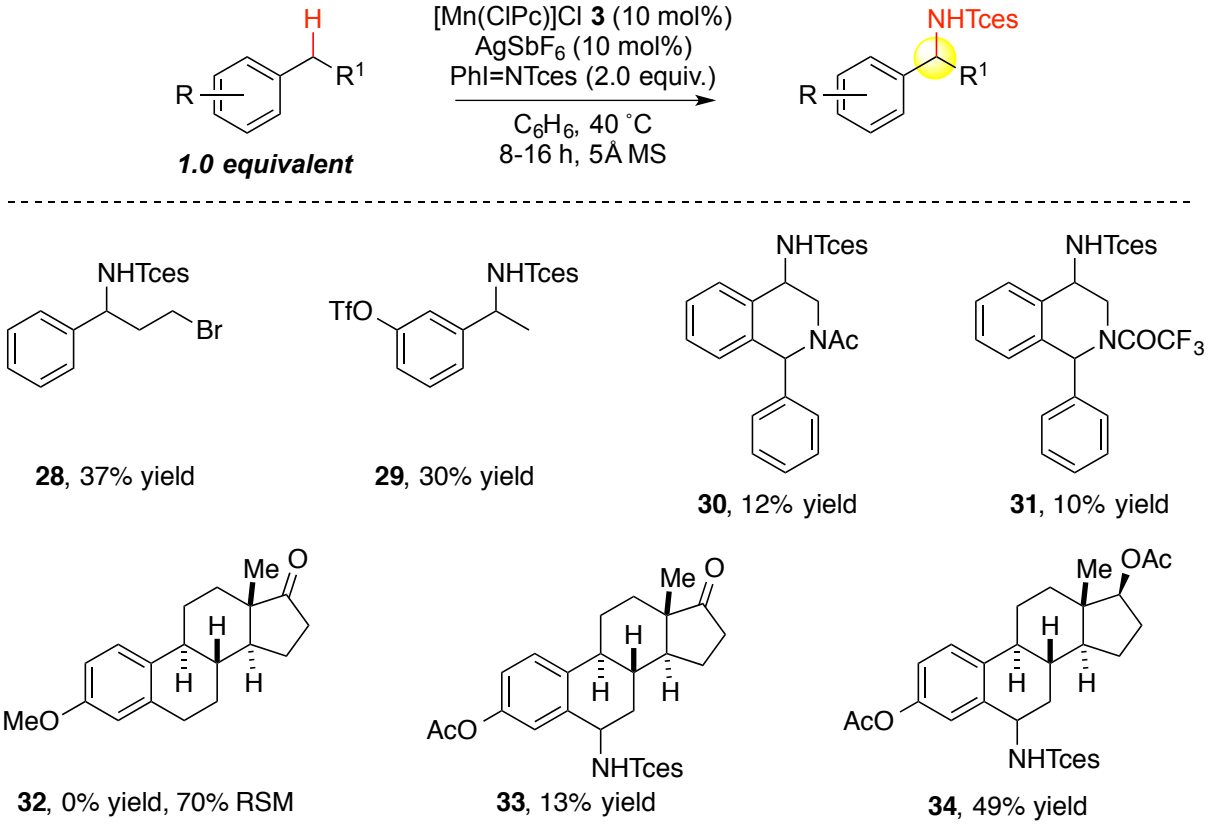
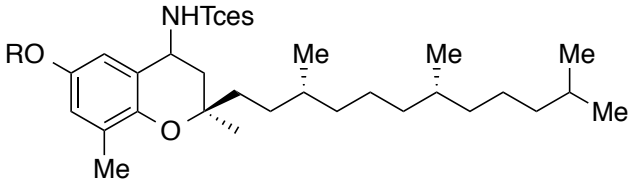


***Figure 12**. Unsuccessful substrates.*

As shown in figure 12, substrates containing alkyl bromides do not work well in this reaction (**28**). We hypothesize that this moiety undergoes deleterious reactivity, because we do not isolate complete recovered starting material. We found that triflate groups were too electron withdrawing for this reaction (**29**). Additionally, we found many substrates where electron-poor groups were too close to the reactive site to furnish good results. For example, in tetrahydroisoquinoline substrates, the electron-deficient amide functionality was only one methylene away from the benzylic site, deactivating this site and lowering yields of desired products (**30** and **31**). Additionally, many different estrone and estradiol derivatives were

explored as substrates for this reaction. Firstly, methoxy-substituted estrone **32** was tested, and we found no desired product. This result was perplexing because we had expected at least some reactivity for this substrate. However, upon closer inspection we found that the starting material was not soluble in the reaction; therefore, we hypothesized that increasing the solubility of the substrate will improve reactivity. Replacing the methoxy group with an acetate improved solubility of the compound and we observed a 13% yield of desired product (**33**). Reduction of the ketone and installation of a second acetate group further increased reactivity to 49% (**34**). From there, we replaced the acetate group with a formyl group, which further increased solubility. We were thus able to achieve high yields of desired product **24** in a highly site-selective reaction.

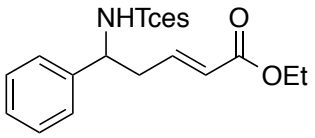


35, R = TBS <5% yield
36, R = Me No product
37, R = Ac 23% yield
38, R = Tf 30% yield

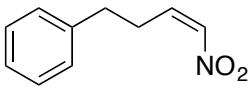
Figure 13*. Exploration of tocopherol substrates.*

Next we explored δ-tocopherol as a potential substrate for this method. Substituting the phenol with a TBS group lead to a substrate that did not work in the reaction. We observed trace product **35** from the reaction; we found that the TBS group had come off during the course of the reaction, which led to deleterious reactivity. Methoxy-substituted tocopherol gave no product formation (**36**) due to overactivation of the aromatic ring. We postulate that this overactivation lead to oxidation of the aromatic ring and eventual destruction of the substrate. This is supported by the fact that we recover no starting material from the reaction. Substituting the phenol with electron-deficient groups helped reactivity: acetate-bearing tocopherol gave a 23% yield of

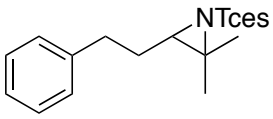
desired product **37** while more electron-deficient triflate-bearing tocopherol gave 30% yield of product (**38**). However, we were ultimately unable to increase the reactivity of this compound above 30%.



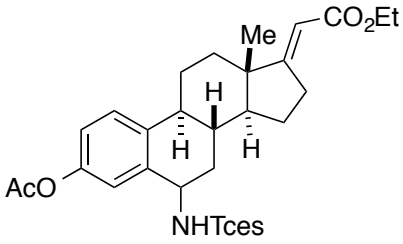
39, 30% yield, no RSM



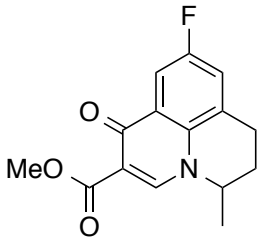
40, 20% yield aziridination



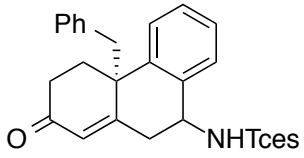
41, 25% yield, no amination



42, 26% yield, 16% RSM



43, 60% RSM, no product

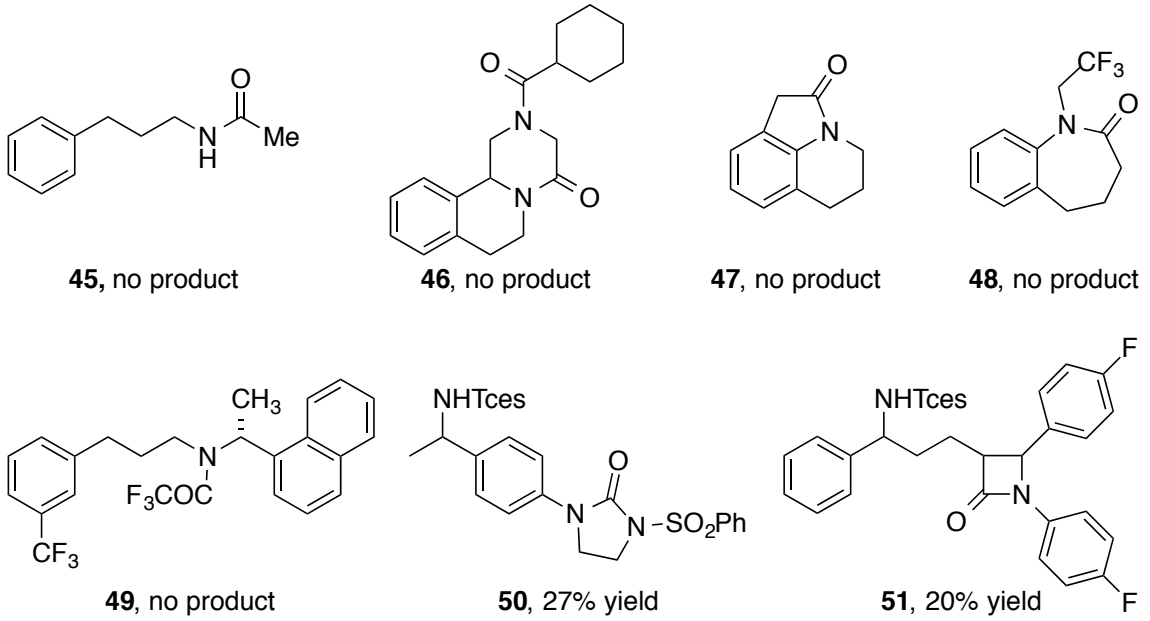


44, 15% yield, 20% RSM

Figure 14*. Exploration of olefin-containing substrates.*

We then turned our attention to olefin-containing substrates to see whether olefins could be tolerated in this reaction. It is known that olefins undergo aziridination under amination reaction conditions; however, we were hoping that by utilizing electron-poor olefins, we could effect C–H amination over aziridination. First we tried ethyl (*E*)-5-phenylpent-2-enoate containing an α,β-unsaturated olefin. This substrate worked in a moderate yield of 30% but we were not able to recover any starting material (**39**). We also tried a substrate containing a nitro-olefin, but found this compound is not reactive enough to give amination and instead gives aziridination product (**40**). We also hypothesized that we could use steric encumbrance around the olefin to favor amination. To test this theory, we tried (4-methylpent-3-en-1-yl)benzene as a substrate, but found only aziridination in the reaction (**41**). Additionally, we tested more complex molecules containing electron-deficient olefins, but found aziridination, low mass balance, or low yields of amination across the board (**42-44**).

The next substrate class we focused on was amides. We tested many amides before finding ones that worked in our system. Simple linear amides such as **45** do not work for



45, no product **46**, no product **47**, no product **48**, no product

49, no product **50**, 27% yield **51**, 20% yield

Figure 15*. Exploration of amide-containing substrates.*

this reaction due to the ability of the nitrogen to bind to the catalyst and shut down reactivity. We hypothesize that the same thing is happening in substrates **46** and **47** as well. Similarly, substrate **48** containing an aniline-derived amide moiety also gives no product. For substrate **49**, we believe the naphthyl ring on the molecule is being oxidized, leading to deleterious side-reactivity which hinders product formation, again leading to no product. We then examined a urea-containing substrate to test if this moiety is tolerated. We were happy to find a 27% yield of desired product **50** in the reaction; however, we were not able to increase the yield of product to a synthetically useful level. Concurrently we tried other heterocycles and found that oxazolidinones and lactams work well (**19** and **20**). Finally, we tried many derivatives of substrate **51** containing an electron-deficient β-lactam and found that in all cases we achieved only moderate yields of desired product (20%).

CHAPTER 5: CONCLUSION

A novel base-metal catalyzed intermolecular benzylic C—H amination was developed that proceeds with unprecedented levels of reactivity, site-selectivity and functional group tolerance. The [Mn(ClPc)] catalyst is synthesized in a one step, scalable reaction from abundant and sustainable commercial starting materials.[21] The [Mn(ClPc)]-catalyzed C—H amination demonstrates high site-selectivities in molecules containing multiple reactive C—H bonds based on steric and electronic differentiation.[22] Collectively, the combination of reactivity and selectivity make this [Mn(ClPc)]-catalyzed intermolecular benzylic C(sp^3)—H amination uniquely effective at preparatively useful late-stage functionalization of bioactive molecules and natural products. Many functional groups were tested, and we found several substrates that work well in this reaction. We found that olefins as well as electron-rich amides are not tolerated. Moreover, substrates with electron poor moieties close to the reactive site give dampened reactivity. Additionally, observed reactivity suggests this method proceeds via a metallonitrene, stepwise C—H amination pathway. The high tunable nature of metallonitrenes bodes well for further development of this method to promote the selective amination of other C(sp^3)—H bond types.

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APPENDIX

General Information

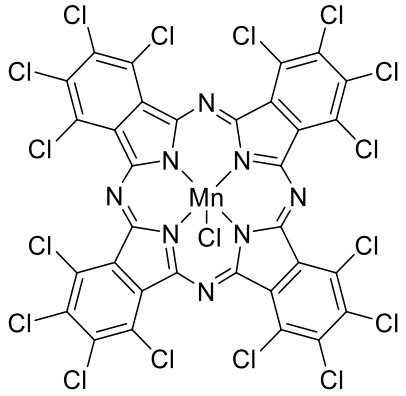
The following commercially obtained reagents were used as received: $Mn(II)Cl_2$ (99.995%-Mn, Strem), tetrachlorophthalonitrile (≥96%, TCI), $PhI(OAc)_2$ (Sigma-Aldrich or Oakwood Chemicals), and powdered 3Å and 5Å molecular sieves (Sigma-Aldrich). 2,2,2-trichloroethyl sulfamate was synthesized according to a previously reported procedure[1] 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 3Å 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).

^{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, 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.

Selected Procedures and Characterization

Catalyst and iminoiodinane synthesis



Manganese (III) Perchloro-Phthalocyanine Chloride [3]. 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, 0.33M) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.243 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 (aq) (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. Manganese (II) perchlorophthalocyanine has been previously reported but there are no reports of the manganese (III) perchlorophthalocyanine chloride catalyst.[2]

UV-Vis (1-Chloronaphthalene, λ_{max} = 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; HRMS (MALDI) m/z calculated for $C_{32}Cl_{16}MnN_8$ $[M\text{-}Cl]^+$: 1110.464, found 1110.507.

UV-Vis Studies: In a 25 mL volumetric flask, 2.0 mg (0.0017 mmol) of manganese (III) perchlorophthalocyanine chloride was taken up in 1-chloronaphthalene to make a 25 mL solution (69 μM). 100 μL of this solution was diluted to 1 mL (6.9 μM) in a 1 mL volumetric flask. A UV-Vis was taken from 1100-350 nm in a quartz cuvette (path length = 1 cm).

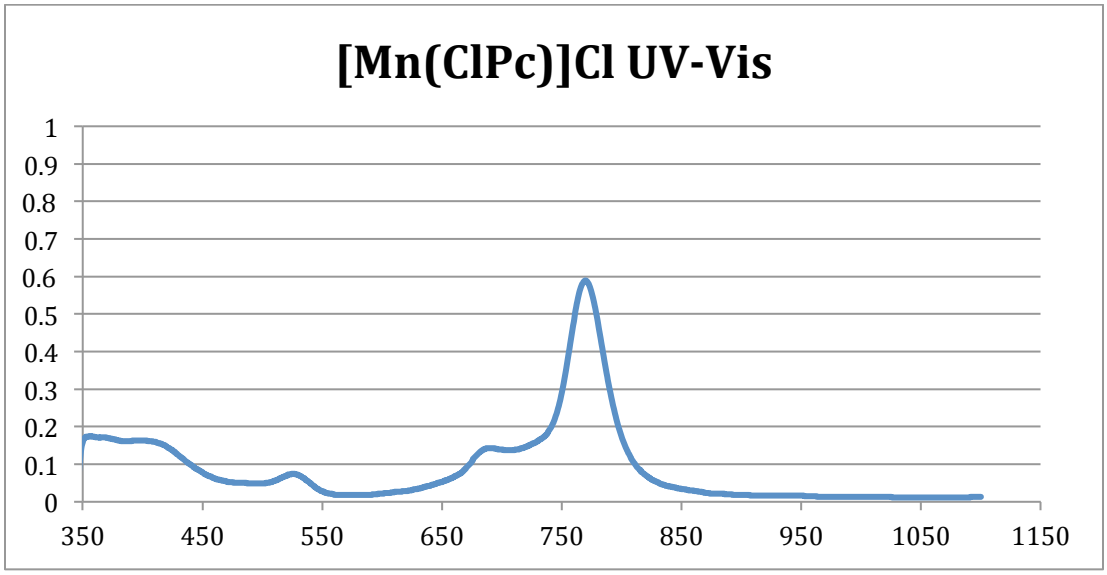
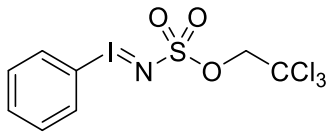


Figure 16. *UV-Vis spectrum for [Mn(ClPc)]Cl.*



2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate [S1]. 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, 0.25M). 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[3] 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).

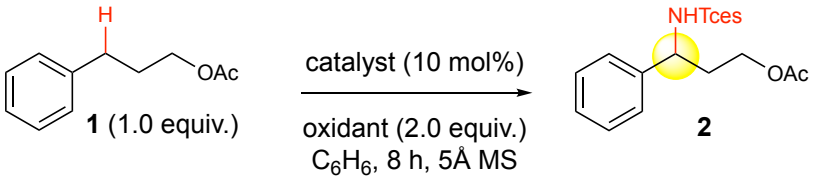
^{13}C NMR (126 MHz, Methanol-d_4)

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.

General amination procedures and optimization data for Table 1



Entry*	Sulfamate Ester	Oxidant	Catalyst (mol%)	Temp	% yield (% rsm)
1	NH_2Tces	$PhI(OPiv)_2$	$[Fe(Pc)]SbF_6$	23 °C	0% (100%)
2	NH_2Tces	$PhI(OPiv)_2$	$[Mn(Pc)]SbF_6$	23 °C	trace (96%)
3†	NH_2Tces	$PhI(OPiv)_2$	$[Mn(Pc)]SbF_6$	23 °C	trace (95%)
4	NH_2Tces	$PhI(OPiv)_2$	$[Mn(^tBuPc)]SbF_6$	23 °C	trace (94%)
5		PhI=NTces	$[Fe(Pc)]SbF_6$	23 °C	9% (85%)
6		PhI=NTces	$[Mn(^tBuPc)]SbF_6$	23 °C	12% (88%)
7		PhI=NTces	$[Mn(Pc)]SbF_6$	23 °C	17% (83%)
8		PhI=NTces	$[Mn(ClPc)]SbF_6$	23 °C	53% (41%)
9		PhI=NTces	$[Mn(ClPc)]SbF_6$	40 °C	68% (32%)
10‡		PhI=NTces	$[Mn(ClPc)]SbF_6$	40 °C	47% (49%)
11§		PhI=NTces	$[Mn(ClPc)]SbF_6$	40 °C	42% (58%)
12‖		PhI=NTces	$[Mn(ClPc)]SbF_6$	40 °C	60% (24%)
13		PhI=NTces	[Mn(ClPc)]Cl	40 °C	50% (43%)
14		PhI=NTces	$AgSbF_6$	40 °C	0% (100%)
15	NH_2Tces	$PhI(OPiv)_2$	$[Mn(ClPc)]SbF_6$	40 °C	trace (87%)

*Reaction Conditions: 1 (0.2 mmol, 1 equiv), catalyst (10 mol%), $AgSbF_6$ (10 mol%), oxidant (2 equiv), C_6H_6 (0.5M), 5Å molecular sieves (40 mg), 8 h. Yields are of isolated product. Trace yield is reported based on ^1H NMR analysis of the crude reaction using 1,3,5-trimethylbenzene as an internal standard and denote a yield of <5%. Recovered starting material (rsm) was determined by ^1H NMR analysis of the crude reaction using 1,3,5-trimethylbenzene as an internal standard. †2.2 equiv of MgO used as an additive in the reaction. ‡5 mol% catalyst used. §1 equivalent of PhI=NTces used. ‖3Å molecular sieves used. 1,2-DCE used as solvent.

Table 2. *Optimization of the base metal C–H amination.*

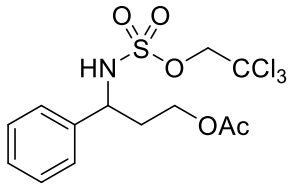
General procedure A for reaction optimization studies (*in situ* formation of iminoiodinane, entries 1-4, 15)

In a 10 mL round bottom flask was added 5Å 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 argon and wrapped in foil to exclude light. Once cooled, solvent (0.40 mL, 0.5 M to substrate), 3-phenylpropyl acetate **1** (35.6 mg, 0.20 mmol, 1 equiv), and 2,2,2-trichloroethyl sulfamate (54.8 mg, 0.24 mmol, 1.2 equiv) were added and stirred for 20 minutes. Catalyst (0.020 mmol, 0.1 equiv) and silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) were massed 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 while maintaining an argon atmosphere. In a 1 dram vial open to air, di-(pivaloyloxy)iodobenzene[4] (162.4 mg, 0.40 mmol, 2 equiv) was massed 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 hours at room temperature. Upon reaction completion, the reaction was filtered through a 1-inch silica gel plug using diethyl ether the eluent. The solvent was evaporated and a crude ^{1}H NMR was obtained using mesitylene (9.3 μL, 0.067 mmol, 0.33 equiv) as an internal standard to obtain the ^{1}H NMR yield.

General procedure B for reaction optimization studies (pre-formed iminoiodinane, entries 5-14)

In a 10 mL round bottom flask was added 5Å 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 **1** (35.6 mg, 0.20 mmol, 1 equiv) were added and stirred for 20 minutes. Catalyst (0.020 mmol, 0.1 equiv) and silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) were massed 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 (172.2 mg, 0.40 mmol, 2 equiv) was massed 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 hours 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 NH_2Tces) 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.

Selected compound characterization



3-phenyl-3-(((2,2,2-trichloroethoxy)sulfonyl)amino)propyl acetate [2]. According to the general amination procedure A, 5Å powdered molecular sieves (40 mg), 3-phenylpropyl acetate **S4** (35.6 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (30 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column using dichloromethane to quantitatively transfer the product. Flash chromatography using gradient elution (500 mL of 100% dichloromethane 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 slightly yellow solid.

Run 1 (53 mg, 0.131 mmol, 66% yield)

Run 2 (54 mg, 0.133 mmol, 67% yield)

Run 3 (57 mg, 0.141 mmol, 71% yield)

Average overall yield: 68% yield ± 2.6

^{1}H NMR: (500 MHz, Chloroform-*d*)

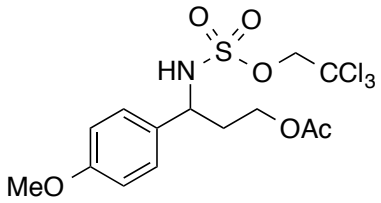
δ 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 3H), 5.73 (d, *J* = 7.7 Hz, 1H), 4.68 (q, *J* = 7.4 Hz, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.18-4.13(m, 1H), 4.05-4.00 (m, 1H), 2.32-2.25 (m, 1H), 2.18-2.11 (m, 1H), 2.04 (s, 3H)

^{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



3-(4-methoxyphenyl)-3-(((2,2,2-trichloroethoxy)sulfonyl)amino)propyl acetate [5]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), 3-(4-methoxyphenyl)propyl acetate **S5** (41.7 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (50 mL), the solvent was concentrated and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography on 75mL of silica using gradient elution (500 mL of 100% dichloromethane then 200 mL of 1% diethyl ether in 99% dichloromethane followed by 400 mL of 2% diethyl ether in 98% dichloromethane then 400 ml of 5% diethyl ether in 95% dichloromethane) gave the pure product as a white solid.

Run 1 (60.9 mg, 0.140 mmol, 70% yield)

Run 2 (56.5 mg, 0.130 mmol, 65% yield)

Run 3 (57.0 mg, 0.131 mmol, 66% yield)

Average overall yield: 67% yield ± 2.6

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

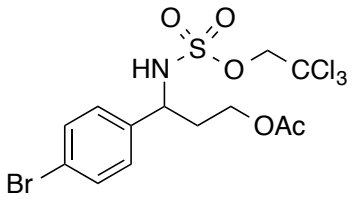
δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.60 (br d, *J* = 7.2 Hz, 1H), 4.63 (q, *J* = 7.2 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.29 (d, *J* = 10.8 Hz, 1H), 4.13 (dt, *J* = 11.6, 5.9 Hz, 1H), 3.99 (dt, *J* = 11.7, 6.3 Hz, 1H), 3.79 (s, 3H), 2.28 (m, 1H), 2.15 – 2.08 (m, 1H), 2.04 (s, 3H).

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

δ 171.22, 159.75, 131.61, 127.99, 114.58, 93.38, 78.11, 61.17, 56.36, 55.49, 35.54, 21.02.

HRMS: (ESI-TOF MS ES-)

m/z calculated for $C_{14}H_{17}Cl_3NO_6S$ $[M-H]^-$: 431.9842, found 431.9839.



3-(4-bromophenyl)-3-(((2,2,2-trichloroethoxy)sulfonyl)amino)propyl acetate [6]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), 3-(4-bromophenyl)propyl acetate **S6** (51.4 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate

(172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (50 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column. Flash chromatography with 75mL of silica using gradient elution (500 mL of 100% dichloromethane then 250 mL of 1% diethyl ether in 99% dichloromethane followed by 250 mL of 2% diethyl ether in 98% dichloromethane) gave the pure product as a white solid.

Run 1 (64.8 mg, 0.106 mmol, 53% yield)

Run 2 (63.0 mg, 0.110 mmol, 55% yield)

Run 3 (63.0 mg, 0.112 mmol, 56% yield)

Average overall yield: 55% yield

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

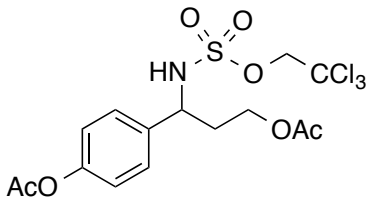
δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.54 (d, *J* = 7.5 Hz, 1H), 4.67 (q, *J* = 7.3 Hz, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.40 (d, *J* = 10.8 Hz, 1H), 4.15 (ddd, *J* = 11.9, 6.8, 5.2 Hz, 1H), 4.04 (ddd, *J* = 11.8, 7.0, 5.2 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.18 – 2.09 (m, 1H), 2.05 (s, 3H).

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

δ 171.17, 138.77, 132.48, 128.53, 122.70, 93.40, 78.25, 61.04, 56.54, 35.61, 21.13.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{15}NO_5NaSCl_3Br$ $[M+Na]^+$: 503.8818, found 503.8807.



4-(3-acetoxy-1-(((2,2,2-trichloroethoxy)sulfonyl)amino)propyl)phenyl acetate [7]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), 3-(4-acetoxyphenyl)propyl acetate **S7** (47.3 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (50 mL), the solvent was concentrated and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography on 75mL silica using gradient elution (500 mL of 100% dichloromethane then 200 mL of 2% diethyl ether in 98% dichloromethane followed by 400 mL of 4% diethyl ether in 96% dichloromethane then 400 ml of 8% diethyl ether in 92% dichloromethane) gave the product as a white solid with a minor impurity that was considered when calculating yield by the addition of mesitylene as an internal standard in the ^{1}H NMR.

Run 1 (53.7 mg, 0.116 mmol, 58% yield)

Run 2 (53.7 mg, 0.116 mmol, 58% yield)

Run 3 (51.8 mg, 0.112 mmol, 56% yield)

Average overall yield: 57% yield ± 1.1

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

δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 5.75 (d, *J* = 6.9 Hz, 1H), 4.68 (q, *J* = 7.1 Hz, 1H), 4.40 (d, *J* = 10.8 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.16 (ddd, *J* = 11.9, 7.1,

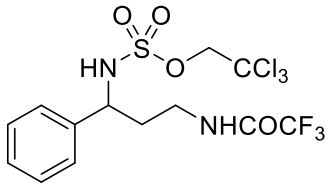
5.2 Hz, 1H), 4.03 (ddd, *J* = 11.8, 6.8, 5.1 Hz, 1H), 2.30 (s, 3H), 2.28 – 2.20 (m, 1H), 2.13 (dtd, *J* = 14.0, 6.8, 5.0 Hz, 1H), 2.03 (s, 3H).

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

δ 171.18, 169.53, 150.70, 137.29, 127.88, 122.38, 93.33, 78.13, 61.03, 56.34, 35.56, 21.26, 21.00.

HRMS: (ESI- TOF MS ES-)

m/z calculated for $C_{15}H_{18}Cl_3NO_7SNa$ $[M+Na]^+$: 483.9767, found 483.9775.



2,2,2-trichloroethyl (1-phenyl-3-(2,2,2-trifluoroacetamido)propyl)sulfamate [9]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 2,2,2-trifluoro-N-(3-phenylpropyl)acetamide **S8** (46.2 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (30 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column using dichloromethane to quantitatively transfer the product. Flash chromatography using gradient elution (500 mL of 100% dichloromethane 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 light yellow solid.

Run 1 (61 mg, 0.133 mmol, 67% yield)

Run 2 (66 mg, 0.144 mmol, 72% yield)

Run 3 (61 mg, 0.133 mmol, 67% yield)

Average overall yield: 69% yield ± 2.9

^{1}H NMR: (500 MHz, Chloroform-*d*)

δ 7.42 – 7.36 (m, 2H), 7.36 – 7.31 (m, 3H), 6.75 (s, 1H), 5.41 (d, *J* = 8.1 Hz, 1H), 4.57 (q, *J* = 7.7 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.31 (d, *J* = 10.8 Hz, 1H), 3.74 – 3.66 (m, 1H), 3.42 – 3.34 (m, 1H), 2.22 – 2.15 (m, 2H)

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

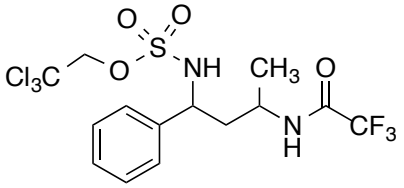
δ 157.9 (q, *J* = 36.2 Hz), 139.6, 129.4, 128.9, 126.6, 115.8 (q, *J* = 287.4 Hz), 93.1, 78.1, 57.2, 37.1, 35.5

^{19}F NMR: (470 MHz, Chloroform-*d*)

δ -76.44

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{14}N_2O_4SCl_3F_3Na$ $[M+Na]^+$: 478.9590, found 478.9555



2,2,2-trichloroethyl (1-phenyl-3-(2,2,2-trifluoroacetamido)butyl)sulfamate [10]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), 2,2,2-trifluoro-*N*-(4-phenylbutan-2-yl)acetamide **S9** (49.1 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver

hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column. Flash chromatography on 75mL silica using gradient elution (500 mL of 100% dichloromethane then 200 mL of 1% diethyl ether in 99% dichloromethane followed by 400 mL of 2% diethyl ether in 98% dichloromethane) gave the pure product as a white solid in a 1:1 diastereomeric mixture. This compound was characterized as a mixture of diastereomers.

Run 1 (61 mg, 0.130 mmol, 65% yield)

Run 2 (58.5 mg, 0.124 mmol, 62% yield)

Run 3 (64.2 mg, 0.136 mmol, 68% yield)

Average overall yield: 65% yield ± 3.0 (1:1 d.r.)

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

δ 7.42 – 7.29 (m, 5H), 6.57 – 6.48 (m, 1H), 6.24 (d, *J* = 7.3 Hz, 0.5H), 5.91 (d, *J* = 7.9 Hz, 0.5H), 4.62 – 4.51 (m, 1H), 4.33 (d, *J* = 10.8 Hz, 0.5H), 4.32 (d, *J* = 10.8 Hz, 0.5H), 4.21 (d, *J* = 10.8 Hz, 0.5H), 4.18 (d, *J* = 10.8 Hz, 0.5H), 4.15 – 3.99 (m, 1H), 2.31 (dt, *J* = 14.6, 7.4 Hz, 0.5H), 2.21 (t, *J* = 7.0 Hz, 0.5H), 1.95 (dt, *J* = 13.9, 6.7 Hz, 1H), 1.33 (d, *J* = 6.7 Hz, 1.5H), 1.29 (d, *J* = 6.7 Hz, 1.5H).

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

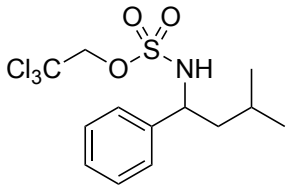
δ157.08 (q, J_{CF} = 37.2 Hz), 156.96 (q, J_{CF} = 37.3 Hz), 139.85, 139.29, 129.46, 129.38, 128.95, 128.82, 126.75, 126.63, 115.77 (q, J_{CF} = 287.4 Hz), 115.75 (q, J_{CF} = 287.9 Hz), 93.20, 93.18, 78.12, 78.09, 56.80, 56.72, 44.43, 44.27, 43.07, 41.91, 20.03, 19.97.

^{19}F NMR: (471 MHz, $CDCl_3$)

δ -75.92, -75.98. (diastereomers).

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{14}H_{20}Cl_3F_3N_3O_4S$ $[M+NH_4]^+$: 488.0192 , found 488.0197.



2,2,2-trichloroethyl (3-methyl-1-phenylbutyl)sulfamate [11]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), isopentylbenzene **S10** (29.7 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (50 mL), the solvent was concentrated and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of 100% hexanes then 400 mL of 5% ethyl acetate in 95% hexanes followed by 200 mL of 10% ethyl acetate in 90% hexanes) gave the pure product as a colorless oil.

Run 1 (37.2 mg, 0.099 mmol, 50% yield)

Run 2 (41.2 mg, 0.110 mmol, 55% yield)

Run 3 (41.2 mg, 0.110 mmol, 55% yield)

Average overall yield: 53% yield ± 2.9

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

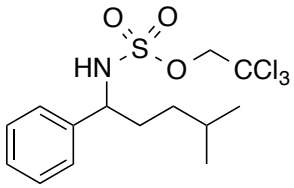
δ 7.41 – 7.23 (m, 5H), 5.15 (br d, *J* = 7.2 Hz, 1H), 4.57 (q, *J* = 7.6 Hz, 1H), 4.26 (d, *J* = 10.8 Hz, 1H), 4.22 (d, *J* = 10.8 Hz, 1H), 1.80 (dt, *J* = 14.5, 7.5 Hz, 1H), 1.67 (dt, *J* = 13.9, 7.2 Hz, 1H), 1.62 – 1.51 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 6H).

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

δ 140.96, 129.14, 128.37, 126.78, 93.36, 78.10, 57.97, 46.29, 24.88, 22.56, 22.32.

HRMS: (ESI- TOF MS ES-)

m/z calculated for $C_{13}H_{17}Cl_3NO_3S$ $[M-H]^-$: 371.9995 , found 371.9991.



2,2,2-trichloroethyl (4-methyl-1-phenylpentyl)sulfamate [12]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), (4-methylpentyl)benzene **S11** (32.5 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (50 mL), the solvent was concentrated and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography on 75mL of silica using gradient elution (100 mL of 100% hexanes then 300 mL of 5% ethyl acetate in 95% hexanes followed by 600 mL of 10% ethyl acetate in 90% hexanes) gave the pure product as a colorless oil.

Run 1 (47 mg, 0.120 mmol, 60% yield)

Run 2 (45.1 mg, 0.116 mmol, 58% yield)

Run 3 (45.2 mg, 0.116 mmol, 58% yield)

Average overall yield: 59% yield ± 1.2

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

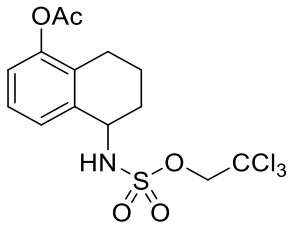
δ 7.41 – 7.27 (m, 5H), 4.97 (br d, *J* = 7.3 Hz, 1H), 4.46 (q, *J* = 7.5 Hz, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.28 (d, *J* = 10.8 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.87 – 1.76 (m, 1H), 1.61 – 1.48 (m, 1H), 1.33 – 1.19 (m, 1H), 1.16 – 1.02 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 6H).

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

δ 140.74, 129.13, 128.39, 126.78, 93.39, 78.13, 60.03, 35.14, 35.00, 27.88, 22.62, 22.52.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{14}H_{19}Cl_3NO_3S$ $[M-H]^-$: 386.0157, found 386.0145.



5-(((2,2,2-trichloroethoxy)sulfonyl)amino)-5,6,7,8-tetrahydronaphthalen-1-yl acetate [13]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 5,6,7,8-tetrahydronaphthalen-1-yl acetate **S12** (38.0 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (30 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel

column using dichloromethane to quantitatively transfer the product. Flash chromatography using gradient elution (100 mL of 100% hexanes then 300 mL of 5% acetone in 95% hexanes followed by 600 mL of 7.5% acetone in 92.5% hexanes) gave the pure product as a clear and yellow oil.

Run 1 (56 mg, 0.134 mmol, 67% yield)

Run 2 (60 mg, 0.144 mmol, 72% yield)

Run 3 (58 mg, 0.139 mmol, 70% yield)

Average overall yield: 70% yield ± 2.5

^{1}H NMR: (500 MHz, Chloroform-*d*)

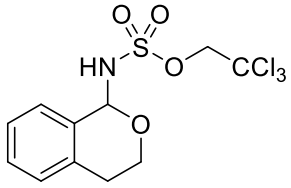
δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.00 – 6.93 (m, 1H), 5.05 (d, *J* = 7.8 Hz, 1H), 4.82 – 4.76 (m, 1H), 4.67 (s, 2H), 2.62 (dt, *J* = 17.4, 5.7 Hz, 1H), 2.51 (dt, *J* = 17.3, 7.1 Hz, 1H), 2.30 (s, 3H), 2.12 – 2.05 (m, 2H), 1.89 – 1.80 (m, 2H)

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

δ 169.4, 149.0, 136.5, 130.4, 127.2, 127.2, 121.8, 93.7, 78.2, 53.3, 29.8, 23.0, 20.9, 18.2

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{14}H_{16}NO_5SCl_3Na$ $[M+Na]^+$: 437.9712, found 437.9707



2,2,2-trichloroethyl isochroman-1-ylsulfamate [14]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), isochroman **S13** (46.2 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg,

0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (30 mL), the solvent was concentrated and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of 100% hexanes then 300 mL of 5% ethyl acetate in 95% hexanes followed by 600 mL of 10% ethyl acetate in 90% hexanes) gave the pure product as a yellow solid.

Run 1 (44 mg, 0.122 mmol, 61% yield)

Run 2 (41 mg, 0.114 mmol, 57% yield)

Run 3 (45 mg, 0.125 mmol, 62% yield)

Average overall yield: 60% yield ± 2.6

^{1}H NMR: (500 MHz, Chloroform-*d*)

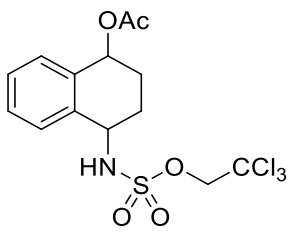
δ 7.33 – 7.22 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.06 (d, *J* = 8.3 Hz, 1H), 5.77 (d, *J* = 8.3 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.06 – 4.01 (m, 2H), 3.00 – 2.91 (m, 1H), 2.79 – 2.72 (m, 1H)

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

δ 134.7, 131.7, 129.1, 129.0, 127.1, 127.0, 93.6, 80.6, 78.6, 59.8, 27.7

HRMS: (ESI-TOF MS ES-)

m/z calculated for $C_{11}H_{11}NO_4SCl_3$ $[M-H]^-$: 357.9474, found 357.9467



4-(((2,2,2-trichloroethoxy)sulfonyl)amino)-1,2,3,4-tetrahydronaphthalen-1-yl acetate [15]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 1,2,3,4-tetrahydronaphthalen-1-yl acetate **S14** (38.0 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl ether as the eluent (30 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column using dichloromethane to quantitatively transfer the product. Flash chromatography using gradient elution (500 mL of 100% dichloromethane 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 in equal amounts of inseparable diastereomers.

Run 1 (50 mg, 0.120 mmol, 60% yield)

Run 2 (52 mg, 0.124 mmol, 62% yield)

Run 3 (48 mg, 0.115 mmol, 58% yield)

Average overall yield: 60% yield ± 2.0 (1:1 d.r.)

^{1}H NMR: (500 MHz, Chloroform-*d*) (mixture of diastereomers)

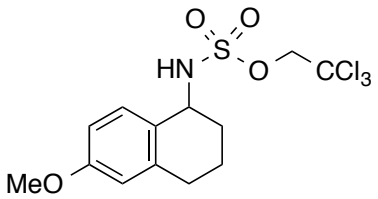
δ 7.59 (d, *J* = 7.4 Hz, 0.5H), 7.53 (d, *J* = 7.4 Hz, 0.5H), 7.40 – 7.35 (m, 1H), 7.35 – 7.30 (m, 2H), 5.99 (t, *J* = 4.4 Hz, 0.5H), 5.92 (t, *J* = 5.2 Hz, 0.5H), 5.05 (d, *J* = 8.0 Hz, 0.5H), 4.94 – 4.88 (m, 0.5H), 4.88 – 4.83 (m, 0.5H), 4.76 (td, *J* = 7.9, 5.1 Hz, 0.5H), 4.70 (s, 1H), 4.69 (s, 1H) 2.40 – 2.31 (m, 0.5H), 2.31 – 2.22 (m, 0.5H), 2.22 – 2.10 (m, 2.5H), 2.09 (s, 1.5H), 2.07 (s, 1.5H), 2.02 – 1.95 (m, 0.5H)

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

δ 170.8, 170.7, 135.7, 135.4, 135.2, 135.1, 129.9, 129.6, 129.5, 129.4, 129.3, 129.1, 128.9, 128.5, 93.7, 93.6, 78.3, 78.2, 69.4, 68.7, 53.5, 52.9, 26.9, 26.0, 25.8, 24.9, 21.5, 21.4.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{14}H_{16}NO_5SCl_3Na$ $[M+Na]^+$: 437.9712, found 437.9704



2,2,2-trichloroethyl (6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)sulfamate [16]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), 6-methoxy-1,2,3,4-tetrahydronaphthalene **S15** (32.5 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was concentrated and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (400 mL of 5% ethyl acetate in hexane followed by 400 mL of 10% ethyl acetate in hexanes) gave the pure product as well as the imine by-product as off-white solids.

Run 1 (46.5 mg, 0.120 mmol, 60% yield + imine (10.2 mg, 0.026 mmol, 13% yield))

Run 2 (47.3 mg, 0.122 mmol, 61% yield + imine (10.0 mg, 0.026 mmol, 13% yield))

Run 3 (41 mg, 0.106 mmol, 53% yield + imine (7.0 mg, 0.014 mmol, 9% yield))

Average overall yield: 58 % yield ± 4.4

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

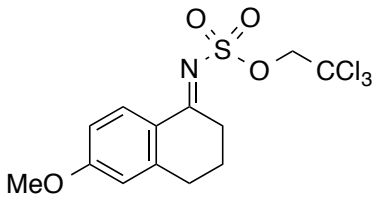
δ 7.39 (d, *J* = 8.6 Hz, 1H), 6.76 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.61 (d, *J* = 2.7 Hz, 1H), 4.83 (d, *J* = 7.7 Hz, 1H), 4.76 – 4.72 (m, 1H), 4.67 (s, 2H), 3.78 (s, 3H), 2.79 (dt, *J* = 17.0, 5.4 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.16 – 2.09 (m, 1H), 2.08 – 2.01 (m, 1H), 1.89 – 1.79 (m, 2H).

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

δ 159.35, 139.22, 130.69, 126.75, 113.77, 113.12, 93.75, 78.18, 55.40, 53.19, 30.46, 29.31, 18.90.

HRMS: (ESI- TOF MS ES-)

m/z calculated for $C_{13}H_{15}Cl_3NO_4S$ $[M-H]^-$: 385.9787, found 385.9784.



2,2,2-trichloroethyl-(6-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)sulfamate [S16].

Isolated as part of the oxidation reaction of 6-methoxy-1,2,3,4-tetrahydronaphthalene.

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

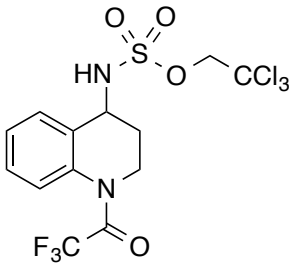
δ 8.17 (d, *J* = 8.9 Hz, 1H), 6.84 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 4.84 (s, 2H), 3.88 (s, 3H), 3.26 – 3.20 (m, 2H), 2.89 (t, *J* = 6.1 Hz, 2H), 2.04 (dq, *J* = 7.1, 6.1 Hz, 2H).

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

δ 182.65, 165.06, 147.98, 130.66, 124.36, 114.17, 113.11, 93.61, 79.28, 55.77, 33.21, 29.96, 22.55.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{13}H_{15}Cl_3NO_4$ $[M+H]^+$: 385.9787, found 385.9778.



2,2,2-trichloroethyl (1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinolin-4-yl)sulfamate [18]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 1-(3,4-dihydroquinolin-1(2*H*)-yl)-2,2,2-trifluoroethan-1-one **S17** (46.0 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using diethyl

ether as the eluent (50 mL), the solvent was concentrated and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography on 75 mL silica using gradient elution (100 mL of 100% hexanes then 400 mL of 5% ethyl acetate in 95% hexanes followed by 200 mL of 10% ethyl acetate in 90% hexanes) gave the pure product as a white solid.

Run 1 (71.1 mg, 0.156 mmol, 78% yield)

Run 2 (68.3 mg, 0.150 mmol, 75% yield)

Run 3 (69.3 mg, 0.152 mmol, 76% yield)

Average overall yield: 76% yield ± 1.5

^{1}H NMR: (500 MHz, $CDCl_3$ at 50 °C)

δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.55 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 5.35 (d, *J* = 7.5 Hz, 1H), 4.85 (q, *J* = 6.3 Hz, 1H), 4.70 – 4.64 (m, 2H), 3.90 (t, *J* = 5.9 Hz, 2H), 2.44 (dq, *J* = 12.3, 6.0 Hz, 1H), 2.33 (dq, *J* = 11.8, 5.9 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$ at 50 °C)

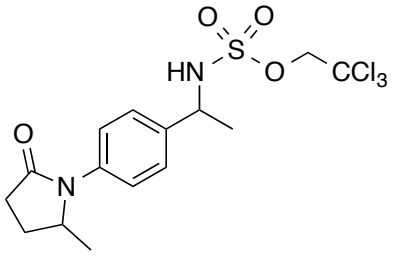
δ 156.16 (q, *J* = 36.3 Hz), 136.86, 129.25, 129.10, 128.75, 127.42, 124.71, 116.63 (q, J_{CF} = 288.3 Hz), 93.68, 78.45, 51.05, 42.80, 31.35.

^{19}F NMR: (471 MHz, DMSO at 23 °C)

δ -68.19, -75.08 (rotational isomers).

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{13}H_{16}Cl_3F_3N_3O_4S$ $[M+NH_4]^+$: 471.9879 , found 471.9880.



2,2,2-trichloroethyl (1-(4-(2-methyl-5-oxopyrrolidin-1-yl)phenyl)ethyl)sulfamate [19]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 1-(4-ethylphenyl)-5-methylpyrrolidin-2-one **S19** (40.7 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column. Flash chromatography on 75 mL silica using gradient elution (500 mL of 100% dichloromethane then 200 mL of 5% diethyl ether in 95% dichloromethane followed by 400 mL of 10% diethyl ether in 90% dichloromethane and then 200 mL of 20% diethyl ether in 80% dichloromethane and finally 400 mL of 50% diethyl ether in 50% dichloromethane) gave the pure product as an off-white oil in a 1:1 diastereomeric mixture. This compound was characterized as a mixture of diastereomers.

Run 1 (56.0 mg, 0.130 mmol, 65% yield)

Run 2 (53.3 mg, 0.124 mmol, 62% yield)

Run 3 (52.0 mg, 0.121 mmol, 61% yield)

Average overall yield: 63% yield ± 2.1 (1:1 d.r.)

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

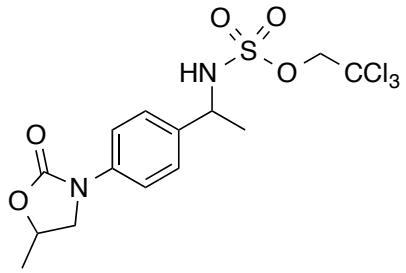
δ 7.41 – 7.34 (m, 4H), 5.64 (d, *J* = 7.5 Hz, 0.5H), 5.61 (d, *J* = 7.4 Hz, 0.5H), 4.71 (dq, *J* = 6.9 Hz, 0.5H), 4.71 (dq, *J* = 6.9 Hz, 0.5H), 4.47 (d, *J* = 10.8 Hz, 0.5H), 4.47 (d, *J* = 10.8 Hz, 0.5H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.36 – 4.25 (m, 1H), 2.71 – 2.62 (m, 1H), 2.60 – 2.51 (m, 1H), 2.43 – 2.34 (m, 1H), 1.82 – 1.71 (m, 1H), 1.60 (d, *J* = 6.5 Hz, 1.5H), 1.58 (d, *J* = 6.5 Hz, 1.5H), 1.26 (d, *J* = 6.2 Hz, 1.5H), 1.24 (d, *J* = 6.2 Hz, 1.5H).

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

δ 174.92, 139.59, 139.52, 137.03, 136.98, 127.15, 127.06, 124.28, 124.21, 93.59, 93.57, 78.05, 55.87, 55.85, 54.38, 54.34, 31.46, 26.71, 26.69, 23.24, 22.92, 20.21.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{15}H_{20}N_2O_4SCl_3$ $[M+H]^+$: 429.0209, found 429.0209.



2,2,2-trichloroethyl (1-(4-(5-methyl-2-oxooxazolidin-3-yl)phenyl)ethyl)sulfamate [20]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 3-(4-ethylphenyl)-5-methyloxazolidin-2-one **S20** (41.1 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel

column. Flash chromatography on 75mL silica using gradient elution (500 mL of 100% dichloromethane then 200 mL of 1% diethyl ether in 99% dichloromethane followed by 400 mL of 2% diethyl ether in 98% dichloromethane and then 200 mL of 5% diethyl ether in 95% dichloromethane) gave the pure product as an off-white solid in a 1:1 diastereomeric mixture. This compound was characterized as a mixture of diastereomers.

Run 1 (45.0 mg, 0.104 mmol, 52% yield)

Run 2 (44.9 mg, 0.104 mmol, 52% yield)

Run 3 (41.4 mg, 0.096 mmol, 48% yield)

Average overall yield: 51% yield ± 2.3 (1:1 d.r.)

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

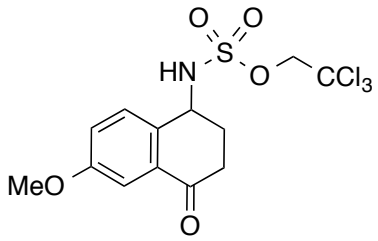
δ 7.50 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 5.47 (s, 1H), 4.79 (sxt, *J* = 6.3 Hz, 1H), 4.75 – 4.66 (m, 1H), 4.50 (d, *J* = 10.8 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.10 (td, *J* = 8.5, 3.5 Hz, 1H), 3.61 (ddd, *J* = 8.6, 7.1, 2.6 Hz, 1H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.53 (d, *J* = 6.2 Hz, 3H).

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

δ 155.15, 138.21, 137.33, 127.19, 118.71, 93.55, 78.21, 69.94, 69.93, 54.43, 52.01, 52.00, 22.92, 22.91, 20.82, 20.80.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{14}H_{18}N_2O_5SCl_3$ $[M+H]^+$: 431.0002, found 431.0006.



2,2,2-trichloroethyl (6-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)sulfamate [17]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), (4-methylpentyl)benzene **S21** (35.2 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column. Flash chromatography on 75mL of silica using gradient elution (500 mL of 100% dichloromethane then 200 mL of 1% diethyl ether in 99% dichloromethane followed by 200 mL of 2% diethyl ether in dichloromethane and then 200 mL of 5% diethyl ether in 95% dichloromethane) gave the pure product as a colorless oil.

Run 1 (42.7 mg, 0.106 mmol, 53% yield)

Run 2 (41.0 mg, 0.102 mmol, 51% yield)

Run 3 (40.3 mg, 0.100 mmol, 50% yield)

Average overall yield: 51% yield ± 1.5

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

δ 7.53 (d, *J* = 8.6 Hz, 1H), 7.41 (d, *J* = 2.8 Hz, 1H), 7.14 (dd, *J* = 8.5, 2.8 Hz, 1H), 5.43 (br d, *J* = 7.8 Hz, 1H), 4.91 (td, *J* = 7.1, 4.0 Hz, 1H), 4.71 (d, *J* = 10.9 Hz, 1H), 4.69 (d, *J*

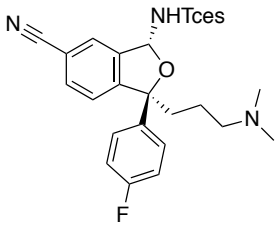
= 10.9 Hz, 1H), 3.82 (s, 3H), 2.86 (ddd, *J* = 17.6, 9.3, 4.6 Hz, 1H), 2.65 (ddd, *J* = 17.7, 7.6, 4.6 Hz, 1H), 2.48 (ddt, *J* = 13.6, 9.0, 4.3 Hz, 1H), 2.41 – 2.32 (m, 1H).

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

δ 196.64, 160.15, 133.38, 133.11, 129.80, 122.43, 109.96, 93.59, 78.26, 55.77, 52.77, 34.73, 29.77.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{13}H_{15}Cl_3NO_5S$ $[M+H]^+$: 401.9737, found 401.9727.



trans-2,2,2-trichloroethyl (6-cyano-3-(3-(dimethylamino)propyl)-3-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)sulfamate [(±)-21]. According to the general amination procedure C, 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile **(±)-S31** (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 3Å 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 d.r.)

Run 2 (78.2 mg, 0.142 mmol, 71% yield, >20:1 d.r.)

Run 3 (77.2 mg, 0.140 mmol, 70% yield, >20:1 d.r.)

Average overall yield: 71% (0% rsm) ±0.6, >20:1 d.r.

^{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, $CDCl_3$)

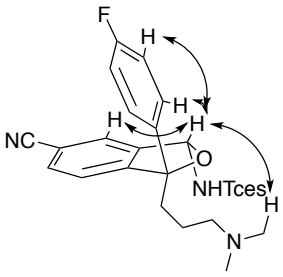
δ 162.40 (d, *J* = 247.4 Hz), 149.62, 142.09, 137.49, 132.63, 128.17, 126.99 (d, *J* = 8.1 Hz), 121.83, 118.56, 115.94 (d, *J* = 21.3 Hz), 112.48, 95.32, 90.96, 90.19, 77.78, 57.00, 42.88, 37.08, 20.67

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

δ -114.82 (s, 1F)

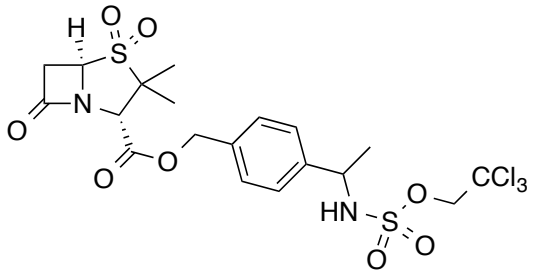
HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{22}H_{24}Cl_3N_3O_4FS$ $[M+H]^+$: 550.0537, found 550.0537.



For COSY and NOESY see Supporting Information: Spectral Data

Stereochemistry was assigned based on ^{1}H NMR and NOESY 1D NMR methods.



4-(1-(((2,2,2-trichloroethoxy)sulfonyl)amino)ethyl)benzyl (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide [22]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 4-ethylbenzyl (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide **S37** (70.3 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was removed by rotary evaporation and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography on 75 mL silica using

gradient elution (400 mL of 20% ethyl acetate in hexane followed by 400 mL of 40% ethyl acetate in hexanes) gave the pure product as a yellow oil in an equal mixture of diastereomers.

Run 1 (57.8 mg, 0.100 mmol, 50% yield)

Run 2 (56.6 mg, 0.098 mmol, 49% yield)

Run 3 (59.0 mg, 0.102 mmol, 51% yield)

Average overall yield: 50% yield ± 1.0 (1:1 d.r.)

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

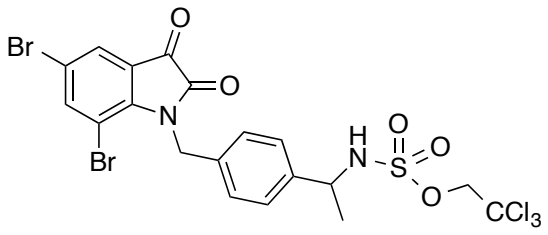
δ 7.41 – 7.33 (m, 4H), 5.27 (br s, 1H), 5.22 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 4.74 (p, *J* = 7.0 Hz, 1H), 4.63 – 4.58 (m, 1H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.45 (d, *J* = 10.9 Hz, 1H), 4.41 (s, 1H), 3.52-3.40 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.56 (s, 3H), 1.32 (s, 3H).

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

δ 171.05, 166.98, 142.61, 134.34, 129.42, 126.87, 93.42, 78.17, 67.79, 63.29, 62.90, 61.21, 54.59, 38.42, 23.07, 20.31, 18.72.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{19}H_{24}Cl_3N_2O_8S_2$ $[M+H]^+$: 577.0015 , found 577.0040.



2,2,2-trichloroethyl (1-(4-((5,7-dibromo-2,3-dioxoindolin-1 yl)methyl)phenyl)ethyl) sulfamate [23]. According to the general procedure B, 5Å powdered molecular sieves (40 mg), 5,7-dibromo-1-(4-ethylbenzyl)indoline-2,3-dione **S38** (84.6 mg, 0.20 mmol, 1 equiv), benzene

(0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was removed by rotary evaporation and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography on 75 mL silica using gradient elution (200 mL of 10% ethyl acetate in hexane followed by 400 mL of 20% ethyl acetate in hexanes, then 400 mL of 40% ethyl acetate in hexanes) gave the pure product as an orange solid.

Run 1 (84.4 mg, 0.130 mmol, 65% yield)

Run 2 (81.8 mg, 0.126 mmol, 63% yield)

Run 3 (81.8 mg, 0.126 mmol, 63% yield)

Average overall yield: 64% yield ± 1.2

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

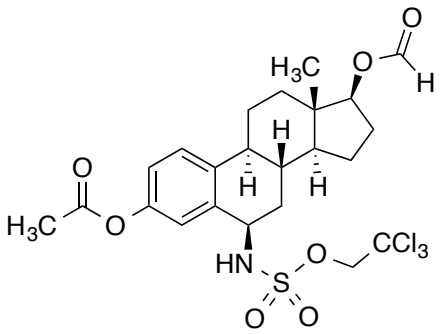
δ 7.82 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.40 (s, 2H), 5.19 (br d, *J* = 7.3 Hz, 1H), 4.71 (dq, *J* = 13.6, 7.1 Hz, 1H), 4.44 (d, *J* = 10.9 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H).

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

δ 181.28, 158.48, 146.62, 145.50, 141.25, 135.84, 127.80, 127.25, 126.95, 121.53, 117.50, 105.31, 93.42, 78.18, 54.57, 44.48, 23.00.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{19}H_{15}N_2O_5SCl_3Br_2Na$ $[M+Na]^+$: 668.8032, found 668.8028.



(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(formyloxy)-13-methyl-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 [24]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), (13*S*,17*S*)-17-(formyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate **46a** (68.5 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was concentrated and the crude brown oil was loaded onto a silica gel column. Flash chromatography on 75 mL of silica gel using gradient elution (500 mL of 100% dichloromethane then 200 mL of 1% diethyl ether in 99% dichloromethane followed by 400 mL of 2% diethyl ether in dichloromethane) gave the pure products as colorless oils and separable diastereomers.

Run 1 (70.5 mg, 0.124 mmol, 62% yield, 1.6:1 d.r.)

Run 2 (74.0 mg, 0.130 mmol, 65% yield, 1.6:1 d.r.)

Run 3 (77.4 mg, 0.136 mmol, 68% yield, 1.6:1 d.r.)

Average overall yield: 65% yield ± 3.0

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

δ 8.10 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.3 Hz, 1H), 5.29 (br d, *J* = 7.5 Hz, 1H), 4.82 (m, 2H), 4.71 (d, *J* = 10.9 Hz, 1H), 4.69 (d, *J* = 10.9 Hz, 1H), 2.39 – 2.22 (m, 2H), 2.30 (s, 3H), 2.23 – 2.15 (m, 1H), 1.95 (d, *J* = 12.3 Hz, 1H), 1.78 (ddd, *J* = 11.8, 9.4, 4.9 Hz, 1H), 1.72 – 1.32 (m, 8H), 0.89 (s, 3H).

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

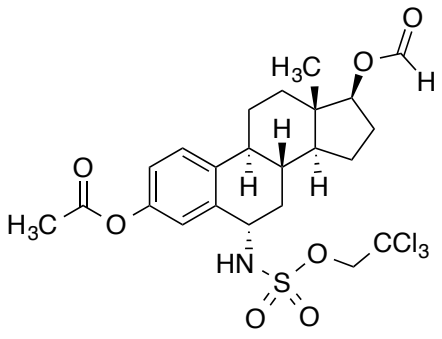
δ 169.87, 161.30, 149.22, 138.29, 135.24, 127.04, 123.16, 122.16, 93.73, 82.30, 78.05, 52.81, 49.17, 43.85, 43.24, 36.68, 34.30, 33.18, 27.57, 25.76, 23.29, 21.15, 12.27.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{23}H_{32}Cl_3N_2O_7S$ $[M+NH_4]^+$: 585.0996, found 585.0995.

*Stereochemistry was assigned based on coupling constant and by analogy to compound **47**.*

Minor diastereomer **S44**:



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

δ 8.09 (s, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.97 (dd, *J* = 8.6, 2.5 Hz, 1H), 5.06 (d, *J* = 8.6 Hz, 1H), 4.87 (td, *J* = 10.0, 7.9 Hz, 1H), 4.79 (t, *J* = 8.5 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.68 (d, *J* = 10.9 Hz, 1H), 2.55 (ddd, *J* = 12.5, 6.5, 2.1 Hz, 1H), 2.36 – 2.20 (m, 2H), 2.30 (s, 3H), 1.96 – 1.88 (m, 1H), 1.77 – 1.69 (m, 1H), 1.67 – 1.58 (m, 3H), 1.51 – 1.30 (m, 5H), 0.84 (s, 3H).

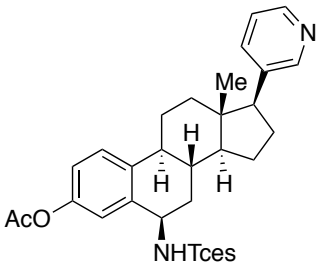
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 169.89, 161.27, 149.36, 138.34, 136.48, 127.07, 121.60, 121.09, 93.75, 82.26, 78.20, 54.96, 49.24, 44.11, 43.01, 38.13, 36.71, 36.52, 27.60, 26.06, 23.34, 21.20, 12.11.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{23}H_{28}NO_7SCl_3Na$ $[M+Na]^+$: 590.0550, found 590.0555.

Stereochemistry was assigned based on coupling constant and by analogy to compound ***S45***.



(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 [25]. 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 **47a** (75.1 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 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 3Å molecular sieves (40 mg) in DCE (0.4 mL), according to the general procedure A. 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 d.r.)

Run 2 (62.7 mg, 0.104 mmol, 52% yield, 1.5:1 d.r.)

Run 3 (60.2 mg, 0.100 mmol, 50% yield, 1.4:1 d.r.)

Average overall yield: 51% (0% rsm) ± 1.0, 1.6:1 d.r.

Data for major diastereomer **47**:

^{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), 1.51 (dq, *J* = 9.3, 5.5 Hz, 2H), 1.43 (td, *J* = 13.1, 4.0 Hz, 1H), 1.32 (td, *J* = 12.6, 3.8 Hz, 1H), 0.37 (s, 3H)

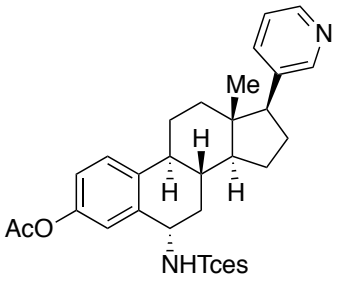
^{13}C NMR: (126 MHz, $CDCl_3$)

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.



Data for minor diastereomer **S45**:

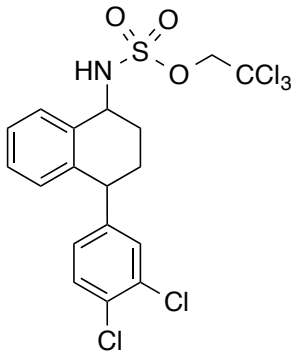
^{1}H NMR: (500 MHz, $CDCl_3$)

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 (4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)sulfamate [(±)-26]. According to the general amination procedure B, 5Å powdered molecular sieves (40 mg), 1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene **S35** (55.4 mg, 0.20 mmol, 1 equiv), benzene (0.40 mL, 0.5M), manganese (III) perchlorophthalocyanine chloride (23.1 mg, 0.020 mmol, 0.1 equiv), silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) and 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) were combined in a 10 mL round-bottom flask and stirred for 8-12 h. After silica plug filtration using ethyl acetate as the eluent (50 mL), the solvent was removed by rotary evaporation and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (400 mL of 5% ethyl acetate in hexane followed by 400 mL of 10% ethyl acetate in hexanes) gave the pure product as an off-white solid as a 1:1 mixture of separable diastereomers.

Run 1 (72.7 mg, 0.144 mmol, 72% yield)

Run 2 (74.7 mg, 0.148 mmol, 74% yield)

Run 3 (73.5 mg, 0.146 mmol, 73% yield)

Average overall yield: 73 % yield ± 1.0 (1:1 d.r.)

Characterized as two diastereomers:

D1 (syn):

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

δ 7.44 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.59 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.68 (q, *J* = 5.6 Hz, 1H), 4.55 – 4.47 (m, 3H), 3.58 (dd, *J* = 8.7, 5.6 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.78 – 1.69 (m, 2H), 1.65 – 1.54 (m, 1H).

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

δ 146.31, 139.02, 134.95, 132.74, 130.75, 130.70, 130.66, 130.28, 129.69, 128.91, 128.25, 127.71, 93.68, 78.22, 53.48, 44.79, 28.66, 28.26.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{18}H_{16}Cl_5NO_3SNa$ $[M+Na]^+$: 523.9191, found 523.9200.

D2 (anti):

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

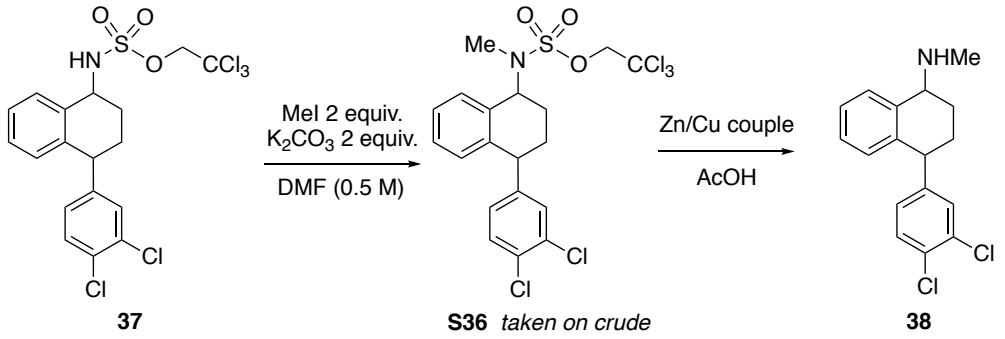
δ 7.61 (d, *J* = 7.0 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.30 (td, *J* = 7.9, 1.5 Hz, 1H), 7.21 (td, *J* = 7.4, 1.4 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.93 – 4.89 (m, 2H), 4.71 (s, 2H), 4.15 (t, *J* = 6.0 Hz, 1H), 2.35 – 2.20 (m, 2H), 2.05 – 1.95 (m, 1H), 1.87 (dddd, *J* = 12.9, 8.3, 6.5, 2.0 Hz, 1H).

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

δ 146.34, 138.60, 135.31, 132.63, 130.65, 130.59, 130.53, 128.99, 128.80, 128.47, 128.12, 127.82, 93.69, 78.26, 53.66, 44.04, 29.06, 27.78.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{18}H_{16}Cl_5NO_3S$ $[M+NaCl]^+$: 558.3 found 557.9.



37 **S36** *taken on crude* **38**

Figure 17. *Synthesis of (±)-Sertraline **27**.*

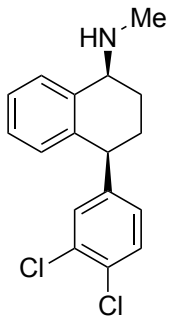
Part 1:

The aminated product **37** was weighed out in a vial and added to a flame dried round bottom under argon (68.7 mg, 0.14 mmol) along with DMF (0.3 mL, 0.5M) and K_2CO_3 (37.6 mg, 0.27 mmol, 2 equiv.) and the reaction was stirred at room temperature for 5 minutes. The reaction was cooled to 0 °C and MeI (29.1 mg, 0.205 mmol, 1.5 equiv.) was added dropwise. The reaction was brought to room temperature and stirred for 2 h (monitored by TLC). Upon reaction completion, water (10 mL) and DCM (10 mL) was added to the round bottom. The phases were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with water (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated using rotary evaporation to give the crude product **S36** in quantitative yield. This

was carried directly to the next step without further purification.

Part 2:

The reaction was performed according to a previously reported procedure.[1] In a 25 mL round bottom flask under N_2 containing a Teflon stir bar was added 2,2,2-trichloroethyl ((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)sulfamate **S36** (70.5 mg, 0.136 mmol, 1 equiv), Zn/Cu couple (96 mg, 1.36 mmol, 10 equiv), and 1:1 MeOH:AcOH (4.3 mL). The reaction was vigorously stirred for 48 h then filtered through celite, using methanol to rinse the filter cake and concentrated using rotary evaporation. To the resulting solid was added methanolic HCl (prepared from mixing 0.41 mL acetyl chloride and 5.4 mL of MeOH) and the reaction heated to 40 °C for 12 h under N_2. Upon reaction completion, 20 mL of EtOAc was added at room temperature and the solution was washed with K_2CO_3 (1 x 10 mL). Additional EtOAc (2 x 20 mL) was used to extract the resulting aqueous layer. The organic layers were combined and dried over K_2CO_3, filtered, and concentrated. Silica gel flash chromatography using gradient elution (0-10% methanol in dichloromethane) gave the pure product as a white solid (39.5 mg, 0.129 mmol, 95% yield).



Characterization matched the reported characterization for the *syn*-diastereomer.[5]

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

δ 7.43 – 7.40 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.21 (t, *J* = 7.4

Hz, 1H), 7.13 (td, J = 7.5, 1.4 Hz, 1H), 7.00 (dd, J = 8.3, 2.1 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 3.99 (dd, J = 9.3, 5.5 Hz, 1H), 3.83 (t, J = 4.3 Hz, 1H), 3.35 (br s, 1H), 2.55 (s, 3H), 2.17 – 1.96 (m, 3H), 1.93 – 1.82 (m, 1H).

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

δ 147.21, 139.01, 137.90, 132.43, 130.89, 130.48, 130.29, 130.06, 129.50, 128.45, 127.79, 126.88, 57.29, 45.43, 33.73, 28.43, 25.36.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{18}NCl_2$ $[M+H]^+$: 306.0816, found 306.0817.

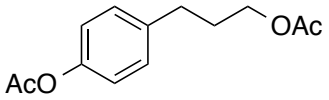
Preparation and characterization of newly reported starting materials

General procedure for acetate protection of an alcohol.

In a flame-dried 100 mL round-bottom flask at room temperature under nitrogen was added a Teflon stir bar, the alcohol substrate (36.7 mmol, 1 equiv), pyridine (37 mL 1.2M to substrate), 4-dimethylaminopyridine (1.84 mmol, 0.05 equiv) and acetic anhydride (73.4 mmol, 2 equiv). The reaction was stirred overnight at room temperature then slowly quenched with $NaHCO_3$ (sat) until bubbling ceased. The mixture was extracted with Et_2O (2 x 150 mL). The organic extracts were combined and washed with $CuSO_4$ (sat) (3 x 100 mL), H_2O (2 x 100 mL) then brine (1 x 100 mL). The organic layer was dried (anhydrous $MgSO_4$), filtered and the solvent removed using rotary evaporation. Purification of the desired compound was performed by either vacuum distillation or flash chromatography.

General procedure for trifluoroacetate protection of an amine.

In a flame-dried 200 mL round-bottom flask at 0 °C under nitrogen was added a Teflon stir bar, the amine substrate (18.79 mmol, 1 equiv), CH_2Cl_2 (47 mL, 0.4M to substrate), and pyridine (56.3 mmol, 3 equiv) followed by dropwise addition of trifluoroacetic anhydride (37.6 mmol, 2 equiv). The reaction was stirred overnight at room temperature then slowly quenched with H_2O, then extracted with CH_2Cl_2 (2 x 75 mL). The organic extracts were combined and washed with H_2O (2 x 100 mL) then brine (1 x 100 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and the solvent removed using rotary evaporation. Purification was of the desired compound was performed by flash chromatography.



3-(4-acetoxyphenyl)propyl acetate [S7]. Prepared using the general procedure for acetate protection.

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

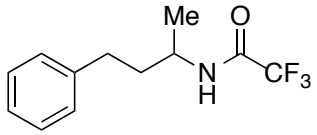
δ 7.20 – 7.18 (m, 1H), 7.20 – 7.15 (m, 1H), 7.02 – 7.00 (m, 1H), 7.00 – 6.98 (m, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 2.70 – 2.66 (m, 2H), 2.28 (s, 3H), 2.05 (s, 3H), 1.98 – 1.91 (m, 2H).

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

δ 171.24, 169.73, 149.01, 138.89, 129.41, 121.57, 63.85, 31.73, 30.27, 21.25, 21.08.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{13}H_{17}O_4$ $[M+H]^+$: 237.1116 , found 237.1127.



2,2,2-trifluoro-*N*-(4-phenylbutan-2-yl)acetamide [S9]. Synthesized via trifluoromethylation of commercially available 4-phenylbutan-2-amine. In a flame-dried round bottom flask equipeed with a septum and stir bar under nitrogen was added 4-phenylbutan-2-amine (2g, 13.4 mmol, 1 equiv.), pyridine (3.18g, 40.2 mmol, 3 equiv.), and DCM (33 mL, 0.4 M). The reaction was cooled to 0 °C and trifluoroacetic anhydride was added dropwise (5.63g, 26.8 mmol, 2 equiv.). The reaction was then warmed to room temperature and stirred to completion (monitored by TLC analysis). Upon completion, the reaction was quenched with H_2O and transferred to a separatory funnel. The mixture is extracted with DCM (2 x 40 mL). The organic layers were washed with H_2O, dried over Na_2SO_4, filtered and the solvent evaporated. The crude product is then purified using silica gel chromatography and eluted with 20% ethyl acetate in 80% hexane to give the product as a white solid (3.12 g, 12.7 mmol, 95% yield).

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

δ 7.32 – 7.27 (m, 2H), 7.23 – 7.16 (m, 3H), 6.02 (s, 1H), 4.13 – 4.03 (m, 1H), 2.70 – 2.64 (m, 2H), 1.90 – 1.84 (m, 2H), 1.27 (d, J = 6.6 Hz, 3H).

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

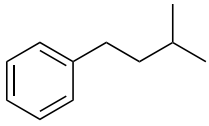
δ 156.63 (q, J = 36.6 Hz), 140.92, 128.75, 128.39, 126.40, 115.96 (q, J = 288.2 Hz), 46.50, 37.99, 32.35, 20.56.

^{19}F NMR: (470.75 MHz, $CDCl_3$)

δ 76.02

HRMS: (ESI- TOF MS ES+)

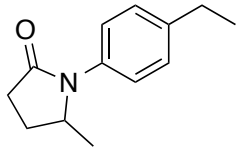
m/z calculated for $C_{12}H_{15}NOF_3[M+H]^+$: 246.1106, found 246.1111.



Isopentylbenzene [S10]. Synthesized using a known procedure.[6]

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

δ 7.30 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 2.68 – 2.58 (m, 2H), 1.65 – 1.56 (m, 1H), 1.55 – 1.48 (m, 2H), 0.95 (d, *J* = 6.6 Hz, 6H).



1-(4-ethylphenyl)-5-methylpyrrolidin-2-one [S19]. 4-ethyl aniline (1.5g, 12.4 mmol, 1 equiv.), levulinic acid (2.88g, 24.76 mmol, 2 equiv.), Et_3N (1.25g, 12.4 mmol, 1 equiv.), and formic acid (0.570g, 12.4 mmol, 1 equiv.) were added to flame-dried round bottom flask equipped with water-cooled condenser. The reagents were dissolved in DMSO (25 mL, 0.5M) and refluxed at 100 °C for 12 h. The reaction was cooled and water (40 mL) and DCM (40 mL) were added. The organic layer was extracted with water (3 x 20 mL). The combined aqueous layers were then extracted with DCM (1 x 40 mL). The combined organic layers were dried over Na_2SO_4. Flash column chromatography on silica gel (1:1 hexanes:ethyl acetate) gives the product as a brown oil (504.2 mg, 2.48 mmol, 10% yield).

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

δ 7.28 – 7.27 (m, 1H), 7.27 – 7.25 (m, 1H), 7.24 – 7.21 (m, 2H), 4.30 – 4.23 (m, 1H), 2.69 – 2.60 (m, 3H), 2.55 (ddd, *J* = 17.0, 9.5, 7.4 Hz, 1H), 2.38 (dddd, *J* = 12.6, 9.5, 7.4,

6.0 Hz, 1H), 1.76 (dddd, *J* = 12.9, 9.5, 7.4, 5.7 Hz, 1H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H).

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

δ 174.34, 142.07, 135.22, 128.55, 124.39, 55.93, 31.43, 28.54, 26.96, 20.39, 15.63.

HRMS (ESI- TOF MS ES+)

m/z calculated for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388, found 204.1395.

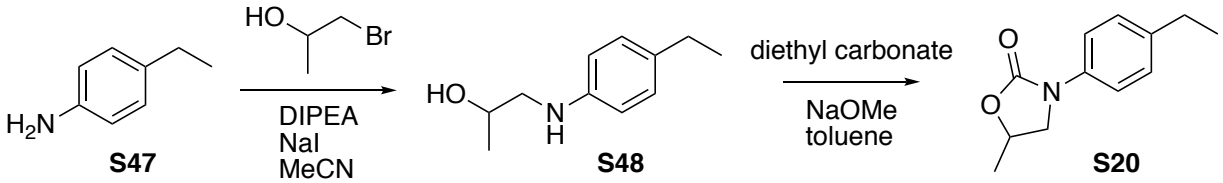
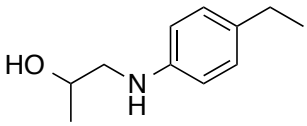


Figure 18. *Synthesis of Oxazolidinone* ***S20****.*

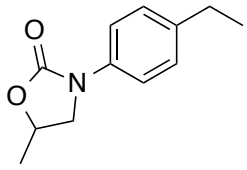


1-((4-ethylphenyl)amino)propan-2-ol [S48]. 4-ethyl aniline (1.45g, 12 mmol, 1 equiv.), 1-bromo-2-propanol **S47** (2 g, 14.4 mmol, 1.2 equiv.), diisopropyl ethyl amine (3.1g, 24 mmol, 2 equiv.), NaI (1.8 g, 12 mmol, 1 equiv.) and acetonitrile (80 mL, 0.15M) were added to a round bottom flask equipped with a water-cooled condenser under a nitrogen atmosphere. The reaction was refluxed overnight and monitored by TLC. Upon completion, the reaction was poured into a separatory funnel and H_2O (20 mL) and DCM (40 mL) were added and shaken. The organic layer was separated and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Flash column chromatography on silica gel using 40% EtOAc in hexanes gives the amino alcohol as a colorless oil in (1.29 g, 7.2 mmol, 60% yield). This substrate contains rotational isomers in NMR, major isomer

reported.

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

δ 7.03 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 4.06 – 3.97 (m, 1H), 3.22 (dd, *J* = 12.9, 3.3 Hz, 1H), 2.98 (dd, *J* = 12.9, 8.7 Hz, 1H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H).



3-(4-ethylphenyl)-5-methyloxazolidin-2-one [S20]. In a flame-dried round bottom flask equipped with a water-cooled condenser was added NaOMe (227 mg, 4.2 mmol, 1.5 equiv.), 1-((4-ethylphenyl)amino)propan-2-ol **S48** (500 mg, 2.8 mmol, 1 equiv.) and toluene (5.6 mL, 0.5M). The mixture was stirred for 5 minutes, then diethyl carbonate was added dropwise (500 mg, 4.2 mmol, 1.5 equiv.). The reaction was refluxed to completion (4 h) and monitored by TLC. Upon completion, the reaction was filtered through celite using DCM and concentrated. The crude product was then purified using silica gel flash chromatography with gradient elution (10% EtOAc in hexane to 50% EtOAc in hexane) to give a white solid (459.8 g, 2.24 mmol, 80% yield).

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

δ 7.43 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 4.78 (ddq, *J* = 8.2, 7.0, 6.2 Hz, 1H), 4.10 (t, *J* = 8.4 Hz, 1H), 3.61 (dd, *J* = 8.6, 7.0 Hz, 1H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.53 (d, *J*

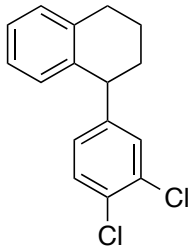
= 6.2 Hz, 3H), 1.22 (t, *J* = 7.6 Hz, 3H).

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

δ 155.12, 140.24, 136.21, 128.54, 118.54, 69.62, 52.22, 28.34, 20.89, 15.82.

HRMS: (ESI- TOF MS ES+)

m/z calculated for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181, found 206.1172.



1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene [S35]. In a round-bottom flask were added 1-(3,4-dichlorophenyl)-1,2-dihydronaphthalene (500 mg, 1.82 mmol, 1 equiv.), EtOAc (3.64 mL, 0.5M) and, Pd/C (5 mol%). The flask was sealed with a rubber septum, purged with hydrogen (3 balloons of hydrogen), and kept on a hydrogen balloon atmosphere at room temperature until reaction completion by TLC (6 h). The reaction was filtered through celite using ethyl acetate as the eluent and concentrated using rotary evaporation. Flash column chromatography on silica gel using hexanes elutes the product as a colorless oil along with minor impurities (approximately 5%) that could not be fully separated and do not affect reactivity (454.6 mg, 1.64 mmol, 90% yield).

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

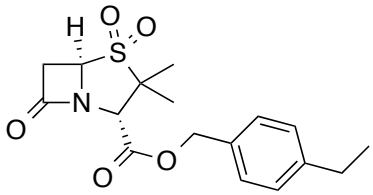
δ 7.34 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.16 – 7.14 (m, 2H), 7.08 – 7.04 (m, 1H), 6.92 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.80 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.09 (t, *J* = 6.5 Hz, 1H), 2.96 – 2.80 (m, 2H), 2.22 – 2.11 (m, 1H), 1.92 – 1.70 (m, 3H).

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

δ 147.99, 138.12, 137.69, 132.33, 130.82, 130.30, 130.12, 130.03, 129.35, 128.39, 126.51, 126.03, 45.00, 33.23, 29.73, 20.86.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{16}H_{14}Cl_2$ [M]: 276.04726, found 276.04669.



4-ethylbenzyl (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide [S37]. Sulbactam (250 mg, 1.07 mmol) was added to a flame-dried round bottom flask along with dichloromethane (3.15 mL, 0.3M). N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC-HCl) (307 mg, 1.6 mmol, 1.6 equiv.) and 4-dimethylaminopyridine (DMAP) (65.4 mg, 0.54 mmol, 0.5 equiv.) under a nitrogen atmosphere and the reaction was stirred at 0 °C for 5 minutes. 4-ethylbenzyl alcohol (218 mg, 1.6 mmol, 1.6 equiv.) was added and stirred at 0 °C for an additional 5 minutes, then warmed to room temperature and stirred for 48 h. After reaction completion, the reaction was diluted with DCM (5 mL) and transferred to separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (1 x 10 mL). The aqueous layer was then extracted with DCM (2 x 10 mL). The combined organic layers were washed with a 10% aqueous citric acid solution (1 x 10 mL). The aqueous layer was again extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered and concentrated using rotary evaporation. Flash column chromatography on silica using gradient elution (20% EtOAc in hexane to 40% EtOAc in

hexane) gave the product as a colorless oil (102 mg, 0.29 mmol, 27% yield).

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

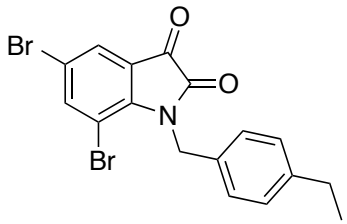
δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.25 (d, *J* = 11.8 Hz, 1H), 5.14 (d, *J* = 11.9 Hz, 1H), 4.59 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.40 (s, 1H), 3.47 (dd, *J* = 16.2, 4.2 Hz, 1H), 3.42 (dd, *J* = 16.2, 2.2 Hz, 1H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.55 (s, 3H), 1.28 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H).

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

δ 170.82, 166.96, 145.45, 131.71, 129.15, 128.43, 68.28, 63.29, 62.89, 61.19, 38.42, 28.74, 20.24, 18.72, 15.59.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{22}NO_5S$ [M+H]+: 352.1219, found 352.1214.



5,7-dibromo-1-(4-ethylbenzyl)indoline-2,3-dione [S38]. Synthesis: In a flame-dried round bottom was added dibromoisatin (500mg, 1.64 mmol), K_2CO_3 (227 mg, 1.64 mmol), and DMF (1.6 mL). The reaction was cooled to 0 °C and stirred for 5 min. Then a solution of 1-(bromomethyl)-4-ethylbenzene (653 mg, 3.28 mmol) in DMF (1.6 mL) was added to the reaction dropwise. The reaction was warmed to room temperature and stirred to completion. After completion by TLC, the reaction was diluted with DCM (40 mL) and poured into a separatory funnel then washed with water (20 mL). The organic layer was separated and washed with water (2 x 20 mL). The combined aqueous layers were extracted with DCM (20 mL), and the organic

layers combined and dried over Na_2SO_4. Column chromatography on silica using gradient elution, 10% EtOAc in Hexane → 40% EtOAc in hexane gave the product as an orange/red solid (487 mg, 1.15 mmol, 70% yield).

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

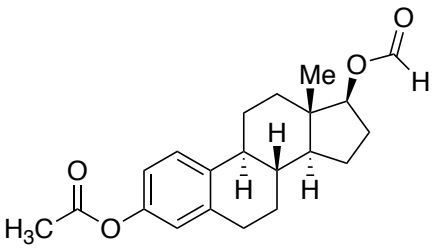
δ 7.81 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.22 – 7.10 (m, 4H), 5.38 (s, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H).

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

δ 181.52, 158.48, 146.99, 145.48, 144.05, 132.95, 128.47, 127.66, 126.69, 121.60, 117.26, 105.43, 44.64, 28.62, 15.60.

HRMS (ESI-TOF MS ES+)

m/z calculated for $C_{17}H_{14}NO_2Br_2$ $[M+H]^+$: 421.9391, found 421.9380.



(13*S*,17*S*)-17-(formyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl acetate [46a]. In a flame-dried round bottom flask equipped with a stir bar under nitrogen was added (8*R*, 9*S*, 13*S*, 14*S*, 17*S*)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[α]phenanthren-3-yl acetate (500 mg, 1.60 mmol, 1 equiv) and DMF (409 mg, 5.6 mmol, 3.5 equiv). The reaction was cooled to 0 °C and oxalyl chloride was added dropwise (630 mg, 4.96 mmol, 3.1 equiv). The reaction was warmed to room temperature and stirred overnight. Upon reaction completion, water (10 mL) was added and the contents were transferred to a separatory funnel. The contents were extracted with DCM

(3 x 10 mL). The combined organic layers were washed with water (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated using rotary evaporation. Silica gel flash column chromatography (20% EtOAc in 80% hexanes) gave the pure product as a white solid (411 mg, 1.2 mmol, 75% yield).

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

δ 7.41 – 7.27 (m, 5H), 4.97 (d, *J* = 7.3 Hz, 1H), 4.46 (q, *J* = 7.5 Hz, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.28 (d, *J* = 10.8 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.87 – 1.76 (m, 1H), 1.61 – 1.48 (m, 2H), 1.33 – 1.19 (m, 1H), 1.16 – 1.02 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 6H).

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

δ 169.97, 161.32, 148.57, 126.54, 121.65, 118.75, 82.69, 49.91, 44.08, 43.08, 38.29, 36.90, 29.61, 27.71, 27.13, 26.10, 23.41, 21.27, 12.19.

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{21}H_{26}O_4$ $[M\text{-}Ac]^+$: 300.18, found 300.2.

HPLC methods for the determination of product selectivity.

HPLC analysis was used to find the detection limit of these compounds to determine the selectivity of our reaction. As shown below, standards for both possible products were made using the reported rhodium catalyzed C—H amination procedure.[1]

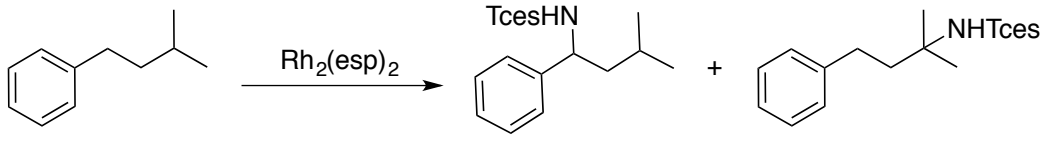


Figure 18. Rh-catalyzed C—H amination of isopentylbenzene.

The products were purified and isolated as mixtures. The purified mixture used for determining the HPLC detection limit contained a 10:1 ratio of benzylic to tertiary amination. A solution of

10 mg of the mixture in 1 mL of acetonitrile (0.0267 mmol/mL concentration) was then diluted by a factor of 10 to give 1 mg in 1 mL. This solution was again diluted to give a final sample containing 0.1 mg in 1 mL of acetonitrile. A 2 μL sample of this mixture was the concentration at which none of the tertiary product was detected by HPLC.

We subjected the starting material of our manganese-catalyzed reaction, analyzed the crude reaction by HPLC, and detected none of the tertiary product. Due to the high detection limit of the HPLC, we concluded that the selectivity of our reaction is at least 100:1 in this case.

Likewise, the same approach was used to determine the detection limit of the minor product in the following reaction.

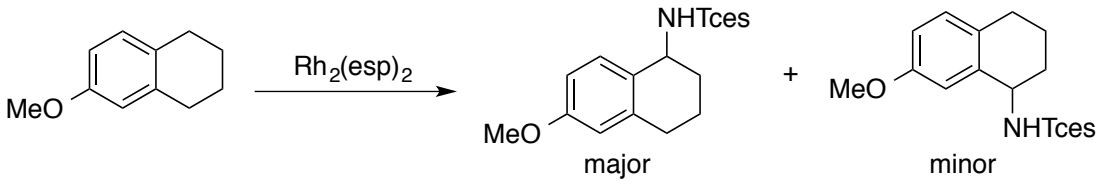


***Figure 19**. Mn-catalyzed C–H amination of 6-methoxytetralin.*

The purified mixture used from the rhodium reaction to determine the HPLC detection limit contained an 8:1 ratio of the major to minor products. A solution of 5 mg of the mixture in 1 mL of acetonitrile was then diluted by a factor of 10 to give 0.5 mg in 1 mL. This solution was again diluted to give a final sample containing 0.05 mg in 1mL of acetonitrile. A 2 μL sample of this mixture was the concentration at which none of the minor product was detected by HPLC.

We subjected the starting material of our manganese-catalyzed reaction, analyzed the crude reaction by HPLC, and detected none of the minor product. Due to the high detection limit of the HPLC, we concluded that the selectivity of our reaction is at least 100:1 in this case.

We also made a standard of the diamination product and did not detect any of this product in our own amination reaction by ^{1}H NMR, however a minor peak was detected by HPLC.