SYNTHESIS AND APPLICATIONS OF SULFAMATES AND RELATED FUNCTIONALITIES

SYNTHESIS AND APPLICATIONS OF SULFAMATES AND RELATED FUNCTIONALITIES

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Descriptive Note

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Lay Abstract

There are thousands of chemical reactions that medicinal and synthetic chemists have at their disposal but many have limitations that hinder their use. This work expands upon previously known reactions and develops novel ones. The first reaction allows for the ability to easily install a pharmaceutically relevant sulfur-containing moiety into alcohol and amine molecules. The second provides a method to further react these moieties using a copper catalyst and inexpensive amine ligand. The final reaction is a substitution reaction of amines. This builds on a discovery originally made 55 years ago but not thoroughly developed until now. Overall, the research described in this thesis can provide future chemists with the ability to perform desired chemical transformations efficiently and thereby grant access to drug-like molecules that were formerly harder to obtain.

Abstract

Sulfur-containing moieties play a crucial role in both medicinal and synthetic chemistry. Chapters 2 and 3 focus on two sulfonamide bioisosteres called sulfamates and sulfamides. Chapter 2 describes the development and scope of a practical new synthesis of sulfamates and sulfamides, which were previously challenging to prepare. This work employs a reagent called hexafluoroisopropyl sulfamate (HFIPS) to synthesize sulfamates and sulfamides from their corresponding alcohols and amines.

Sulfamates and sulfamides are known to undergo numerous chemical transformations, primarily metal catalyzed. The most common transformations are CH aminations in which the NH_2 reacts and inserts between a C-H bond. A lesser explored reaction is that of the NH_2 with aryl bromides. As described in Chapter 3, this *N*-arylation of sulfamates and sulfamides through copper catalysis provides access to their arylated products that have previously been difficult or even impossible to synthesize.

Sulfur-containing functionalities are often versatile intermediates in organic chemistry. The aryl trifluoromethylsulfonate (triflate; Ar-OSO_2CF_3) moiety is considered a "pseudohalide" as it is a useful alternative to aryl halides in the context of cross-coupling chemistry. Chapter 4 describes the development and scope of a practical substitution of alkyl amines by iodine salts via *N*-bistriflimide intermediates that act as *N*-leaving groups in substitution chemistry to yield their corresponding alkyl iodide product.

Acknowledgements

They say that if you do what you love, you'll never work a day in your life. Thank you, Jake, for allowing and encouraging me to do what I love. Rarely have the last five years felt like "work," and that can only be attributed to the trust you've had in me to be independent and accomplish what I needed to.

To my committee members Prof. Wright and Prof. Li, thank you for being encouraging and uplifting to a young grad student. I still remember all the kind words from my first committee meeting years ago. You two saw the potential in me that I was years away from realizing. I am very grateful for your time and support, especially because what I presented was not in your primary fields of expertise.

To all the past and present Magolan lab members, thank you for tolerating me and enhancing my grad school experience in so many ways. There are way too many people to name but I'd like to specifically thank Jarrod for teaching me so much in our collaborations and being patient with me in the early days of grad school.

To my family and friends outside of the lab, thank you for showing me so much love and support over the years. Anytime I needed a distraction from school, you were there without hesitation. From talking with me on the phone for hours, to golfing on the weekends, to having Sunday dinners with my family; all of that was needed to stay balanced and focused over the years. Thank you so much.

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List of abbreviations

AcSH: acetyl thiol

ArBr: aryl bromide

ArCl: aryl chloride

ArI: aryl iodide

ArOTf: aryl triflate

aq.: aqueous

B^-: base

Bn: benzyl

Boc: *tert*-butyloxycarbonyl

bp: boiling point

cat.: catalytic

Cbz – benzyloxycarbonyl

$CDCl_3$: deuterated chloroform

$CHCl_3$: chloroform

CH_2Cl_2: dichloromethane (DCM)

COOH: carboxylic acid

COSY: correlation spectrometry

CSI: chlorosulfonyl isocyanate

CuI: copper (I) iodide

$Cu(OAc)_2$: copper acetate

DABCO: 1,4-diazabicyclo[2.2.2]octane

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DIPEA: *N,N*-diisopropylethylamine (Hunig's base)

DMA: dimethylacetamide

DMAP: 4-dimethyl-aminopyridine

DMF: *N*,*N*-dimethylformamide

EDG: electron-donating group

Et: ethyl

Et_3N: triethylamine

EtOH: ethanol

EtOAc: ethyl acetate

EWG: electron-withdrawing group

FDA: U.S Food and Drug Administration

g: grams

GABA: γ-aminobutyric acid

h: hour(s)

H_2O: water

H_2S: hydrogen sulfide

HCl: hydrogen chloride

HCO_2H: formic acid

HFIP: hexafluoroisopropanol

HFIPS: hexafluoroisopropyl sulfamate

HMBC: heteronuclear multiple quantum coherence

HRMS: high-resolution mass spectrometry

HSBC: heteronuclear single quantum coherence

KI: potassium iodide

KOAc: potassium acetate

L: liter

L*: chiral ligand

LiCl: lithium chloride

Lutidine: 2,6-dimethylpyridine

M: molar

Me: methyl

MeCN: acetonitrile

MeOH: methanol

mg: milligrams

MgO: magnesium oxide

$MgSO_4$: magnesium sulfate

mL: milliliters

mmol: millimoles

Mp: melting point

Ms: mesyl (methane sulfonic)

Na_2S: sodium sulfide

NaH: sodium hydride

NaI: sodium iodide

NIS: *N*-Iodosuccinimide

NMI: *N*-methylimidazole

NMR: nuclear magnetic resonance

np: no product

PCPS: pentachlorophenyl sulfamate

$Pd(OAc)_2$: palladium (II) acetate

PIDA: (diacetoxyiodo)benzene

Ph: phenyl

$PhI(OAc)_2$: PIDA ((diacetoxyiodo)benzene)

PhMe: toluene

PFPS: pentafluorophenyl sulfamate

PMA: phosphomolybdic acid

PMP: *para*-methoxyphenyl

Py: pyridine

$Rh_2(esp)_2$: bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]

$Rh_2(oct)_4$: rhodium (II) octanoate, dimer

$[RhCl(COD)]_2$: cyclooctadiene rhodium chloride dimer

$[Rh(COD)_2]BF_4$: cyclooctadiene rhodium tetrafluoroborate

RSH: general thiol

rt: room temperature

S_8: elemental sulfur

sec: second(s)

S_N2: nucleophilic substitution (bimolecular)

S_NAr: nucleophilic aromatic substitution

tBu: *tert*-butyl

$TcesNH_2$: 2,2,2-trichloroethoxysulfonamide

THF: tetrahydrofuran

Tf: triflate (trifluoromethanesulfonate)

Tf_2O: trifluoromethanesulfonic anhydride

TFA: trifluoroacetic acid

TLC: thin-layer chromatography

Ts: tosyl (*p*-toluenesulfonyl)

W: watt

XantPhos: 9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane)

α – alpha

β – beta

γ – gamma

δ – delta / chemical shift in parts per million

°C – degree Celsius

Δ – reflux

Authors declaration

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

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

The academic achievements discussed in this thesis consist of:

Chapter 2:

1. Sguazzin, M. A., Johnson, J. W., Magolan, J. Hexafluoroisopropyl Sulfamate: A Useful Reagent for the Synthesis of Sulfamates and Sulfamides. *Organic Letters* **2021**, *23* (9), 3373-3378.

The experimental work was conducted by Matthew Sguazzin. The project was initiated by Dr. Johnson. The manuscript was written by Matthew Sguazzin and Dr. Johnson.

Chapter 3:

2. Sguazzin, M. A., Samokhin, P. A., Saliba, P., Johnson, J. W., Magolan, J. Copper-Catalyzed *N*-Arylation of Sulfamates and Sulfamides (manuscript in preparation).

The project was proposed and initiated by Matthew Sguazzin. The experimental work was conducted by Matthew Sguazzin, Philip Samokhin and Paul Saliba. Dr. Johnson was an advisor to the project and assisted with manuscript writing and creation of figures.

Chapter 4:

3. Sguazzin, M. A., MacIver, M., Magolan, J. A Practical Substitution of Amines (manuscript in preparation).

The project was initiated and drafted by Matthew Sguazzin. The experimental work was conducted by Matthew Sguazzin and Marissa MacIver.

Chapter 1 – Introduction

1.1 Background

1.1.1 Importance of Sulfur-Containing Functional Groups

Sulfur-containing functionalities are ubiquitous in natural products, synthetic chemistry, drug discovery, and more.[1-4] In both natural products and FDA-approved drugs sulfur atom(s) typically appear as disulfides, thioethers, sulfones, sulfoxides, sulfonates, sulfates, thiazoles, sulfonamides, sulfamates and sulfamides (Figure 1-1). There are over 150 sulfur-containing FDA-approved drugs on the market.[5] These compounds can exist in many forms while having a variety of biological functions because of sulfur's ability to exist in different valence states (S^{2-} to S^{6+}).[5, 6] Due to the vast amount of sulfur-containing moieties, there is an interest for chemists to develop new methodologies to synthesize them.

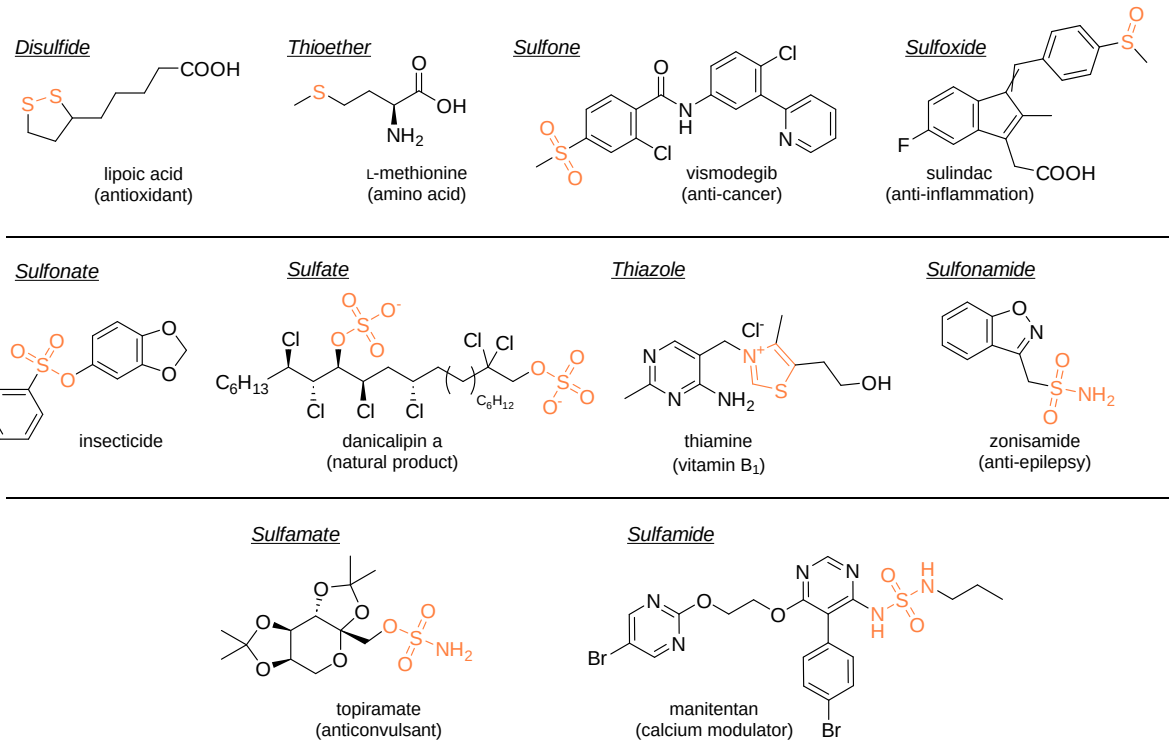


Figure 1-1: Examples and applications of biologically relevant sulfur-containing moieties.

In synthetic chemistry, sulfur-containing functionalities are commonly introduced by sulfurization reagents. The most simple one being elemental sulfur (S_8), a stable solid at room temperature that has been known to undergo numerous organic reactions for sulfur-incorporation.[7] Moreover, there are a plethora of organic and inorganic sulfuration reagents for a variety of applications such as H_2S (**i-11**), Na_2S (**i-12**), AcSH (**i-13**), and cysteine (**i-14**) (Figure 1-2A).[8] However, the relevant examples for this body of work are reagents that not only form relevant sulfur-containing products, but also sulfur-containing intermediates (Figure 1-2B).

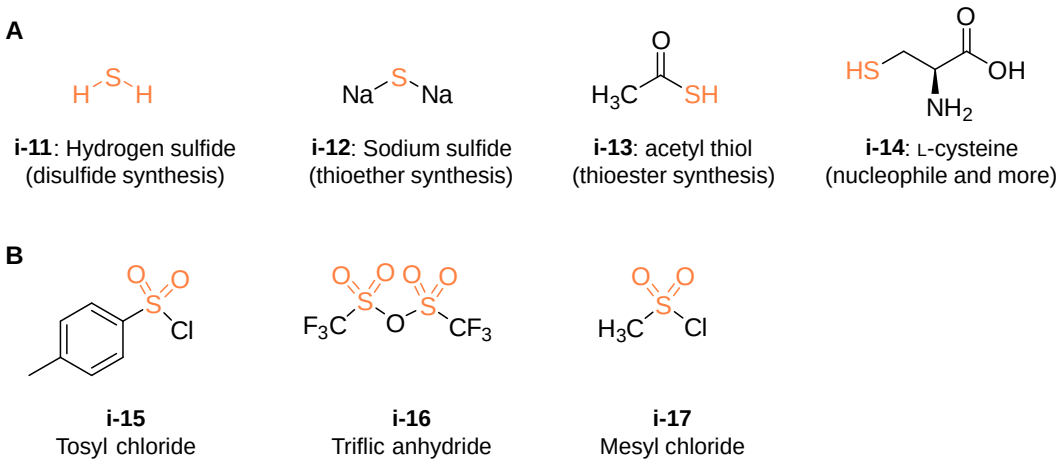


Figure 1-2: Common sulfurization reagents for medicinal and synthetic chemistry.

For example, if an amine (**i-18**) is reacted with either tosyl chloride (**i-15**), triflic anhydride (**i-16**), or mesyl chloride (**i-17**) and a non-nucleophilic base, its corresponding sulfonamide (**i-19)** is formed (Figure 1-3A). This substitution happens at the electrophilic sulfur atom and displaces the chlorine atom. This is a simple yet powerful reaction because sulfonamides are commonly found in pharmaceutical products.[9] However, if an alcohol nucleophile (**i-20**) is reacted with tosyl chloride (**i-15**), the corresponding tosylate is formed (**i-21**) (Figure 1-3B). Unlike sulfonamides, tosylates are not desirable functional groups in drug

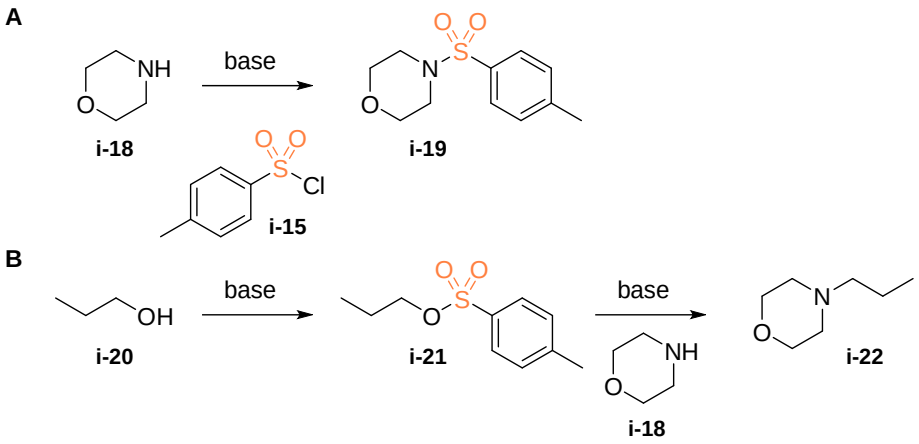
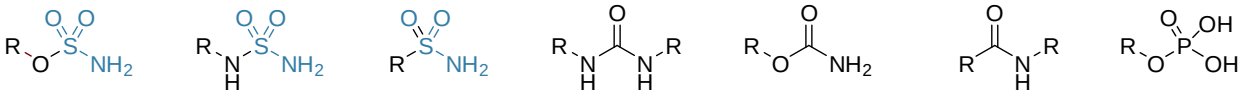


Figure 1-3: Different uses for sulfurization reagents in synthetic chemistry.

candidates. Instead, they are commonly employed as reactive intermediates in substitution, elimination, and cross-coupling reactions.[10-12] Alcohols are very poor leaving groups because hydroxide ($^{-}$OH) is a strong base; however, once functionalized as its corresponding sulfonate, it becomes an excellent leaving group.[13] Therefore, if tosylate **i-21** is treated with amine **i-18**, the S_N2 product **i-22** will be formed (Figure 1-3B). Although the sulfur-containing moiety was required for this chemistry, it does not appear in the final product. Chapter 4 of this report will employ and expand upon similar principles to this ideology.

1.1.2 Significance of Sulfamates and Sulfamides

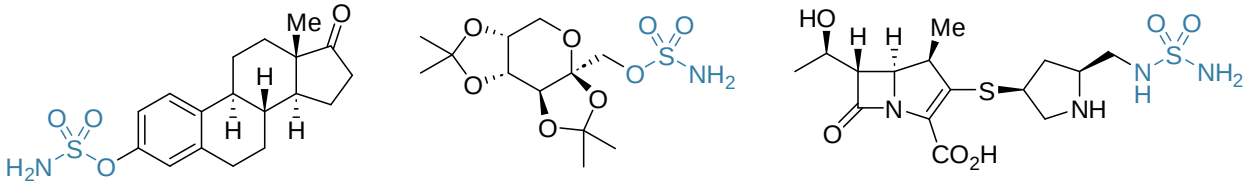
Sulfamates (**i-23**) and sulfamides (**i-24**) are sulfur-containing bioisosteres of sulfonamides (**i-25**), ureas (**i-26**), carbamates (**i-27**), amides (**i-28**), and phosphates (**i-29**) (Figure 1-4).[14] These moieties are able to form unique electrostatic interactions with cell membranes and proteins.[14]



i-23 (sulfamates) **i-24** (sulfamides) **i-25** (sulfonamides) **i-26** (ureas) **i-27** (carbamates) **i-28** (amides) **i-29** (phosphates)

Figure 1-4: Sulfamates, sulfamides, and related functionalities.

Sulfamate and sulfamide-containing compounds represent an important class of biologically relevant molecules with therapeutic uses including anti-cancer, anti-viral, antibiotic, and neurological indications (Figure 1-5).[15, 16]



i-30 (EMATE) **i-9** (topiramate) **i-32** (doripenem)

Figure 1-5: Biologically relevant sulfamate and sulfamide compounds.

Estrone-3-O-sulfamate (EMATE, **i-30**) is the first known irreversible inhibitor of steroid sulfatase for the treatment of endometriosis and estrogen dependent tumors.[15] Additionally, the sulfamate moiety of **i-30** was found to be responsible for carbonic anhydrase binding, giving it a dual inhibition mode of action.[17] Topiramate (**i-9**), the first FDA-approved sulfamate drug was originally developed as an anticonvulsant and is now primarily prescribed for the treatment of epilepsy and migraines.[18] Topiramate's mechanism of action has not been fully elucidated; however, it is known to modulate calcium and sodium-gated channels, and inhibit GABA and glutamate receptors.[18] Doripenem (**i-31**) is a clinically important FDA-approved carbapenem broad-spectrum sulfamide antibiotic. More specifically, it was used to treat infections from

Pseudomonas aeruginosa and highlights the medicinally relevant properties of this functional group.[19] Sulfamates and sulfamides are relatively underrepresented in medicinal chemistry potentially due to challenges related to their synthesis.

1.1.3 Synthesis of Sulfamates and Sulfamides

The traditional route to sulfamate and sulfamide synthesis involves the reaction of chlorosulfonyl isocyanate (CSI, **i-32**) with formic acid. This generates in situ an unstable intermediate (**i-33**) which can be treated with a desired nucleophile (Figure 1-6).[20] In the

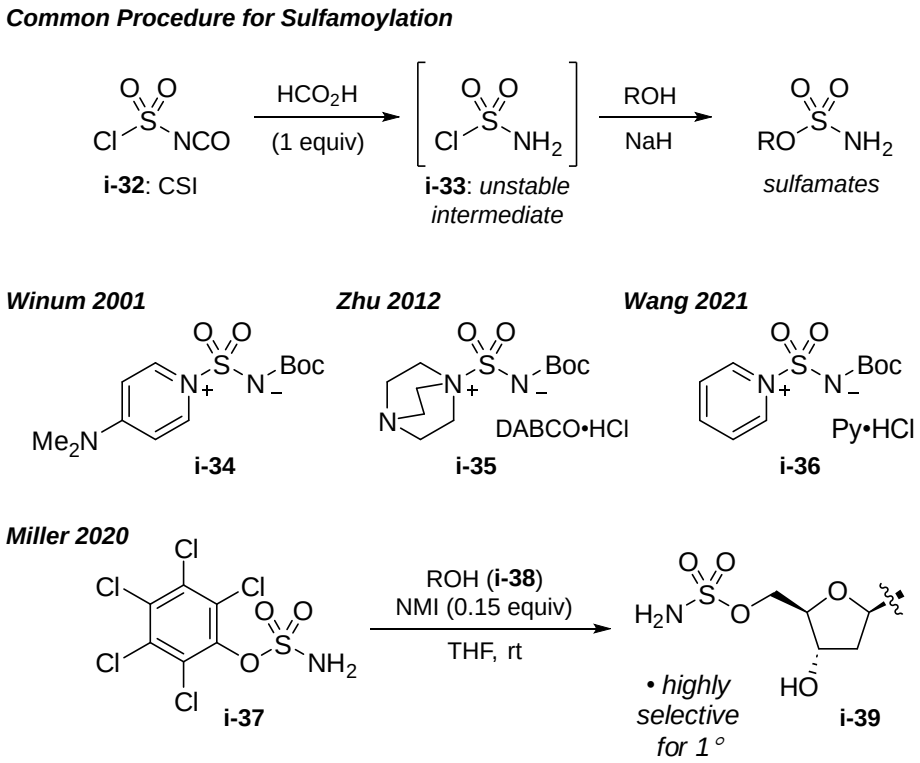


Figure 1-6: Previous methods for sulfamoylation.

Magolan laboratory, we have found this reaction to be unreliable with poor and inconsistent yields. Furthermore, CSI is prone to spontaneous decomposition and is thus used in large

excess, and DMA (bp. 165 °C) is the main solvent suitable for this chemistry due to safety concerns. As others have experienced these issues in the past, there have been multiple attempts to find alternative methods. The most common developments involve Burgess-like amine salt reagents and have been reported by Winum (2001), Zhu (2012), and Wang (2021) (Figure 1-6).[21-23] While an improvement upon the original procedure, these reagents are not ideal because of their lack of substrate versatility, shelf-instability, and requirements of an acidic second step to remove the -Boc group. As we investigated alternative reagents, the Miller Lab at Yale University coincidently published a pentachlorophenyl sulfamoylating reagent (Figure 1-6).[24] Moreover, they also disclosed other potential reagents; many of which we were simultaneously investigating. After discussing future directions with Prof. Miller, we independently pursued a different sulfamoylating reagent, hexafluoroisopropyl sulfamate (HFIPS), and published in *Organic Letters* a complementary method to theirs which can be found in Chapter 2.

1.1.4 Importance and Common Methods for *N*-Arylation

An analysis of the synthetic routes leading to FDA-approved drugs found that the most common reaction type in medicinal chemistry is heteroatom arylation and alkylation.[25] Furthermore, *N*-arylation with aryl halides made up the largest number of reactions in this subset.[25] Arylation of amines with aryl halides is commonly achieved by S_NAr (nucleophilic aromatic substitution) chemistry, however, this reaction has a number of limitations (Figure 1-7). Firstly, electronics dictate that more nucleophilic amines react faster, and that the aryl group must be “activated” (electron deficient); usually achieved by electron-withdrawing groups

(EWG) or heteroatom incorporation. Furthermore, aryl fluorides and chlorides are the most reactive for this chemistry and high temperatures are often required.[26] These limitations have led to the pioneering work of Buchwald and Hartwig's discovery of the palladium-catalyzed arylation of amines. The "Buchwald-Hartwig" amination (Figure 1-7) has been expanded through the development of powerful ligands and catalysts to be compatible with a diverse number of nitrogen nucleophiles and (hetero)aryl halide coupling partners.[27] With transition-

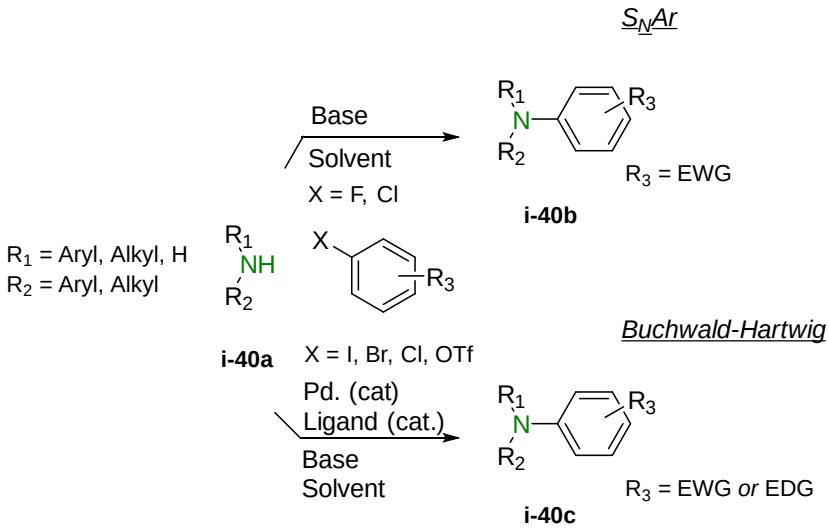


Figure 1-7: Generalized methods for *N*-arylation.

metal catalyzed arylations, both electron deficient and electron rich aryl groups are tolerated. [28] Also, leaving groups such as iodides, bromides, chlorides, and triflates are all compatible. Lastly, through the research and development of ligands and catalysts, these reactions are often conducted at mild temperatures and without the need for strong bases.[29, 30]

Although palladium catalyzed aminations allow for powerful *N*-functionalizations, they also work best with more nucleophilic nitrogens.[31] To circumvent the issues with weaker amine nucleophiles, powerful ligands have been developed. Such ligands are often very expensive and

difficult handle.[31] A complementary method to the Buchwald-Hartwig amination is the Ullmann-like copper-catalyzed aminations.[32, 33] The benefit of this method is that copper has an affinity for more acidic nitrogens, opposite to that of palladium.[31-33]

After discovering this I decided to apply copper catalysis to the weakly nucleophilic sulfamate NH_2; a class of compounds we now had easy access to (see Chapter 3). Previously, this transformation had only been reported a single time.[34] Roizen et al. revealed a methodology employing an expensive iridium photocatalyst, nickel ligand, and blue light (Figure 1-8A). Moreover, they disclose that they attempted traditional Buchwald-Hartwig conditions, however, it proved to be challenging and a very poor yield was obtained (Figure 1-8B).[34] A copper-catalyzed arylation of sulfamates would be complementary to this photochemistry methodology, and have the benefit of employing more common reagents.

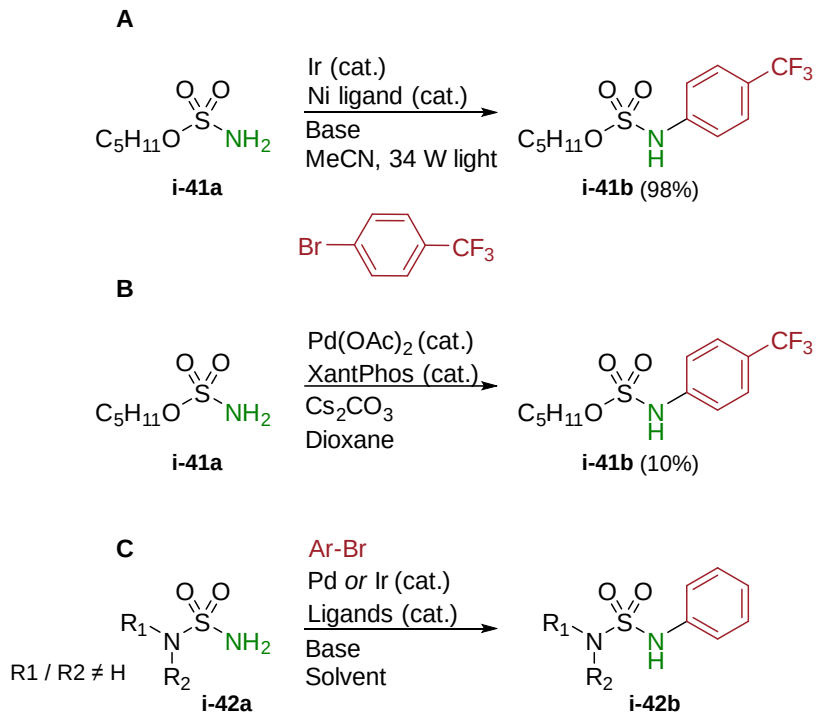


Figure 1-8: Previously disclosed sulfamate and sulfamide *N*-arylations.

Contrary to sulfamates, the *N*-arylation of sulfamides has been reported a few times; even with palladium (Figure 1-8C).[35-37] In 2004, researchers at AstraZeneca disclosed the palladium-catalyzed *N*-heteroarylation of sulfamides with heteroaryl bromides.[35] Notably, no examples with aryl bromides were disclosed. A year later, aryl bromide substrates were shown to be compatible with modified palladium conditions by Muniz and Nieger.[36] Over a decade after that, the Roizen Group published an iridium catalyzed (hetero)arylation of sulfamides, similar to their previously disclosed sulfamate *N*-arylation chemistry.[37] These previously reported methods are impactful, however, they all have one limitation in common. None of R_1 or R_2 on the sulfamide can be hydrogen (H) (Figure 1-8C). This means that only functionalized, cyclic, or protected sulfamides can be successfully *N*-arylated. It can be hypothesized that under palladium or iridium-catalyzed conditions, the free sulfamide NH can coordinate to and "poison" the metal catalyst.[38] We envisioned accomplishing this transformation by utilizing a copper catalyst. As proven in Chapter 3, we were able to successfully have compatibility with free NH sulfamides and utilize more common reagents.

1.1.5 The Chemical Importance of Aliphatic Amines

Aliphatic amines are one of the most relevant functional groups in natural products, drug discovery, and synthetic chemistry. The most biologically significant examples are those that are commonly found in amino acids, neurotransmitters, hormones, proteins, are more (Figure 1-9A).[39-42] In respect to drug discovery, in 2014 the FDA approved 1086 novel small molecule drugs, and 874 of them included at least one nitrogen atom (Figure 1-9B).[43] They are

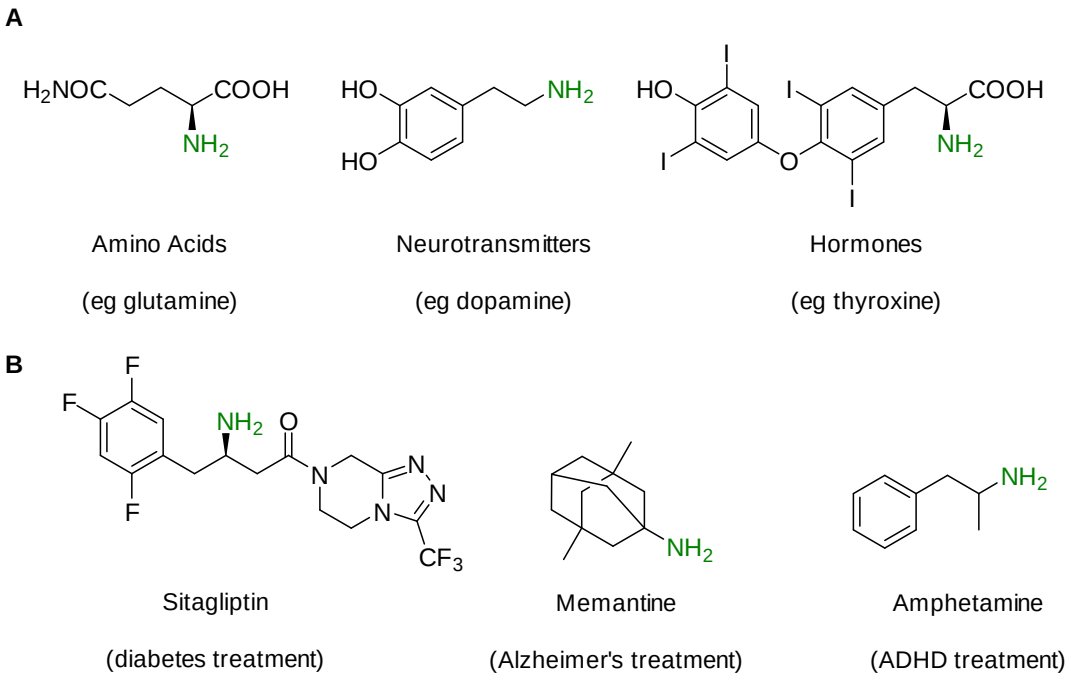


Figure 1-9: Aliphatic amines found in natural products (A) and FDA-approved drugs (B).

able to facilitate bioactivity in molecules because of their ability to modulate solubility, increase polarity, and be recognized by enzymes.[44, 45] Furthermore, the lone pair on the nitrogen atom can allow for certain molecules to cross cell membranes and the blood-brain barrier.

Due to their ubiquity, aliphatic amines are also ideal starting materials in organic chemistry and are known to undergo numerous transformations.[46-48] Because of the intrinsic properties of the nitrogen atom, amines have been traditionally employed as nucleophiles and undergo reactions with electrophiles. Conversely, their ability to react as electrophiles has rarely been explored.[48-50] In classical S_N2 substitution reactions, a nucleophile displaces an electrophile, breaking a bond, and a new bond is formed (Figure 1-10A).[51]

Alcohols are not great electrophiles, however, once functionalized with an electron

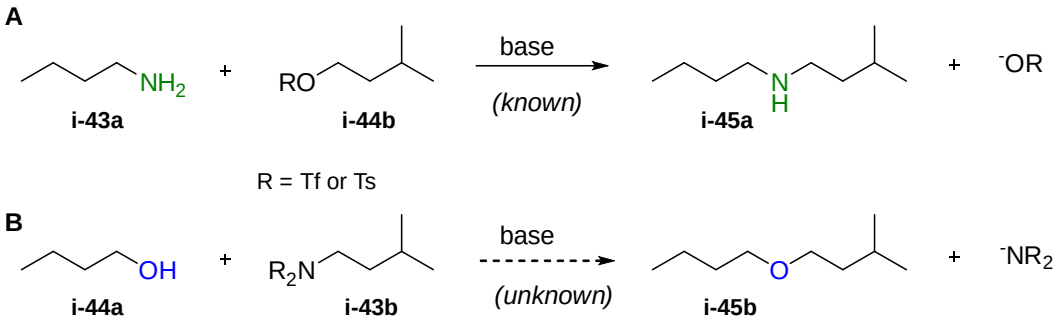


Figure 1-10: S_N2 substitution reactions.

withdrawing group into their corresponding triflate (OTf) or tosylate (OTs), they become excellent leaving groups.[52] This rudimentary idea initiated our interests to see what would occur if the conventional roles of amines (nucleophile) and alcohols (electrophiles) were reversed (Figure 1-10B). We envisioned functionalizing an amine into its corresponding NTf_2 and subjecting it to numerous nucleophiles (see Chapter 4).

In the literature there are currently >250,000 hits for aromatic NTf_2 compounds, however, there are <250 hits for aliphatic NTf_2. Aromatic *N*-ditriflate molecules, such as Comins reagent, are commonly utilized for synthesizing aryl or vinyl triflates under mild conditions.[53] For aliphatic *N*-ditriflate molecules, the vast majority of these results were for the synthesis of ionic liquids, however, there was one relevant paper from 1971 with limited citations.[50, 54, 55] In this publication, Dr. Glass disclosed the transformation of two aliphatic NTf_2 compounds to their corresponding nitriles (CN) (Figure 1-11).[50] Looking through the citations of that manuscript, a 1969 *JACS* paper appeared involving the harder to make and less reactive NTs_2 substrates.[21] This was the first published example of amines being utilized as electrophile precursors (Figure 1-11).

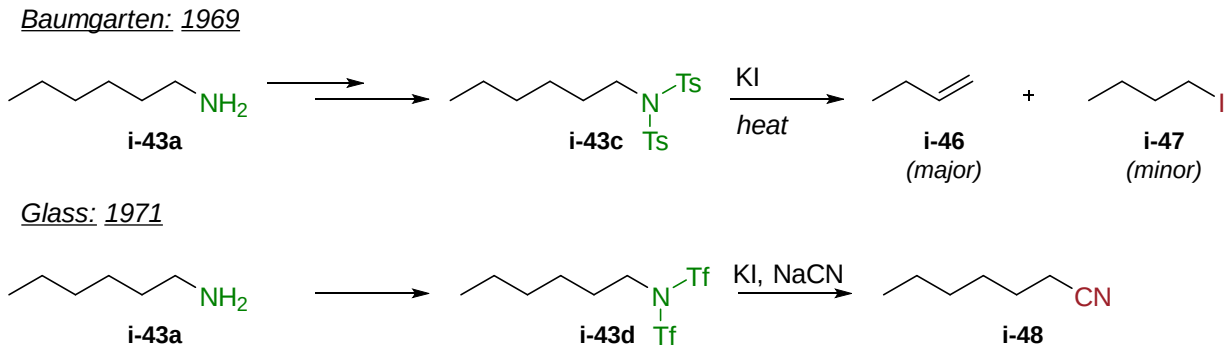


Figure 1-11: Initially disclosed examples of nitrogen leaving groups.

We decided that it was worthwhile to attempt to improve upon this reaction. We envisioned accomplishing the transformations above, however, in a single step and with a variety of relevant applications. As shown in Chapter 4, we successfully achieved this through the reaction of in situ generated NTf_2 intermediates and iodine salts.

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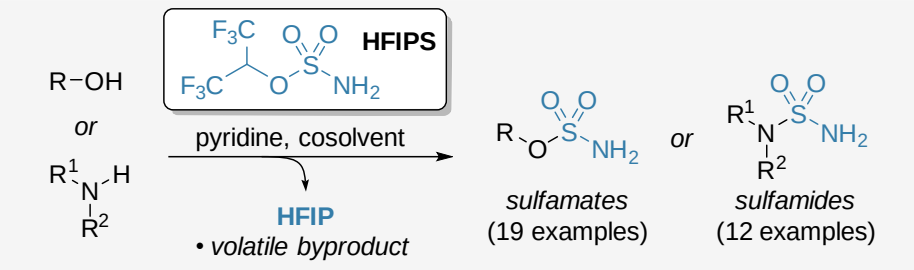
Chapter 2 - Hexafluoroisopropyl Sulfamate

2.1 A Useful Reagent for the Synthesis of Sulfamates and Sulfamides

As introduced in sections 1.1.2 and 1.1.3, attached is the manuscript of our *Organic Letters* paper entitled "Hexafluoroisopropyl Sulfamate: A Useful Reagent for the Synthesis of Sulfamates and Sulfamides."[56]

ABSTRACT: Sulfamates and sulfamides are most often synthesized from alcohols and amines with sulfamoyl chloride, an unstable reagent. We have identified hexafluoroisopropyl sulfamate (HFIPS) as a bench-stable solid that reacts readily with a wide variety of alcohols, amines, phenols, and anilines under mild reaction conditions. The sole byproduct of the reaction is hexafluoroisopropanol (HFIP) and reaction products can often be isolated in high purity after an aqueous workup (optional) and removal of solvents by evaporation.



Sulfamates and sulfamides are important functional groups in both biology and chemistry (Figure 2-1). Sulfamoyl substituents are often used in drug discovery to modulate polarity, solubility, and basicity, and to act as versatile hydrogen-bond donor-acceptor or Zn-binding functionalities.[14, 15] In the case of the anti-epileptic drug topiramate, the sulfamate is essential for potent inhibition of carbonic anhydrase[15, 16] and for the antibiotic doripenem, the

sulfamide sidechain improves activity against Gram-negative bacteria.[57, 58] Sulfamates and sulfamides can also be used as nitrene precursors in Rh-, Ag-, Fe-, or Mn-catalyzed C–H aminations or aziridinations, which are powerful methods for the stereoselective synthesis of amines and aziridines (Figure 2-1B).[59-69] Aryl sulfamate esters are also used in ortho-metalation reactions[70] and in metal-catalyzed cross-couplings.[71]

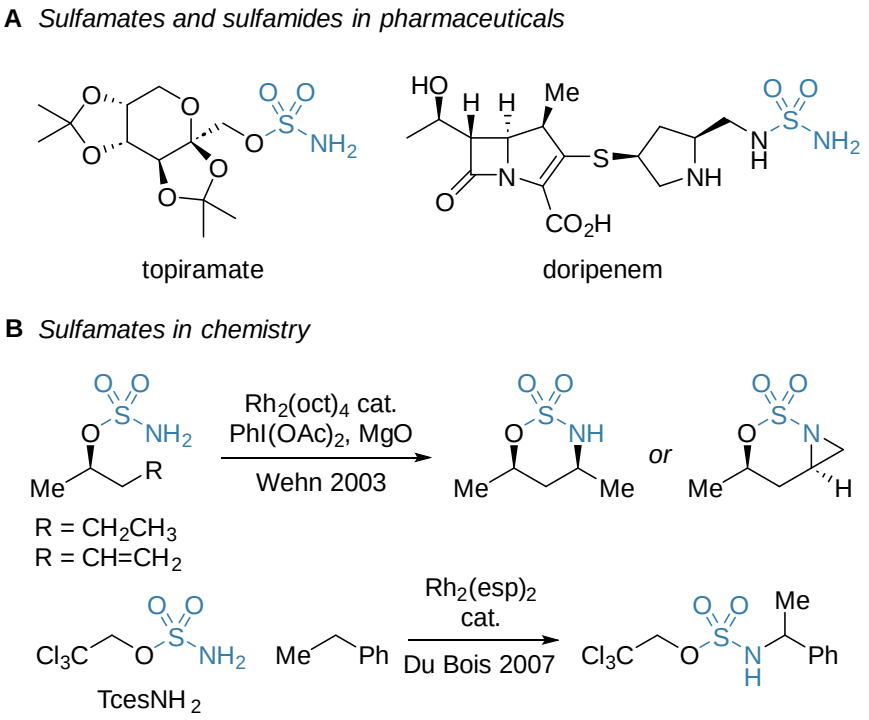


Figure 2-1: Sulfamoyl functionalities in (A) biology, and (B) in intra- and intermolecular C–H amination and aziridination chemistry.

The most commonly employed method for the synthesis of primary sulfamates and sulfamides has long-been a two-step procedure that involves the conversion of chlorosulfonyl isocyanate (CSI, **ii-1**) to sulfamoyl chloride (**ii-2**) in situ, followed by the addition of the alcohol or amine nucleophile (Figure 2-2).[20] Sulfamoyl chloride (**ii-2**) is highly reactive, but a large excess of reagent is often required due to its tendency to decompose in solution. Its high sensitivity to hydrolysis also prevents long-term storage. Boc-protected Burgess-type salts **ii-**

3a–**3c** have been developed as sulfamoylation reagents with improved safety and stability, but Boc removal requires an additional step and strongly acidic conditions.[22, 23] In 2020, the Miller lab disclosed a useful process employing pentachloro- (PCPS, **ii-4**) or pentafluorophenyl sulfamate (PFPS, **ii-5**) and catalytic NMI for the synthesis of sulfamates, with high selectivity for primary over secondary alcohols (e.g., N^6-Bz-deoxyadenosine, **ii-6a**).[24]

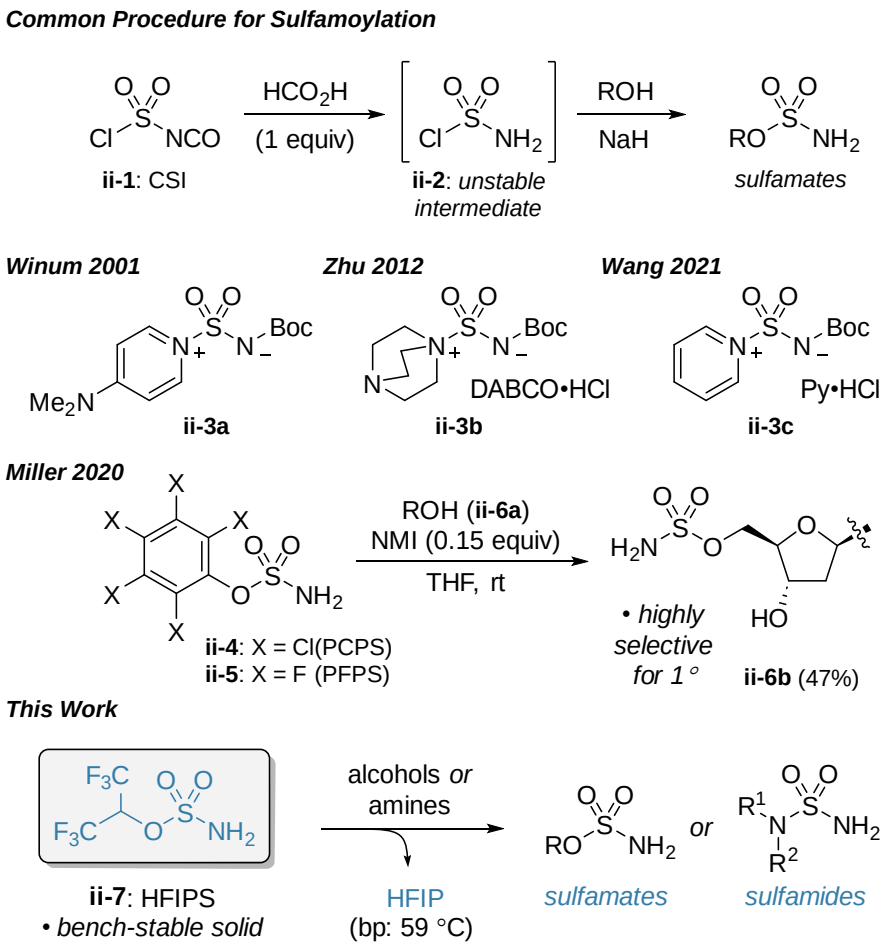


Figure 2-2: Common procedures and improved reagents for the sulfamoylation of alcohols and amines.

Here, we demonstrate the utility of 1,1,1,3,3,3-hexafluoro-isopropyl sulfamate (HFIPS, **ii-7**) as a versatile sulfamoylation reagent and complementary alternative to PCPS and PFPS. The reactivities of PCPS and PFPS permit sulfamoylation in the presence of catalytic NMI,

whereas HFIPS (**ii-7**) offers enhanced stability, improved safety,[24] and convenient scalability, with the only reaction byproduct being hexafluoroisopropanol (HFIP), a volatile solvent easily removed by evaporation. HFIPS (**ii-7**) reacts under mild conditions with both alcohols and amines to generate sulfamates and sulfamides in good yields.

HFIPS (also known as Hfs-NH_2) has been investigated previously as a nitrogen atom donor for intermolecular C–H aminations,[60, 63, 72] intermolecular aziridinations,[65, 73] and as a carbonic anhydrase inhibitor,[74] but has not been investigated extensively as a sulfamoylation reagent. Among the previous preparations of HFIPS, we have found the methods of Roizen[60] and Okada[75] to be the most reproducible. The 2-step, 1-pot procedure involves the addition of formic acid to a solution of CSI in MeCN,[60] rather than neat CSI, to generate sulfamoyl chloride (**ii-2**) in situ, followed by the addition of HFIP (hexafluoro-2-propanol) as a solution in dimethylacetamide (DMA), without an additional base.[75] Following an aqueous workup, HFIPS was isolated in 74% yield and sufficient purity (>98%) to be used in sulfamoylations without chromatography (Figure 2-3). We used less CSI (1.3 equiv) than is typically required (2–4 equiv) and achieved a more atom-economical procedure.

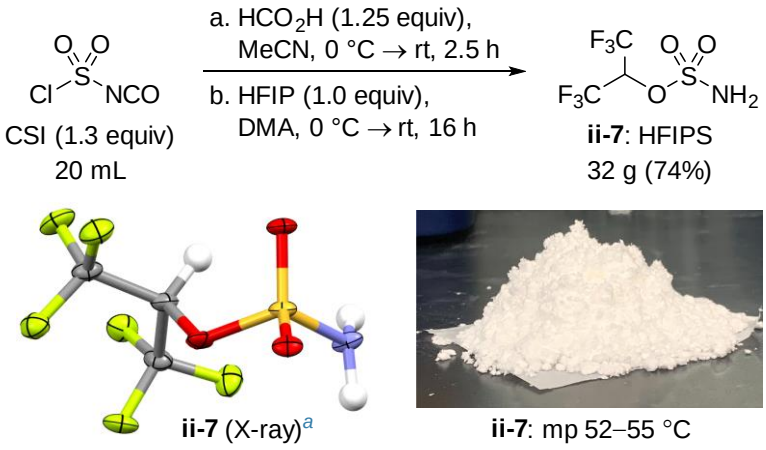
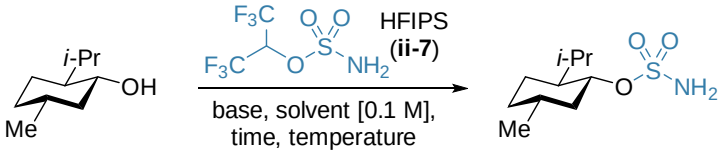


Figure 2-3: Synthesis and crystal structure of HFIPS.

With the goal of developing mild and general sulfamoylation conditions with HFIPS, we began our investigation with secondary alcohol **ii-8a** and commonly used soluble amine bases (Table 2-1). Although the sulfamoylation was low-yielding with Et_3N and DBU, improved yields of sulfamate **ii-8b** were obtained using DMAP, NMI, lutidine, and pyridine (entries 1–6). The use of pyridine as the solvent significantly improved the reaction time and also permitted a reduction in HFIPS, from 1.5 to 1.2 equivalents (entry 7). The sulfamoylation remained high yielding when pyridine was used as a cosolvent with CH_2Cl_2, THF, PhMe, MeCN, and DMF (entries 8–13), and this versatility is beneficial for substrates with different solubility requirements. The reaction performed equally well on gram-scale (entry 9).

Table 2-1: Sulfamoylation of menthol with HFIPS.



ii-8a: (–)-L-menthol (0.5 mmol) → **ii-8b**

Entry	HFIPS (equiv)	Solvent, Base	Temp (°C)	Time (h)	Yield (%)[c]
1	1.5	CH_2Cl_2, Et_3N (2 equiv)	30	20	3
2	1.5	CH_2Cl_2, DBU (2 equiv)	30	20	0
3	1.5	CH_2Cl_2, DMAP (2 equiv)	30	20	18
4	1.5	CH_2Cl_2, NMI (2 equiv)[d]	30	20	53
5	1.5	CH_2Cl_2, lutidine (2 equiv)	30	20	30
6	1.5	CH_2Cl_2, pyridine (2 equiv)	30	20	73
7	1.2	pyridine	30	4	88
8[b]	1.2	CH_2Cl_2, pyridine (7:3)	30	9	89
9[c]	1.2	CH_2Cl_2, pyridine (7:3)	30	16	86
10	1.2	THF, pyridine (7:3)	30	9	88
11	1.2	PhMe, pyridine (7:3)	30	9	89

12	1.2	MeCN, pyridine (7:3)	30	9	75
13	1.2	DMF, pyridine (7:3)	30	9	74

[a] Isolated yields. [b] Reaction conditions for entry 8: L-menthol (78 mg, 0.50 mmol), HFIPS (148 mg, 0.60 mmol), pyridine (1.5 mL, 19 mmol, 39 equiv), CH_2Cl_2 (3.5 mL). [c] 1.2 g (7.5 mmol) scale. [d] Sulfamate **ii-8b** was isolated in 61% yield using NMI (2 equiv) in THF. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-dimethyl-aminopyridine; NMI = N-methylimidazole; lutidine = 2,6-dimethyl pyridine; THF = tetrahydrofuran; DMF = N,N-dimethylformamide.

With a variety of mild reaction conditions established, we chose the CH_2Cl_2-pyridine (7:3) solvent mixture to evaluate the scope of the sulfamoylation reaction with a diverse collection of substrates (**ii-9a**–**39a**) that includes alcohols, phenols, amines, and anilines (Figure 2-4). Primary and secondary alcohols reacted efficiently under the standard reaction conditions. Upon completion, the reaction mixtures were simply concentrated under reduced pressure and subjected to silica gel chromatography, but it should be noted that crude products often showed relatively high purity prior to chromatography. Alkyl sulfamates **ii-9b**–**21b** were stable under these conditions and elimination products were not detected.

Phenols also reacted readily with HFIPS, despite its diminished reactivity compared to other reagents such as sulfamoyl chloride (**ii-2**) and PCPS (**ii-4**). Phenols **ii-25a**–**27a** were slower to react with HFIPS than alcohols, but reaction rates were improved with additional HFIPS (1.5 equiv) and the aryl sulfamate products **ii-25b**–**27b** were isolated in good yield. Since aryl sulfamate esters are known to be sensitive to base-induced decomposition,[76] pyridine was removed with aqueous workups rather than rotary evaporation.

The sulfamoylation of quinine (**ii-19a**) was low-yielding under standard conditions, but sulfamate **ii-19b** was isolated in 60% yield using 3 equiv HFIPS and an extended reaction time (48 h). Tertiary alcohol **ii-22a** was unreactive under the standard conditions, presumably due to

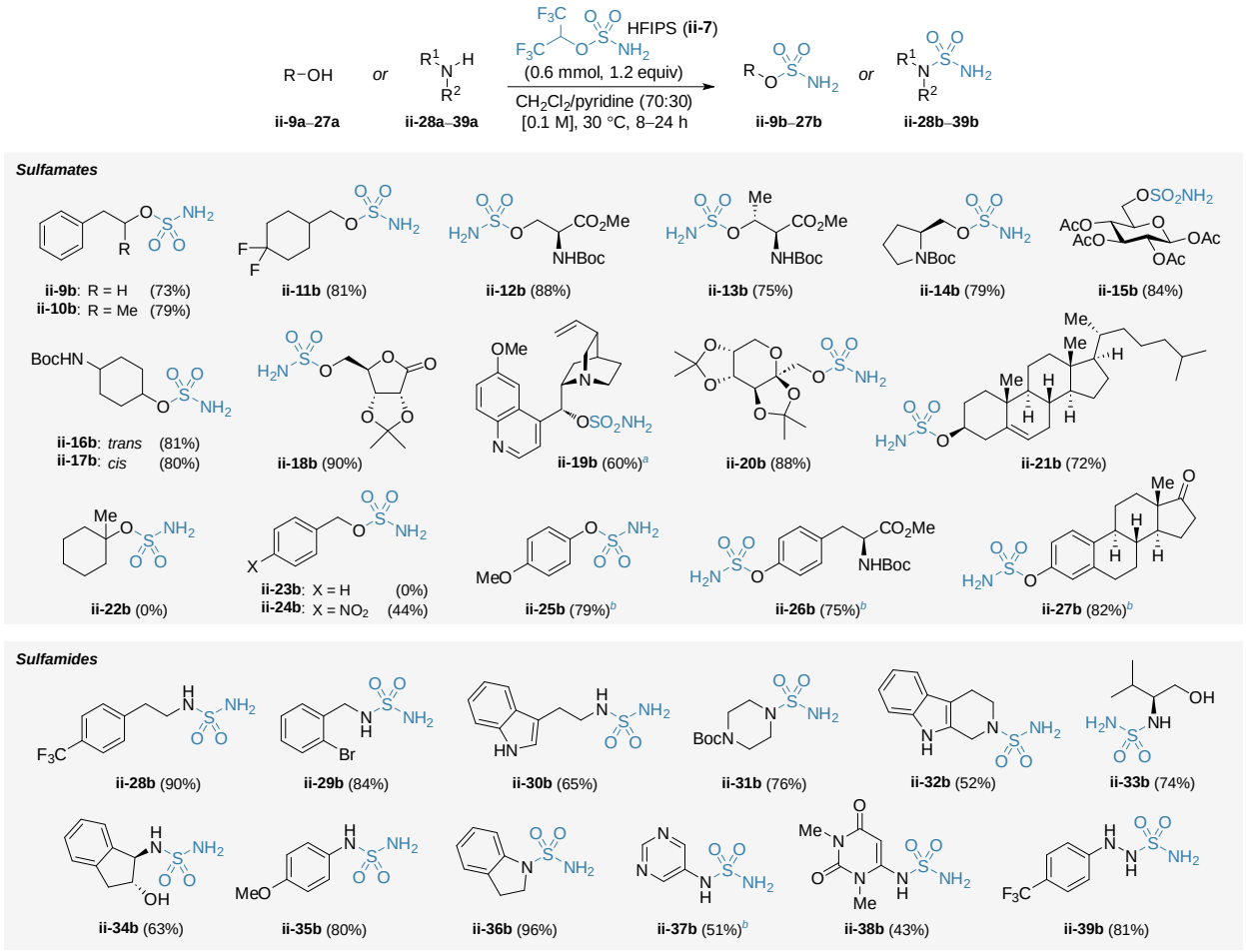


Figure 2-4: Sulfamates and sulfamides synthesized with HFIPS.

steric hindrance, and starting material was recovered.

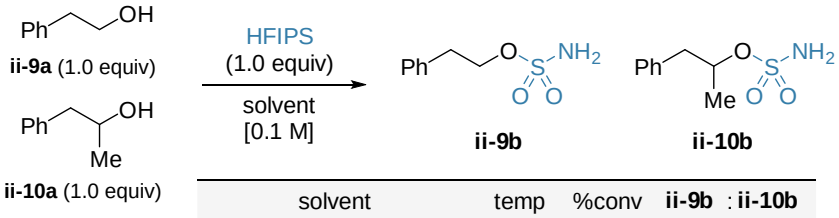
Starting material was also isolated after unsuccessful attempts to synthesize benzyl sulfamate (**ii-23b**) from benzyl alcohol (**ii-23a**). We identified precipitates formed during the reaction as benzyl pyridinium salts by ^{1}H NMR, supporting our hypothesis that the benzyl sulfamate product (**ii-23b**) was generated in situ, but sensitive to pyridine-catalyzed hydrolysis. The p-nitrobenzyl derivative is more stable, although the isolated yield of **ii-24b** was moderate (44%).

As expected, the reaction conditions optimized for the sulfamoylation of alcohols were

also fully compatible with more nucleophilic amines. Primary and secondary amines (**ii-28a**–**34a**), anilines (**ii-35a**, **ii-36a**), and phenyl hydrazine **ii-39a** all reacted readily with HFIPS to generate the corresponding sulfamide products in good to high yields. Heterocyclic amines **ii-37a** and **ii-38a** reacted more slowly to provide sulfamides **ii-37b** and **ii-38b** in moderate yields.

Amino alcohols **ii-33a** and **ii-34a** reacted predictably with HFIPS, with sulfamoylation occurring at the amines. Sulfamides **ii-33b** and **ii-34b** were isolated cleanly in good yield, with no detectable sulfamate or aziridine byproducts.

The Burgess-type sulfamoylation reagents **ii-3b** and **ii-3c** and PCPS (**ii-4**) are highly selective toward primary- over secondary alcohols in diol- or polyol substrates.[22-24] In order to probe the inherent selectivity of HFIPS toward primary and secondary alcohols, we designed a competition experiment involving alcohols **ii-9a** and **ii-10a** that was followed by ^{1}H NMR (Figure 2-5). Alcohols **ii-9a** and **ii-10a** were combined with HFIPS in equimolar amounts and stirred in $CDCl_3$/pyridine-d_5 (7:3) or neat pyridine-d_5 at 30 °C. Sulfamate product ratios were determined prior to reaction completion so that ratios reflect the inherent reactivity. Modest selectivity for alcohol **ii-9a** over **ii-10a** was observed in both $CDCl_3$/pyridine-d_5 and neat pyridine-d_5 (1.5:1 and 1.9:1, respectively). Reduction of the reaction temperature to rt improved selectivity (2.7:1), but also reduced reaction rate.



solvent	temp	%conv	ii-9b	:	ii-10b
$CDCl_3$, pyridine-d_5 (7:3)	30 °C	57	1.5	:	1.0
pyridine-d_5 (neat)	30 °C	38	1.9	:	1.0
pyridine-d_5 (neat)	23 °C	25	2.7	:	1.0

Figure 2-5: Sulfamoylation selectivity.

Sulfamoylation with HFIPS was also site-selective in the synthesis of dealanylascamycin (**ii-41**), a sulfamate-containing natural product produced by Streptomyces sp. JCM9888 (Figure 2-6).[77-79] Dealanylascamycin (**ii-41**, also known as AT-265) is an adenosine-based nucleoside antibiotic with a broad-spectrum of activity against Gram-positive and Gram-negative bacteria.[80] The sulfamoylation of adenosine derivatives is commonly done with either NaH (1.5 equiv) and $ClSO_2NH_2$ (1.5 equiv),[81] or $ClSO_2NH_2$ (2–4 equiv) in DMA[75, 82] but these methods can be unreliable for some substrates, including **ii-40**.[83-85] In other sulfamoylations of **ii-40**, Ubukata et al.[86, 87] and Castro-Pichel et al.[88] used $(Bu_3Sn)_2O$ (3 equiv), to generate the 5'-O-tributyltin ether in situ,[83] followed by $ClSO_2NH_2$ (8 equiv). Each of the methods above involves the tedious preparation of $ClSO_2NH_2$ and multiple operations with toxic or moisture-sensitive reagents. In the present study, alcohol **ii-40** was treated with shelf-stable HFIPS in reagent-grade CH_2Cl_2/pyridine and the sulfamate product was obtained in 78% yield (unoptimized). Subsequent acetonide hydrolysis completed an operationally simple two-step synthesis of dealanylascamycin (**ii-41**).

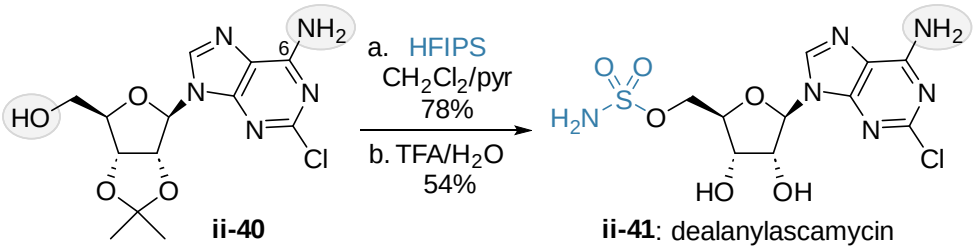


Figure 2-6: Synthesis of dealanylascamycin.

Several kinetic and computational studies with aryl sulfamates demonstrate that the mechanisms of hydrolysis and aminolysis at neutral or alkaline pH involve E2 or E1cB elimination pathways, rather than direct nucleophilic attack at the sulfur atom.[24, 76, 89-94] The

elimination generates $HN{=}SO_2$ (**ii-42**, also known as aza-sulfene) in situ as a reactive intermediate that is attacked rapidly by nucleophiles.

In the sulfamoylation of menthol (**ii-8a**) with HFPIS (Table 2-1), we were surprised to find weaker bases to be more effective than stronger bases (pyridine > NMI > lutidine > DMAP >> Et_3N > DBU), since the reactive intermediate $HN{=}SO_2$ (**ii-42**) should be generated more effectively with stronger bases (Figure 2-7A). One possible rationale for the results involves the reversibility of the elimination reaction. In reactions with bases that are stronger than hexafluoroisopropoxide (HFIP pK_a 9.3),[95] such as DBU (pK_{BH} 13.5) and Et_3N (pK_{BH} 10.7),[96] $HfipO^-$ can compete with alcohols to attack **ii-42**. In reactions with weaker bases, such as pyridine (pK_{BH} 5.2), lutidine (pK_{BH} 6.8), NMI (pK_{BH} 7.2), and DMAP (pK_{BH} 9.2), $HfipO^-$ is protonated to a greater extent by the conjugate acids (BH^+) to form HFIP, which is less nucleophilic than other alcohols toward **ii-42**.

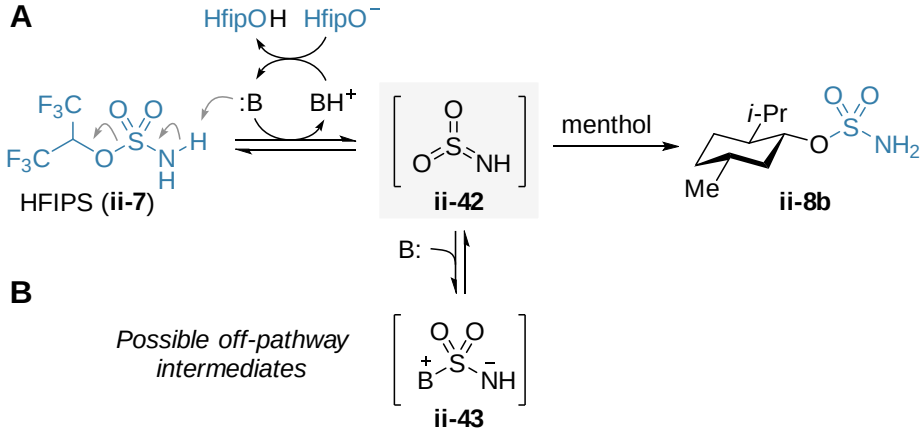


Figure 2-7: Possible mechanisms for sulfamoylations with HFIPS.

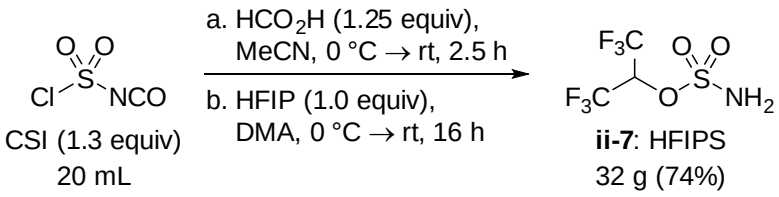
It is also possible that stronger bases could induce polymerization if $HN{=}SO_2$ is generated too rapidly[97] or that bases could act as nucleophiles toward **ii-42** to form inactive Burgess-type salts **ii-43** (Figure 2-7B). Stronger bases such as DBU and Et_3N may act to

sequester the sulfamoyl group, while the interactions with weaker bases such as pyridine may be reversible and allow $HN{=}SO_2$ to be more available to react with alcohols. More detailed kinetic and mechanistic studies will be required to evaluate the reversibility of the elimination and the possible role of internal salts **ii-43** in HFIPS sulfamoylation reactions.

In conclusion, we have developed a general and versatile method for the synthesis of sulfamates and sulfamides using hexafluoroisopropyl sulfamate (HFIPS, **ii-7**) and have demonstrated the utility of this method with a broad scope of alcohol and amine substrates. The HFIPS method is preferable to sulfamoylation using $ClSO_2NH_2$ and is complementary to the catalytic method developed by the Miller group.[24] Overall, the HFIPS sulfamoylation method offers significant improvements in both operational simplicity and time economy.

2.2 Supporting Information

1,1,1,3,3,3-Hexafluoroisopropyl sulfamate (HFIPS, ii-7)

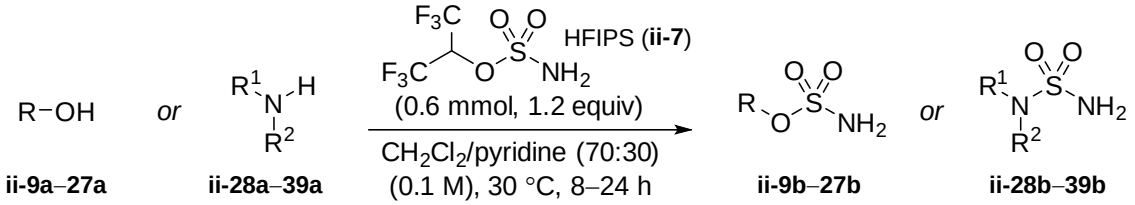


Formic acid (8.26 mL, 219 mmol) was added at 0 °C dropwise over a period of 5 min to a vigorously stirring solution of CSI (20.1 mL, 228 mmol) in MeCN (20 mL) in a 250 mL RBF. *CAUTION: Strong evolution of CO and CO_2 gas upon addition*. The solution was stirred at 0 °C for an additional 10 min and then allowed to warm to rt. After stirring at rt for 2.5 h, the reaction mixture was cooled to 0 °C and a solution of HFIP (18.4 mL, 175 mmol) in DMA (20 mL) was added slowly dropwise over 20 min via syringe pump. The reaction mixture was stirred at 0

°C for 10 min and then at rt for 16 h. The reaction was carefully quenched with the slow addition of H_2O (50 mL) and transferred to a separatory funnel with additional H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 75 mL) and the combined organic extracts were washed with H_2O (4 × 75 mL), satd aq. NaCl (75 mL), and 10% LiCl (2 × 25 mL) (to aid in DMA removal), dried over Na_2SO_4, and concentrated under reduced pressure to provide HFIPS (**ii-7**) as a colorless oil that solidified under vacuum (32.2 g, 131 mmol, 74%). The resulting solid was broken up into a white powder that was determined to be >98% pure by ^{1}H NMR and used in sulfamoylation reactions without further purification. Mp: 52–55 °C (lit. 50–52 °C). ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.50 (s, 2H), 6.21 (sept, $^3J_{HF}$ = 6.0 Hz, 1H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 120.5 (q, $^1J_{CF}$ = 284 Hz, 2C), 70.7 (sept, $^2J_{CF}$ = 33.5 Hz). ^{19}F NMR (659 MHz, DMSO-d_6): δ –71.9. Spectral data are consistent with previous reports.[60]

A small portion of the HFIPS isolated above (117 mg) was chromatographed on silica gel (0→100% EtOAc/Hex) to provide an analytical sample of HFIPS (113 mg) as a white amorphous solid. Mp: 49–51 °C. HFIPS is difficult to visualize on TLC plates and is resistant to most standard TLC stains, but its presence can be inferred by negative staining with iodine: R_f = 0.61 (33% EtOAc/Hex).[24] ^{1}H NMR (700 MHz, $CDCl_3$): δ 5.18 (sept, $^3J_{HF}$ = 5.6 Hz, 1H), 5.18–5.09 (brs, 2H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 120.1 (qq, $^1J_{CF}$ = 283 Hz, $^3J_{CF}$ = 3.7 Hz, 2C), 73.5 (sept, $^2J_{CF}$ = 35.3 Hz). ^{19}F NMR (659 MHz, $CDCl_3$): δ –73.67.

General Procedures for Sulfamoylation



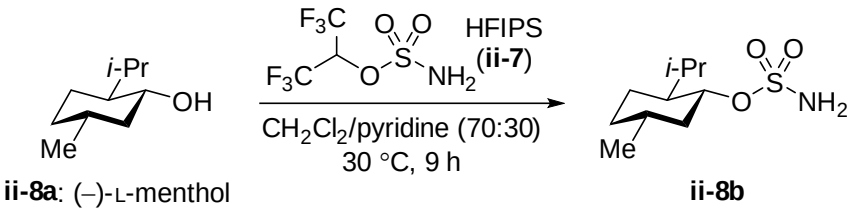
ii-9a–**27a** **ii-28a**–**39a** **ii-9b**–**27b** **ii-28b**–**39b**

General Procedure A, for sulfamides and alkyl sulfamates. HFIPS (148 mg, 0.6 mmol) was added to a solution of alcohol (0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 8–18 h. The reaction mixture concentrated under reduced pressure via rotary evaporation (with a bath temperature up to 50 °C) and often co-evaporated with PhMe (15 mL) to aid in pyridine removal. The crude mixture was chromatographed on silica gel to provide the sulfamate or sulfamide product.

General Procedure B, for aryl sulfamates and other sulfamates sensitive to thermal and/or base-induced decomposition. HFIPS (148 mg, 0.6 mmol) was added to a solution of a phenol or alcohol (0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The solution was then diluted with CH_2Cl_2* (20 mL) and washed with 10% HCl (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2* (3 × 20 mL) and the combined organic extracts were washed with H_2O (3 × 20 mL), and satd NaCl (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Sulfamate products were purified by silica gel chromatography.

* Some sulfamates showed poor solubility in CH_2Cl_2 and were extracted more efficiently with Et_2O or EtOAc.

L-Menthyl sulfamate (ii-8b)



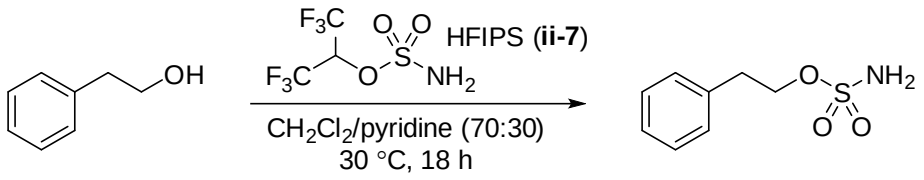
ii-8a: (–)-L-menthol **ii-8b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of L-menthol (78 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 9 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→40% EtOAc/Hex) to provide sulfamate **ii-8b** as a white powder (104.4 mg, 89%).

R_f = 0.45 (20% EtOAc/Hex), visualized with PMA stain. Mp: 103–105 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.72–4.64 (brs, 2H), 4.44 (td, *J* = 10.9, 4.6 Hz, 1H), 2.37 (dddd, *J* = 12.2, 4.6, 3.4, 2.0 Hz, 1H), 2.12 (dsept, *J* = 2.5, 7.0 Hz, 1H), 1.72 (dq, *J* = 13.3, 3.4 Hz, 1H), 1.69 (dddt, *J* = 13.2, 3.5, 3.2, 2.0 Hz, 1H), 1.47 (ttq, *J* = 12.1, 6.5, 3.5 Hz, 1H), 1.41 (dddd, *J* = 12.2, 10.9, 3.6, 2.5, 1H), 1.24 (dt, *J* = 12.2, 11.0 Hz, 1H), 1.06 (app dq, *J* = 13.0, 3.3 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 84. 9, 47.8, 41.7, 34.0, 31.8, 25.8, 23.2, 22.1, 21.0, 15.9. Spectral data are consistent with data reported previously for this compound.[34]

The same reaction was also done on a larger scale. HFIPS (2224 mg, 9.0 mmol) was added to a solution of L-menthol (1172 mg, 7.5 mmol) in CH_2Cl_2 (50 mL) and pyridine (20 mL) and stirred at 30 °C for 16 h. Following aqueous workup and chromatography, as above, menthyl sulfamate **ii-8b** was isolated as a white solid (1518 mg, 86%).

Phenethyl sulfamate (ii-9b)

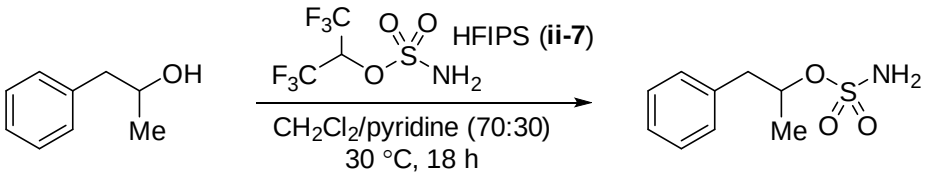


ii-9a **ii-9b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of 2-phenylethanol (61 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→40% EtOAc/Hex) to provide sulfamate **ii-9b** as a colorless oil (80 mg, 73%).

R_f = 0.65 (33% EtOAc/Hex), visualized by PMA stain. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.48–7.45 (brs, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 4.23 (t, J = 6.9 Hz, 2H), 2.97 (t, J = 6.9 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 137.4, 128.9 (2C), 128.4 (2C), 126.5, 69.2, 34.5. Spectral data are consistent with data reported previously for this compound.[34]

1-Phenylpropan-2-yl sulfamate (ii-10b)



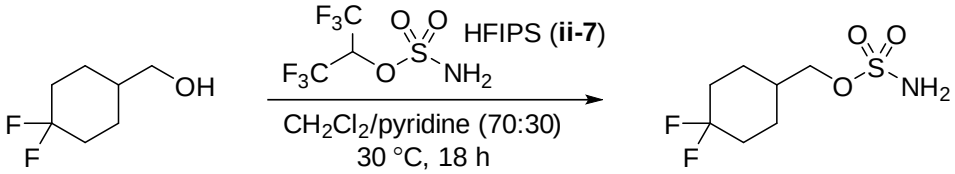
ii-10a **ii-10b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of 1-phenyl-2-propanol (68 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at

30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→33% EtOAc/Hex) to provide sulfamate **ii-10b** as a colorless oil (85 mg, 79%).

R_f = 0.50 (33% EtOAc/Hex), visualized by PMA stain. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.24 (t, J = 7.6 Hz, 2H), 7.19–7.14 (m, 3H), 4.75 (ddq, M of $ABMX_3$, J_{MA} = 7.7, J_{MB} = 5.6, J_{MX} = 6.2 Hz, 1H), 4.31–4.16 (brs, 2H), 2.93 (dd, A of $ABMX_3$, J_{AB} = 13.9, J_{AM} = 7.7 Hz, 1H), 2.82 (dd, B of $ABMX_3$, J_{AB} = 13.9, J_{BM} = 5.6 Hz, 1H), 1.36 (d, X of $ABMX_3$, J_{MX} = 6.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 137.0, 129.8 (2C), 128.8 (2C), 127.2, 82.1, 42.9, 20.7. The synthesis of this compound has been reported previously.[34]

(4,4-Difluorocyclohexyl)methyl sulfamate (ii-11b)



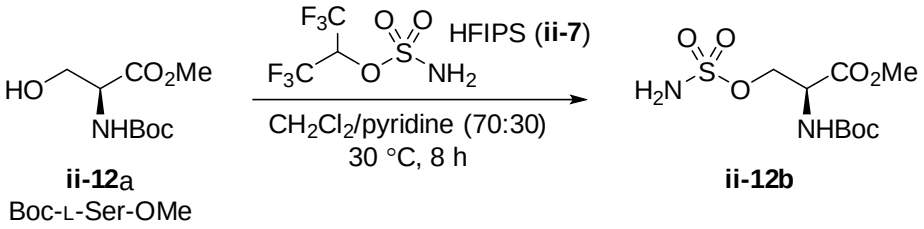
ii-11a **ii-11b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of (4,4-difluorocyclohexyl)methanol (81 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→50% EtOAc/Hex) to provide sulfamate **ii-11b** as a clear oil (99 mg, 81%).

R_f = 0.35 (33% EtOAc/Hex), visualized with PMA stain. ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.84–4.73 (brs, 2H), 4.07 (d, J = 6.3 Hz, 2H), 2.17–2.10 (m, 2H), 1.91–1.82 (m, 3H), 1.73 (app dddt, $^3J_{HF}$ = 33 Hz, J = 13.6, 13.2, 4 Hz, 2H), 1.39 (app dddt, J = 14, 12, 4, 2 Hz, 2H). ^{13}C NMR (176 MHz,

$CDCl_3$): δ 123.1 (dd, $^1J_{CF}$ = 242.6 Hz, $^1J_{CF}$ = 239.6 Hz), 74.6 (d, $^5J_{CF}$ = 3.2 Hz), 35.5 (d, $^4J_{CF}$ = 1.8 Hz), 33.0 (dd, $^2J_{CF}$ = 25.7 Hz, $^2J_{CF}$ = 23.2 Hz), 25.4 (d, $^3J_{CF}$ = 9.6 Hz). ^{19}F NMR (659 MHz, $CDCl_3$): δ −92.5 (d, $^2J_{FF}$ = 237 Hz), −102.7 (d, $^2J_{FF}$ = 237 Hz). HRMS (ESI) *m/z*: $[M + Na]^+$ 252.0476 Calcd for $C_7H_{13}F_2NO_3SNa^+$; Found 252.0484.

Boc-L-Serine-O-sulfamate methyl ester (ii-12b)



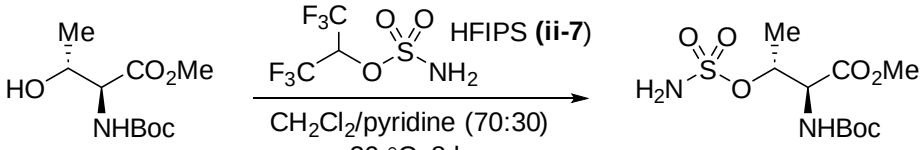
ii-12a
Boc-L-Ser-OMe

ii-12b

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of *N*-Boc-L-serine methyl ester (**ii-12a**) (130 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 8 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→80% EtOAc/Hex) to provide sulfamate **ii-12b** as a viscous oil (156 mg, 88%).

R_f = 0.75 (67% EtOAc/Hex), visualized by $KMnO_4$ stain. ^{1}H NMR (700 MHz, $CDCl_3$): δ 5.59–5.49 (brs, 1H), 5.44–5.23 (brs, 2H), 4.67–4.59 (brs, X of ABX, 1H), 4.52 (dd, A of ABX, J_{AB} = 10.2 Hz, J_{AX} = 2.9 Hz, 1H), 4.49–4.42 (brd, B of ABX, J_{BA} = 10.2 Hz, 1H), 3.80 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.7, 155.5, 81.0, 70.2, 53.3, 53.1, 28.4 (3C). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for 299.0908 $C_9H_{19}N_2O_7S^+$; Found 299.0910.

Boc-L-Threonine-O-sulfamate methyl ester (ii-13b)



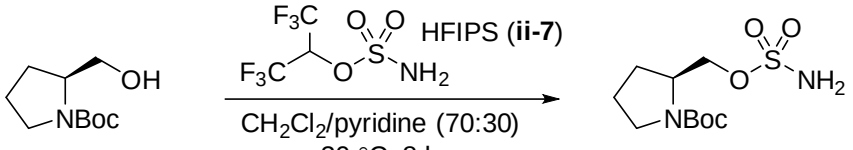
ii-13a
Boc-L-Thr-OMe

ii-13b

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of Boc-L-Thr-OMe (**ii-13a**) (117 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 8 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→40% EtOAc/Hex) to provide sulfamate **ii-13b** as white crystals (118 mg, 75%).

R_f = 0.75 (50% EtOAc/Hex), visualized with $KMnO_4$ stain. Mp: 112–115 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.55–7.48 (brs, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 4.83 (dd, *J* = 6.4, 3.4 Hz, 1H), 4.34 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.65 (s, 3H), 1.39 (s, 9H), 1.32 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 170.2, 156.1, 79.2, 76.5, 57.9, 52.6, 28.6, 28. 6, 17.6. HRMS (ESI) *m/z*: $[M + H]^+$ 313.1064 Calcd for $C_{10}H_{21}N_2O_7S^+$; Found 313.1069.

N-Boc-(2S)-Sulfamoyloxymethyl pyrrolidine (ii-14b)



ii-14a
Boc-L-prolinol

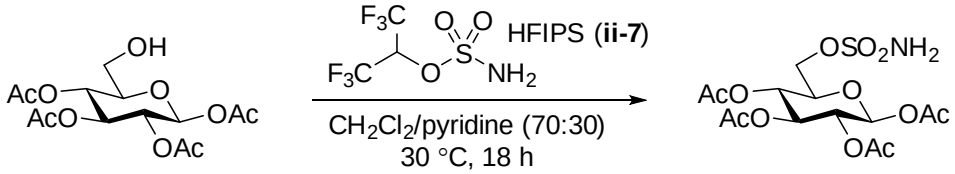
ii-14b

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of Boc-L-prolinol (101 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C

for 8 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→40% EtOAc/Hex) to provide sulfamate **ii-14b** as a clear oil (111 mg, 79% yield).

R_f = 0.62 (50% EtOAc/Hex), visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.53–7.44 (brs, 2H), 4.11–4.01 (m, 1H), 3.96–3.85 (m, 2H), 3.28–3.17 (m, 2H), 2.00–1.89 (m, 1H), 1.88–1.71 (m, 3H), 1.41 (s, 9H). Carbamate rotamers were observed in the ^{13}C spectrum (approx. 1:1). ^{13}C NMR (176 MHz, DMSO-d_6): δ 153.7/153.3, 78.8/78.7, 68.7/68.1, 55.2, 46.6/46.3, 28.1 (3C), 28.1/27.2, 22.4/23.2. HRMS (ESI) *m/z*: $[M + H]^+$ 281.1166 Calcd for $C_{10}H_{21}N_2O_5S^+$; Found 281.1165.

1,2,3,4-Tetra-O-acetyl-6-sulfamoyl-β-D-glucopyranose (ii-15b)



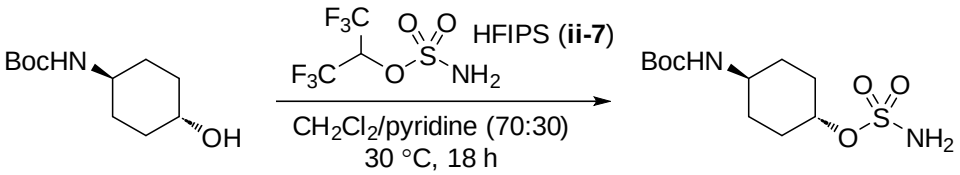
ii-15a **ii-15b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (**ii-15a**) (174 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→60% EtOAc/Hex) to provide sulfamate **ii-15b** as a white powder (180 mg, 84%).

R_f = 0.44 (50% EtOAc/Hex), visualized with PMA stain. Mp: 163–164 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.60–7.56 (brs, 2H), 5.98 (d, *J* = 8.3 Hz, 1H), 5.45 (t, *J* = 9.6 Hz, 1H), 4.95 (d, *J*

= 9.7, 8.3 Hz, 1H), 4.94 (dd, *J* = 8.9, 9.6 Hz, 1H), 4.28 (ddd, *J* = 9.6, 5.8, 2.5 Hz, 1H), 4.03 (dd, *J* = 11.2, 2.5 Hz, 1H), 3.99 (dd, *J* = 11.2, 5.8 Hz, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 169.5, 169.2, 169.1, 168.7, 90.7, 71.8, 71.3, 69.9, 67.8, 66.6, 20.5, 20.4, 20.3, 20.2. HRMS (ESI) *m/z*: $[M + Na]^+$ 450.0677 Calcd for $C_{14}H_{21}NO_{12}SNa^+$; Found 450.0696.

trans-4-(Boc-amino)cyclohexyl sulfamate (ii-16b)

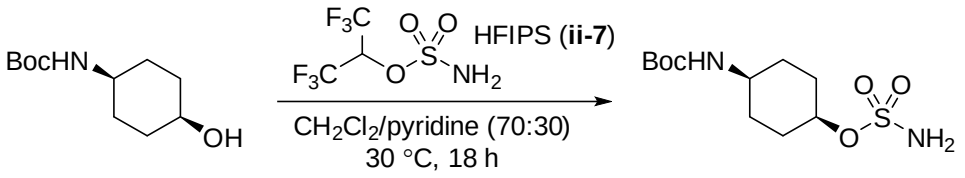


ii-16a (*trans*) **ii-16b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of *trans*-*tert*-butyl(4-hydroxycyclohexyl)carbamate (**ii-16a**) (161 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→60% EtOAc/Hex) to provide sulfamate **ii-16b** as a white powder (180 mg, 81%).

R_f = 0.42 (50% EtOAc/Hex). PMA stain. Mp: 142–144 °C. ^{1}H NMR (700 MHz, acetone-d_6): δ 6.62–6.55 (brs, 2H), 5.90–5.82 (brs, 1H), 4.43 (tt, *J* = 10.6, 4.3 Hz, 1H), 3.43–3.35 (m, 1H), 2.17–2.11 (m, 2H), 2.00–1.93 (m, 2H), 1.58 (ddt, *J* = 13.1, 10.6, 3.7 Hz, 2H), 1.39 (s, 9H), 1.37–1.32 (m, 2H).^{13}C NMR (176 MHz, acetone-d_6): δ 155.9, 80.0, 78.5, 48.9, 31.6 (2C), 31.0 (2C), 28.6 (3C). HRMS (ESI) *m/z*: $[M + Na]^+$ 317.1142 Calcd for $C_{11}H_{22}N_2O_5SNa^+$; Found 317.1143.

cis-4-(Boc-amino)cyclohexyl sulfamate (ii-17b)

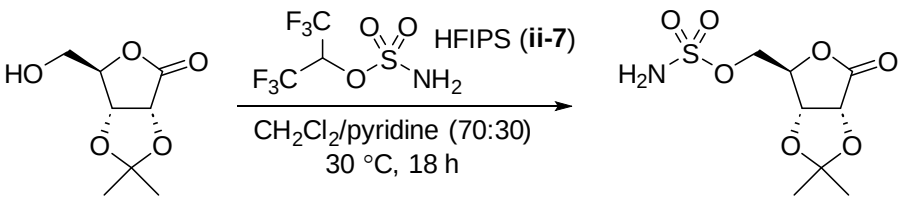


ii-17a (*cis*) **ii-17b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of *cis*-*tert*-butyl(4-hydroxycyclohexyl)carbamate (**ii-17a**) (161 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→60% EtOAc/Hex) to provide sulfamate **ii-17b** as a white powder (177 mg, 80%).

R_f = 0.42 (50% EtOAc/Hex). PMA stain. Mp: 88–91 °C. ^{1}H NMR (700 MHz, acetone-d_6): δ 6.64–6.51 (brs, 2H), 5.96–5.84 (brs, 1H), 4.72–4.65 (brs, 1H), 3.49–3.39 (m, 1H), 2.04–1.99 (m, 2H), 1.76–1.67 (m, 4H), 1.64–1.55 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (176 MHz, acetone-d_6): δ 155.9, 78.4, 77.6, 48.6, 29.9 (2C), 28.6 (3C), 28.1 (2C). HRMS (ESI) *m/z*: $[M + Na]^+$ 317.1142 Calcd for $C_{11}H_{22}N_2O_5SNa^+$; Found 317.1128.

2,3-O-Isopropylidene-D-ribonic-γ-lactone-5'-sulfamate (ii-18b)



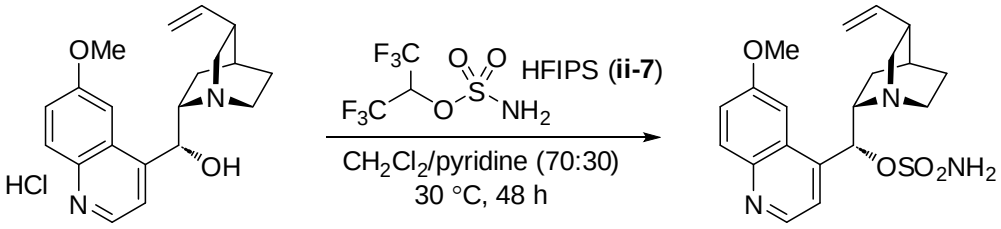
ii-18a **ii-18b**

According to General Procedure A, HFIPS (185 mg, 0.75 mmol) was added to a solution

of 2,3-*O*-isopropylidene-D-ribonic-γ-lactone (**ii-18a**) (161 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C. The crude oil was partitioned between Et_2O (20 mL) and H_2O (15 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL) and the organic phases were combined. The organic extracts were washed with H_2O (3 × 20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to provide sulfamate **ii-18b** as a viscous oil (120 mg, 90%).

R_f = 0.52 (50% EtOAc/Hex), visualized with PMA stain. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.73–7.70 (brs, 2H), 4.88 (dd, *J* = 3.3, 3.0 Hz, 1H), 4.84 (A of AB, *J* = 5.6 Hz, 1H), 4.82 (B of AB, *J* = 5.6 Hz, 1H), 4.33 (dd, *J* = 11.4, 3.4 Hz, 1H), 4.25 (dd, *J* = 11.4, 3.0 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 173.6, 112.5, 79.3, 77.2, 74.5, 67.7, 26.5, 25.2. HRMS (ESI) *m/z*: $[M + Na]^+$ 290.0305 Calcd for $C_8H_{13}NO_7SNa^+$; Found 290.0297.

Quinine sulfamate (ii-19b)



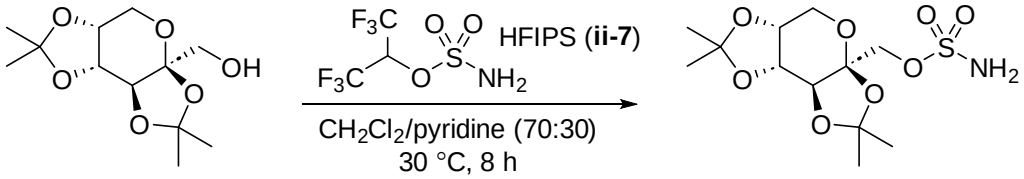
ii-19a: quinine•HCl **ii-19b**

According to General Procedure A, HFIPS (371 mg, 1.5 mmol) was added to a solution of quinine·HCl (180 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 48 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→5%

MeOH/CH_2Cl_2) to provide sulfamate **ii-19b** as a viscous oil (121 mg, 60%).

R_f = 0.25 (5% MeOH/CH_2Cl_2), visualized by UV. ^{1}H NMR (700 MHz, CD_3OD): δ 8.73–8.66 (brs, 1H), 7.99–7.92 (m, 1H), 7.79 (d, *J* = 4.6 Hz, 1H), 7.45 (s, 1H), 7.45–7.39 (m, 1H), 6.16–6.08 (m, 1H), 5.81–73 (m, 1H), 5.11 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.31–4.23 (brs, 1H), 4.03 (s, 3H), 3.67–3.58 (m, 2H), 3.31–3.25 (m, 1H), 2.84–2.78 (m, 1H), 2.28–2.16 (m, 2H), 2.12–2.06 (brs, 1H), 1.99–1.93 (m, 1H), 1.60–1.52 (m, 1H). ^{13}C NMR (176 MHz, CD_3OD): δ 160.2, 148.1, 147.1, 144.7, 139.3, 131.6, 127.5, 123.7, 120.5, 117.1, 102.1, 68.3, 61.4, 57.1, 55.5, 45.3, 38.5, 28.3, 25.2, 19.4. HRMS (ESI) *m/z*: $[M + H]^+$ 404.1639 Calcd for $C_{20}H_{26}N_3O_4S^+$; Found 404.1658.

Topiramate (ii-20b)



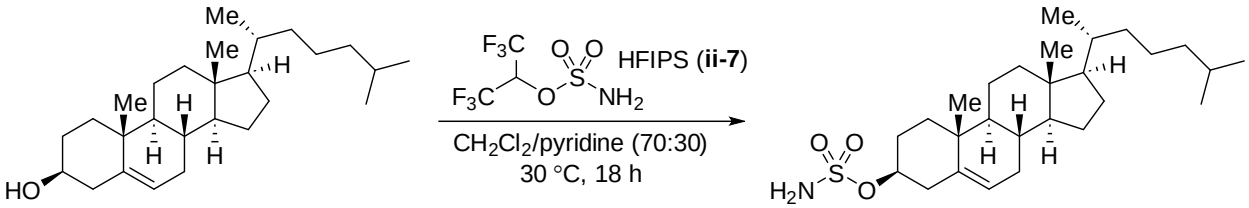
ii-20a **ii-20b**: topiramate

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of diacetone-β-D-fructopyranose (**ii-20a**) (132 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 8 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→30% EtOAc/Hex) to provide topiramate (**ii-20b**) as a white foam (150 mg, 88%).

R_f = 0.45 (33% EtOAc/Hex), visualized by PMA stain. Mp: 123–126 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.64–7.60 (brs, 2H), 4.60 (dd, *J* = 7.9, 2.6 Hz, 1H), 4.25 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.24

(d, *J* = 2.6 Hz, 1H), 4.00 (A of AB, J_{gem} = 10.1 Hz, 1H), 3.96 (B of AB, J_{gem} = 10.1 Hz, 1H), 3.75 (dd, *J* = 13.1, 1.8 Hz, 1H), 3.62 (d, *J* = 13.1 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 108.4, 108.2, 100.6, 69.9, 69.7, 69.2, 68.7, 60.5, 26.2, 25.7, 25.0, 24.0. Spectral data is consistent with data previously reported in the literature for this compound.[67]

Cholesterol sulfamate (ii-21b)



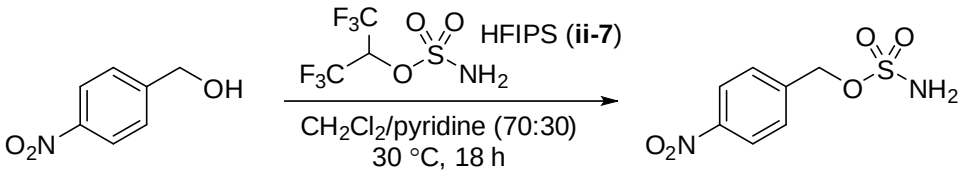
ii-21a: cholesterol **ii-21b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of cholesterol (**ii-21a**) (193 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→20% EtOAc/Hex) to provide sulfamate **ii-21b** as white crystals (168 mg, 72%).

R_f = 0.10 (10% EtOAc/Hex), visualized by PMA stain. Mp: 168–171 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.41–7.37 (brs, 2H), 5.37 (d, *J* = 5.2 Hz, 1H), 4.20 (tt, *J* = 11.4, 4.8 Hz, 1H), 2.42 (ddd, *J* = 13.2, 5.2, 2.2 Hz, 1H), 2.39–2.33 (m, 1H), 1.98–1.90 (m, 3H), 1.86 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.78 (dtd, *J* = 13.3, 9.5, 6.1 Hz, 1H), 1.62 (dtd, *J* = 15.3, 12.5, 3.8 Hz, 1H), 1.57–1.45 (m, 4H), 1.44–1.26 (m, 5H), 1.23 (dtd, *J* = 13.2, 11.2, 3.0 Hz, 1H), 1.18–0.98 (m, 8H), 0.97 (s, 3H), 0.93–0.87 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.65 (s, 3H).

^{13}C NMR (176 MHz, DMSO-d_6): δ 139.3, 122.6, 79.6, 56.1, 55.6, 49.5, 41.9, 39.2, 39.0, 38.5, 36.5, 36.0, 35.7, 35.2, 31.4, 31.4, 28.2, 27.8, 27.4, 23.9, 23.2, 22.7, 22.4, 20.6, 18.9, 18.6, 11.7. Spectral data is consistent with data previously reported in the literature for this compound.[67]

***p*-Nitrobenzyl sulfamate (ii-24b)**

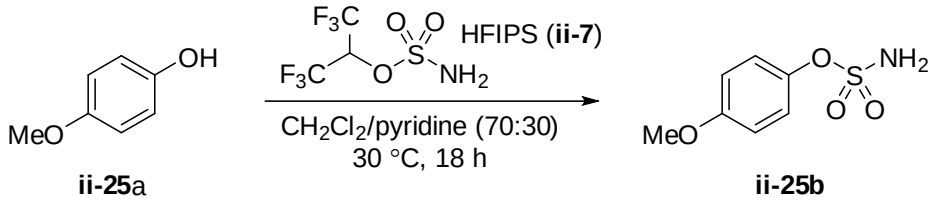


ii-24a **ii-24b**

According to General Procedure B, HFIPS (148 mg, 0.6 mmol) was added to a solution of p-nitrobenzyl alcohol (77 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The solution was diluted with CH_2Cl_2 (15 mL) and neutralized with 10% HCl (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phases were combined. The resulting organic solution was washed with H_2O (3 × 20 mL) followed by brine (20 mL). The organic solution was dried with Na_2SO_4 and concentrated under reduced pressure to provide sulfamate **ii-24b** as white crystals (51 mg, 44%).

R_f = 0.20 (33% EtOAc/Hex), visualized by UV. Mp: 104–106 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.27 (d, J = 8.8 Hz, 2H), 7.73 (brs, 2H), 7.69 (d, 2H), 5.23 (s, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 147.4, 142.6, 128.8 (2C), 123.6 (2C), 68.7. HRMS (ESI) *m/z*: $[M + Na]^+$ 255.0046 Calcd for $C_7H_8N_2O_5SNa^+$; Found 255.0051.

4-Methoxyphenyl sulfamate (ii-25b)

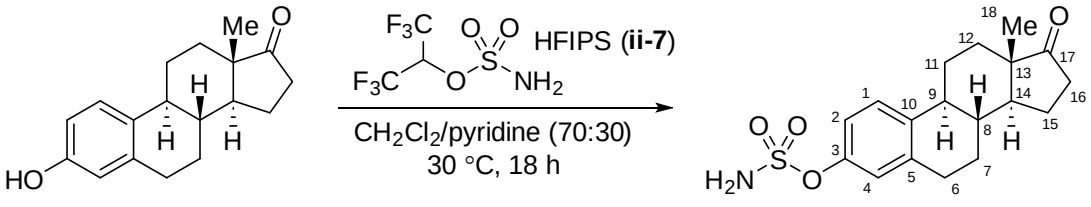


ii-25a **ii-25b**

According to General Procedure B, HFIPS (185 mg, 0.75 mmol) was added to a solution of *p*-methoxyphenol (**ii-25a**) (62 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The solution was diluted with CH_2Cl_2 (15 mL) and neutralized with 10% HCl (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phases were combined. The resulting organic solution was washed with H_2O (3 × 20 mL) followed by brine (20 mL). The organic solution was dried with Na_2SO_4, concentrated under reduced pressure, and chromatographed (0→30% EtOAc/Hex) to provide sulfamate **ii-25b** as clear oil (73 mg, 79%).

R_f = 0.33 (33% EtOAc/Hex), visualized by PMA stain. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.24 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.13–5.06 (brs, 2H), 3.80 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 158.6, 143.6, 123.3 (2C), 114.9 (2C), 55.8. Spectral data are consistent with data reported previously for this compound.[98]

Estrone Sulfamate (Emate, ii-27b)

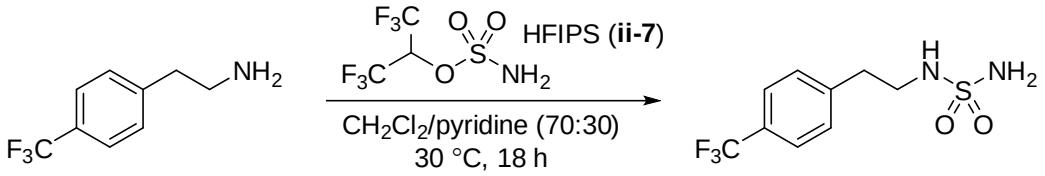


ii-27a: estrone **ii-27b**

According to General Procedure B, HFIPS (185 mg, 0.75 mmol) was added to a solution of estrone (**ii-27a**) (135 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The solution was diluted with CH_2Cl_2 (15 mL) and neutralized with 10% HCl (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phases were combined. The resulting organic solution was washed with H_2O (3 × 20 mL) followed by brine (20 mL). The organic solution was dried with Na_2SO_4, concentrated under reduced pressure, and chromatographed (0→50% EtOAc/Hex) to provide sulfamate **ii-27b** as a white fluffy powder (143 mg, 82%).

R_f = 0.30 (33% EtOAc/Hex), visualized by PMA stain. Mp: 196–198 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.91–7.87 (brs, 2H, SO_2NH_2), 7.35 (d, *J* = 8.5 Hz, 1H, H1), 7.03 (dd, *J* = 8.5, 2.4 Hz, 1H, H2), 6.99 (d, *J* = 2.4 Hz, 1H, H4), 2.90–2.84 (m, 2H, H6α + H6β), 2.44 (dd, *J* = 18.7, 8.8 Hz, 1H, H16β), 2.41–2.34 (m, 1H, H11α), 2.29–2.22 (m, 1H, H9α), 2.07 (dt, *J* = 18.7, 8.8 Hz, 1H, H16α), 2.00–1.92 (m, 2H, H7β + H15α), 1.81–1.75 (m, 1H, H12β), 1.62–1.47 (m, 3H, H8β + H14α + H15β), 1.45–1.34 (m, 3H, H7α + H11α + H12α), 0.84 (s, 3H, H18). ^{13}C NMR (176 MHz, DMSO-d_6): δ 219.5 (C17), 148.0 (C3), 138.0 (C5), 138.0 (C10), 126.6 (C1), 121.9 (C2), 119.3 (C4), 49.5 (C14), 47.3 (C13), 43.6 (C9), 37.5 (C8), 35.4 (C16), 31.3 (C12), 28.9 (C6), 25.8 (C7), 25.4 (C11), 21.1 (C15), 13.5 (C18). Spectral data were consistent with data reported previously for this compound.[99]

2-(4-(Trifluoromethyl)phenylethyl sulfamide (ii-28b)

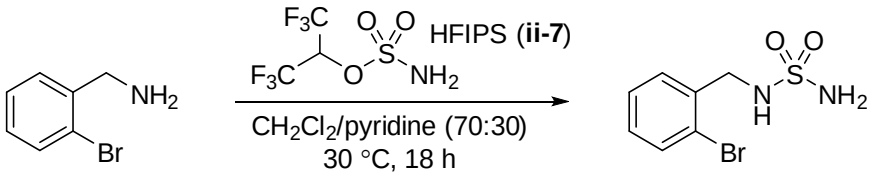


ii-28a **ii-28b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of 2-(4-(trifluoromethyl)phenyl)ethan-1-amine (95 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→5% MeOH/CH_2Cl_2) to provide sulfamide **ii-28b** as a white powder (120 mg, 90%).

R_f = 0.40 (5% MeOH/ CH_2Cl_2), visualized by $KMnO_4$ stain. Mp: 123–125 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.65 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 6.60 (t, J = 5.9 Hz, 1H), 6.57–7.53 (brs, 2H), 3.13 (dt, J = 7.4, 5.9 Hz, 2H), 2.88 (t, J = 7.4 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 144.4, 129.6 (2C), 126.9 (q, $^2J_{CF}$ = 31.7 Hz, 2C), 125.1 (q, $^3J_{CF}$ = 3.8 Hz, 2C), 124.4 (q, $^1J_{CF}$ = 272 Hz), 43.6, 34.8. ^{19}F NMR (659 MHz, DMSO-d_6): δ −60.3. HRMS (ESI) m/z: $[M + Na]^+$ 291.0386 Calcd for $C_9H_{11}N_2O_2F_3SNa^+$; Found 291.0374.

2-Bromobenzyl sulfamide (ii-29b)

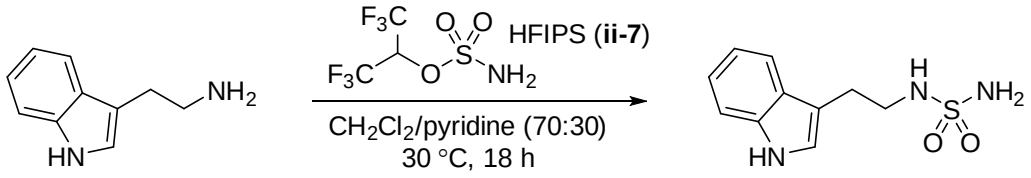


ii-29a **ii-29b**

According to modified General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of 2-bromobenzylamine (93 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C. The crude oil was dissolved in Et_2O (20 mL) and H_2O (15 mL). The aqueous layer was extracted with ether (3 × 15 mL) and the organic phases were combined. The resulting organic solution was washed with H_2O (3 × 20 mL) followed by brine (20 mL). The organic solution was dried with Na_2SO_4 and concentrated under reduced pressure to provide sulfamide **ii-29b** as a yellow powder (111 mg, 84%).

R_f = 0.62 (5% MeOH/CH_2Cl_2), visualized by UV. Mp: 115–118 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.39 (app t, *J* = 7.6 Hz, 1H), 7.21 (app t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 6.4 Hz, 1H), 6.76–6.68 (brs, 2H), 4.13 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 137.5, 132.2, 129.3, 128.9, 127.6, 122.1, 46.1. HRMS (ESI) *m/z*: [M + H]$^+$ 264.9641 calcd for $C_7H_{10}N_2O_2BrS^+$; Found 264.9633.

_N_-Sulfamoyl tryptamine (ii-30b)



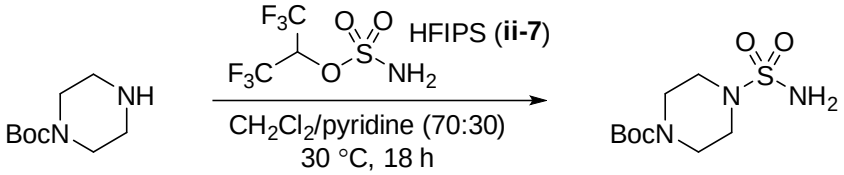
ii-30a: tryptamine **ii-30b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of tryptamine (80 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced

pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→50% EtOAc/Hex) to provide sulfamide **ii-30b** as a white solid (78 mg, 65%).

R_f = 0.46 (EtOAc/Hex 50:50), visualized by PMA stain. Mp: 143–145 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 10.83–10.78 (brs, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.33 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.98 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 6.55 (t, *J* = 6.1, 1H), 6.53–6.51 (brs, 2H), 3.17–3.12 (m, 2H), 2.89 (app t, *J* = 7.7 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 136.2, 127.1, 122.7, 120.9, 118.2, 118.2, 111.6, 111.4, 43.5, 25.3. HRMS (ESI) *m/z*: $[M + H]^+$ 240.0801 Calcd for $C_{10}H_{14}N_3O_2S^+$; Found 240.0793.

1-Boc-4-sulfamoylpiperazine (ii-31b)



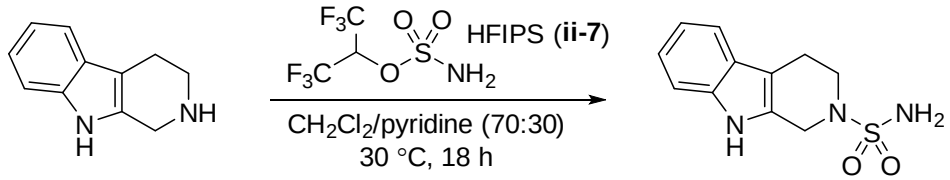
ii-31a **ii-31b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of *tert*-butyl piperazine-1-carboxylate (**ii-31a**) (93 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→5% MeOH/CH_2Cl_2) to provide sulfamide **ii-31b** as a white powder (101 mg, 76% yield).

R_f = 0.70 (5% MeOH/CH_2Cl_2), visualized by $KMnO_4$ stain. Mp: 173–174 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 6.83–6.79 (brs, 2H), 3.44–3.38 (brs, 4H), 2.89 (t, *J* = 5.2 Hz, 4H), 1.41 (s, 9H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 153.6, 79.2, 45.7 (2C), 43.1 (br), 42.1 (br), 28.0 (3C). HRMS

(ESI) *m/z*: $[M + Na]^+$ 288.0989 Calcd for $C_9H_{19}N_3O_4SNa^+$; Found 288.0977.

_N_-Sulfamoyl tryptoline (ii-32b)

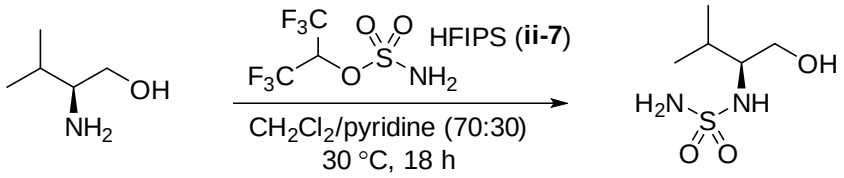


ii-32a: tryptoline **ii-32b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of tryptoline (86 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→5% MeOH/CH_2Cl_2) to provide sulfamide **ii-32b** as a white powder (65 mg, 52% yield).

R_f = 0.48 (50% MeOH/CH_2Cl_2), visualized by PMA stain. Mp: 234–238 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 10.90–10.86 (brs, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.31 (dt, *J* = 8.0 Hz, 1H), 7.05 (app t, *J* = 8.1 Hz, 1H), 6.97 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.94 (s, 2H), 4.26 (d, *J* = 1.6 Hz, 2H), 3.36 (t, *J* = 5.7 Hz, 2H), 2.85–2.78 (m, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 136.5, 130.3, 126.3, 120.8, 118.5, 117.6, 111.0, 106.2, 44.3, 43.6, 20.9. HRMS (ESI) *m/z*: $[M + Na]^+$ 274.0621 Calcd for $C_{11}H_{13}N_3O_2SNa^+$; Found 274.0601.

_N_-Sulfamoyl L-valinol (ii-33b)

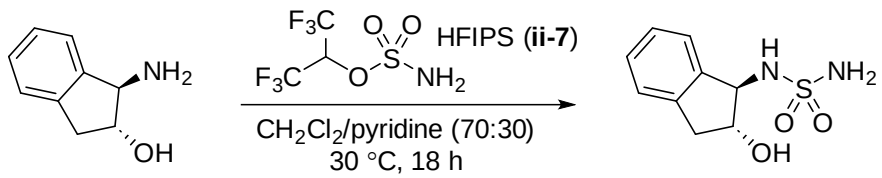


ii-33a : L-valinol **ii-33b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of L-valinol (52 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 8 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→100% EtOAc/Hex) to provide sulfamide **ii-33b** as translucent crystals (68 mg, 74%).

R_f = 0.34 (100% EtOAc), visualized by $KMnO_4$ stain. Mp: 72–74 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 6.41–6.38 (s, 2H), 6.19 (d, J = 8.6 Hz, 1H), 4.53 (t, J = 5.5 Hz, 1H), 3.48 (dt, J_{gem} = 10.9, J = 5.5 Hz, 1H), 3.42 (ddd, J_{gem} = 10.9, 6.5, 5.5 Hz, 1H), 2.99 (ddt, J = 8.6, 6.5, 5.2 Hz, 1H), 1.86 (dp, J = 6.9, 5.2 Hz, 1H), 0.88 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 61.4, 59.7, 27.9, 19.5, 17.5. HRMS (ESI) *m/z*: $[M + H]^+$ 183.0798 Calcd for $C_5H_{15}N_2O_3S^+$; Found 183.0796.

1*R*-Sulfamido-2*S*-indanol (ii-34b)



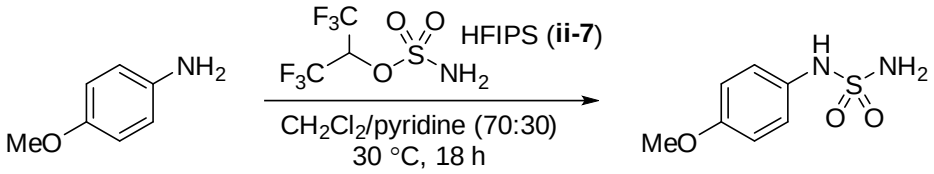
ii-34a: *trans* **ii-34b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of

(1*R*,2*S*)-1-amino-2-indanol (**ii-34a**) (75 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 8 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→70% EtOAc/Hex) to provide sulfamide **ii-34b** as a white solid (91 mg, 63% yield).

R_f = 0.48 (67% EtOAc/Hex), visualized by PMA stain. Mp: 163–165 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.41–7.37 (m, 1H), 7.23–7.17 (m, 3H), 6.77–6.70 (s, 2H), 6.33 (d, *J* = 8.9 Hz, 1H), 4.92 (d, *J* = 4.4 Hz, 1H), 4.64 (dd, *J* = 8.7, 4.9 Hz, 1H), 4.52 (ddt, *J* = 4.9, 4.4, 1.6 Hz, 1H), 3.00 (dd, *J* = 16.0, 4.9 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 141.7, 140.2, 127.4, 126.2, 124.8, 124.7, 71.8, 60.7, 39.3. HRMS (ESI) *m/z*: $[M + Na]^+$ 251.0461 Calcd for $C_9H_{12}N_2O_3SNa^+$; Found 251.0441.

4-Methoxyphenyl sulfamide (ii-35b)



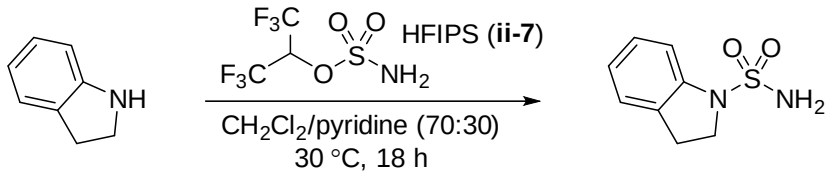
ii-35a **ii-35b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of 4-methoxyaniline (100 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→50% EtOAc/Hex) to provide sulfamide **ii-35b** as white crystals (132 mg, 80%).

R_f = 0.30 (50% EtOAc/Hex), visualized by UV. Mp: 128–130 °C. ^{1}H NMR (700 MHz, DMSO-

d_6): δ 9.04–8.96 (brs, 1H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.89–6.85 (brs, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.71 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 155.3, 132.3, 121.5 (2C), 114.0 (2C), 55.2. Spectral data is consistent with data previously reported for this compound.[100]

_N_-Sulfamoyl indoline (ii-36b)

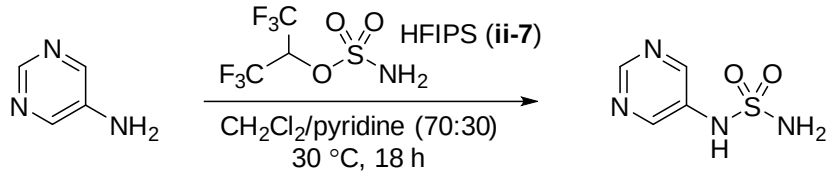


ii-36a: indoline **ii-36b**

According to modified General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of indoline (60 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture was dissolved in Et_2O (20 mL) and H_2O (15 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL) and the organic phases were combined. The resulting organic solution was washed with H_2O (3 × 20 mL) followed by brine (20 mL). The organic solution was dried with Na_2SO_4 and concentrated under reduced pressure to provide sulfamide **ii-36b** as a beige powder (106 mg, 96%)

R_f = 0.30 (33% EtOAc/Hex), visualized by UV. Mp: 148–150 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.27 (d, *J* = 8.0, 1H), 7.25–7.22 (brs, 2H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.15 (app t, *J* = 7.7 Hz, 1H), 6.95 (app t, *J* = 7.0 Hz, 1H), 3.79 (t, *J* = 8.4 Hz, 2H), 3.04 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 143.0, 131.5, 127.2, 125.0, 122.4, 113.7, 49.9, 27.3. HRMS (ESI) *m/z*: [M + Na]$^+$ 221.0355 Calcd for $C_8H_{10}N_2O_2SNa^+$; Found 221.0340.

5-Pyrimidinyl sulfamide (ii-37b)

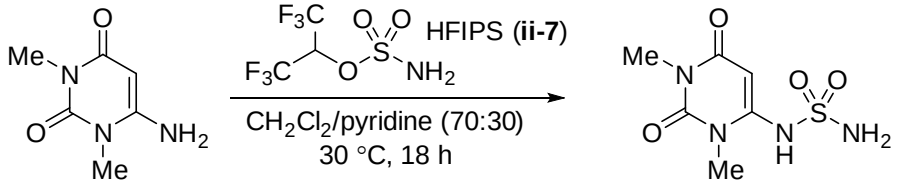


ii-37a **ii-37b**

According to General Procedure A, HFIPS (148 mg, 0.75 mmol) was added to a solution of pyrimidin-5-amine (48 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0⟶10% MeOH/CH_2Cl_2) to provide sulfamide **ii-37b** as a white powder (44 mg, 51% yield).

R_f = 0.32 (10% MeOH/CH_2Cl_2), visualized by UV. Mp: 180–182 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 10.08–9.96 (brs, 1H), 8.83 (s, 1H), 8.58 (s, 2H), 7.47–7.40 (brs, 2H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 152.1, 146.8 (2C), 134.7. HRMS (ESI) *m/z*: $[M + H]^+$ 175.0284 Calcd for $C_4H_6N_4O_2S$; 175.0286.

6-Sulfamido-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (ii-38b)



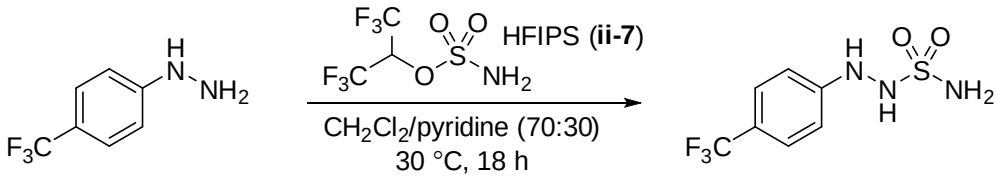
ii-38a **ii-38b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of 1,3-dimethyluracil (78 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30

°C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0⟶10% MeOH/CH_2Cl_2) to provide sulfamide **ii-38b** as white crystals (50 mg, 43%).

R_f = 0.30 (10% MeOH/CH_2Cl_2), visualized by UV. Mp: 192−195 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.03–7.72 (br s, 2H), 6.86–6.80 (brs, 2H), 3.33 (s, 3H), 3.14 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 158.7, 152.9, 149.7, 91.7, 30.1, 27.4. HRMS (ESI) *m/z*: $[M + Na]^+$ 257.0315 Calcd for $C_6H_{10}N_4O_4SNa^+$; Found 257.0310.

1-Sulfamoyl-2-(4-Trifluoromethylphenyl)hydrazine (ii-39b)



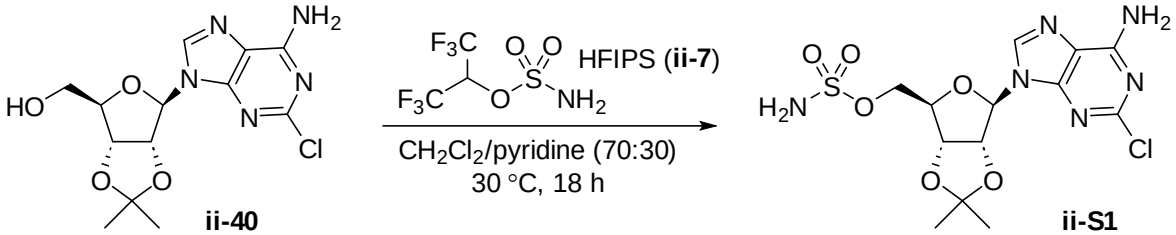
ii-39a **ii-39b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of (4-(trifluoromethyl)phenyl)hydrazine (88 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0⟶50% EtOAc/Hex) to provide sulfamide **ii-39b** as a yellow powder (103 mg, 81%).

R_f = 0.10 (20% EtOAc/Hex). $KMnO_4$ stain. Mp: 158–161 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.25 (s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.96 (s, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 152.2, 125.9 (q, $^3J_{CF}$ = 3.6 Hz, 2C), 125.1 (q, $^1J_{CF}$ = 274 Hz), 117.8 (q, $^2J_{CF}$ = 31.7 Hz), 111.8 (2C). ^{19}F NMR (659 MHz, DMSO-d_6) δ −58.7. HRMS (ESI) *m/z*: $[M + Na]^+$ 278.0182

Calcd for $C_7H_8N_3O_2F_3SNa^+$; Found 278.0159.

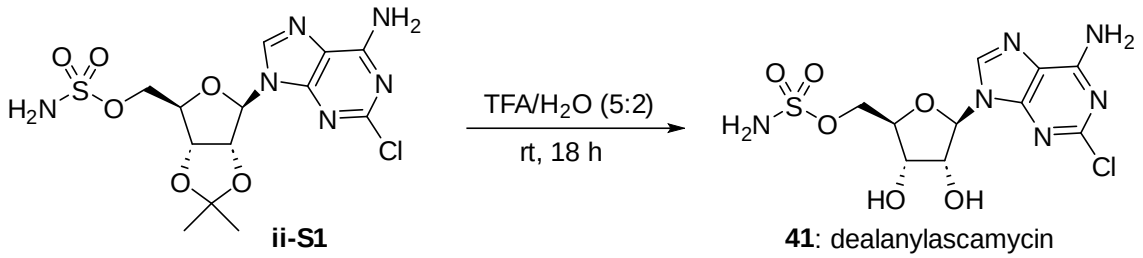
2′,3′-O-Isopropylidenedealanylascamycin (ii-S1)



According to General Procedure A, HFIPS (185 mg, 0.75 mmol) was added to a solution of 2-Chloro-2′,3′-*O*-isopropylideneadenosine (**ii-40**) (171 mg, 0.5 mmol) in CH_2Cl_2 (3.5 mL) and pyridine (1.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (15 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→10% MeOH/CH_2Cl_2) to provide dealanylascamycin acetonide (**ii-S1**) as a white powder (165 mg, 78%).

R_f = 0.62 (10% MeOH/CH_2Cl_2), visualized by UV. Mp: 198 °C (dec.) ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.31 (s, 1H), 7.94–7.91 (brs, 2H), 7.60 (s, 2H), 6.16 (d, *J* = 2.4 Hz, 1H), 5.35 (dd, *J* = 6.2, 2.4 Hz, 1H), 5.01 (dd, *J* = 6.2, 3.4 Hz, 1H), 4.41 (ddd, *J* = 6.3, 4.9, 3.4 Hz, 1H), 4.22 (dd, *J* = 10.9, 4.9 Hz, 1H), 4.16 (dd, *J* = 10.9, 6.3 Hz, 1H), 1.55 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 156.9, 153.2, 149.8, 139.9, 118.1, 113.7, 88.8, 83.7, 83.4, 80.9, 68.1, 26.9, 25.2. Spectral data is consistent with data previously reported for this compound.[85]

Dealanylascamycin (ii-41)



ii-S1 **41**: dealanylascamycin

Acetonide **ii-S1** (63 mg, 0.15 mmol) was stirred in a mixture of trifluoroacetic acid (TFA) and H_2O (5:2, 1.5 mL) at rt for 18 h. The reaction mixture was diluted with EtOH (1.5 mL) and PhMe (3 mL) and concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel (0→15% MeOH/CH_2Cl_2) and dealanylascamycin (**ii-41**) was isolated as white crystals (31 mg, 54%).

R_f = 0.15 (EtOAc), visualized by UV. Mp: 215 °C (dec). ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.31 (s, 1H), 7.92–7.77 (brs, 2H), 7.63–7.56 (brs, 2H), 5.87 (d, *J* = 5.4 Hz, 1H), 5.70–5.76 (brs, 1H), 5.56–5.38 (brs, 1H), 4.52 (dd, *J* = 5.4, 5.2 Hz, 1H), 4.28 (dd, *J* = 10.8, 3.7 Hz, 1H), 4.21–4.17 (m, 2H), 4.15 (ddd, *J* = 5.9, 3.9, 3.7 Hz, 1H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 157.3, 153.8, 150.9, 140.1, 118.6, 88.0, 82.3, 73.8, 70.8. Spectral data is consistent with data reported previously for this compound.[85]

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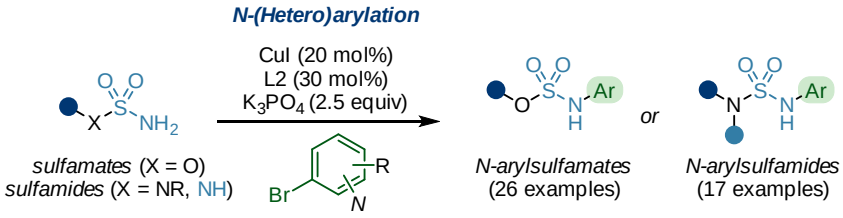
Chapter 3 - Sulfamate and Sulfamide Cross-Couplings

3.1 Copper-Catalyzed *N*-Arylation of Sulfamates and Sulfamides

As introduced in section 1.1.4, attached is the unpublished manuscript of our future publication entitled "Copper-Catalyzed *N*-Arylation of Sulfamates and Sulfamides."

ABSTRACT: Sulfamates and sulfamides are emerging moieties in drug discovery; however, there are limitations to their functionalizations. Herein, we report a simple and efficient methodology to (hetero)arylate both sulfamates and sulfamides



with aryl bromides via copper catalysis with a diamine ligand. This chemistry is applied to medicinally relevant molecules. This method is complementary to previous arylations in this space, and in addition, allows for the arylation of sulfamides without the need to protect the second nitrogen.

The arylation of heteroatoms with aryl halides is one of the most common types of reactions performed in organic and medicinal chemistry.[25] This is because heteroatom-containing molecules make up a large majority of FDA-approved drugs, natural products and more.[101] Heteroatoms allow for the ability to modulate properties such as: lipophilicity,

solubility, polarity and toxicity.[46] Further functionalizations, such as arylations, are a powerful and strategic methods to fine-tune these properties.[102]

Specific heteroatom-containing functionalities such as amides, ureas, sulfonamides, and carbamates are ubiquitous in drug candidates.[14] The less common, although emerging bioisosteres of the aforementioned moieties are the sulfamate and sulfamide functionalities.[16, 103] These substrates can be challenging to functionalize because they are often not conducive to common types of nitrogen functionalizations such as S_NAr and Buchwald-Hartwig couplings due to their poorly nucleophilic NH_2. Recognizing the importance of *N*-(hetero)aryl sulfamates and sulfamides, as well as their inaccessibility, Roizen et al. recently reported an effective photochemical (hetero)arylation (Figure 3-1).[34, 37] Palladium-catalyzed Buchwald-Hartwig cross-couplings of sulfamides had previously been reported (Figure 3-1).[35, 36] While being versatile and high-yielding, these methods lack operational simplicity and require costly palladium and iridium metal catalysts. We envisioned a simple and efficient copper-catalyzed reaction to achieve this transformation while utilizing inexpensive and ubiquitous reagents (Figure 3-1).

We recognized that although a limitation of palladium-catalyzed cross-couplings is the difficulties associated with weakly nucleophilic amines, copper catalysts have a preference for them.[31] Thus, an efficient transformation with mild conditions was developed using copper-catalysis. Pleasantly, the reaction proceeded without the need to functionalize the second nitrogen in sulfamide containing substrates (Figure 3-1). To our knowledge, this is the first report of a sulfamide *N*-arylation containing a free NH. Previous reports of sulfamide arylations involve either cyclic, functionalized, or protected sulfamides.[35-37]

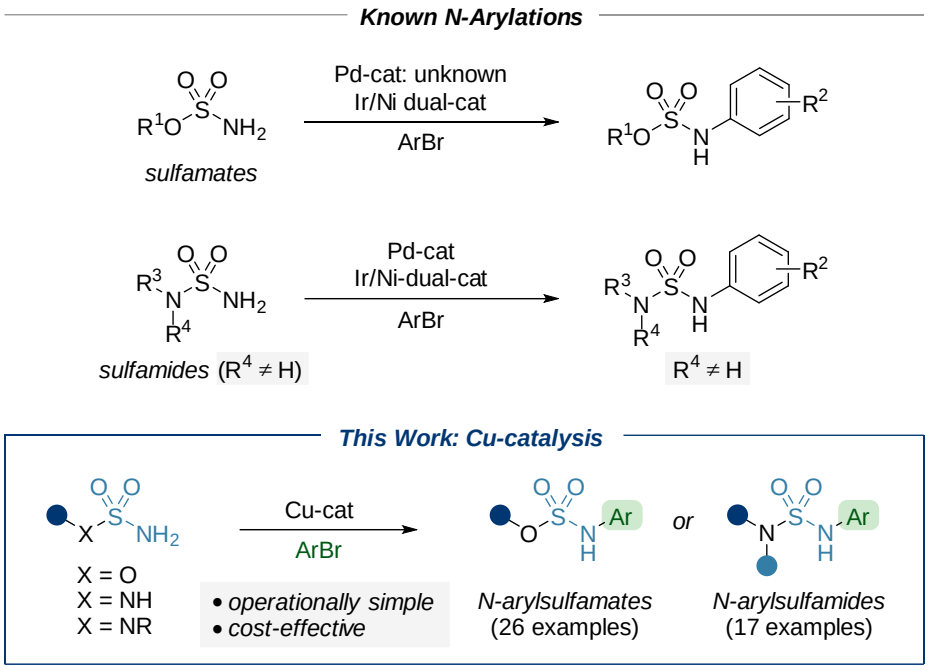
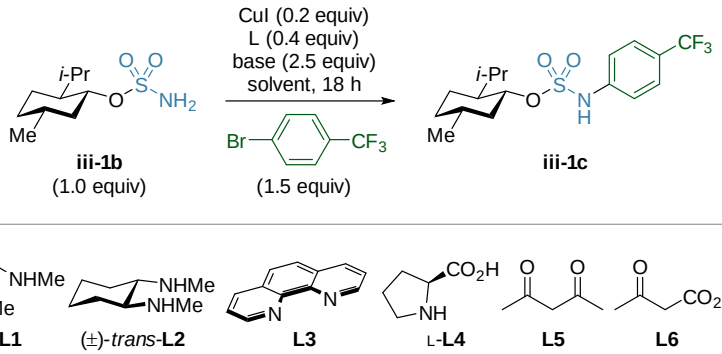


Figure 3-1: Previous and proposed *N*-arylations of sulfamates and sulfamides.

A major determinant for the success of this reaction under mild conditions is the ligand employed. Contrary to that of palladium, phosphine ligands are uncommon in copper catalysis and are instead replaced with bidentate oxygen and nitrogen-based ancillary ligands (Table 3-1).[104, 105] Furthermore, the pioneering work of Buchwald and co-workers have shown great success with diamine ligands for copper catalysis.[104] A ligand screen was conducted with standard arylation conditions to arylate menthyl sulfamate ester **iii-1b** (Table 3-1). Interestingly, only two of the ligands screened yielded any of the desired product: *N*,*N*-dimethylethane-1,2-diamine (**L1,** 7%) and *N*,*N*-dimethylcyclohexane-1,2-diamine (**L2,** 44%). Further optimizations were then performed with **L2** to determine the most successful conditions for the desired transformation (Table 3-1).

Initially, toluene was used as the solvent and a base screen was conducted

Table 3-1: *N*-arylation of menthyl sulfamate.



Entry	Ligand	Base	Solvent, Temperature [a]	Yield (%) [b]
1	L1	K_2CO_3	PhMe, 80 °C	7
2	L2	K_2CO_3	PhMe, 80 °C	44
3	L3–L6	K_2CO_3	PhMe, 80 °C	0
4	L2	Cs_2CO_3	PhMe, 80 °C	29
5	L2	KOAc	PhMe, 80 °C	20
6	L2	pyridine	PhMe, 80 °C	11
7	L2	K_3PO_4	PhMe, 80 °C	77
8	L2	K_3PO_4	MeCN, 80 °C	0
9	L2	K_3PO_4	THF, 80 °C	0
10	L2	K_3PO_4	DMF, 80 °C	trace
11	L2	K_3PO_4	DMSO, 80 °C	trace
12 [c]	L2	K_3PO_4	dioxane, 80 °C	90
13 [d]	L2	K_3PO_4	dioxane, 80 °C	83

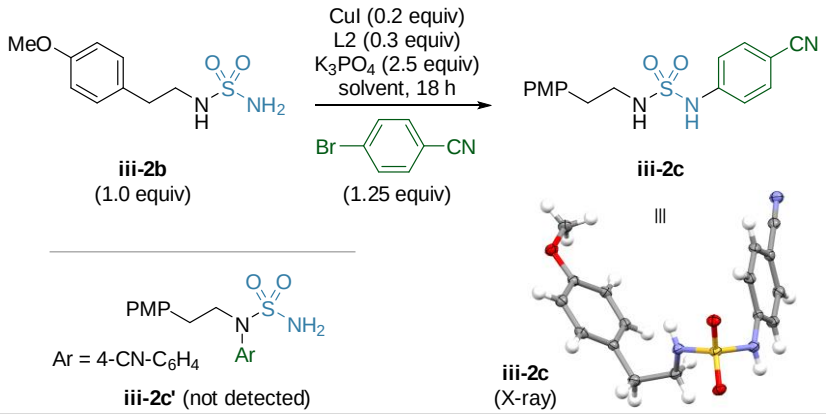
[a] Reactions were conducted under inert atmosphere. [b] NMR yields. [c] Reaction conditions for entry 12: sulfamate **iii-1b** (71 mg, 0.30 mmol), ArBr (101 mg, 0.45 mmol), K_3PO_4 (159 mg, 0.75 mmol), dioxane (3.0 mL). [d] 1.59 g (5.0 mmol) scale.

(entries 2 & 4-7). It was determined that potassium phosphate (entry 7) was superior to carbonate (entries 2/4), acetate (entry 5), and organic bases (entry 6). Then, potassium phosphate was consistently employed, and a solvent screen was conducted (entries 7-12). Polar solvents such as THF, MeCN, DMF, and DMSO performed poorly compared to non-polar

solvents (entries 7/12). The highest yielding combination of solvent and base with CuI and **L2** was 90% (Entry 12). Furthermore, this reaction was performed on a gram scale and pleasantly recorded an 83% yield (entry 13). After completing the optimization, the catalyst stoichiometry was slightly increased to 0.25 equivalents to ensure that more difficult substrates reached completion. We were apprehensive to increase the temperature because it was thought that alkyl sulfamates may be at risk of elimination, therefore, we decided to keep the temperature mild and slightly increase the amount of catalyst instead. It should be noted that not once was any sulfamate elimination detected under our final set of conditions.

With optimized conditions for the *N*-arylation of sulfamates accomplished, we applied them to sulfamides (Table 3-2). Overall, the chemistry was conducive with only a solvent

Table 3-2: Regioselective *N*-arylation of sulfamide **iii-2b**.



Entry	Solvent	Temperature [a]	Yield **iii-2c** (%) [b]
1	PhMe	80 °C	4
2	dioxane	80 °C	61
3 [c]	DMF	80 °C	72

[a] Reactions were conducted under inert atmosphere. [b] Isolated yields. [c] Reaction conditions for entry 3: sulfamide **iii-2b** (69 mg, 0.30 mmol), ArBr (68 mg, 0.38 mmol), K_3PO_4 (159 mg, 0.75 mmol), dioxane (3.0 mL).

change from dioxane to DMF being adjusted (entry 3). Pleasantly, this transformation was able to tolerate the sulfamide free NH to produce **iii-2c**, and the regioisomer **iii-2c'** was not detected. To our knowledge, this is the first example of a sulfamide substitution with an unprotected regioisomeric NH. A crystal structure confirmed that **iii-2c** was the sole product (Table 3-2). We observed sulfamides to be less stable than sulfamates under the standard reaction conditions and opted to not increase the temperature. Once the conditions were finalized for both sulfamates and sulfamides, substrate scopes were independently conducted (Figures 3-2A-D).

Menthyl sulfamate **iii-1b** was coupled to a variety of (hetero)aryl halides in good to excellent yields. The cross-couplings performed effectively with both electron withdrawing (**iii-1d**-**f,** 71-86%) and donating (**iii-1g**-**i,** 40-82%) halide substrates.

Bromo-indole (**iii-1j**), benzofuran (**iii-1k**), and benzothiophene (**iii-1l**) also coupled in good to excellent yields (38%, 66%, and 80% respectively). Notably, similar copper catalyzed cross-coupling conditions have been previously reported for the *N*-arylation of indoles, however, we did not observe any indole *N*-arylation.[106] Electron-rich benzodioxole also coupled well to produce compound **iii-1m** in a 70% yield.

Once an adequate variety of aryl halides were successfully coupled, heteroaryl halides were examined. Pleasantly, most heterocycles reacted as intended. 2-bromopyridines coupled well to yield substrates **iii-1n** and **iii-1o** in good to excellent yields (82% and 44% respectively). However, with these extremely electron poor heteroaryl bromides, we determined that a solvent change from dioxane to DMF was necessary. Furthermore, 5-bromopyrimidine coupled adequately to produce compound **iii-1p** in a 62% yield.

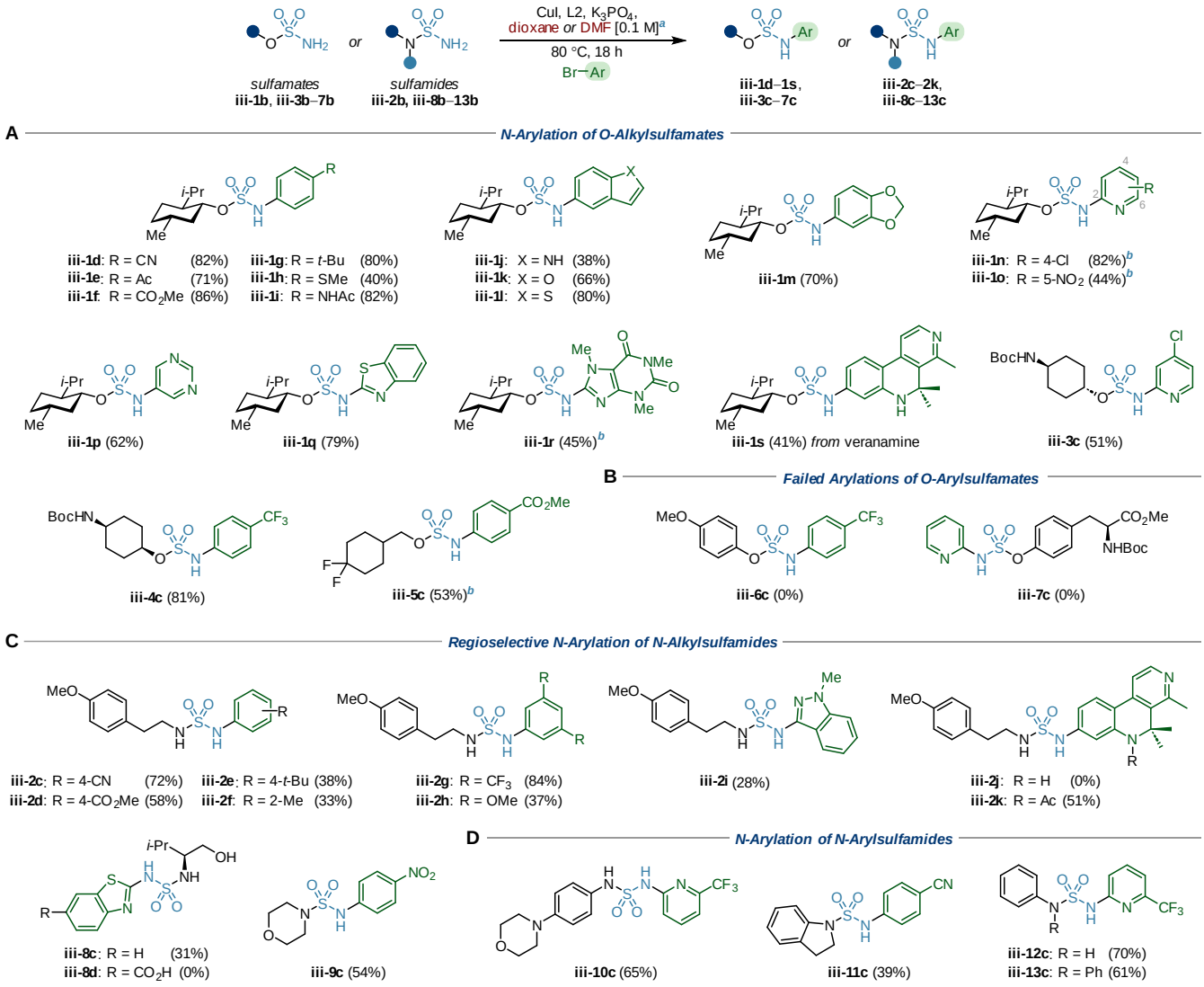


Figure 3-2: *N*-arylation of sulfamates and sulfamides.

[a] Dioxane was used as the solvent for couplings with sulfamates and DMF for sulfamides, except where noted. [b] DMF used.

Bromo thiazole coupled without issue to produce **iii-1q** in a 79% yield. Pleasantly, bromo caffeine reacted well to produce caffeine-derivative **iii-1r** in a 44% yield. Additionally, the bromine-containing natural product veranamine, isolated from a marine sponge, was cross-coupled under our standard conditions to afford compound **iii-1s** in a 41% yield.[107]

Lastly, the reactivity of other sulfamates such as **iii-3c**-**5c** were explored. Having not

detected any sulfamate elimination, trans (**iii-3b**) and cis (**iii-4b**) cyclohexyl sulfamates were investigated. Once again, no stability issues were observed and **iii-3c** and **iii-4c** were synthesized in 51% and 81% yields respectively. These reactions also display the compatibility with -Boc protecting groups. Furthermore, difluorocyclohexyl sulfamate **iii-5b** reacted in a 53% yield to produce **iii-5c**. Interestingly this reaction required DMF and appeared sluggish in dioxane.

Unsurprisingly, aryl sulfamates such as the electron rich **iii-6b** and tyrosine-derived **iii-7b** did not couple under our conditions (Figure 3-2B). Aryl sulfamates are known to eliminate under basic conditions and were not stable enough to react.[56] After exploring the reaction with many sulfamates, we subjected sulfamides to the newly developed reaction conditions (Figure 3-2C-D).

When expanding the substrate scope our goal was to cross-couple unprotected and non-cyclic sulfamides. The sulfamide NH may have poisoned previously employed metal catalysts; however, this was not observed with copper and these substrates coupled in good to excellent yields (Figure 3-2C-D). For example, phenethyl sulfamide **iii-2b** was coupled to electron rich, electron poor, mono and di-substituted aryl bromides to yield compounds **iii-2c**-**2h** in 33%-84% yields. Moreover, electron-deficient aryl bromides coupled in higher yields than those electronically rich. Sulfamide **iii-2b** was also coupled to nitrogen containing heterocycles to produce diazole **iii-2i** and acylated veranamine derivative **iii-2k** in 28% and 51% yield respectively. Notably, unprotected veranamine failed to react in the sulfamide reaction.

When the free alcohol containing sulfamide **iii-8b** was coupled to bromobenzothiazole, compound **iii-8c** was produced in a 31% yield; however, with a free carboxylic acid present,

compound **iii-8d** was not formed.

Next, cyclic morpholine sulfamide **iii-9b** was reacted to produce compound **iii-9c** in a 54% yield. This example demonstrates that our chemistry works well with both free NH and cyclic sulfamides.

Unlike aryl sulfamates, aryl sulfamides are base stable and were compatible with the reaction conditions (Figure 3-2D). The morpholine-functionalized *N*-arylsulfamide **iii-10b** was able to couple with a substituted bromopyridine to yield **iii-10c** in a 65% yield. As with morpholine sulfamide, the cyclic indoline sulfamide was successfully coupled to produce compound **iii-11c** in a 39% yield. Lastly, we cross-coupled phenylsulfamide **iii-12b**, and diphenylsulfamide **iii-13b** to yield their corresponding *N*-aryl products in a 70% and 61% yield respectively.

Unexpectedly, when we were exploring the reactivity of different halides and pseudohalides, we noticed an incompatibility with *para*-nitro bromobenzene and menthyl sulfamate (Figure 3-3A). The cross-coupling did not proceed as expected in that a low yield of product was obtained and both starting materials remained present after 18 h. However, when testing other halides, we were able to access **iii-1t** in a 71% yield by using *para*-nitro iodobenzene. Notably, chloro and triflate *p*-nitrobenzene failed to yield any of the desired product.

Surprisingly, phenethyl sulfamide **iii-2b** was able to couple with *para*-nitro bromobenzene to produce **iii-9j** in a 55% yield (Figure 3-3A). This yield was further increased to 80% with the utilization of para-nitro iodobenzene. As with sulfamates, the chlorine and triflate coupling partners did not yield any product when reacted with sulfamides. This data indicates

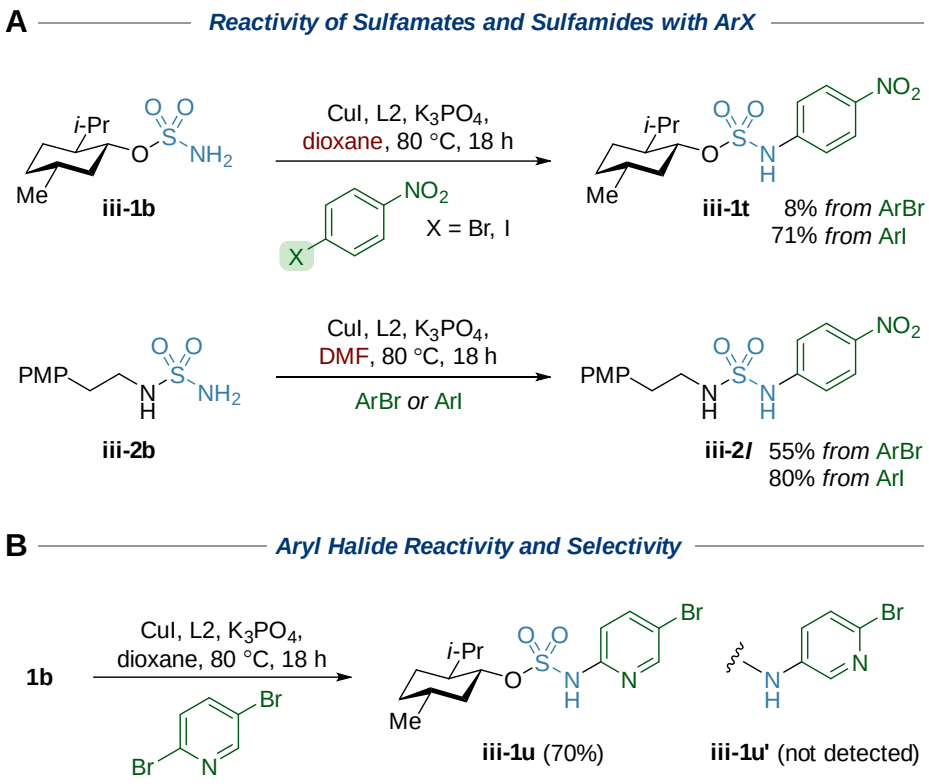


Figure 3-3: Reactivity and selectivity experiments.

that aryl iodide partners should be utilized if reaction difficulties occur with bromides.

Next, we were curious about selectivity between two bromines on the same substrate (Figure 3-3B). When differentiating between the same halide, electronics are the primary factor for selectivity.[108] The ability to conduct sequential cross-couplings on the same substrate allows for complex compounds to be synthesized from inexpensive starting materials. 2,5-dibromopyridine was reacted with menthyl sulfamate (**iii-1b**) and as predicted, compound **iii-1u** was generated in a 70% yield. However, there was no detection of the other regioisomer or disubstituted product. We also attempted the reaction in DMF to try and produce a change in selectivity, although none was observed.

Our last goal was to apply this chemistry to bioactive molecules (Figure 3-4).

Furthermore, we attempted to synthesize these complex *N*-aryl bioactive molecules without purifying the intermediate sulfamate and sulfamides. Having previously reported a volatile sulfamoylating reagent (hexafluoroisopropyl sulfamate, HFIPS, see Chapter 2), we applied that chemistry to the alcohol and amine precursors.[56] After the in situ formation of the corresponding sulfamates and sulfamides, the volatiles were evaporated and the crude reaction mixture was treated with our cross-coupling conditions.

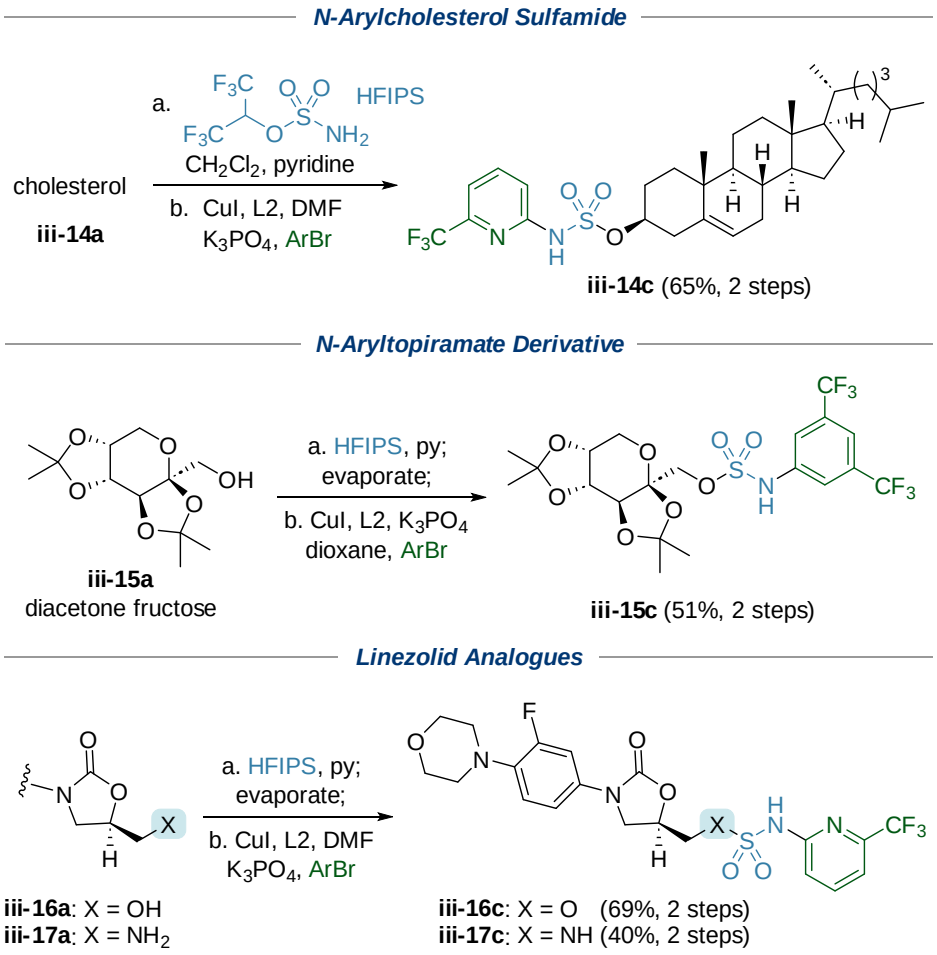


Figure 3-4: One-pot sulfamoylation and *N*-arylation.

We were able to synthesize *N*-heteroaryl cholesterol sulfamate **iii-14c** in a 65% yield

over two steps. When the alcohol precursor to the FDA-approved drug topiramate was subjected to the two step one-pot conditions, *N*-aryl topiramate **iii-15c** was synthesized in a 51% yield over two steps.[109] Lastly, when the amine and alcohol precursors of the FDA-approved drug linezolid were treated with our conditions, we were able to synthesize the *N*-heteroaryl sulfamate **iii-16c** and sulfamide **iii-17c** linezolid derivatives in 69% and 40% yields respectively. This two step one-pot procedure proved to be a powerful tool for the rapid functionalization of relevant alcohols and amines into their corresponding *N*-aryl sulfamates and sulfamides.

Although generally robust, there were unpredictable circumstances in which our chemistry failed to proceed. To help us rationalize potential issues, we found it appropriate to model the cross-coupling catalytic cycle and logically interpret the trends of our results (Figure 3-5). When searching for inconsistencies in the literature for previously reported copper-

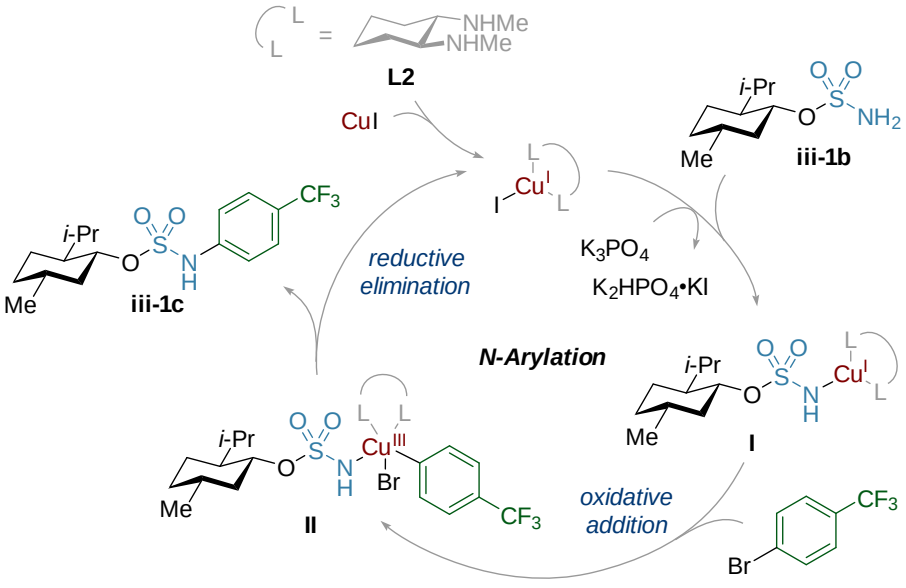


Figure 3-5: Mechanism for the *N*-arylation of sulfamates and sulfamides.

catalyzed arylations, we found that a CuI catalyzed heteroarylation of sulfonamides by Baffoe et al., noted issues with non-polar solvents, that were resolved once switching to DMF.[110] Interestingly, this paper focused solely on heteroaryl bromides, and we noticed a similar trend when these were employed with our chemistry. They determined experimentally that product inhibition was not significant, and they hypothesized that there were instability issues with the heteroaryl-metal catalytic intermediates (**II**). In our case, this instability appeared to be more prominent in dioxane, and was stabilized in DMF for certain substrates. This solvent change allowed us to couple both aryl and heteroaryl bromides and was predictable, however, sulfamate and sulfamide failures were not. Likewise, changing the sulfamate or sulfamide substrate can also cause stability issues to the catalytic cycle intermediates (**I** or **II**). This leads to potential amine-metal catalytic intermediates issues that may be resolved by further optimizations that were not explored. Moreover, a simple change to the more reactive aryl iodide may circumvent these issues by increasing the rate of the reaction, and not requiring prolonged intermediate stability.

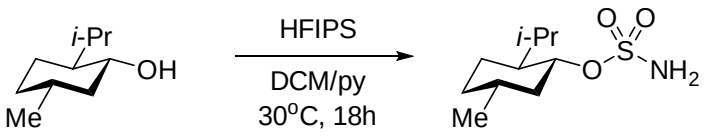
To summarize, we have disclosed a robust copper catalyzed *N*-arylation that is compatible with alkyl sulfamates, and unprotected and protected aryl and alkyl sulfamides. Furthermore, this *N*-arylation can be applied to in situ generated sulfamates and sulfamides allowing for one-pot reactions from alcohol and amine precursors.

3.2 Supporting Information

General Procedure A: Sulfamoylation of Alcohols and Amines - HFIPS (148 mg, 0.6 mmol) was added to a solution of alcohol or amine (0.5 mmol) in CH_2Cl_2 (2.5 mL) and pyridine (2.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (25 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture was chromatographed to provide sulfamate or sulfamide. (NOTE: an acidic workup with 1 M HCl could be performed instead of azeotroping with PhMe on stable substrates)

General Procedure B: *N*-Arylation of Sulfamates and Sulfamides - Sulfamate *or* sulfamide (0.30 mmol), (hetero)aryl halide (0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane or DMF (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O or 10% LiCl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography provided aryl sulfamates *or* sulfamides. (NOTE: dioxane was commonly employed as the solvent for sulfamate *N*-arylation and DMF for sulfamides)

L-Menthyl Sulfamate (iii-1b)

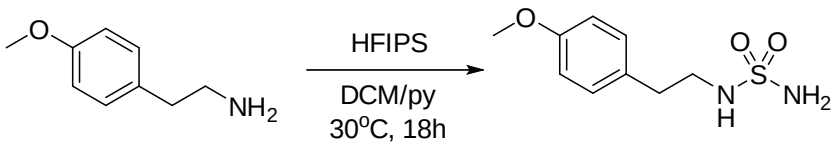


iii-1a **iii-1b**

According to General Procedure A, HFIPS (2.24 g, 9 mmol) was added to a solution of L-menthol **iii-1a** (1.17 g, 7.5 mmol) in CH_2Cl_2 (50 mL) and pyridine (20 mL) and stirred at 30 °C for 18 h. It was then quenched with 1M HCl (60 mL), extracted into CH_2Cl_2 (3 x 40 mL), the combined organic layers washed with 1M HCl (60 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→40% EtOAc/Hexanes) provided sulfamide **iii-1b** as a white powder (1.52 g, 86%).

R_f = 0.45 (20% EtOAc/Hex), visualized with PMA stain. Mp: 103–105 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.72–4.64 (brs, 2H), 4.44 (td, *J* = 10.9, 4.6 Hz, 1H), 2.37 (dddd, *J* = 12.2, 4.6, 3.4, 2.0 Hz, 1H), 2.12 (dsept, *J* = 2.5, 7.0 Hz, 1H), 1.72 (dq, *J* = 13.3, 3.4 Hz, 1H), 1.69 (dddt, *J* = 13.2, 3.5, 3.2, 2.0 Hz, 1H), 1.47 (ttq, *J* = 12.1, 6.5, 3.5 Hz, 1H), 1.41 (dddd, *J* = 12.2, 10.9, 3.6, 2.5, 1H), 1.24 (dt, *J* = 12.2, 11.0 Hz, 1H), 1.06 (app dq, *J* = 13.0, 3.3 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 84. 9, 47.8, 41.7, 34.0, 31.8, 25.8, 23.2, 22.1, 21.0, 15.9. Spectral data are consistent with data reported previously for this compound.[56]

2-(4-(methoxy)phenyl)ethyl sulfamide (iii-2b)

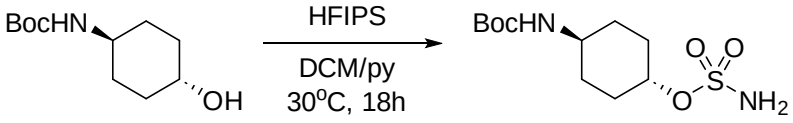


iii-2a **iii-2b**

According to General Procedure A, HFIPS (4.9 g, 19.8 mmol) was added to a solution of phenethylamine **iii-2a** (2.0 g, 13.2 mmol) in CH_2Cl_2/pyridine (3:7, 10 mL). After stirring the reaction mixture at 30 °C for 18 h, it was quenched with 1M HCl (30 mL), extracted into CH_2Cl_2 (3 x 20 mL), the combined organic layers washed with 1M HCl (30 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→60% EtOAc/Hexanes) provided sulfamide **iii-2b** as a pale grey solid powder (1.96 g, 63%).

R_f = 0.31 (50% EtOAc/Hex). Mp: 102.5-104.5 °C. ^{1}H NMR (700 MHz, MeOD): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.85 (s, 3H), 3.76 (s, 3H), 3.23 – 3.18 (m, 2H), 2.82 – 2.76 (m, 2H).^{13}C NMR (176 MHz, MeOD): δ 150.3, 122.9, 121.3 (2C), 105.4 (2C), 46.2, 36.6, 26.7. HRMS (ESI) *m/z*: 231.0798 calcd for $C_9H_{15}N_2O_3S^+$ $[M + H]^+$; Found 231.0799.

(1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl sulfamate (iii-3b)



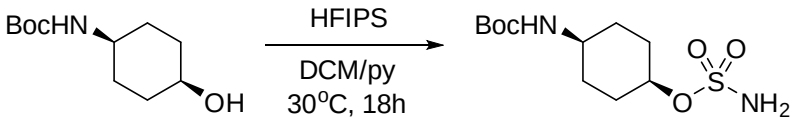
iii-3a **iii-3b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of tert-butyl ((1r,4r)-4-hydroxycyclohexyl)carbamate (161 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) and pyridine (2.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (25 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude

mixture chromatographed (0→60% EtOAc/Hex) to provide sulfamate **iii-3b** as a white powder (180 mg, 81%).

R_f = 0.42 (50% EtOAc/Hex), visualized with PMA stain. ^{1}H NMR (700 MHz, acetone-d_6): δ 6.62–6.55 (brs, 2H), 5.90–5.82 (brs, 1H), 4.43 (tt, *J* = 10.6, 4.3 Hz, 1H), 3.43–3.35 (m, 1H), 2.17–2.11 (m, 2H), 2.00–1.93 (m, 2H), 1.58 (ddt, *J* = 13.1, 10.6, 3.7 Hz, 2H), 1.39 (s, 9H), 1.37–1.32 (m, 2H).^{13}C NMR (176 MHz, acetone-d_6): δ 155.9, 80.0, 78.5, 48.9, 31.6 (2C), 31.0 (2C), 28.6 (3C). Spectral data are consistent with data reported previously for this compound.[56]

(1s,4s)-4-((tert-butoxycarbonyl)amino)cyclohexyl sulfamate (iii-4b)

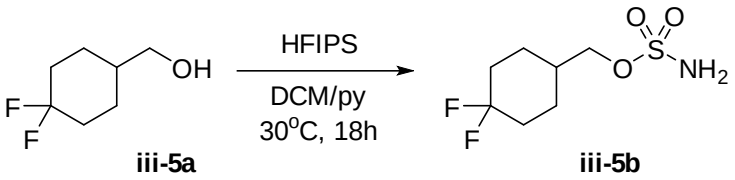


iii-4a **iii-4b**

According to General Procedure A, HFIPS (148 mg, 0.6 mmol) was added to a solution of tert-butyl ((1s,4s)-4-hydroxycyclohexyl)carbamate **iii-4a** (161 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) and pyridine (2.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (25 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→60% EtOAc/Hex) to provide sulfamate **iii-4b** as a white powder (177 mg, 80%).

R_f = 0.42 (50% EtOAc/Hex), visualized with PMA stain. ^{1}H NMR (700 MHz, acetone-d_6): δ 6.64–6.51 (brs, 2H), 5.96–5.84 (brs, 1H), 4.72–4.65 (brs, 1H), 3.49–3.39 (m, 1H), 2.04–1.99 (m, 2H), 1.76–1.67 (m, 4H), 1.64–1.55 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (176 MHz, acetone-d_6): δ 155.9, 78.4, 77.6, 48.6, 29.9 (2C), 28.6 (3C), 28.1 (2C). Spectral data are consistent with data reported previously for this compound.[56]

(4,4-Difluorocyclohexyl)methyl sulfamate (iii-5b)

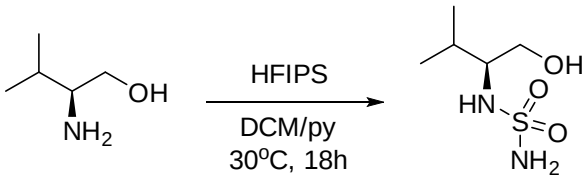


iii-5a **iii-5b**

According to General Procedure A, HFIPS (2.24 g, 9 mmol) was added to a solution of (4,4-difluorocyclohexyl)methanol **iii-5a** (81 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) and pyridine (2.5 mL) and stirred at 30 °C for 18 h. The reaction mixture was diluted with PhMe (25 mL) and concentrated under reduced pressure via rotary evaporation at 50 °C and the crude mixture chromatographed (0→50% EtOAc/Hex) to provide sulfamate **iii-5b** as a clear oil (97 mg, 80%).

R_f = 0.35 (33% EtOAc/Hex), visualized with PMA stain. ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.84–4.73 (brs, 2H), 4.07 (d, J = 6.3 Hz, 2H), 2.17–2.10 (m, 2H), 1.91–1.82 (m, 3H), 1.73 (app dddt, $^3J_{HF}$ = 33 Hz, J = 13.6, 13.2, 4 Hz, 2H), 1.39 (app dddt, J = 14, 12, 4, 2 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 123.1 (dd, $^1J_{CF}$ = 242.6 Hz, $^1J_{CF}$ = 239.6 Hz), 74.6 (d, $^5J_{CF}$ = 3.2 Hz), 35.5 (d, $^4J_{CF}$ = 1.8 Hz), 33.0 (dd, $^2J_{CF}$ = 25.7 Hz, $^2J_{CF}$ = 23.2 Hz), 25.4 (d, $^3J_{CF}$ = 9.6 Hz). ^{19}F NMR (659 MHz, $CDCl_3$): δ –92.5 (d, $^2J_{FF}$ = 237 Hz), –102.7 (d, $^2J_{FF}$ = 237 Hz). Spectral data are consistent with data reported previously for this compound.[56]

***N*-Sulfamoyl L-valinol (iii-8b)**



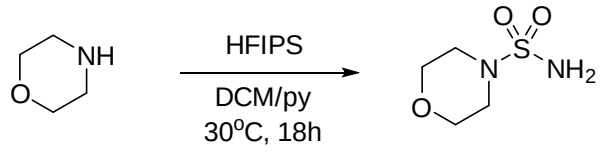
iii-8a **iii-8b**

According to General Procedure A, HFIPS (897 mg, 3.63 mmol) was added to a solution

of amino alcohol **iii-8a** (250 mg, 2.42 mmol) in CH_2Cl_2/pyridine (3:7, 5 mL). After stirring the reaction mixture at 30 °C for 18 h, it was quenched with 1M HCl (15 mL), extracted into CH_2Cl_2 (3 x 20 mL), the combined organic layers washed with 1M HCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→100% EtOAc/Hexanes) provided sulfamide **iii-8b** as a white powder (107 mg, 24%).

R_f = 0.37 (100% EtOAc). ^{1}H NMR (700 MHz, DMSO-d_6): δ 6.41–6.38 (s, 2H), 6.19 (d, J = 8.6 Hz, 1H), 4.53 (t, J = 5.5 Hz, 1H), 3.48 (dt, J_{gem} = 10.9, J = 5.5 Hz, 1H), 3.42 (ddd, J_{gem} = 10.9, 6.5, 5.5 Hz, 1H), 2.99 (ddt, J = 8.6, 6.5, 5.2 Hz, 1H), 1.86 (dp, J = 6.9, 5.2 Hz, 1H), 0.88 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 61.4, 59.7, 27.9, 19.5, 17.5. Spectral data are consistent with data reported previously for this compound.[56]

4-Morpholinesulfonamide (iii-9b)



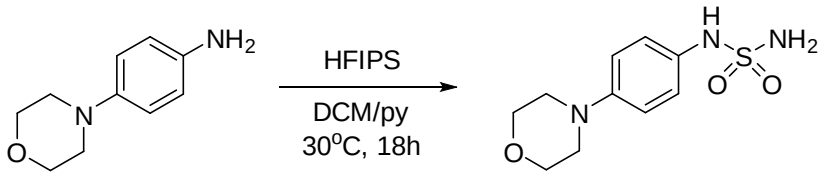
iii-9a **iii-9b**

According to General Procedure A, HFIPS (185 mg, 0.75 mmol) was added to a solution of morpholine **iii-9a** (40 μL, 0.50 mmol) in CH_2Cl_2/pyridine (3:7, 10 mL). After stirring the reaction mixture at 30 °C for 18 h, it was quenched with 1M HCl (30 mL), extracted into CH_2Cl_2 (3 x 20 mL), the combined organic layers washed with 1M HCl (30 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided sulfamide **iii-9b** as a yellow powder (78 mg, 94%).

R_f = 0.30 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (s, 1H), 3.66 – 3.61 (m, 2H), 2.94 – 2.87 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 65.28 (2C), 45.98 (2C). Spectral data

are consistent with data reported previously for this compound.[37]

4-morpholinosulfamide (iii-10b)

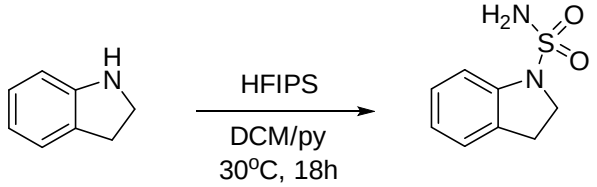


iii-10a **iii-10b**

According to General Procedure A, HFIPS (1.48 g, 6 mmol) was added to a solution of aniline **iii-10a** (890 mg, 5 mmol) in CH_2Cl_2/pyridine (3:7, 20 mL). After stirring the reaction mixture at 30 °C for 18 h, it was quenched with 1M HCl (20 mL), extracted into CH_2Cl_2 (3 x 20 mL), the combined organic layers washed with 1M HCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→10% CH_2Cl_2/MeOH) provided sulfamide **iii-10b** as a grey powder (1.28 g, 69%).

R_f = 0.42 (10% CH_2Cl_2/MeOH). Mp: 173–176 °C. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.94 (s, 1H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.84 (s, 2H), 3.77 – 3.69 (m, 4H), 3.05 – 2.97 (m, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 147.3, 131.5, 121.2 (2C), 115.8 (2C), 66.1 (2C), 49.2 (2C). HRMS (ESI) *m/z*: 258.0907 calcd for $C_{10}H_{16}N_3O_3S^+$ [M + H]$^+$; Found 258.0915.

***N*-Sulfamoyl indoline (iii-11b)**



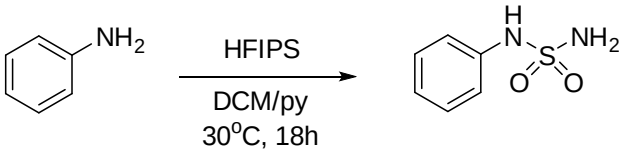
iii-11a **iii-11b**

According to General Procedure A, HFIPS (341 mg, 1.24 mmol) was added to a solution

of indoline **iii-11a** (100 mg, 0.83 mmol) in CH_2Cl_2/pyridine (3:7, 5 mL). After stirring the reaction mixture at 30 °C for 18 h, it was quenched with 1M HCl (10 mL), extracted into CH_2Cl_2 (3 x 20 mL), the combined organic layers washed with 1M HCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided sulfamide **iii-11b** as a white powder (111 mg, 67%).

R_f = 0.18 (30% EtOAc/Hex). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, J = 8.0 Hz, 1H), 7.23 (brs, 2H), 7.21 (d, J = 7.9 Hz, 1H), 7.15 (t, J = 7.7 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 3.79 (t, J = 8.4 Hz, 2H), 3.04 (t, J = 8.4 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 143.0, 131.5, 127.2, 125.0, 122.4, 113.7, 49.9, 27.3. Spectral data are consistent with data reported previously for this compound.[56]

Phenylsulfamide (iii-12b)



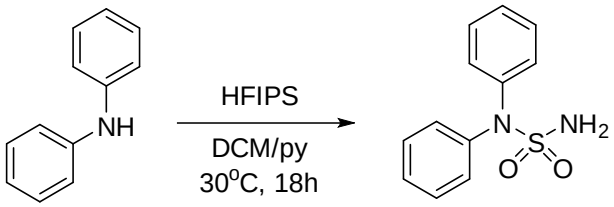
iii-12a **iii-12b**

According to General Procedure A, HFIPS (1.90 g, 8.05 mmol) was added to a solution of aniline **iii-12a** (500 mg, 5.40 mmol) in CH_2Cl_2/pyridine (3:7, 10 mL). After stirring the reaction mixture at 30 °C for 18 h, it was quenched with 1M HCl (30 mL), extracted into CH_2Cl_2 (3 x 20 mL), the combined organic layers washed with 1M HCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided sulfamide **iii-12b** as a white powder (490 mg, 53%).

R_f = 0.50 (50% EtOAc/Hex). ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.26 (dd, J = 8.5,

7.4 Hz, 2H), 7.15 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.07 (s, 2H), 6.96 (tt, *J* = 7.4, 1.1 Hz, 1H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 139.50, 128.76 (2C), 121.85, 117.94 (2C). Spectral data are consistent with data reported previously for this compound.[111]

Diphenylsulfamide (iii-13b)

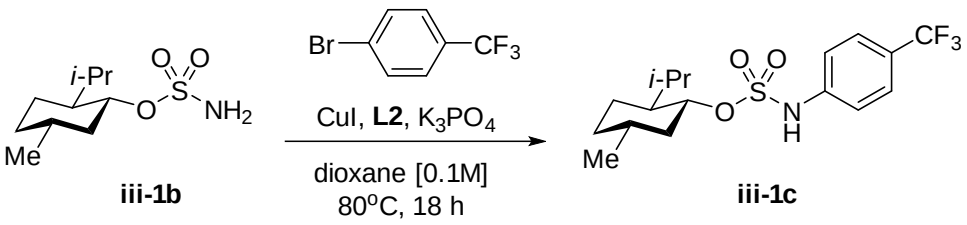


iii-13a **iii-13b**

According to General Procedure A, HFIPS (485 mg, 1.77 mmol) was added to a solution of diphenyl aniline **iii-13a** (200 mg, 1.18 mmol) in CH_2Cl_2/pyridine (3:7, 5 mL). After stirring the reaction mixture at 30 °C for 18 h, it was quenched with 1M HCl (10 mL), extracted into CH_2Cl_2 (3 x 20 mL), the combined organic layers washed with 1M HCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided sulfamide **iii-13b** as a white powder (81 mg, 28%).

R_f = 0.57 (50% EtOAc/Hex). Mp: 145–147 °C. ^{1}H NMR (700 MHz, Acetone-d_6) δ 7.47 – 7.43 (m, 4H), 7.38 – 7.34 (m, 4H), 7.26 – 7.22 (m, 2H), 6.67 (s, 2H). ^{13}C NMR (176 MHz, Acetone-d_6) δ 144.2 (2C), 129.8 (4C), 128.5 (4C), 127.2 (2C). HRMS (ESI) *m/z*: 249.0692 calcd for $C_{12}H_{13}N_2O_2S^+$ $[M + H]^+$; Found 249.0695.

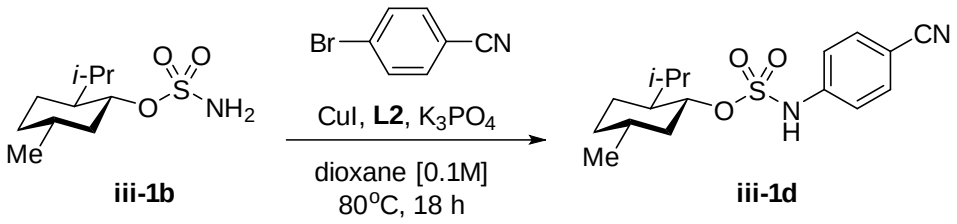
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-(trifluoromethyl)phenyl)sulfamate (iii-1c)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 1-bromo-4-(trifluoromethyl)benzene (86 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamate **iii-1c** as a white powder (100 mg, 88%).

R_f = 0.34 (25% EtOAc/Hex), visualized with PMA stain. Mp: 89-91 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.71 (s, 1H), 4.50 (td, *J* = 10.9, 4.5 Hz, 1H), 2.22 (dddd, *J* = 12.2, 5.1, 3.7, 1.9 Hz, 1H), 1.92 (dqd, *J* = 9.5, 7.0, 3.5 Hz, 1H), 1.71 – 1.63 (m, 2H), 1.46 – 1.38 (m, 2H), 1.21 – 1.13 (m, 1H), 1.01 (qd, *J* = 12.9, 3.3 Hz, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.87 – 0.84 (m, 1H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.68 (d, *J* = 6.9 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.75 (3F). ^{13}C NMR (176 MHz, $CDCl_3$) δ 139.95, 126.82 (q, $^3J_{CF}$ = 3.6 Hz, 3C), 124.07 (q, $^1J_{CF}$ = 271.5 Hz), 118.85 (2C), 86.43, 47.77, 41.36, 33.77, 31.83, 25.52, 23.13, 21.98, 20.87, 15.63. HRMS (ESI) *m/z*: 378.1356 calcd for $C_{17}H_{23}F_3NO_3S^-$; $[M - H]^-$ 378.1370 obsd.

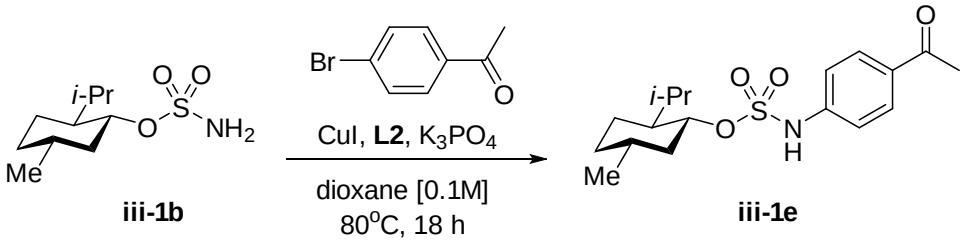
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-cyanophenyl)sulfamate (iii-1d)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 4-bromobenzonitrile (69 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamate **iii-1d** as a white powder (86 mg, 82%).

R_f = 0.45 (25% EtOAc/Hex), visualized with PMA stain. Mp: 191-195 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H), 7.24 – 7.21 (m, 2H), 6.94 (s, 1H), 4.51 (td, *J* = 10.9, 4.6 Hz, 1H), 2.23 (dddd, *J* = 12.1, 5.1, 3.4, 1.9 Hz, 1H), 1.93 (heptd, *J* = 7.0, 2.4 Hz, 1H), 1.71 – 1.64 (m, 2H), 1.44 – 1.38 (m, 2H), 1.22 – 1.14 (m, 1H), 1.02 (qd, *J* = 13.1, 3.4 Hz, 1H), 0.93 (dd, *J* = 9.2, 6.8 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.69 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 140.97, 133.75 (2C), 118.59, 118.48 (2C), 107.64, 86.83, 47.74, 41.33, 33.72, 31.84, 25.55, 23.13, 21.99, 20.87, 15.64. HRMS (ESI) *m/z*: 335.1435 calcd for $C_{17}H_{23}N_2O_3S^-$; $[M-H]^-$ 335.1447 obsd.

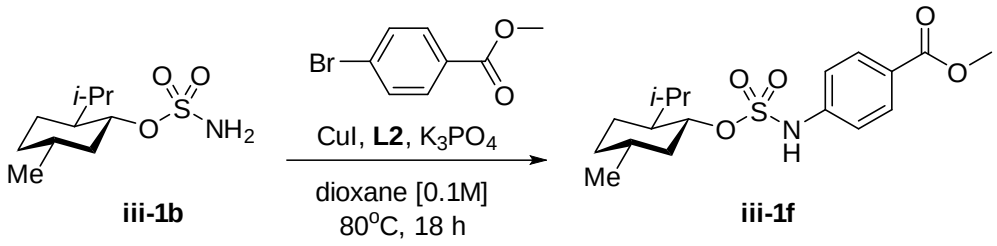
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-acetylphenyl)sulfamate (iii-1e)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 1-(4-bromophenyl)ethan-1-one (76 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→35% EtOAc/Hexanes) provided aryl sulfamate **iii-1e** as a white powder (75 mg, 71%).

R_f = 0.20 (20% EtOAc/Hex), visualized with PMA stain. Mp: 140-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 2H), 7.24 – 7.16 (m, 2H), 6.97 (s, 1H), 4.50 (td, *J* = 10.9, 4.5 Hz, 1H), 2.58 (s, 3H), 2.24 (dddd, *J* = 12.1, 5.0, 3.4, 1.8 Hz, 1H), 1.97 (pd, *J* = 7.0, 2.4 Hz, 1H), 1.75 – 1.59 (m, 2H), 1.41 (dddd, *J* = 14.7, 10.7, 3.9, 1.9 Hz, 2H), 1.18 (td, *J* = 12.2, 11.0 Hz, 1H), 1.10 – 0.95 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.88 – 0.79 (m, 4H), 0.69 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.93, 141.20, 133.14, 130.18 (2C), 117.91 (2C), 86.42, 47.76, 41.32, 33.77, 31.83, 26.60, 25.50, 23.13, 22.01, 20.91, 15.66. HRMS (ESI) *m/z*: 352.1588 calcd for $C_{18}H_{26}NO_4S^-$; $[M - H]^-$ 352.1599 obsd.

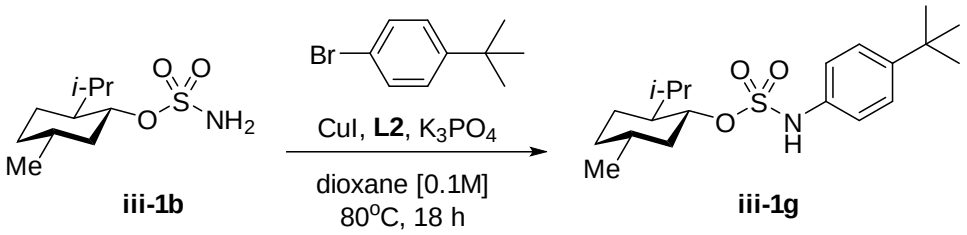
Methyl 4-(((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)sulfonyl)amino)benzoate (iii-1f)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 4-bromobenzoate (82 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→20% EtOAc/Hexanes) provided aryl sulfamate **iii-1f** as a white powder (95 mg, 86%).

R_f = 0.22 (15% EtOAc/Hex), visualized with PMA stain. Mp: 132-134 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.02 - 8.01 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.99 (s, NH), 4.49 (td, *J* = 10.9, 4.5 Hz, 1H), 3.91 (s, 3H), 2.25 – 2.22, m (1H), 1.99 – 1.93 (m, 1H), 1.70 – 1.63 (m, 2H), 1.45 – 1.37 (m, 2H), 1.17 (dd, *J* = 23.4, 12.2 Hz, 1H), 1.01 (qd, *J* = 13.1, 3.2 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.86 - 0.84 (m, 1H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.68 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.59, 141.05, 131.28 (2C), 125.96, 117.86 (2C), 86.36, 52.29, 47.76, 41.32, 33.77, 31.81, 25.47, 23.11, 21.99, 20.89, 15.63. HRMS (ESI) *m/z*: 368.1537 calcd for $C_{18}H_{26}NO_5S^-$; $[M-H]^-$ 368.1549 obsd.

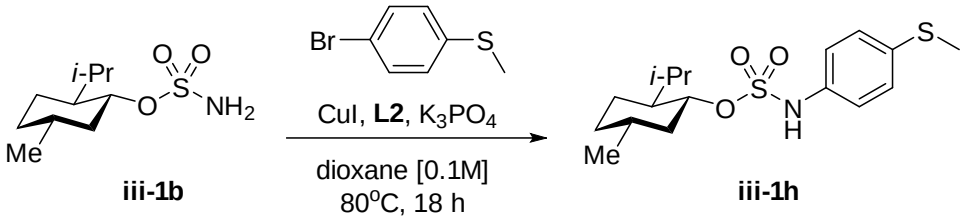
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-(tert-butyl)phenyl)sulfamate (iii-1g)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 1-bromo-4-(tert-butyl)benzene (69 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→10% EtOAc/Hexanes) provided aryl sulfamate **iii-1g** as a white powder (88 mg, 80%).

R_f = 0.55 (10% EtOAc/Hex), visualized with PMA stain. Mp: 81-83 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.08 – 7.03 (m, 2H), 6.52 – 6.45 (m, 1H), 4.35 (td, *J* = 10.9, 4.5 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.83 (dqd, *J* = 13.9, 7.0, 2.5 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.36 – 1.26 (m, 2H), 1.23 (s, 9H), 1.06 (td, *J* = 12.3, 11.0 Hz, 1H), 0.96 – 0.89 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.79 – 0.74 (m, 1H), 0.73 (d, *J* = 7.0 Hz, 3H), 0.57 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 148.43, 133.89, 126.28 (2C), 120.73 (2C), 85.48, 77.34, 77.16, 76.98, 47.79, 41.46, 34.53, 33.88, 31.75, 31.48 (3C), 25.41, 23.11, 22.01, 20.93, 15.65. HRMS (ESI) m/z: 366.2108 calcd for $C_{20}H_{32}NO_3S^-$; $[M - H]^-$ 366.2121 obsd.

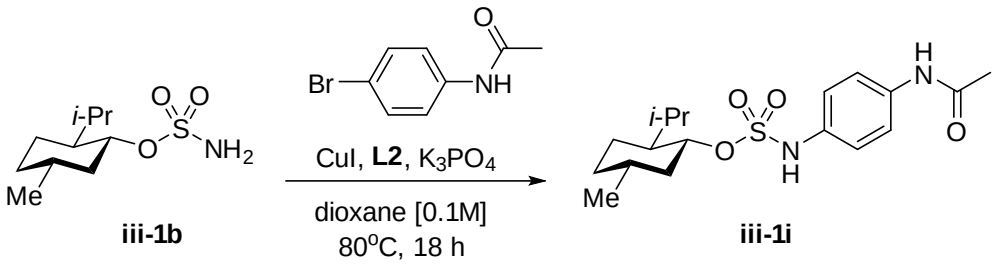
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-(methylthio)phenyl)sulfamate (iii-1h)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), (4-bromophenyl)(methyl)sulfane (77 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→15% EtOAc/Hexanes) provided aryl sulfamate **iii-1h** as a white powder (43 mg, 40%).

R_f = 0.70 (20% EtOAc/Hex), visualized with PMA stain. Mp: 86-88 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.60 (s, NH), 4.44 (td, *J* = 10.9, 4.5 Hz, 1H), 2.47 (s, 3H), 2.21 – 2.18 (m, 1H), 1.96 – 1.90 (m, 1H), 1.69 – 1.63 (m, 2H), 1.44 – 1.35 (m, 2H), 1.14 (dd, *J* = 23.5, 12.1 Hz, 1H) 1.00 (qd, *J* =13.0, 3.2 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 – 0.81 (m, 4H), 0.68 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 135.11, 134.11, 128.25 (2C), 121.31 (2C), 85.71, 47.77, 41.43, 33.84, 31.77, 25.48, 23.12, 22.01, 20.92, 16.70, 15.67. HRMS (ESI) *m/z*: 356.1360 calcd for $C_{17}H_{26}NO_3S_2^-$; $[M - H]^-$ 356.1371 obsd.

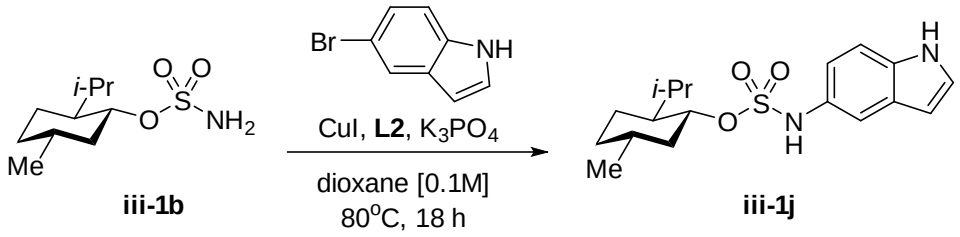
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-acetamidophenyl)sulfamate (iii-1i)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), N-(4-bromophenyl)acetamide (81 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamate **iii-1i** as a yellow powder (91 mg, 82%).

R_f = 0.38 (50% EtOAc/Hex), visualized with PMA stain. Mp: (decomp.) 296-300 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.34 (s, NH), 7.14 (d, *J* = 8.8 Hz, 2H), 6.84 (s, NH), 4.44 (td, *J* = 10.9, 4.5 Hz, 1H), 2.22 – 2.20 (m, 1H), 2.17 (s, 3H), 1.99 – 1.93 (m, 1H), 1.68 – 1.63 (m, 2H), 1.43 – 1.35 (m, 2H), 1.14 (dd, *J* = 23.5, 12.1 Hz, 1H), 1.00 (qd, *J* = 12.9, 3.1 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.83 – 0.81, (m, 1H), 0.69 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, $CDCl_3$): δ 168.61, 135.19, 132.83, 121.50 (2C), 120.99 (2C), 85.54, 47.78, 41.42, 33.85, 31.77, 25.50, 24.63, 23.13, 22.02, 20.93, 15.68. HRMS (ESI) *m/z*: 367.1697 calcd for $C_{18}H_{27}N_2O_4S^-$; $[M - H]^-$ 367.1707 obsd.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (1H-indol-5-yl)sulfamate (iii-1j)

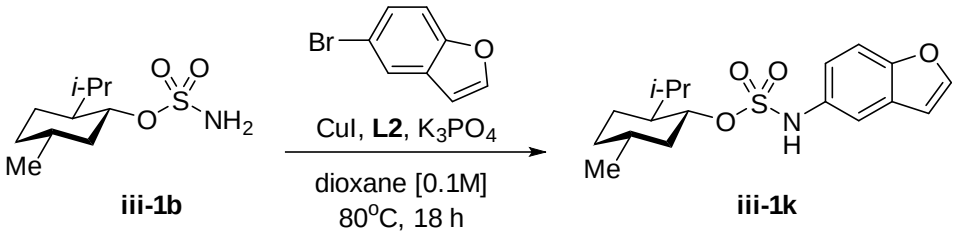


iii-1b **iii-1j**

According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 5-bromo-1H-indole (74 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→25% EtOAc/Hexanes) provided aryl sulfamate **iii-1j** as a yellow powder (40 mg, 38%).

R_f = 0.22 (20% EtOAc/Hex), visualized with PMA stain. Mp: (decomp.) 325-330 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.19 (s, NH), 7.54 (d, *J* = 1.9 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.24 – 7.23 (m, 1H) 7.09 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.53 (ddd, *J* = 3.0, 2.0, 0.8 Hz, 1H), 6.38 (s, NH), 4.42 (td, *J* = 10.9, 4.5 Hz, 1H), 2.18 – 2.15 (m, 1H), 1.96 – 1.89 (m, 1H), 1.65 – 1.60 (m, 2H), 1.41 – 1.34 (m, 2H), 1.12 (dd, *J* = 23.4, 12.2 Hz, 1H), 0.97 (qd, *J* = 12.9, 3.1 Hz, 1H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.81 – 0.79 (m, 1H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.61 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, $CDCl_3$): δ 134.27, 128.72, 128.36, 125.61, 118.45, 115.49, 111.55, 103.06, 85.13, 47.80, 41.55, 33.92, 31.73, 25.44, 23.11, 21.98, 20.92, 15.58. HRMS (ESI) *m/z*: 349.1591 calcd for $C_{18}H_{25}N_2O_3S^-$; $[M - H]^-$ 349.1605 obsd.

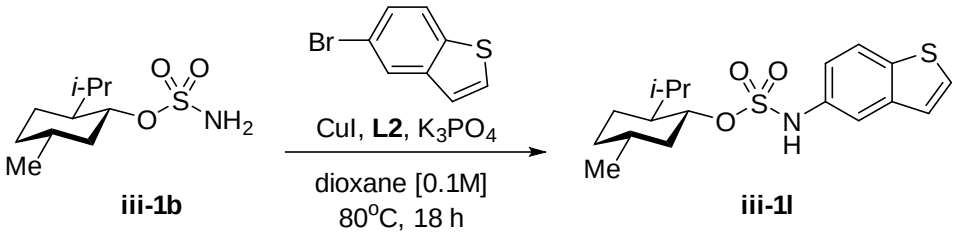
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzofuran-5-ylsulfamate (iii-1k)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 5-bromobenzofuran (75 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→15% EtOAc/Hexanes) provided aryl sulfamate **iii-1k** as a white powder (70 mg, 66%).

R_f = 0.71 (20% EtOAc/Hex), visualized with PMA stain. Mp: 102-104 °C. ^{1}H NMR (700 MHz, $CDCl_3$): 7.65 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.13 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.75 (dd, *J* = 2.1, 0.9 Hz, 1H), 6.48 (s, 1H), 4.44 (td, *J* = 10.9, 4.5 Hz, 1H), 2.19 – 2.16 (m, 1H), 1.91 – 1.86 (m, 1H), 1.67 -1.61 (m, 2H), 1.43 – 1.34 (m, 2H), 1.13 (dd, *J* = 23.4, 12.2 Hz, 1H), 0.98 (qd, *J* = 13.1, 3.0 Hz, 1H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.82 – 0.80 (m, 1H), 0.79 (d, *J* = 7.1 Hz, 3H), 0.61 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, $CDCl_3$): δ 152.95, 146.40, 131.64, 128.26, 119.27, 114.81, 111.94, 106.82, 85.49, 47.78, 41.51, 33.85, 31.73, 25.44, 23.09, 21.97, 20.88, 15.57. HRMS (ESI) *m/z*: 350.1432 calcd for $C_{18}H_{24}NO_4S^-$; $[M - H]^-$ 350.1447 obsd.

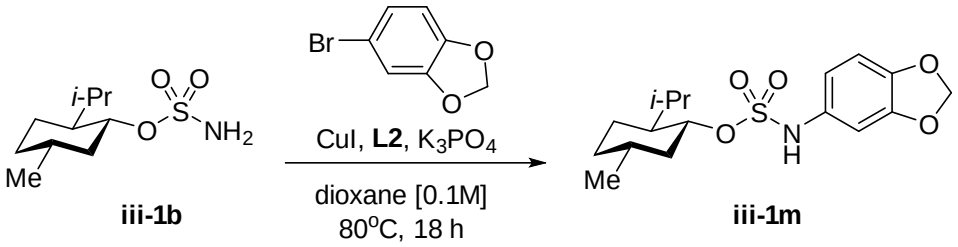
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzo[b]thiophen-5-ylsulfamate (iii-1l)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 5-bromobenzo[b]thiophene (81 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→25% EtOAc/Hexanes) provided aryl sulfamate **iii-1l** as a white powder (88 mg, 80%).

R_f = 0.28 (20% EtOAc/Hex), visualized with PMA stain. Mp 99-101 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.49 (d, *J* = 5.4 Hz, 1H), 7.30 (d, *J* = 5.4 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.89 (s, NH), 4.47 (td, *J* = 10.9, 4.5 Hz, 1H), 2.22 – 2.19 (m, 1H), 1.93 – 1.87 (m, 1H), 1.66 – 1.61 (m, 2H), 1.43 – 1.34 (m, 2H), 1.13 (dd, *J* = 23.4, 12.2 Hz, 1H), 0.98 (qd, *J* = 13.0, 3.2 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.80 (dd, *J* = 12.4, 2.8 Hz, 1H), 0.77 (d, *J* = 7.1 Hz, 3H), 0.62 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR DEPTQ (176 MHz, $CDCl_3$): δ 140.43, 136.72, 133.47, 128.26, 123.82, 123.28, 118.44, 115.56, 85.71, 47.78, 41.46, 33.83, 31.75, 25.43, 23.09, 21.97, 20.88, 15.59. HRMS (ESI) *m/z*: 366.1203 calcd for $C_{18}H_{24}NO_3S_2^-$; $[M - H]^-$ 366.1202 obsd.

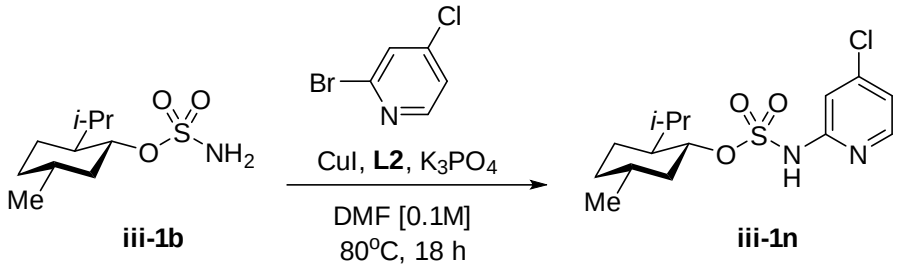
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzo[d][1,3]dioxol-5-ylsulfamate (iii-1m)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 5-bromobenzo[d][1,3]dioxole (76 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→20% EtOAc/Hexanes) provided aryl sulfamate **iii-1m** as a white powder (74 mg, 70%).

R_f = 0.64 (20% EtOAc/Hex), visualized with PMA stain. Mp: 62-65 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.82 (d, *J* = 2.2 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.56 (s, NH), 5.96 (s, 2H), 4.43 (td, *J* = 10.9, 4.5 Hz, 1H), 2.21 – 2.18 (m, 1H), 1.97 - 1.91 (m, 1H), 1.69 – 1.63 (m, 2H), 1.44 – 1.35 (m, 2H), 1.14 (dd, *J* = 23.4, 12.1 Hz, 1H), 1.00 (qd, *J* = 13.2, 3.0 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.83 – 0.80 (m, 1H), 0.69 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, $CDCl_3$): δ 148.28, 145.77, 130.41, 115.63, 108.37, 104.48, 101.69, 85.53, 47.78, 41.51, 33.87, 31.75, 25.50, 23.12, 22.01, 20.94, 15.67. HRMS (ESI) *m/z*: 354.1381 calcd for $C_{17}H_{24}NO_5S^-$; $[M - H]^-$ 354.1387 obsd.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-chloropyridin-2-yl)sulfamate (iii-1n)

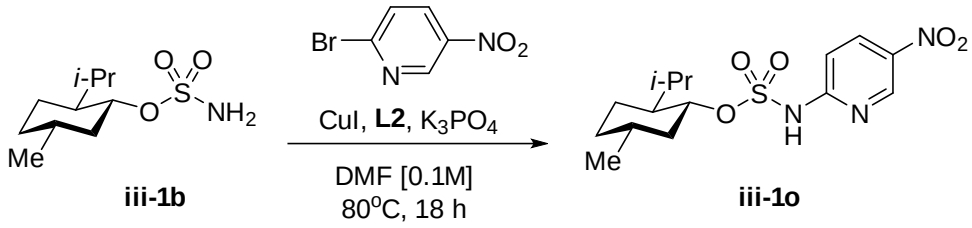


iii-1b **iii-1n**

According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 2-bromo-4-chloropyridine (73 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous DMF (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→25% EtOAc/Hexanes) provided aryl sulfamate **iii-1n** as a white powder (85 mg, 82%).

R_f = 0.30 (20% EtOAc/Hex), visualized with PMA stain. Mp: 124-126 °C. ^{1}H NMR (700 MHz, $CDCl_3$): 8.13 (d, J = 6.5 Hz, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 6.84 (dd, *J* = 6.6, 1.9 Hz, 1H), 4.40 (td, *J* = 10.9, 4.5 Hz, 1H), 2.39 – 2.36 (m, 1H), 2.06 – 2.01 (m, 1H), 1.70 – 1.65 (m, 2H), 1.45 – 1.36 (m, 2H), 1.19 (dd, *J* = 23.4, 12.1 Hz, 1H), 1.01 (qd, *J* = 13.0, 3.2 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.84 – 0.82 (m, 1H), 0.75 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, $CDCl_3$): δ 155.95, 150.87, 140.28, 115.97, 115.28, 83.62, 47.93, 41.75, 33.98, 31.83, 25.62, 23.10, 22.12, 21.03, 15.71. HRMS (ESI) *m/z*: 345.1045 calcd for $C_{15}H_{22}ClN_2O_3S^-$; $[M - H]^-$ 345.1053 obsd.

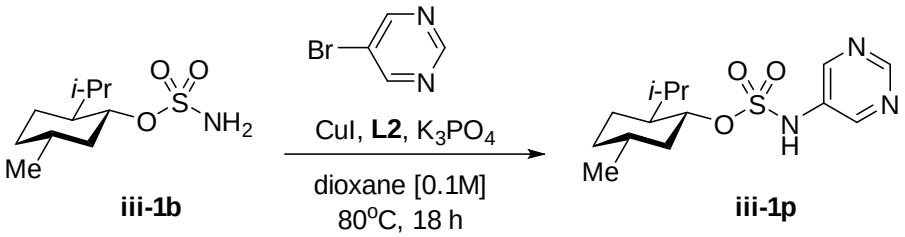
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (5-nitropyridin-2-yl)sulfamate (1o)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 2-bromo-5-nitropyridine (77 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous DMF (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→25% EtOAc/Hexanes) provided aryl sulfamate **iii-1o** as a white powder (47 mg, 44%).

R_f = 0.30 (20% EtOAc/Hex), visualized with PMA stain. Mp: 100-103 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.88 (br s, 1H), 9.29 (s, 1H), 8.55 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.57 (d, *J* = 9.2 Hz, 1H), 4.58 (td, *J* = 10.9, 4.5 Hz, 1H), 2.34 – 2.28 (m, 1H), 1.95 (heptd, *J* = 7.0, 2.5 Hz, 1H), 1.72 – 1.65 (m, 2H), 1.48 – 1.39 (m, 2H), 1.26 – 1.19 (m, 1H), 1.02 (qd, *J* = 13.1, 3.5 Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 – 0.86 (m, 1H), 0.85 (d, *J* = 7.1 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.38, 145.01, 140.25, 134.83, 111.30, 87.30, 47.74, 41.36, 33.68, 31.87, 25.70, 23.10, 21.99, 20.86, 15.63. HRMS (ESI) *m/z*: 356.1286 calcd for $C_{15}H_{22}N_3O_5S^-$; $[M - H]^-$ 356.1294 obsd.

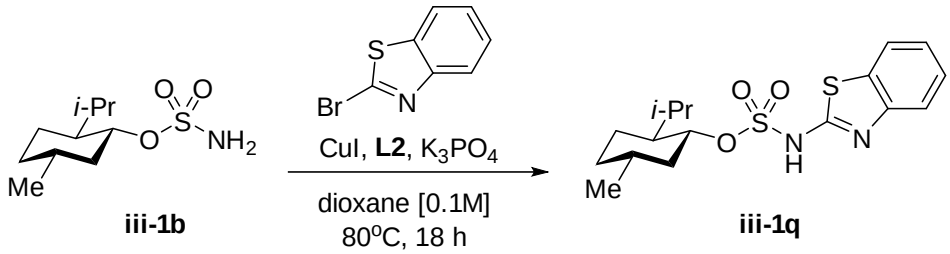
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl pyrimidin-5-ylsulfamate (iii-1p)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 5-bromopyrimidine (60 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→25% EtOAc/Hexanes) provided aryl sulfamate **iii-1p** as a white powder (58 mg, 62%).

R_f = 0.34 (33% EtOAc/Hex), visualized with PMA stain. Mp: 133-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.68 (s, 2H), 7.12 (s, 1H), 4.54 (td, *J* = 10.9, 4.5 Hz, 1H), 2.30 – 2.19 (m, 1H), 1.91 (pd, *J* = 7.0, 2.6 Hz, 1H), 1.79 – 1.62 (m, 2H), 1.55 – 1.36 (m, 2H), 1.20 (td, *J* = 12.1, 11.0 Hz, 1H), 1.02 (qd, *J* = 14.2, 13.7, 3.8 Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.84 – 0.79 (m, 1H), 0.71 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.98, 148.25 (2C), 132.55, 87.04, 47.73, 41.48, 33.72, 31.84, 25.70, 23.14, 21.98, 20.85, 15.58. HRMS (ESI) *m/z*: 312.1387 calcd for $C_{14}H_{22}N_3O_3S^-$; $[M - H]^-$ 312.1398 obsd.

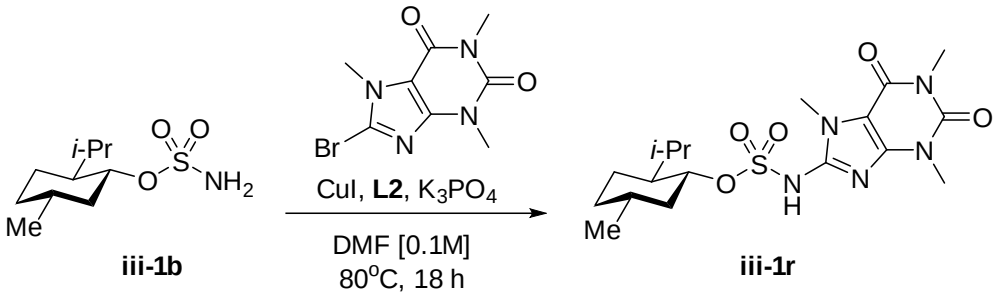
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzo[d]thiazol-2-ylsulfamate (iii-1q)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 2-bromobenzo[d]thiazole (81 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→10% EtOAc/Hexanes) provided aryl sulfamate **iii-1q** as a white powder (87 mg, 79%).

R_f = 0.63 (10% EtOAc/Hex), visualized with PMA stain. Mp: 122-125 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 11.86 (s, NH), 7.84 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 11.4, 4.2 Hz, 1H), 7.30 (dd, *J* = 11.3, 4.0 Hz, 1H), 4.44 (td, *J* = 10.9, 4.5 Hz, 1H), 2.44 – 2.41 (m, 1H), 2.15 – 2.09 (m, 1H), 1.67 – 1.61 (m, 2H), 1.38 – 1.33 (m, 2H), 1.21 (dd, *J* = 23.3, 12.1 Hz, 1H), 0.99 (qd, *J* = 13.0, 3.2 Hz, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.85 – 0.83 (m, 1H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR DEPTQ (176 MHz, $CDCl_3$): δ 170.18, 136.15, 127.80, 124.87, 124.58, 122.04, 114.67, 84.02, 47.91, 41.80, 33.97, 31.81, 25.60, 23.15, 22.10, 20.99, 15.86. HRMS (ESI) *m/z*: 367.1156 calcd for $C_{17}H_{23}N_2O_3S_2^-$; $[M - H]^-$ 367.1158 obsd.

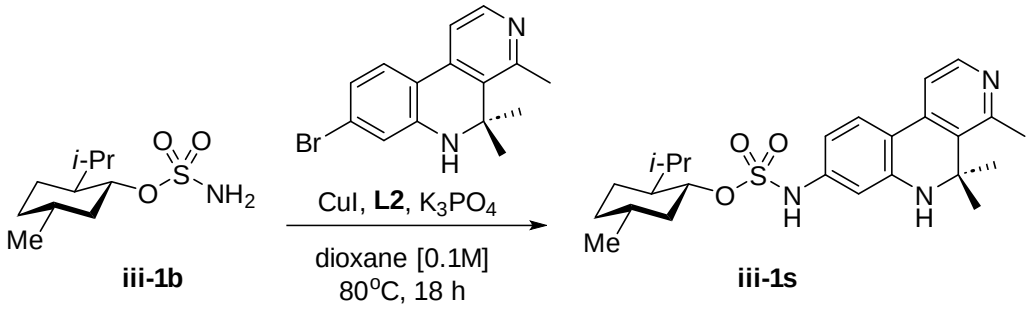
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)sulfamate (iii-1r)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 8-bromo-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (104 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous DMF (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→10% MeOH/DCM) provided aryl sulfamate **iii-1r** as a white powder (58 mg, 45%).

R_f = 0.51 (10% MeOH/DCM), visualized with PMA stain. Mp: (decomp.) 320-330 °C. ^{1}H NMR (700 MHz, DMSO-d_6) δ 4.09 (td, *J* = 10.7, 4.3 Hz, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 3.17 (s, 3H), 2.40 (dtd, *J* = 12.4, 4.0, 2.0 Hz, 1H), 2.36 (td, *J* = 6.9, 2.2 Hz, 1H), 1.62 – 1.51 (m, 2H), 1.38 – 1.27 (m, 1H), 1.18 – 1.10 (m, 1H), 0.99 – 0.88 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.81 – 0.76 (m, 4H), 0.57 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (176 MHz, DMSO) δ 154.28, 152.82, 151.08, 148.20, 101.04, 78.11, 47.64, 41.87, 39.88, 39.76, 39.64, 39.52, 39.40, 39.28, 39.16, 33.83, 31.07, 29.55, 29.11, 27.10, 24.23, 22.65, 22.13, 21.03, 15.67. HRMS (ESI) *m/z*: 426.1817 calcd for $C_{18}H_{28}N_5O_5S^-$; $[M - H]^-$ 426.1828 obsd.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4,5,5-trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridin-8-yl)sulfamate (iii-1s)



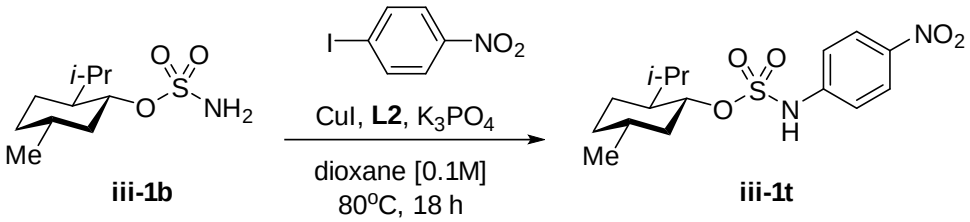
iii-1b **iii-1s**

According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), veranamine (115 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→10% MeOH/DCM) provided aryl sulfamate **iii-1s** as a yellow powder (62 mg, 45%).

R_f = 0.51 (10% MeOH/DCM), visualized with PMA stain. Mp: 108-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 4.8 Hz, 1H), 6.55 (d, *J* = 2.2 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.46 (td, *J* = 10.9, 4.5 Hz, 1H), 3.82 (br s, 1H), 2.69 (s, 3H), 2.32 – 2.22 (m, 1H), 2.03 – 1.95 (m, 1H), 1.71 – 1.65 (m, 2H), 1.64 (s, 3H), 1.61 (s, 3H), 1.48 – 1.35 (m, 2H), 1.18 (td, *J* = 12.2, 11.0 Hz, 1H), 1.01 (qd, *J* = 13.7, 3.7 Hz, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 – 0.80 (m, 4H), 0.70 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.22, 145.40, 144.59, 144.11, 139.14, 138.72, 138.51, 125.72, 115.52, 109.62, 104.57, 85.89, 77.48, 77.16, 76.84, 54.36, 47.80, 41.39, 33.84, 31.83, 29.99, 29.74, 26.96, 25.52, 23.16, 22.05, 20.97, 15.73. HRMS

(ESI) *m/z*: 456.2326 calcd for $C_{25}H_{34}N_3O_3S^-$; $[M - H]^-$ 456.2338 obsd.

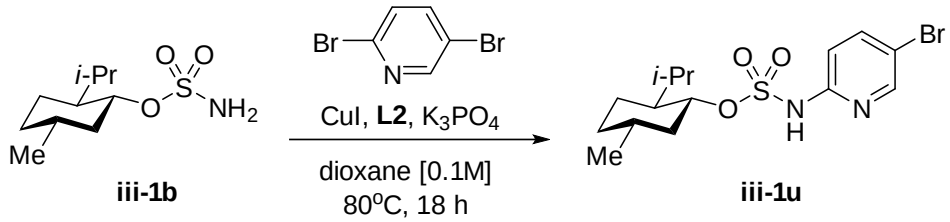
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (4-nitrophenyl)sulfamate (iii-1t)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 1-iodo-4-nitrobenzene (95 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamate **iii-1t** as a yellow powder (78 mg, 73%).

R_f = 0.22 (15% EtOAc/Hex), visualized with PMA stain. Mp: 94-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.19 (m, 2H), 7.43 – 7.34 (m, 1H), 7.30 – 7.23 (m, 2H), 4.54 (td, *J* = 10.9, 4.5 Hz, 1H), 2.29 – 2.18 (m, 1H), 1.95 (pt, *J* = 6.9, 3.4 Hz, 1H), 1.75 – 1.61 (m, 2H), 1.50 – 1.36 (m, 2H), 1.19 (td, *J* = 12.2, 11.0 Hz, 1H), 1.02 (qd, *J* = 13.4, 3.5 Hz, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.87 – 0.81 (m, 4H), 0.70 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.86, 142.78, 125.56 (2C), 117.81 (2C), 87.12, 47.73, 41.30, 33.68, 31.84, 25.56, 23.11, 21.98, 20.86, 15.63. HRMS (ESI) *m/z*: 355.1333 calcd for $C_{16}H_{23}N_2O_5S^-$; $[M - H]^-$ 355.1343 obsd.

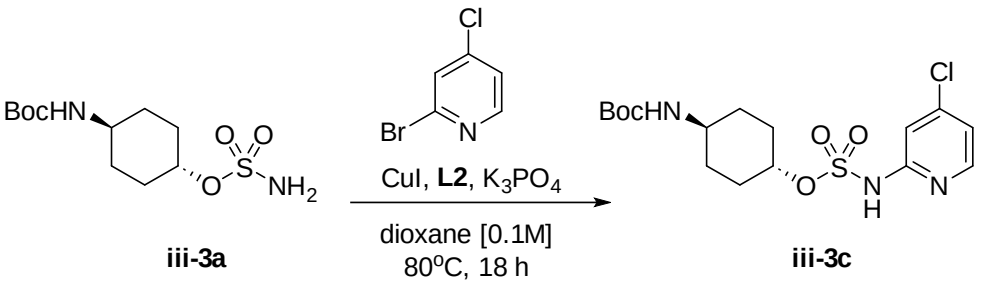
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (5-bromopyridin-2-yl)sulfamate (iii-1u)



According to General Procedure B, sulfamate **iii-1b** (71 mg, 0.30 mmol), 2,5-dibromopyridine (90 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→20% EtOAc/Hexanes) provided aryl sulfamate **iii-1u** as a white powder (82 mg, 70%).

R_f = 0.67 (20% EtOAc/Hex), visualized with PMA stain. Mp: 117-120 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.18 (br s, 1H), 8.45 (s, 1H), 7.83 (ddd, *J* = 8.9, 2.4, 0.7 Hz, 1H), 7.37 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.47 (td, *J* = 10.9, 4.5 Hz, 1H), 2.33 – 2.26 (m, 1H), 1.94 (hd, *J* = 6.9, 2.5 Hz, 1H), 1.73 – 1.60 (m, 2H), 1.44 – 1.32 (m, 1H), 1.17 (td, *J* = 12.2, 11.0 Hz, 1H), 1.00 (qd, *J* = 12.9, 3.3 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.88 – 0.80 (m, 4H), 0.69 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.24, 148.41, 141.93, 114.01, 113.70, 85.95, 77.34, 77.16, 76.98, 47.77, 41.33, 33.79, 31.83, 25.56, 23.10, 22.03, 20.94, 15.67. HRMS (ESI) *m/z*: 391.0540 calcd for $C_{15}H_{22}BrN_2O_3S^-$; $[M - H]^-$ 391.0529 obsd.

(1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl (4-chloropyridin-2-yl)sulfamate (iii-3c)

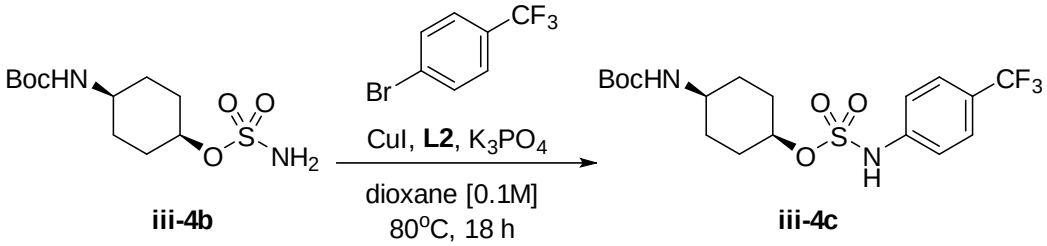


iii-3a **iii-3c**

According to General Procedure B, sulfamate **iii-3b** (71 mg, 0.30 mmol), 2-bromo-4-chloropyridine (73 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→5% MeOH/DCM) provided aryl sulfamate **iii-3c** as a grey powder (62 mg, 51%).

R_f = 0.66 (5% MeOH/DCM), visualized with PMA stain. Mp: 167-169 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 13.53 (app. br. s, 1H), 8.10 (app. br. s, 1H), 7.49 (app. br. s, 1H), 6.83 (app. br. s, 1H), 4.49 (app. br. s, 1H), 4.39 (s, 1H), 3.46 (app. br. s, 1H), 2.22 – 1.99 (m, 4H), 1.70- 1.60 (m, 2H), 1.43 (s, 9H), 1.28 – 1.19 (m, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 156.27, 155.30, 151.40, 139.87, 116.14, 115.18, 79.93, 79.62, 48.29, 30.92 (2C), 30.77 (2C), 28.54 (3C). HRMS (ESI) *m/z*: 404.1052 calcd for $C_{16}H_{23}ClN_3O_5S^-$; $[M - H]^+$ 404.1065 obsd.

(1s,4s)-4-((tert-butoxycarbonyl)amino)cyclohexyl (4-(trifluoromethyl)phenyl)sulfamate (iii-4c)

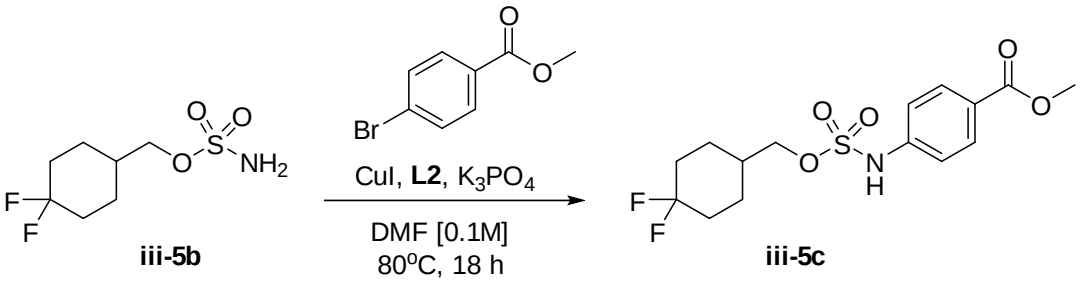


iii-4b **iii-4c**

According to General Procedure B, sulfamate **iii-4b** (71 mg, 0.30 mmol), 1-bromo-4-(trifluoromethyl)benzene (86 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hex) provided aryl sulfamate **iii-4c** as a white powder (106 mg, 81%).

R_f = 0.62 (50% EtOAc/Hex), visualized with PMA stain. Mp: 157-160 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.06 (br.s, 1H), 4.81 (tt, *J* = 4.8, 2.7 Hz, 1H), 4.45 (s, 1H), 3.49 (br.s, 1H), 2.02 – 1.93 (m, 2H), 1.85 – 1.74 (m, 2H), 1.66 (tt, *J* = 15.1, 3.4 Hz, 2H), 1.55 – 1.48 (m, 2H), 1.43 (s, 9H). ^{19}F NMR (659 MHz, $CDCl_3$) δ -62.73 (3F). ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.29, 139.95, 127.01 (q, $^3J_{CF}$ = 3.6 Hz, 2C), 126.57 (q, $^2J_{CF}$ = 33.4 Hz), 124.95 – 116.35 (app m), 118.21 (2C), 80.53, 79.65, 47.71, 29.46 (2C), 28.54 (3C), 27.56 (2C). HRMS (ESI) *m/z*: 437.1364 calcd for $C_{18}H_{24}F_3N_2O_5S^-$; $[M - H]^-$ 437.1379 obsd.

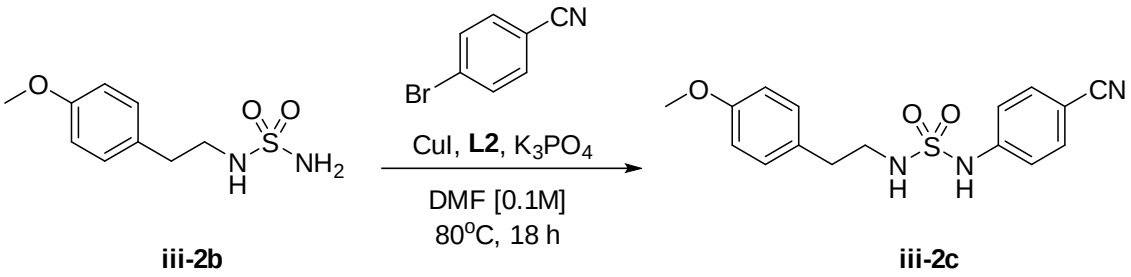
Methyl 4-((((4,4-difluorocyclohexyl)methoxy)sulfonyl)amino)benzoate (iii-5c)



According to General Procedure B, sulfamate **iii-5b** (71 mg, 0.30 mmol), 4-bromobenzoate (82 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous DMF (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→40% EtOAc/Hexanes) provided aryl sulfamate **iii-5c** as a white powder (56 mg, 52%).

R_f = 0.29 (33% EtOAc/Hex), visualized with PMA stain. Mp: 123-126 °C. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.05 – 7.89 (m, 2H), 7.33 – 7.19 (m, 2H), 4.02 (d, J = 6.2 Hz, 2H), 3.90 (s, 3H), 2.07 – 1.93 (m, 2H), 1.88 – 1.72 (m, 4H), 1.35 – 1.16 (m, 2H). ^{19}F NMR (377 MHz, Methanol-d_4) δ -91.89 (d), -102.36 (d). ^{13}C NMR (101 MHz, MeOD) δ 168.02, 143.76, 132.00 (2C), 126.61 – 120.38 (app m), 126.05, 118.49 (2C), 75.62 (d, $^5J_{CF}$ = 3.0 Hz), 52.52, 36.40 (d, $^4J_{CF}$ = 1.6 Hz), 33.72 (dd, $^2J_{CF}$ = 25.6, 23.4 Hz, 2C), 26.34 (d, $^3J_{CF}$ = 9.8 Hz, 2C). HRMS (ESI) *m/z*: 362.0879 calcd for $C_{15}H_{18}F_2NO_5S^-$; $[M - H]^-$ 362.0892 obsd.

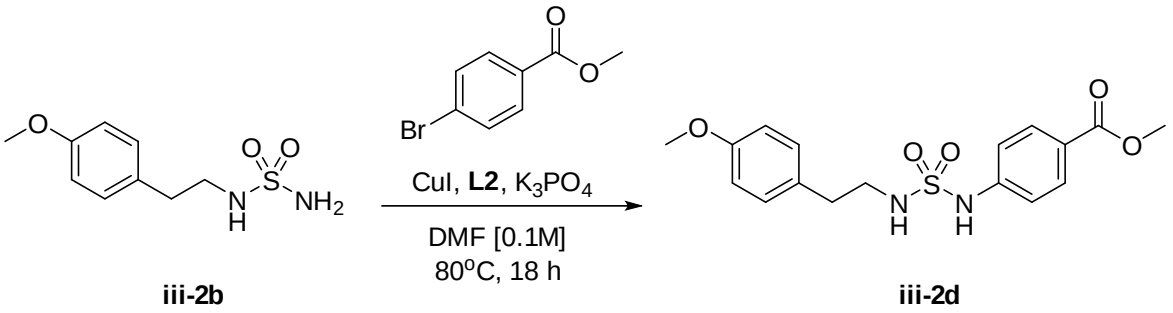
_N_-(4-cyanophenyl)-_N'_-(4-methoxyphenethyl)sulfamide (iii-2c)



According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 4-bromobenzonitrile (68 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamide **iii-2c** as a white powder (72 mg, 72%).

R_f = 0.37 (50% EtOAc/Hex). Mp: 113–115 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.01 (br s, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 4.57 (t, *J* = 5.1 Hz, 1H), 3.30 (q, *J* = 6.3 Hz, 2H), 2.73 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.8, 141.3, 133.8 (2C), 129.7 (2C), 129.0, 118.7, 118.0 (2C), 114.4 (2C), 107.0, 55.4, 44.6, 34.5. HRMS (ESI) *m/z*: 332.1063 calcd for $C_{16}H_{18}N_3O_3S^+$ $[M + H]^+$; Found 332.1072.

_N_-(4-methylbenzoate)-_N'_-(4-methoxyphenethyl)sulfamide (iii-2d)

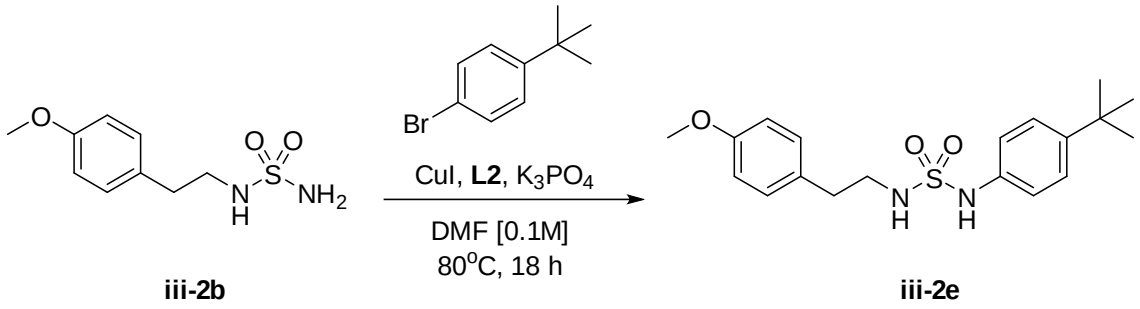


iii-2b **iii-2d**

According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 4-bromobenzoate (81 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamide **iii-2d** as a white powder (64 mg, 58%).

R_f = 0.46 (50% EtOAc/Hex). Mp: 83–85 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.85 (br s, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.54 (t, *J* = 5.6 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.28 (q, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.6, 158.7, 141.4, 131.4 (2C), 129.8 (2C), 129.2, 125.6, 117.5 (2C), 114.4 (2C), 55.4, 52.2, 44.6, 34.6. HRMS (ESI) *m/z*: 365.1166 calcd for $C_{17}H_{21}N_2O_5S^+$ $[M + H]^+$; Found 365.1173.

_N_-(4-_tert_-butylphenyl)-_N'_-(4-methoxyphenethyl)sulfamide (iii-2e)

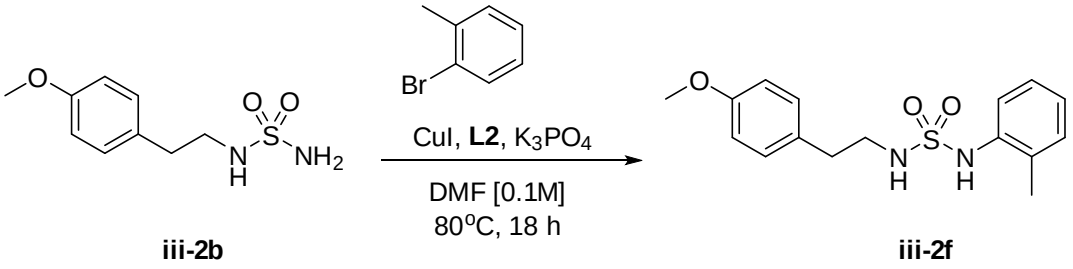


iii-2b **iii-2e**

According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 1-bromo-4-*tert*-butylbenzene (64 μL, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamide **iii-2e** as a yellow oil (42 mg, 38%).

R_f = 0.34 (30% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.58 (s, 1H), 4.45 (t, *J* = 6.0 Hz, 1H), 3.78 (s, 3H), 3.30 (q, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 1.30 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.6, 148.1, 134.4, 129.9 (2C), 129.7, 126.5 (2C), 120.4 (2C), 114.3 (2C), 55.4, 44.6, 34.8, 34.5, 31.5 (3C). HRMS (ESI) *m/z*: 363.1737 calcd for $C_{19}H_{27}N_2O_3S^+$ $[M + H]^+$; Found 363.1742.

_N_-(2-methylphenyl)-_N'_-(4-methoxyphenethyl)sulfamide (iii-2f)

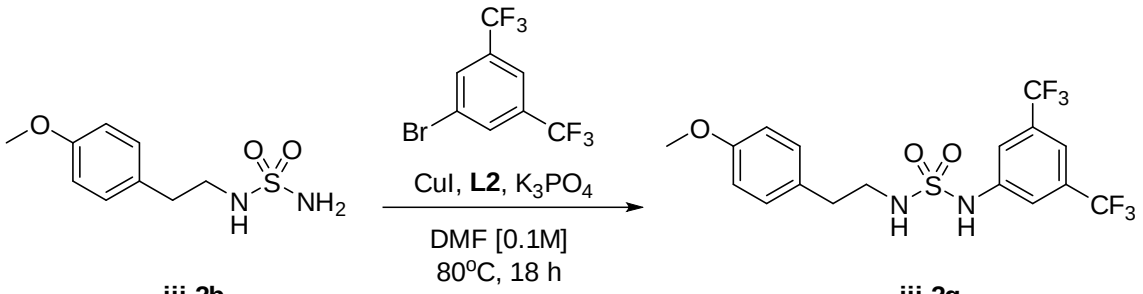


iii-2b **iii-2f**

According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 1-bromo-2-methylbenzene (40 μL, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamide **iii-2f** as a yellow oil (32 mg, 33%).

R_f = 0.40 (30% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 11.5, 4.0 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.25 (s, 1H), 4.46 (s, 1H), 3.78 (s, 3H), 3.28 (q, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.6, 135.4, 131.1, 129.8 (2C), 129.6, 128.9, 127.3, 125.2, 120.9, 114.4 (2C), 55.4, 44.7, 34.7, 17.9. HRMS (ESI) *m/z*: 321.1267 calcd for $C_{16}H_{21}N_2O_3S^+$ $[M + H]^+$; Found 321.1279.

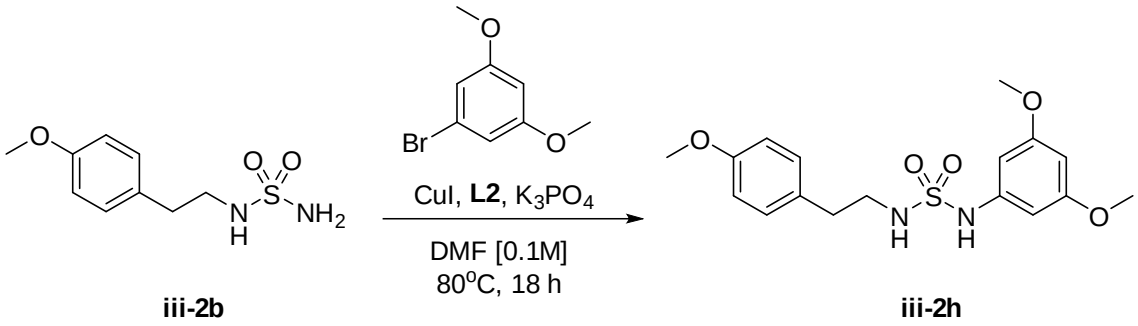
_N_-(3,5-bis(trifluoromethyl)phenyl)-_N'_-(4-methoxyphenethyl)sulfamide (iii-2g)



According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 1-bromo-3,5-bis(trifluoromethyl)benzene (64 μL, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamide **iii-2g** as white crystals (112 mg, 84%).

R_f = 0.48 (30% EtOAc/Hex). Mp: 88–89 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.49 (s, 2H), 7.41 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 4.74 (t, *J* = 5.3 Hz, 1H), 3.75 (s, 3H), 3.33 (q, *J* = 6.2 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.6, 138.8, 132.9 (q, $^2J_{CF}$ = 35.2 Hz, 2C), 129.5 (2C), 128.8, 123.0 (q, $^1J_{CF}$ = 272.4 Hz, 2C), 118.1 (d, $^3J_{CF}$ = 2.6 Hz, 2C), 117.3 (p, $^3J_{CF}$ = 3.7 Hz), 114.3 (2C), 55.2, 44.5, 34.4. ^{19}F NMR (659 MHz, $CDCl_3$) δ -63.6 (6F). HRMS (ESI) *m/z*: 465.0678 calcd for $C_{17}H_{17}F_6N_2O_3S^+$ $[M + H]^+$; Found 465.0692.

_N_-(3,5-bis(methoxy)phenyl)-_N'_-(4-methoxyphenethyl)sulfamide (iii-2h)

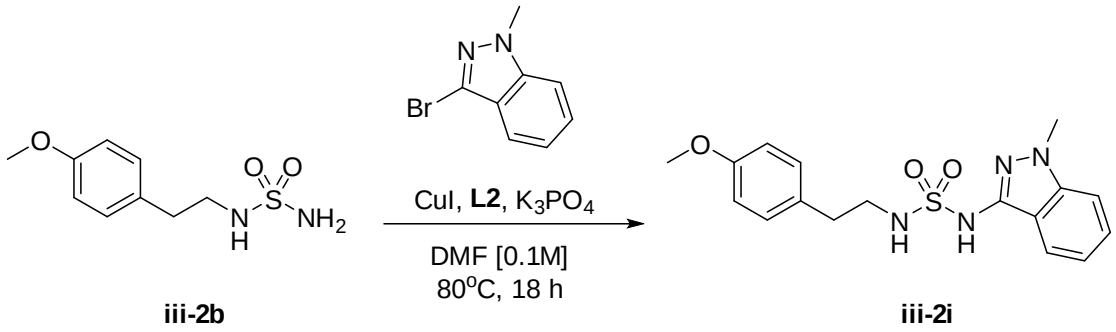


iii-2b **iii-2h**

According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 1-bromo-3,5-bis(methoxy)benzene (81 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamide **iii-2h** as a yellow oil (41 mg, 37%).

R_f = 0.23 (30% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.64 (s, 1H), 6.27 (d, *J* = 2.0 Hz, 2H), 6.22 (t, *J* = 1.9 Hz, 1H), 4.52 (t, *J* = 6.0 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 6H), 3.27 (q, *J* = 6.6 Hz, 2H), 2.72 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.7, 158.6, 139.0, 129.8 (2C), 129.4, 114.3 (2C), 97.7 (2C), 96.5, 55.5 (2C), 55.4, 44.5, 34.6. HRMS (ESI) *m/z*: 367.1322 calcd for $C_{17}H_{23}N_2O_3S^+$ $[M + H]^+$; Found 367.1333.

_N_-(1-methyl-1H-indazol-3-yl)-$_N$'-(4-methoxyphenethyl)sulfamide (iii-2i)

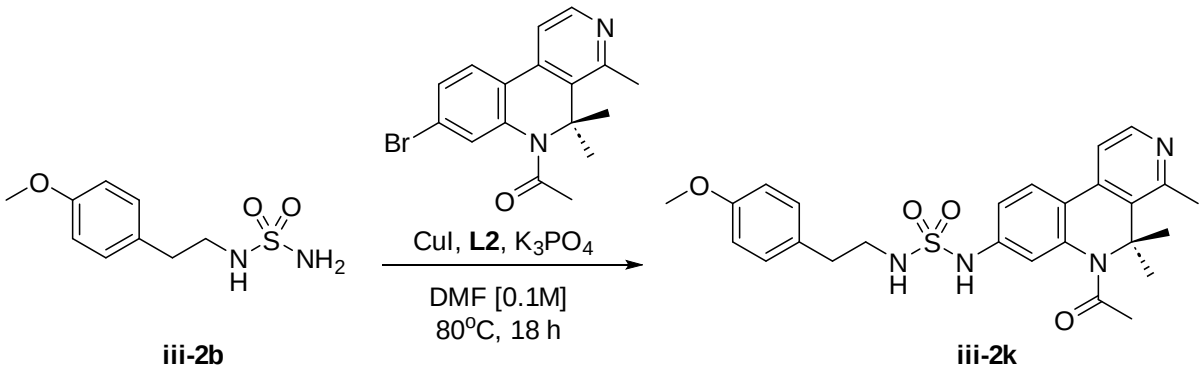


iii-2b **iii-2i**

According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 3-bromo-1-methyl-1H-indazole (79 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamide **iii-2i** as a yellow oil (31 mg, 28%).

R_f = 0.25 (30% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.64 (s, 1H), 7.40 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.13 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 4.80 (t, *J* = 6.1 Hz, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.34 (q, *J* = 6.8 Hz, 2H), 2.76 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.5, 141.2, 137.9, 129.9 (2C), 127.5, 120.9, 120.5, 117.1, 114.2 (2C), 109.1, 55.4, 44.9, 35.5, 34.6. HRMS (ESI) *m/z*: 361.1329 calcd for $C_{17}H_{21}N_4O_3S^+$ $[M + H]^+$; Found 361.1339.

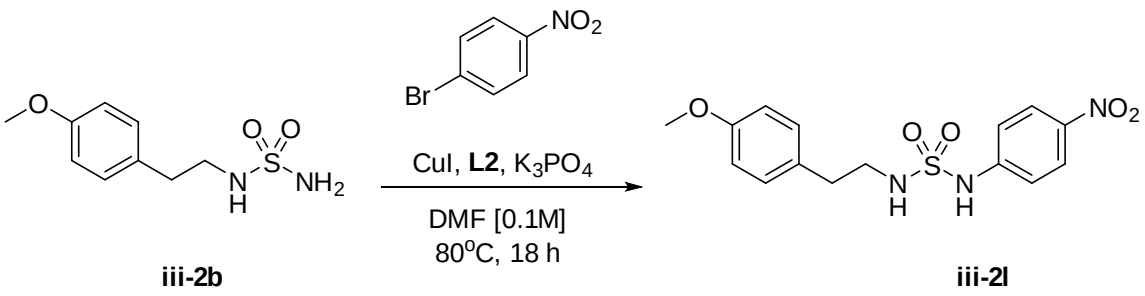
***N*-(*N*-acetylveranamine)-*N*'-(4-methoxyphenethyl)sulfamide (iii-2k)**



According to General Procedure B, sulfamide **iii-2b** (32 mg, 0.13 mmol), *N*-acetylveranamine (60 mg, 0.17 mmol), copper (I) iodide (6 mg, 0.039 mmol), and K_3PO_4 (69 mg, 0.33 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (1.5 mL) and **L2** (6 μL, 0.033 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamide **iii-2k** as a green oil (32 mg, 50%).

R_f = 0.10 (50% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.0 Hz, 1H), 7.72 (br s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 5.1 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.85 (t, *J* = 6.0 Hz, 1H), 3.73 (s, 3H), 3.33 (q, *J* = 6.7 Hz, 2H), 2.78 (s, 3H), 2.76 (t, *J* = 6.9 Hz, 2H), 1.90 (s, 3H), 1.78 (br s, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.2, 158.7, 153.8, 147.5, 141.5, 139.5, 138.9, 137.7, 129.8, 129.4 (2C), 126.3, 126.2, 117.54, 117.46, 116.6, 114.4 (2C), 60.7, 55.4, 44.7, 34.8, 29.3, 26.6, 26.1. HRMS (ESI) *m/z*: 495.2061 calcd for $C_{26}H_{31}N_4O_4S^+$ $[M + H]^+$; Found 495.2064.

_N_-(4-nitrophenyl)-_N'_-(4-methoxyphenethyl)sulfamide (iii-2l)

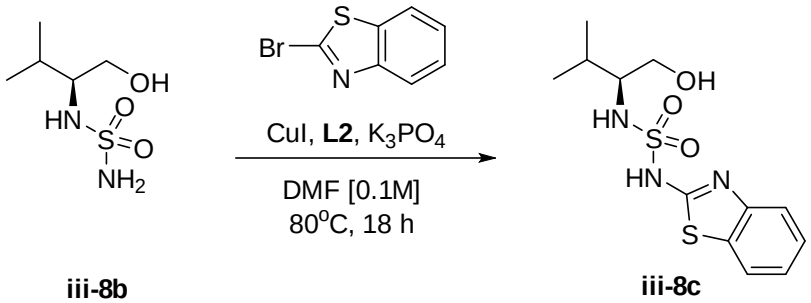


iii-2b **iii-2l**

According to General Procedure B, sulfamide **iii-2b** (69 mg, 0.30 mmol), 4-nitrobromobenzene (75 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamide **iii-2l** as a yellow powder (58 mg, 55%).

R_f = 0.27 (30% EtOAc/Hex). Mp: 129–132 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.1 Hz, 2H), 7.09 (d, *J* = 9.1 Hz, 2H), 7.01 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.58 (t, *J* = 5.5 Hz, 1H), 3.76 (s, 3H), 3.32 (q, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.9, 143.5, 143.0, 129.7 (2C), 129.0, 125.6 (2C), 117.3 (2C), 114.4 (2C), 55.4, 44.7, 34.5. HRMS (ESI) *m/z*: 352.0962 calcd for $C_{15}H_{18}N_3O_5S^+$ $[M + H]^+$; Found 352.0967.

_N_-(benzo[d]thiazol-2-yl)-_N'_-(_L_-valinol)sulfamide (iii-8c)

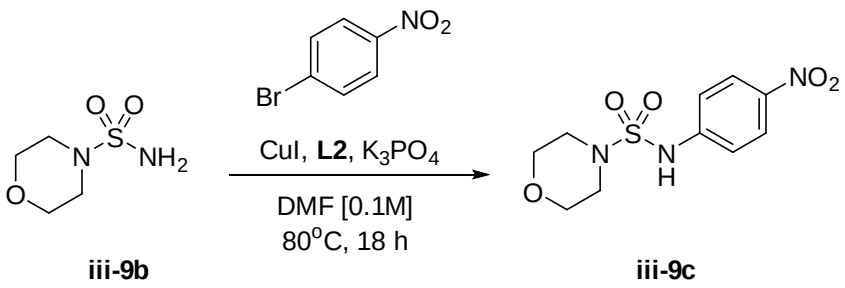


iii-8b **iii-8c**

According to General Procedure B, sulfamide **iii-8b** (36 mg, 0.2 mmol), *N*-acetylveranamine (53 mg, 0.25 mmol), copper (I) iodide (10 mg, 0.05 mmol), and K_3PO_4 (106 mg, 0.50 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (2 mL) and **L2** (9 μL, 0.06 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→70% EtOAc/Hexanes) provided aryl sulfamide **iii-8c** as a brown oil (20 mg, 31%).

R_f = 0.33 (70% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.31 (m, 1H), 7.21 – 7.17 (m, 1H), 5.29 (d, *J* = 8.6 Hz, 1H), 3.77 (dd, *J* = 11.5, 3.7 Hz, 1H), 3.60 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.30 (ddd, *J* = 12.5, 9.1, 3.7 Hz, 1H), 1.88 – 1.79 (m, 1H), 0.94 (dd, *J* = 9.1, 6.8 Hz, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 168.5, 136.3, 127.5, 124.9, 124.1, 122.0, 113.9, 63.6, 62.0, 30.3, 19.4, 18.6. HRMS (ESI) *m/z*: 316.0784 calcd for $C_{12}H_{18}N_3O_3S_2^+$ [M + H]$^+$; Found 316.0793.

_N_-(4-nitrophenyl)morpholine-4-sulfamide (iii-9c)

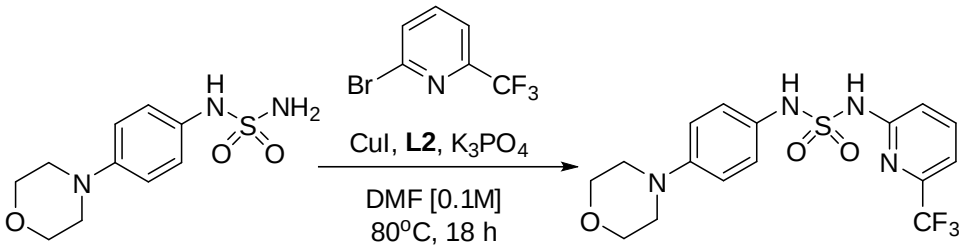


iii-9b **iii-9c**

According to General Procedure B, sulfamide **iii-9b** (49 mg, 0.30 mmol), 4-nitrobromobenzene (75 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamide **iii-9c** as a yellow powder (47 mg, 54%).

R_f = 0.55 (50% EtOAc/Hex). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.22 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H), 3.59 – 3.52 (m, 4H), 3.17 – 3.09 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.97, 142.04, 125.33 (2C), 117.64 (2C), 65.31 (2C), 45.89 (2C). Spectral data are consistent with data reported previously for this compound.[35]

_N_-(4-morpholinophenyl)-_N'_-((6-(trifluoromethyl)pyridin-2-yl)sulfamide (iii-10c)

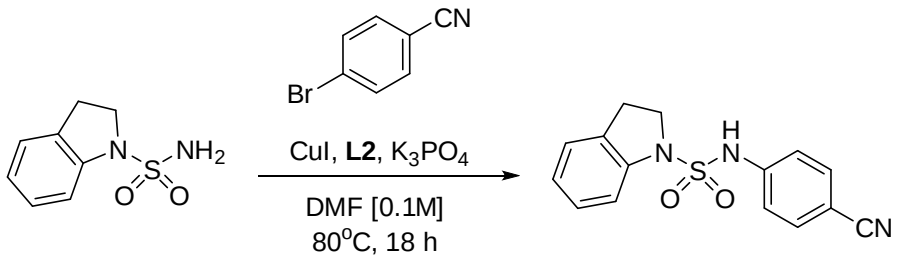


iii-10b **iii-10c**

According to General Procedure B, sulfamide **iii-10b** (77 mg, 0.30 mmol), 2-bromo-6-(trifluoromethyl)pyridine (84 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamide **iii-10c** as a brown powder (79 mg, 65%).

R_f = 0.36 (50% EtOAc/Hex). Mp: 177–180 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.82 (t, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.89 (s, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 3.84 – 3.81 (m, 4H), 3.11 – 3.07 (m, 4H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 151.3, 150.4, 146.9 (q, $^2J_{CF}$ = 35.0 Hz), 140.0, 127.5, 125.5 (2C), 121.2 (q, $^1J_{CF}$ = 273.7 Hz), 116.2 (2C), 115.4, 114.6, 66.9 (2C), 49.2 (2C). ^{19}F NMR (659 MHz, $CDCl_3$) δ -68.82 (3F). HRMS (ESI) *m/z*: 403.1046 calcd for $C_{16}H_{18}F_3N_4O_3S^+$ $[M + H]^+$; Found 403.1045.

_N_-(4-cyanophenyl)indoline-1-sulfamide (iii-11c)

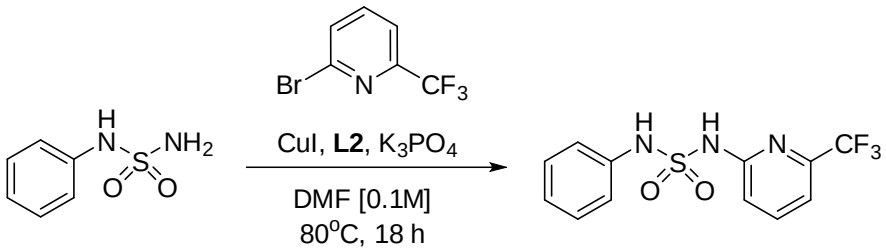


iii-11b **iii-11c**

According to General Procedure B, sulfamide **iii-11b** (59 mg, 0.30 mmol), 4-bromobenzonitrile (68 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamide **iii-11c** as a brown powder (35 mg, 39%).

R_f = 0.47 (50% EtOAc/Hex). Mp: 137–139 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.15 (m, 3H), 7.03 (t, *J* = 7.2 Hz, 1H), 4.01 (t, *J* = 8.4 Hz, 2H), 3.00 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 141.5, 141.1, 133.7 (2C), 131.4, 128.1, 125.6, 124.3, 119.6 (2C), 118.6, 114.3, 107.9, 51.4, 28.2. HRMS (ESI) *m/z*: 322.0621 calcd for $C_{15}H_{13}N_3O_2SNa^+$ $[M + Na]^+$; Found 322.0622.

_N_-(phenyl)-_N'_-((6-(trifluoromethyl)pyridin-2-yl)sulfamide (iii-12c)

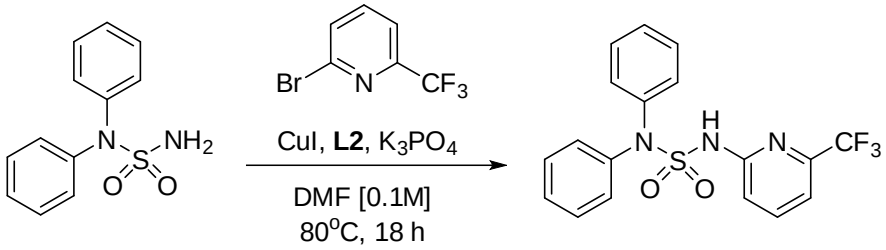


iii-12b **iii-12c**

According to General Procedure B, sulfamide **iii-12b** (51 mg, 0.30 mmol), 2-bromo-6-(trifluoromethyl)pyridine (84 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→40% EtOAc/Hexanes) provided aryl sulfamide **iii-12c** as a brown powder (67 mg, 70%).

R_f = 0.44 (50% EtOAc/Hex). Mp 142–143.0 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.70 (t, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 10.0 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.22 – 7.16 (m, 3H), 7.08 (m, 3H), 6.94 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 151.1, 146.7 (q, $^2J_{CF}$ = 35.0 Hz), 140.0, 136.0, 129.6 (2C), 126.4, 122.3 (2C), 121.2 (q, $^1J_{CF}$ = 274.0 Hz), 115.42, 114.62. ^{19}F NMR (659 MHz, $CDCl_3$) δ -68.78 (3F). HRMS (ESI) *m/z*: 318.0519 calcd for $C_{12}H_{11}F_3N_3O_2S^+$ $[M + H]^+$; Found 318.0522.

***N*, *N*-(diphenyl)-*N*'-((6-(trifluoromethyl)pyridin-2-yl)sulfamide (iii-13c)**

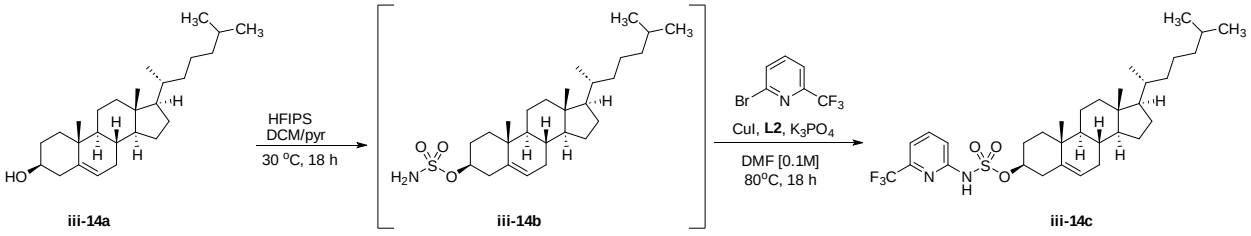


iii-13b **iii-13c**

According to General Procedure B, sulfamide **iii-13b** (75 mg, 0.30 mmol), 2-bromo-6-(trifluoromethyl)pyridine (84 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dimethylformamide (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→50% EtOAc/Hexanes) provided aryl sulfamide **iii-13c** as a brown powder (72 mg, 61%).

R_f = 0.72 (50% EtOAc/Hex). Mp: 100–103 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.70 (t, *J* = 7.9 Hz, 1H), 7.38 (m, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 4H), 7.24 (t, *J* = 7.7 Hz, 4H), 7.18 (m, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 151.2, 147.0 (q, $^2J_{CF}$ = 35.4 Hz), 141.3, 139.9, 129.7 (4C), 128.3 (4C), 128.2 (2C), 121.3 (q, $^1J_{CF}$ = 274.4 Hz), 116.0, 115.5. ^{19}F NMR (659 MHz, $CDCl_3$) δ -68.79 (3F). HRMS (ESI) *m/z*: 394.0832 calcd for $C_{18}H_{15}F_3N_3O_2S^+$ $[M + H]^+$; Found 394.0829.

N-Aryl Cholesterol Sulfamate (iii-14c)



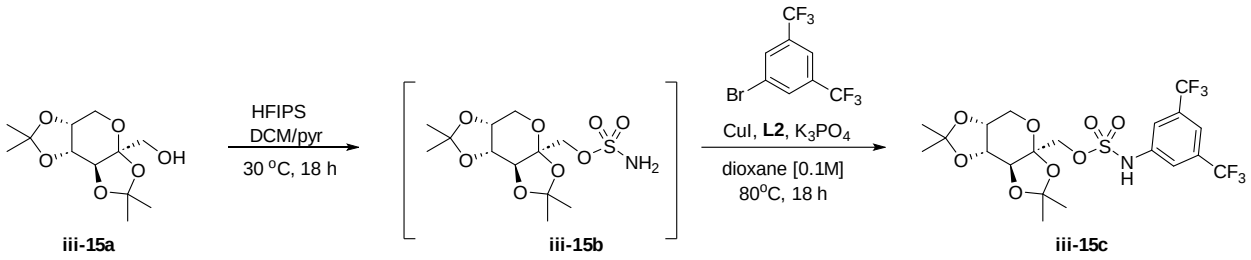
iii-14a iii-14b iii-14c

HFIPS (111 mg, 0.45 mmol) was added to a solution of cholesterol **iii-14a** (116 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) /pyridine (1 mL). After stirring the reaction mixture at 30 °C for 18 h, the reaction was the reaction was concentrated under reduced pressure via rotary evaporation with PhMe (10 mL x 2). Then, the resultant crude sulfamate yellow solid, 2-bromo-6-(trifluoromethyl)pyridine (86 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous DMF (3mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamate **iii-14c** as a white powder (119 mg, 65% over 2-steps).

R_f = 0.49 (33% EtOAc/Hex), visualized with PMA stain. Mp: 144-147 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.89 (t, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 5.36 (dt, *J* = 5.4, 2.1 Hz, 1H), 4.53 (tt, *J* = 11.6, 4.9 Hz, 1H), 2.49 – 2.43 (m, 1H), 2.40 – 2.35 (m, 1H), 2.02 – 1.92 (m, 3H), 1.89 – 1.80 (m, 2H), 1.77 – 1.70 (m, 1H), 1.62 – 1.55 (m, 2H), 1.55 – 1.48 (m, 2H), 1.48 – 1.39 (m, 3H), 1.41 – 1.30 (m, 3H), 1.29 – 1.22 (m, 2H), 1.18 – 1.02 (m, 7H), 1.01 – 0.99 (m, 1H), 0.98 (s, 3H), 0.93 – 0.89 (m, 3H), 0.86 (dd, *J* = 6.6, 3.2 Hz, 6H), 0.66 (s, 3H). ^{19}F NMR (659

MHz, $CDCl_3$) δ -68.89 (3F). ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.75, 147.11 (q, $^2J_{CF}$ = 35.5 Hz), 140.27, 138.41, 124.31, 121.08 (q, $^1J_{CF}$ = 274.1 Hz), 116.07 (q, $^3J_{CF}$ = 3.0 Hz), 114.70, 85.19, 56.75, 56.26, 50.04, 42.44, 39.78, 39.66, 38.72, 36.95, 36.50, 36.31, 35.91, 32.00, 31.89, 28.57, 28.34, 28.16, 24.40, 23.96, 22.96, 22.71, 21.16, 19.29, 18.85, 11.99. HRMS (ESI) *m/z*: 609.3343 calcd for $C_{33}H_{48}F_3N_2O_3S^-$; $[M - H]^-$ 609.3337 obsd.

_N_-Aryl Topiramate (iii-15c)

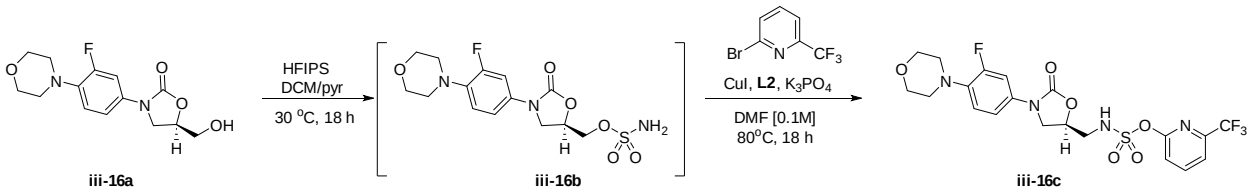


HFIPS (111 mg, 0.45 mmol) was added to a solution of diacetone fructose **iii-15a** (78 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) /pyridine (1 mL). After stirring the reaction mixture at 30 °C for 18 h, the reaction was the reaction was concentrated under reduced pressure via rotary evaporation with PhMe (10 mL x 2). Then, the resultant crude sulfamate oil, 1-bromo-3,5-bis(trifluoromethyl)benzene (111 mg, 0.38 mmol), copper (I) iodide (14 mg, 0.075 mmol), and K_3PO_4 (159 mg, 0.75 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous dioxane (3 mL) and **L2** (14 μL, 0.09 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with H_2O (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with H_2O (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→30% EtOAc/Hexanes) provided aryl sulfamate **iii-15c** as an opaque oil (70

mg, 42% over 2-steps).

R_f = 0.62 (33% EtOAc/Hex), visualized with PMA stain. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.69 (s, 2H), 7.68 (s, 1H), 7.47 (br s, 1H), 4.57 (dd, *J* = 7.9, 2.6 Hz, 1H), 4.34 (dd, *J* = 10.6, 1.0 Hz, 1H), 4.25 (dd, *J* = 10.6, 1.1 Hz, 1H), 4.23 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.17 (d, *J* = 2.7 Hz, 1H), 3.89 (dd, *J* = 13.0, 1.9 Hz, 1H), 3.74 (d, *J* = 13.0 Hz, 1H), 1.52 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.54 (6F). ^{13}C NMR (176 MHz, $CDCl_3$) δ 138.09, 133.08 (q, $^2J_{CF}$ = 33.9 Hz, 2C), 125.28 - 120.63 (app m, 2C), 120.58 (q, $^3J_{CF}$ = 3.7 Hz, 2C), 118.84 (q, *J* = 3.8 Hz), 109.77, 109.45, 100.68, 72.26, 70.60, 70.58, 69.81, 61.50, 26.42, 25.81, 24.94, 24.04. HRMS (ESI) *m/z*: 550.0976 calcd for $C_{20}H_{22}F_6NO_8S^-$; $[M-H]^-$ 550.0985 obsd.

_O_-((deacetamido)linezolid)-_N_-((6-(trifluoromethyl)pyridin-2-yl)sulfamate (iii-16c)

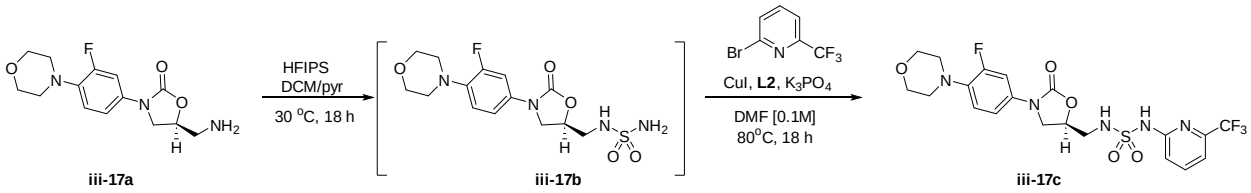


HFIPS (185 mg, 0.75 mmol) was added to a solution of hydroxy(deacetamido)linezolid **iii-16a** (150 mg, 0.5 mmol) in CH_2Cl_2/pyridine (1:1, 5 mL). After stirring the reaction mixture at 30 °C for 18 h, the reaction was concentrated under reduced pressure via rotary evaporation with PhMe (25mL). Then, the resultant solid (246 mg, 0.66 mmol), 2-bromo-6-(trifluoromethyl)pyridine (184 mg, 0.82 mmol), copper (I) iodide (31 mg, 0.17 mmol), and K_3PO_4 (351 mg, 1.7 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous DMF (6mL) and **L2** (31 μL, 0.20 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl

acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→70% EtOAc/Hexanes) provided aryl sulfamate **iii-16c** as a white solid (178 mg, 0.34 mmol, 69%).

R_f = 0.33 (70% EtOAc/Hex). Mp: 199–201 °C. ^{1}H NMR (700 MHz, Acetone-d_6) δ 8.04 (t, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 15.0, 2.6 Hz, 1H), 7.15 (ddd, *J* = 8.8, 2.6, 1.0 Hz, 1H), 7.05 – 7.01 (m, 1H), 5.08 (dddd, *J* = 9.2, 6.0, 4.9, 3.0 Hz, 1H), 4.72 (dd, *J* = 11.4, 3.0 Hz, 1H), 4.66 (dd, *J* = 11.4, 4.8 Hz, 1H), 4.26 (t, *J* = 9.2 Hz, 1H), 3.92 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.80 – 3.76 (m, 4H), 3.03 – 2.99 (m, 4H). ^{13}C NMR (176 MHz, Acetone-d_6) δ 156.2 (d, $^1J_{CF}$ = 244.1 Hz), 154.5, 152.2, 146.9 (q, $^2J_{CF}$ = 34.3 Hz), 140.6, 137.0 (d, $^2J_{CF}$ = 9.0 Hz), 134.6 (d, $^3J_{CF}$ = 10.2 Hz), 122.3 (q, $^1J_{CF}$ = 273.3 Hz), 119.9 (d, $^4J_{CF}$ = 4.2 Hz), 116.6 (m), 116.2, 114.6, 107.6 (d, $^2J_{CF}$ = 54.7 Hz), 72.2, 70.7, 67.5 (2C), 52.0 (2C), 47.00. ^{19}F NMR (659 MHz, Acetone-d_6) δ -67.56 (3F), -121.20. HRMS (ESI) *m/z*: 521.1112 calcd for $C_{20}H_{21}F_4N_4O_6S^+$ $[M + H]^+$; Found 521.1131.

_N_-(deacetyl linezolid)-_N'_-((6-(trifluoromethyl)pyridin-2-yl)sulfamide (iii-17c)



iii-17a iii-17b iii-17c

HFIPS (185 mg, 0.75 mmol) was added to a solution of deacetyl linezolid **iii-17a** (150 mg, 0.5 mmol) in CH_2Cl_2/pyridine (1:1, 5 mL). After stirring the reaction mixture at 30 °C for 18 h, the reaction was concentrated under reduced pressure via rotary evaporation with PhMe

(25mL). Then, the resultant solid (207 mg, 0.55 mmol), 2-bromo-6-(trifluoromethyl)pyridine (153 mg, 0.68 mmol), copper (I) iodide (24 mg, 0.13 mmol), and K_3PO_4 (275 mg, 1.3 mmol) were added to a vial charged with a stir bar, and the vial was degassed with argon. Then, anhydrous DMF (5mL) and **L2** (25 μL, 0.16 mmol) were added. After stirring the reaction mixture at 80 °C for 18 h, it was quenched with 10% LiCl (10 mL), extracted into ethyl acetate (3 x 20 mL), the combined organic layers washed with 10% LiCl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (0→70% EtOAc/Hexanes) provided aryl sulfamide **iii-17c** as a yellow oil (103 mg, 40%).

R_f = 0.37 (70% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.36 (dd, *J* = 14.2, 2.6 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.88 (t, *J* = 9.1 Hz, 1H), 6.06 (t, *J* = 6.6 Hz, 1H), 4.83 – 4.76 (m, 1H), 4.02 (t, *J* = 9.0 Hz, 1H), 3.88 – 3.85 (m, 4H), 3.85 – 3.82 (m, 1H), 3.59 – 3.54 (m, 1H), 3.47 – 3.42 (m, 1H), 3.05 – 3.02 (m, 4H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.5 (d, $^1J_{CF}$ = 246.6 Hz), 154.6, 151.3, 146.6 (q, $^2J_{CF}$ = 34.7 Hz), 140.1, 136.8 (d, $^3J_{CF}$ = 8.62 Hz), 132.7 (d, $^3J_{CF}$ = 10.4 Hz), 121.2 (q, $^1J_{CF}$ = 274.2 Hz), 119.0 (d, $^4J_{CF}$ = 4.0 Hz), 115.2 (d, $^4J_{CF}$ = 2.3 Hz), 114.7, 114.3 (d, $^4J_{CF}$ = 2.5 Hz), 107.8 (d, $^2J_{CF}$ = 26.0 Hz), 71.3, 67.1 (2C), 51.1 (d, $^4J_{CF}$ = 2.3 Hz, 2C), 47.6, 46.2. ^{19}F NMR (659 MHz, $CDCl_3$) δ -68.67 (3F), -120.58. HRMS (ESI) *m/z*: 520.1272 calcd for $C_{20}H_{22}F_4N_5O_5S^+$ $[M + H]^+$; Found 520.1288

3.3 References

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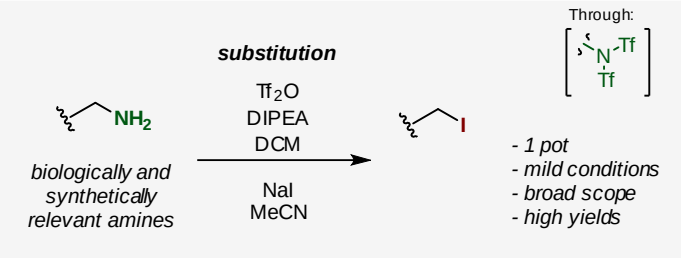
Chapter 4 – Amine Substitution

4.1 A Practical Substitution of Amines

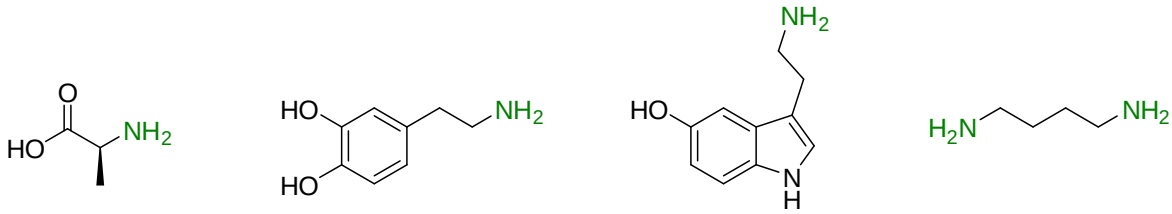
As introduced in section 1.1.5, attached is the unpublished manuscript of our future publication entitled "A Practical Substitution of Amines."

ABSTRACT: Amines are ubiquitous substrates in organic and medicinal chemistry. Because of their nucleophilicity, amines are often reacted with electrophiles to perform substitution reactions. However, amines have rarely been investigated for their ability to react as electrophiles. Herein, we have investigated the ability of ditriflyl amines to undergo nucleophilic substitution through the displacement of $^{-}NTf_2$. With easy access to this powerful leaving group, we have demonstrated the ability of iodine salts to react with relevant amine substrates to produce their corresponding iodides.



Aliphatic amines are one of the most relevant functional groups in drug discovery and organic chemistry.[43, 44, 112] They are responsible for the biological activity of a plethora of molecules that are imperative to life because of their ability to modulate solubility, increase polarity, and be recognized by enzymes.[44, 45] Furthermore, the lone pair on the nitrogen atom is a necessary feature for certain molecules to cross cell-membranes and the blood-brain barrier.[44] They are commonly found in natural products such as amino acids (e.g. alanine), phenethylamines (e.g. dopamine), tryptamines (e.g. serotonin), polyamines (e.g. putrescine)

and more (Figure 4-1).[113-115] Because of their commonality and commercial availability, aliphatic amines are ideal starting materials in organic chemistry and are known to undergo numerous transformations.[48, 116-120]



Amino Acids (*e.g. alanine*) | *Phenethylamines* (*e.g. dopamine*) | *Tryptamines* (*e.g. serotonin*) | *Polyamines* (*e.g. putrescine*)

Figure 4-1: Relevant classes of aliphatic amine-containing natural products.

Due to the intrinsic properties of the nitrogen atom, amines are commonly employed as nucleophiles and undergo reactions with electrophiles.[121, 122] Conversely, their ability to react as electrophiles has rarely been explored.[49, 50] We envisioned creating an electrophilic amine by attaching two electron-withdrawing substituents and subsequently reacting it with a nucleophile to displace it as $^{-}NR_2$. Previously, this has been explored half a century ago by Baumgaren et al., where *N*-ditosyl amines were displaced by a nucleophile, such as an iodine salt, to yield the corresponding alkyl iodide and styrene (Figure 4-2).[49] However, this procedure requires three steps and due to the harsh reaction conditions, results in a mixture of the alkyl iodide (minor product) and its eliminated styrene (major product).[49] Our explorations initiated with the rarely explored and more electrophilic *N*-ditrifyl amines, therefore, allowing us to employ mild reaction conditions and expand the utility of this transformation (Figure 4-2). To generalize the applications of our chemistry, we targeted a one-step procedure for the

transformation of alkyl amines into their corresponding alkyl iodides. Alkyl iodides are fundamental building blocks in organic chemistry and are commonly synthesized from their corresponding alcohols (Figure 2).[123-126] The synthesis of iodinated compounds offers a handle for diverse applications in pharmaceuticals, materials science, and more.[127] By expanding the utilization of amines as precursors for this chemistry, we have increased the accessibility of substrates that cannot be obtained as the alcohol, such as those in Figure 4-1.

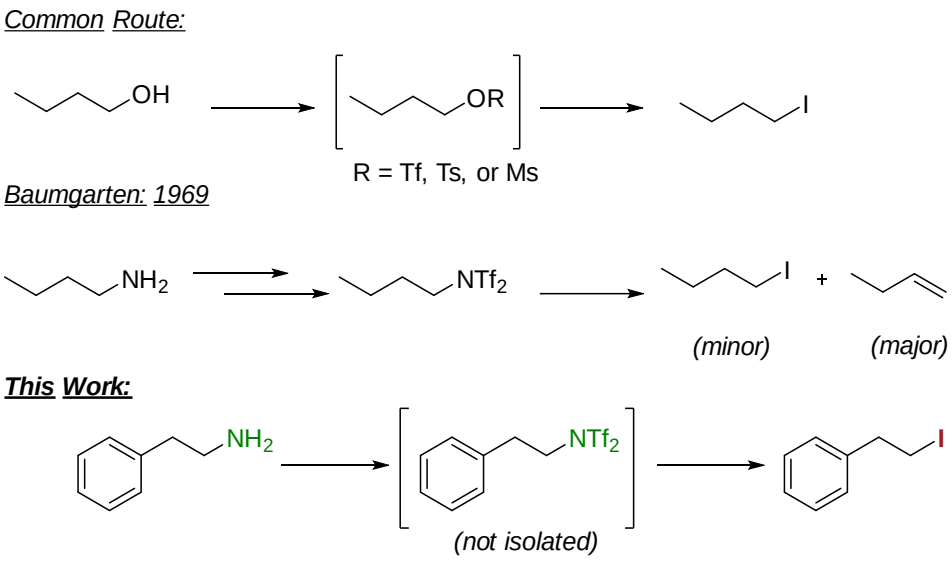


Figure 4-2: Iodination routes through substitution.

To begin our investigations, the biologically relevant phenethylamine (**iv-1a**) was subjected to triflic anhydride (Tf_2O) and various conditions.[128] Although *N*-ditriflation conditions are known, they are primarily applied to aromatic amines and there is little literature on aliphatic amines undergoing this transformation.[53] Pleasantly, the *N*-ditriflyl phenethylamine **iv-1aa** was synthesized in a high crude yield (81%) and proved to be stable on silica chromatography. This intermediate was reacted with a variety of nucleophilic salts; however, only iodine salts resulted in appreciable yields (Figure 4-3).

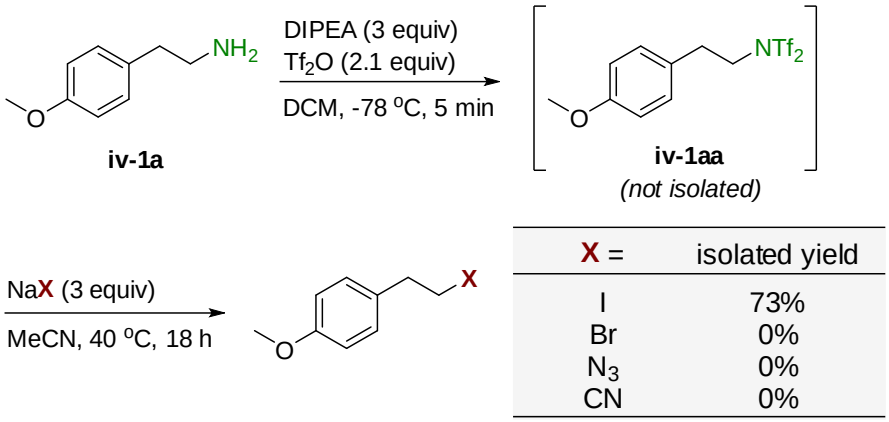
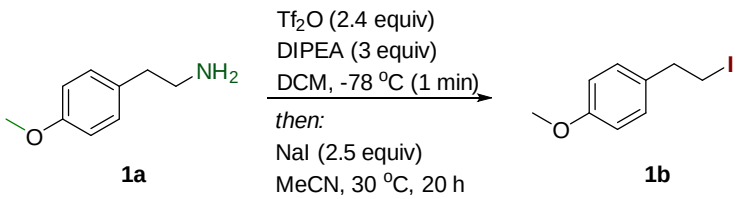


Figure 4-3: Unoptimized reactions of a *N*-ditriflyl intermediate with nucleophilic salts.

After obtaining conditions for two high-yielding reactions, we sought to combine them into a single step (Table 4-1). This was successfully achieved by reacting phenethylamine (**iv-1a**) in DCM with DIPEA at -78 °C and slowly adding Tf_2O. Once the dropwise addition was complete, the reaction vessel was removed from the cold bath, and the immediate addition of NaI and MeCN with slight heat resulted in the desired iodide (**iv-1b**) overnight in a 96% yield (entry 1). When attempting the reaction at 0 °C or in a higher boiling point solvent, the reaction yield was reduced, yet impressive nonetheless (entries 2-3). Conducting the reaction in the absence of a polar co-solvent resulted in a significantly diminished yield (entry 4). Changing amine bases can be tolerated, however, only to triethylamine (entries 5-6). Notably, a slight reduction in excess Tf_2O from 2.4 to 2.1 equivalences resulted in a significant reduction in yield (entry 8). Lastly, other iodine salts were also high yielding, however, sodium iodide was the most tolerated when reacted with numerous substrates (entry 9).

Table 4-1: Optimization for the iodination of amines.



1a **1b**

entry	variation from standard conditions	isolated yield (%)
1 [a]	none	96
2	0 °C instead of -78 °C	81
3	DCE instead of DCM	90
4	without MeCN	64
5	NEt_3 instead of DIPEA	83
6	DMAP instead of DIPEA	trace
7	5 equiv of DIPEA	91
8	2.1 equiv of Tf_2O	78
9	KI instead of NaI	93

[a] Reaction conditions for entry 1: *p*-methoxyphenethylamine (76 mg, 0.50 mmol), DIPEA (0.26 mL, 1.50 mmol), Tf_2O (0.20 mL, 1.2 mmol), DCM (4.0 mL), NaI (188 mg, 1.25 mmol) and MeCN (2 mL).

With high yielding and optimized conditions for the one-step iodination of amines achieved, our chemistry was explored on other substrates bearing relevant functionalities (Figure 4). Due to phenethylamines being one of the most prominent amine natural products, we explored the reaction of mono and di-substituted electron rich (**iv-4b**) and electron poor (**iv-2b + iv-3b)** aryl systems.[129] All phenethylamines that were investigated reacted in high to quantitative yields. Similarly, the benzylamine derivative of **iv-3a** underwent iodination in an 87% yield (**iv-5b**). Next, other drug-like and complex amines were investigated. Pleasantly, benzyl protected glycine reacted in an 81% yield to furnish its corresponding iodide **iv-6b**. The Boc-protected saturated amine **iv-8a** reacted in a 61% yield to furnish **iv-8b**, which displays

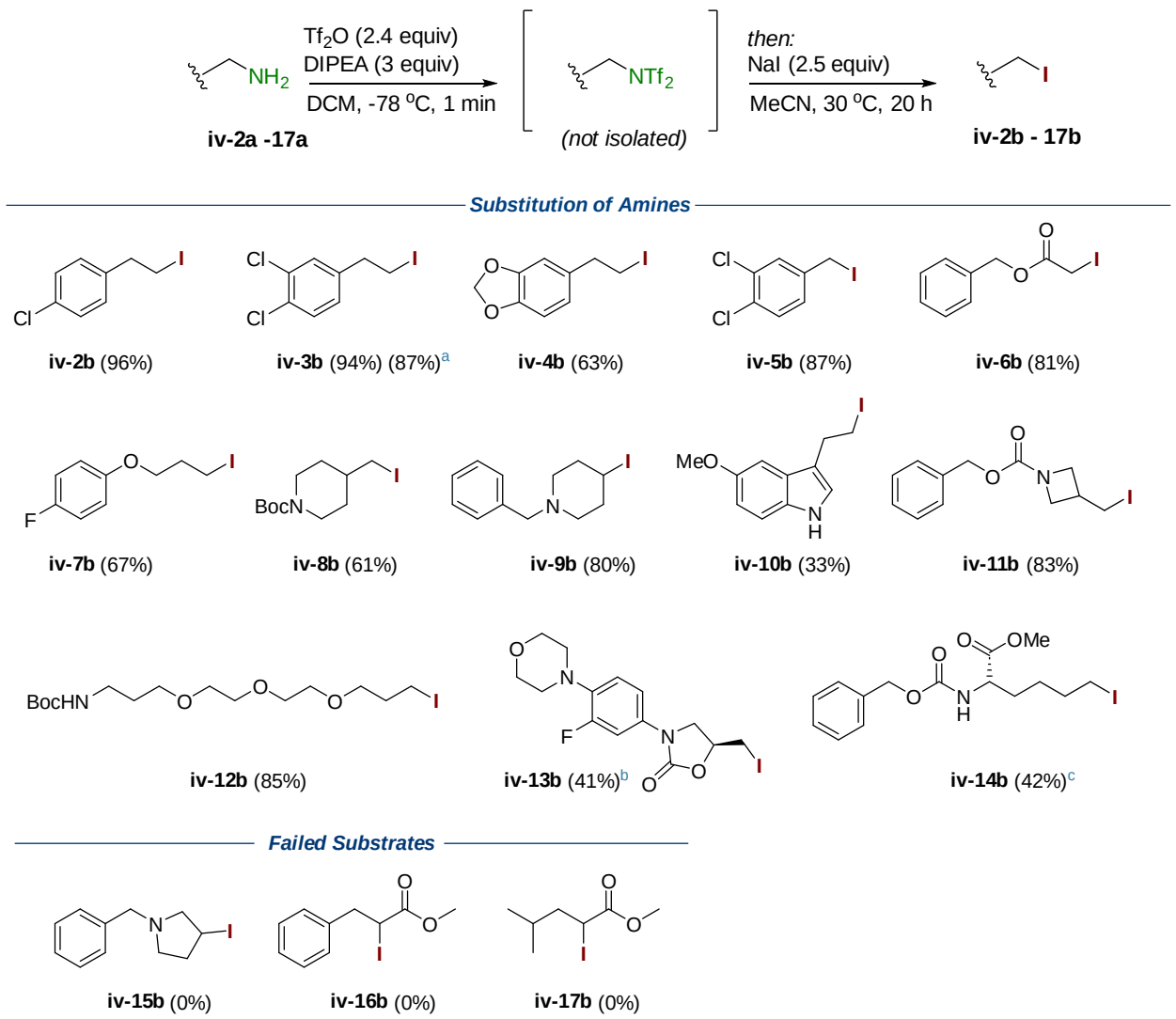


Figure 4-4: Iodination of amines substrate scope.

Reaction conditions: amine (0.50 mmol), DIPEA (0.26 mL, 1.50 mmol), Tf_2O (0.20 mL, 1.2 mmol), DCM (4.0 mL), NaI (188 mg, 1.25 mmol) and MeCN (2 mL). [a] Reaction was conducted on a 5 mmol (gram) scale. [b] NMR yield. [c] Two-step procedure and yield.

compatibility with this ubiquitous protecting group. An alkylated phenol (**iv-7b**) and cyclic amide (**iv-11b**) containing substrates yielded their corresponding iodides in 67% and 83% yield respectively. Tryptamines are another subset of biologically relevant amines because of their prominence in natural products and neurotransmitters.[130] When 5-methoxytryptamine was reacted, the corresponding iodide was achieved in a 33% yield (**iv-10b**). Notably, this amino

compound (**iv-10a**) is not commercially available as the alcohol. The lower yield for this reaction may be rationalized by the free NH of the indole reacting with Tf_2O or the nucleophilic indole performing side-chemistry. Furthermore, a polyethylene glycol containing a free NH on the -Boc group (**iv-12b**) reacted in an 85% yield. This is important because the -Boc group can be readily removed to furnish a free amine that can cyclize intramolecularly, or the iodine product can be reacted, and the *N*-Boc amine can then be deprotected to allow for further amine chemistry.

Pleasantly, deacetyl linezolid **iv-13a** underwent the reaction in a 41% yield. This is important because iodide **iv-13b** can be used as a precursor to synthesize analogues of the FDA approved antibiotic.[131] Lysine derivative **iv-14a** proved to have purification issues between the iodide product and $-NTf_2$ intermediate. To circumvent this, a two-step procedure was employed and the desired iodide **iv-14b** was obtained in a 42% yield. Notably, this compound is often synthesized from its corresponding alcohol, however, that alcohol is synthesized bio enzymatically from the amine.[132] Furthermore, if cyclized, **iv-14b** can become an enantiomerically pure protected version of the unnatural amino acid pipecolic acid.[133]

Lastly, when sterically hindered amines were employed, no reaction was observed (**iv-15-17b**). For these examples, the amines were successfully ditriflated, however, the steric bulk prevented the iodine salt from displacing the NTf_2 leaving group. Conversely, the -Boc protected aminated piperazine **iv-9a** successfully reacted in high yield (80%, **iv-9b**). This reaction may have been successful due to anchimeric assistance. The lack of reactivity for phenylalanine methyl ester **iv-16a** and leucine methyl ester **iv-17a** was disappointing because of their biological and synthetic importance. The issues with these substrates required a separate optimization and have subsequently been addressed (Figure 4-6).

With an optimized procedure established and a substrate scope explored, further applications of our chemistry were investigated. Having access to a plethora of iodinated substrates, subsequent nucleophilic displacement with relevant nucleophiles was examined (Figure 4-5). The biologically relevant *O*-benzyl protected glycine was iodinated on a 2.5 mmol scale which resulted in half a gram of product. This intermediate was divided into four reaction vessels and nucleophilic substitution furnished relevant products (Figure 4-5).

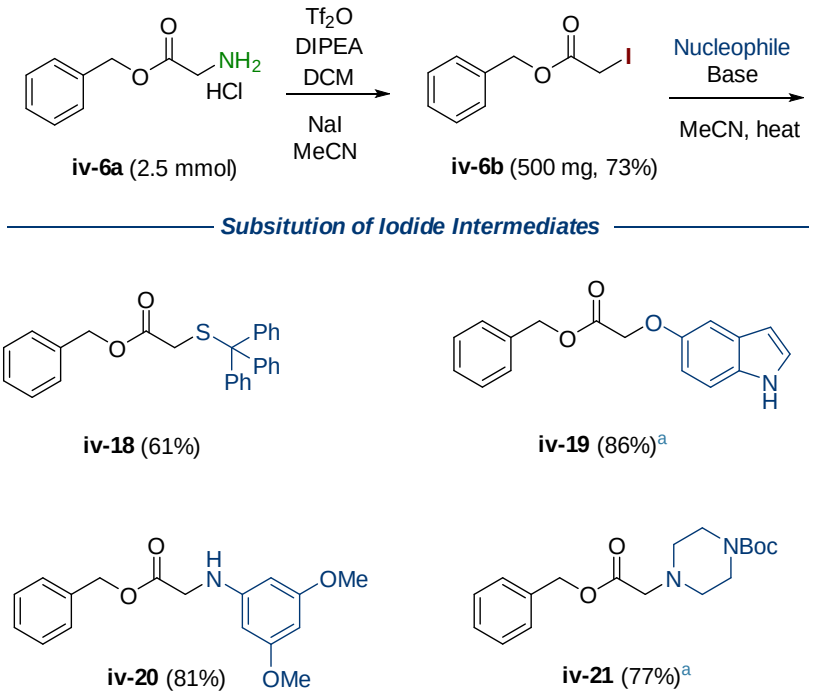


Figure 4-5: Functionalizations of iodinated products.

Reaction conditions: **iv-6b** (85 mg, 0.30 mmol), DIPEA (0.09 mL, 0.50 mmol), nucleophile (0.25 mmol), and MeCN (2.5 mL) at 50 °C for 18 h. [a] **iv-6b** (85 mg, 0.30 mmol), K_2CO_3 (86 mg, 0.625 mmol), nucleophile (0.25 mmol), and MeCN (2.5 mL) at 70 °C for 18 h.

For example, trityl thiol was reacted to yield the thioether product **iv-18** in a 61% yield. If desired, this compound can be deprotected to provide the free thiol analogue of glycine. 5-hydroxyindole was reacted with intermediate **iv-6b** to produce the alkylated indole **iv-19** in an 86% yield. An electron rich aniline was reacted to furnish the alkylated product **iv-20** in an 81%

yield. Notably, this substrate was chosen because of its inability to be synthesized via S_NAr chemistry due to being electronically rich. This product further demonstrates the utility of this chemistry by easily transforming the free amine **iv-6a** into the cyclic amine **iv-21**. The conversion of primary amines into cyclic amines often involves complex metal catalysts and high temperatures.[134, 135] This method allows for a relatively simple way to achieve the same transformation.

After many unsuccessful attempts to react amino ester substrates, it was determined that a one-step procedure would not be viable. To circumvent any potential issues, the triflation and substitution were independently optimized (SI Table 4-2). With optimized conditions for the separate steps obtained, we were able to combine them with only a workup in-between (Figure 4-6).

The triflation was once again performed in DCM at -78 °C and went to completion in 2 min. Notably, the success of this reaction came from lowering the amount of base and increasing the amount of Tf_2O. Also, it was necessary for MeCN to be substituted to DMF to allow for the complete conversion of all substrates. If the reaction did not go to completion, the separation of the NTf_2 intermediate and iodine product was often unachievable. Furthermore, an aqueous workup between the two steps also proved to be essential for the substitution to reach completion. Pleasantly, every amino ester yielded the desired product except for the sulfur-containing methionine **iv-30a**. Thiol ethers are known to react with Tf_2O and this may have prevented the desired reaction.[136]

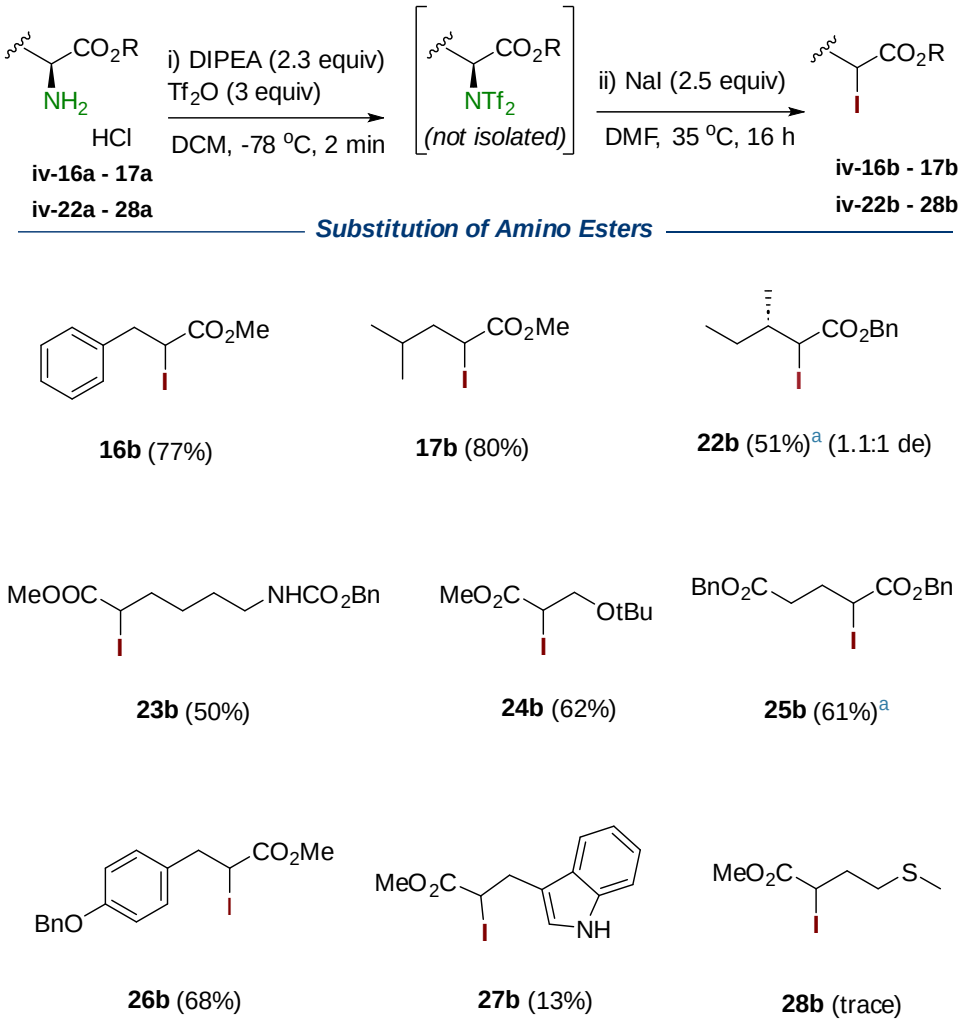


Figure 4-6: Successful iodination of amino esters.

Reaction conditions: i) Amino ester HCl (0.50 mmol), DIPEA (0.20 mL, 1.15 mmol), Tf_2O (0.30 mL, 1.5 mmol) and DCM (4.0 mL). ii) NaI (188 mg, 1.25 mmol) and DMF (4 mL). [a] Free base amino ester and 1.3 equiv of DIPEA.

With the new reaction conditions, the previously unobtainable product of the phenylalanine methyl ester was obtained in a 77% yield (**iv-16b**). We were uncertain if the benzylic protons were responsible for complicating the previous reaction, however, now we know that to not be the case. Leucine methyl ester also now reacted excellently to produce iodide **iv-17b** in an 80% yield.

Compound **iv-22b** informed us about the stereochemical outcome of the reaction. Due to isoleucine having a second chiral center, we were able to identify the diastereomeric ratio via NMR. Unsurprisingly, the stereochemistry was scrambled and in a 55:45 ratio. The more commonly available L-amino esters were used for this chemistry; however, racemic mixtures would have provided the same products.

Interestingly, two compounds were purchased as the tosylate salt instead of the HCl salt: isoleucine ester **iv-22a** and glutamic acid ester **iv-25a**. When subjected to the standard reaction conditions, poor yields were obtained. However, when these compounds were reacted as their free base, iodides **iv-22b** and **iv-25b** were obtained in 51% and 61% yields, respectively.

Other amino esters such as those derived from lysine **iv-23a**, serine **iv-24a**, and tyrosine **iv-26a** also provided the desired iodide products in good yields; 50%, 62%, and 68% respectively.

Lastly, when the tryptophan methyl ester **iv-27a** was reacted, its corresponding product **iv-27b** was only isolated in a 13% yield. Many byproducts were observed from this reaction, predictably from the indole.

With a robust one-pot two-step procedure obtained, we were curious as to if other nucleophilic salts were compatible now that a second step was required (SI Figure 4-9). Leucine NTf_2 methyl ester was reacted with an azide ($^-N_3$), cyanide (^-CN), and bromide (^-Br) salt, however, only the bromide provided the desired product. Furthermore, all the starting material was consumed for each reaction, indicating that it was not stable enough to survive the reaction conditions.

Next, we attempted to react NaBr in our two-step one-pot procedure (Figure 4-7). By

substituting NaBr for NaI, increased reaction temperatures were required due to the lower nucleophilicity of bromide. However, this proved to be problematic because of the instability of the NTf_2 intermediate, resulting in low yields of bromide products. Nonetheless, we were able to synthesize the bromo esters of phenylalanine (**iv-16c**, 23%), leucine (**iv-17c**, 29%) and lysine derivatives (**iv-23c**, 20%), albeit in lower yields.

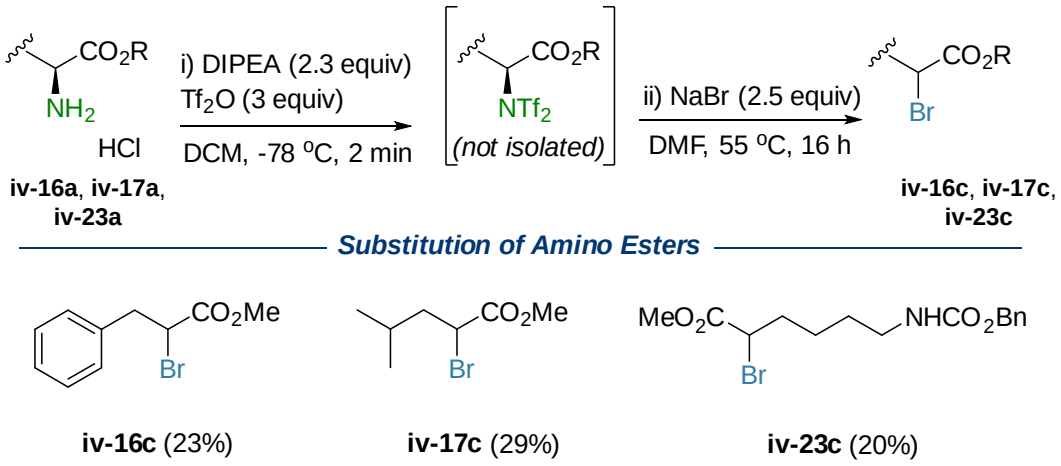


Figure 4-7: Bromination of amino esters.

Reaction conditions: i) Amino ester HCl (0.50 mmol), DIPEA (0.20 mL, 1.15 mmol), Tf_2O (0.30 mL, 1.5 mmol) and DCM (4.0 mL). ii) NaI (188 mg, 1.25 mmol) and DMF (4 mL).

For the iodo-esters, stability issues once isolated were observed. They were able to be successfully isolated and stored at 0 °C, however, at room temperature they would eventually decompose. In attempts to potentially circumvent this issue, we were curious as to if we could react an iodo-ester in situ, without the need to isolate it (Figure 4-8). After the formation of **iv-24b** in situ, a cyclic amine nucleophile and base were added directly to the reaction mixture to yield the corresponding products. Pleasantly, all desired compounds were synthesized in good

yields over two steps. Boc-protected piperazine yielded compound **iv-29** in a 63% yield, and a bridged piperazine derivative yielded **iv-31** in 71% yield. The bridged morpholine nucleophile

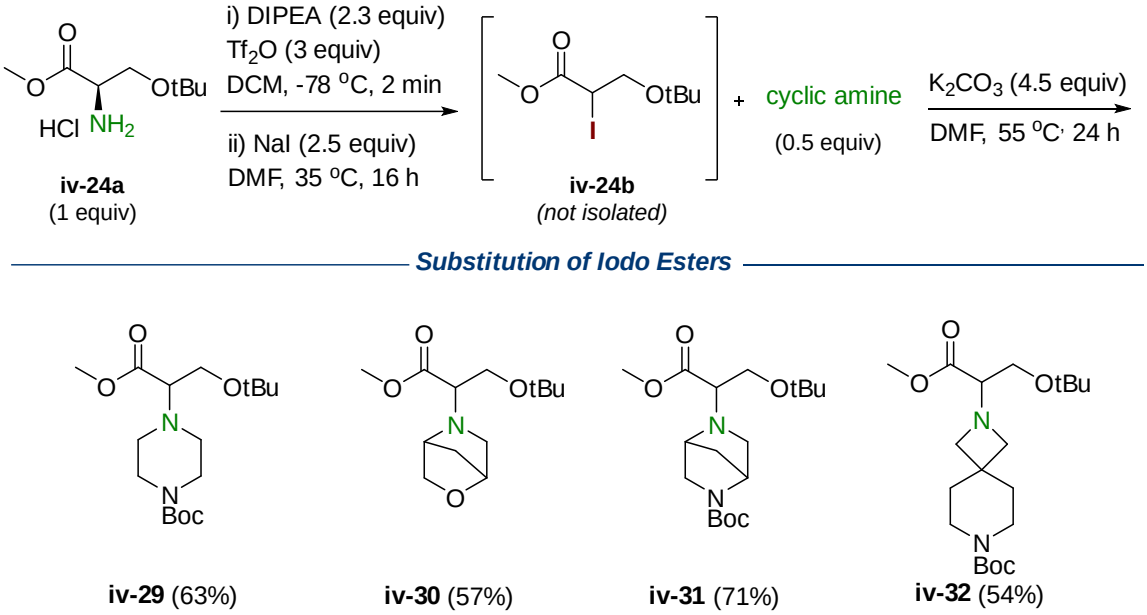


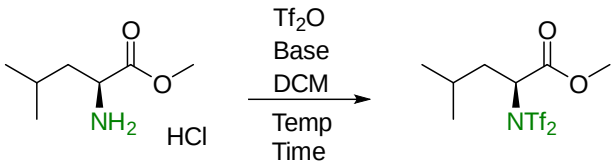
Figure 4-8: Iodo-ester in situ substitution.

Reaction conditions: i) Amino ester HCl (0.50 mmol), DIPEA (0.20 mL, 1.15 mmol), Tf_2O (0.30 mL, 1.5 mmol) and DCM (4.0 mL). ii) NaI (188 mg, 1.25 mmol) and DMF (4 mL). iii) amine nucleophile (0.25 mmol), K_2CO_3 (138 mg, 1 mmol).

produced **iv-30** in a 57% yield and an azetidine spirocycle formed compound **iv-32** in a 54% yield. Notably, these cyclic amino ester compounds are present in pharmaceutical chemistry and are sometimes made on process scale.[137, 138] Our chemistry offers an alternative way to access these difficult to synthesize and biologically relevant molecules.

4.2 Supporting Information

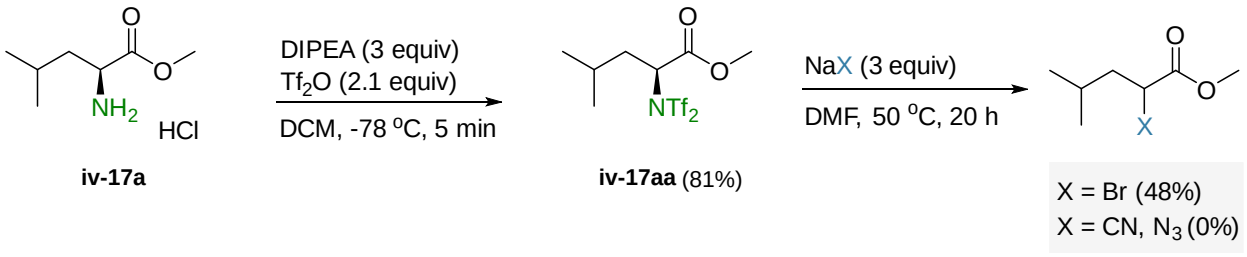
Table 4-2: Optimization for the *N*-ditriflation of amino esters.



iv-17a **iv-17aa**

Entry	Base (equiv)	Tf_2O (equiv)	Temp (°C)	Time	Isolated Yield (%)
1	DIPEA (4)	2.4	-78	5 min	38%
2	DIPEA (3.5)	2.4	-78	5 min	39%
3	DIPEA (5)	2.4	-78	5 min	31%
4	DIPEA (5)	3.5	-78	5 min	41%
5	DIPEA (4)	3	-78	5 min	51%
6	DIPEA (4)	4	-78	5 min	43%
7	DIPEA (4)	3	-78 -> 30	18 h	44%
8	DIPEA (3.5)	3	-78	1 min	52%
9	DIPEA (3)	3	-78	1 min	64%
10	DIPEA (2.5)	3	-78	1 min	78%
11	DIPEA (2.4)	3	-78	1 min	80%
12	DIPEA (2.3)	3	-78	1 min	84%
13	DIPEA (2.2)	3	-78	1 min	76%
14	DIPEA (2.3)	2.4	-78	1 min	57%
15	DIPEA (2)	2.4	-78	1 min	80%
16[a]	DIPEA (1.3)	3	-78	1 min	82%
17	DIPEA (3.5)	3	-78	1 min	52%

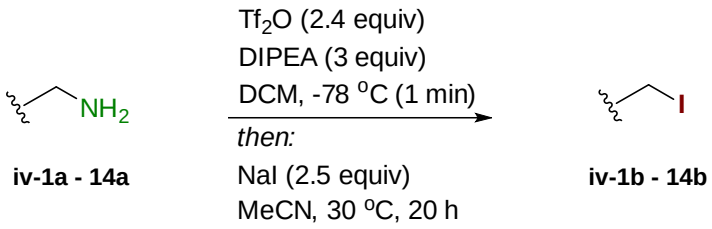
[a] Free base starting material



iv-17a **iv-17aa** (81%)

Figure 4-9: Two-step reaction of nucleophilic salts with amino triflimide intermediate.

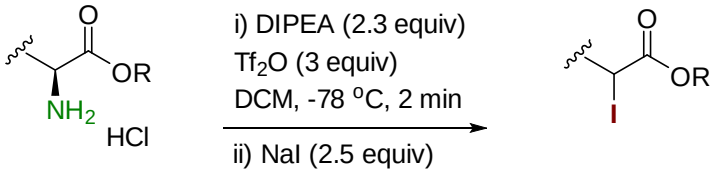
General Procedure A: Iodination of Amines



iv-1a - 14a **iv-1b - 14b**

Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of amine (0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed on silica gel to provide the desired iodide products. *(NOTE: most iodide products stain the TLC plate yellow under prolonged UV exposure)*

General Procedure B: Iodination of Amino Esters



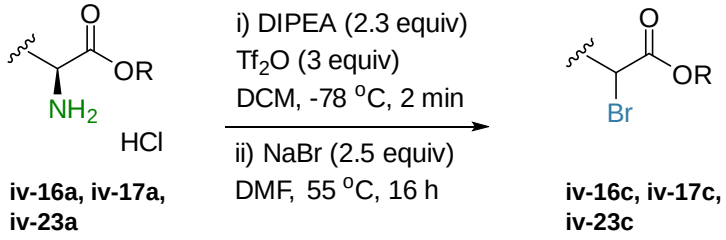
iv-16a - 17a
iv-22a - 28a

iv-16b - 17b
iv-22b - 28b

Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of amino ester HCl (0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the

combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Iodo-ester products were purified via column chromatography. *(NOTE: most iodo-ester products stain the TLC plate yellow under prolonged UV exposure)*

General Procedure C: Bromination of Amino Esters

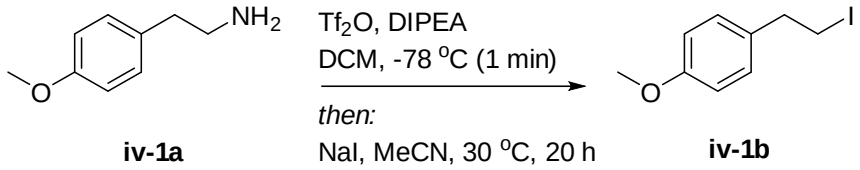


iv-16a, iv-17a, iv-23a → **iv-16c, iv-17c, iv-23c**

Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of amino ester HCl (0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting oil, NaBr (129 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with

DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Bromo ester products were purified via column chromatography.

1-(2-iodoethyl)-4-methoxybenzene (iv-1b)

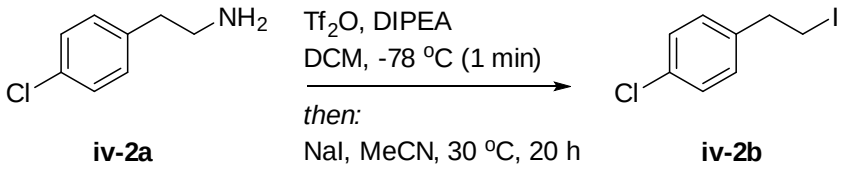


iv-1a **iv-1b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of 2-(4-methoxyphenyl)ethan-1-amine (0.07 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-5% EtOAc/Hex) to provide iodide **iv-1b** as a clear oil (126 mg, 96%).

R_f = 0.65 (EtOAc/Hex 5:95). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 7.03 (m, 2H), 6.90 – 6.80 (m, 2H), 3.80 (s, 3H), 3.32 (t, *J* = 8.3, 7.2, 1.0 Hz, 2H), 3.12 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.60, 132.96, 129.46 (2C), 114.13 (2C), 55.38, 39.65, 6.52. Spectra data are consistent with data previously reported for this compound.[139]

1-chloro-4-(2-iodoethyl)benzene (iv-2b)

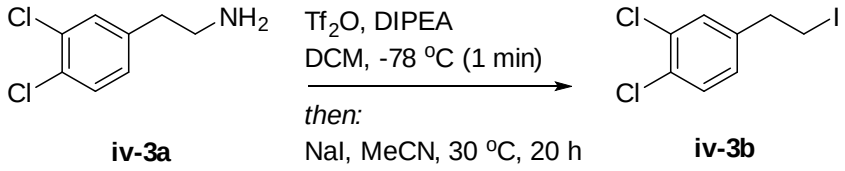


iv-2a **iv-2b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of 2-(4-chlorophenyl)ethan-1-amine (0.07 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-5% EtOAc/Hex) to provide iodide **iv-2b** as a clear oil (120 mg, 90%).

R_f = 0.80 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 2H), 7.15 – 7.10 (m, 2H), 3.33 (t, *J* = 7.6, 2H), 3.15 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.06, 132.84 (2C), 129.83 (2C), 128.93, 39.59, 5.30. Spectra data are consistent with data previously reported for this compound.[140]

1,2-dichloro-4-(2-iodoethyl)benzene (iv-3b)



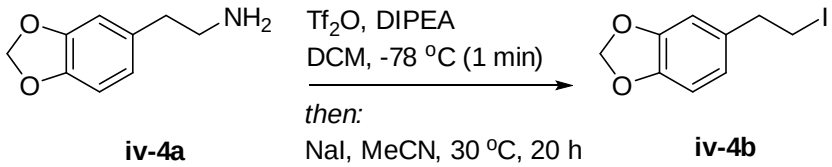
iv-3a **iv-3b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of 2-(3,4-dichlorophenyl)ethan-1-amine (0.08 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an

additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-5% EtOAc/Hex) to provide iodide **iv-3b** as a clear oil (144 mg, 94%).

R_f = 0.80 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 – 7.50 (m, 2H), 7.27 (dd, *J* = 8.3, 2.1 Hz, 1H), 3.49 (t, *J* = 7.3 Hz, 2H), 3.14 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 141.78, 130.85, 130.52, 130.37, 129.14, 128.96, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 37.68, 7.28. HRMS (ESI) *m/z*: 172.9919 calcd for $C_8H_7Cl_2^+$; $[M\text{-}HI+H]^+$ 172.9922 obsd.

5-(2-iodoethyl)benzo[d][1,3]dioxole (iv-4b)



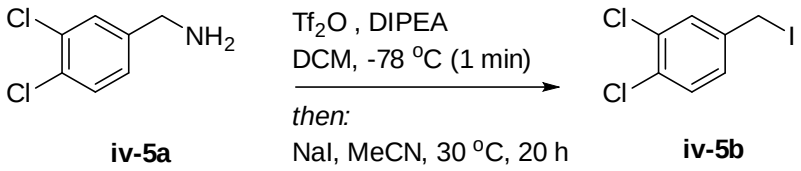
iv-4a **iv-4b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-amine (0.07 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-4b** as a clear oil (87 mg, 63%).

R_f = 0.72 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 7.8 Hz, 1H), 6.69 –

6.62 (m, 2H), 5.94 (s, 2H), 3.30 (t, *J* = 7.7 Hz, 2H), 3.08 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.91, 146.56, 134.64, 121.57, 108.84, 108.52, 101.14, 40.20, 6.21. Spectra data are consistent with data previously reported for this compound.[141]

1,2-dichloro-4-(iodomethyl)benzene (iv-5b)

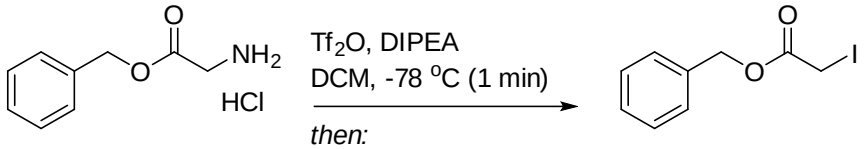


iv-5a **iv-5b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of (3,4-dichlorophenyl)methanamine (0.07 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-5% EtOAc/Hex) to provide iodide **iv-5b** as a white crystalline solid (125 mg, 87%).

R_f = 0.78 (EtOAc/Hex 15:85), Mp: 28-30 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.2 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.2 Hz, 1H), 4.36 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.64, 132.81, 132.05, 130.92, 130.68, 128.22, 2.68. Spectra data are consistent with data previously reported for this compound.[142, 143]

Benzyl 2-iodoacetate (iv-6b)

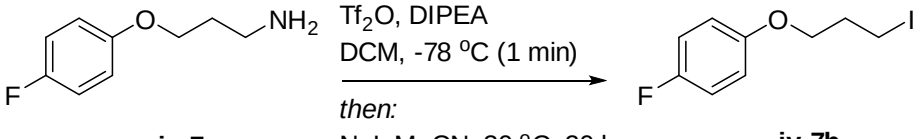


iv-6a **iv-6b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of benzyl glycinate HCl (101 mg, 0.50 mmol) and DIPEA (0.35 mL, 2.0 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-6b** as a yellowish oil (116 mg, 81%).

R_f = 0.55 (EtOAc/Hex 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 5H), 5.18 (s, 2H), 3.74 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.72, 135.26, 128.77 (2C), 128.66, 128.45 (2C), 67.93, -5.43. Spectra data are consistent with data previously reported for this compound.[144]

1-fluoro-4-(3-iodopropoxy)benzene (iv-7b)



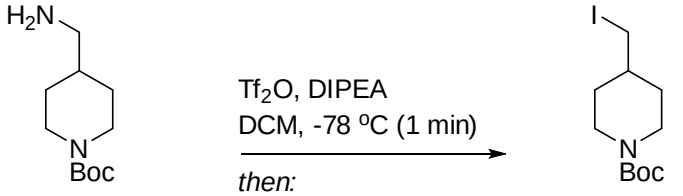
iv-7a **iv-7b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of 3-(4-fluorophenoxy)propan-1-amine (0.08 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an

additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-7b** as a clear oil (94 mg, 67%).

R_f = 0.70 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 – 6.93 (m, 2H), 6.93 – 6.78 (m, 2H), 4.00 (t, *J* = 5.8 Hz, 2H), 3.37 (t, *J* = 6.7 Hz, 2H), 2.26 (tt, *J* = 6.7, 5.8 Hz, 2H). ^{19}F NMR (377 MHz, $CDCl_3$) -124.26. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.51 (d, $^1J_{CF}$ = 238.6 Hz), 154.94 (d, $^4J_{CF}$ = 2.1 Hz), 116.10, 115.87, 115.74, 115.66, 68.08, 33.07, 2.58. HRMS (ESI) *m/z*: 153.0710 calcd for $C_9H_{10}FO^+$; $[M\text{-}HI+H]^+$ 153.0713 obsd.

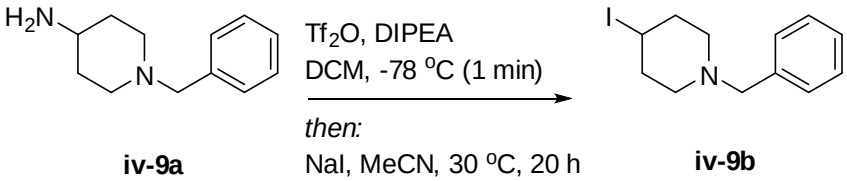
tert-butyl 4-(iodomethyl)piperidine-1-carboxylate (iv-8b)



According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (0.11 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-8b** as a clear oil (100 mg, 61%).

R_f = 0.30 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (d, *J* = 13.3 Hz, 2H), 3.10 (d, *J* = 6.5 Hz, 2H), 2.74 – 2.60 (m, 2H), 1.89 – 1.77 (m, 2H), 1.65 – 1.56 (m, 1H), 1.45 (s, 9H), 1.13 (ddd, *J* = 12.4, 4.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.82, 79.66, 43.63 (2C), 38.81 (2C), 32.73, 28.59 (3C), 13.62. Spectra data are consistent with data previously reported for this compound.[145]

1-benzyl-4-iodopiperidine (iv-9b)

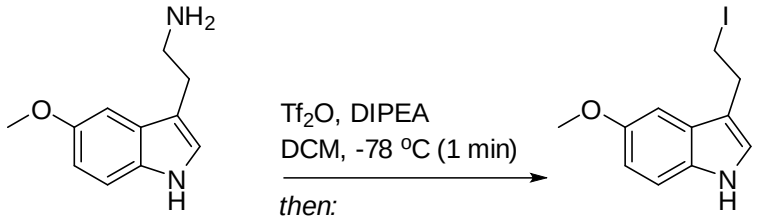


iv-9a **iv-9b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of 1-benzylpiperidin-4-amine (0.10 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-15% EtOAc/Hex) to provide iodide **iv-9b** as a clear oil (120 mg, 80%).

R_f = 0.25 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 4H), 7.26 – 7.21 (m, 1H), 4.29 (br.s, 1H), 3.48 (s, 2H), 2.69 – 2.57 (m, 2H), 2.32 – 2.05 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.40, 129.18, 128.39, 127.22, 63.27, 53.92 (2C), 38.41 (2C), 26.81. Spectra data are consistent with data previously reported for this compound.[146]

3-(2-iodoethyl)-5-methoxy-1H-indole (iv-10b)

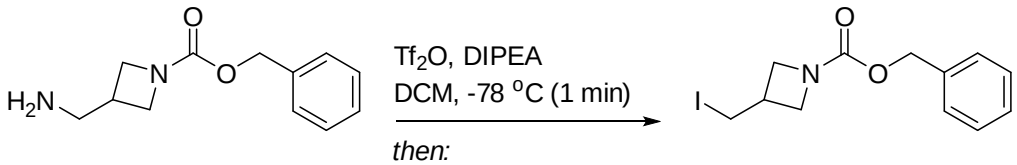


iv-10a **iv-10b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of 2-(5-methoxy-1H-indol-3-yl)ethan-1-amine (95 mg, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-10b** as a yellow viscous oil (50 mg, 33%).

R_f = 0.47 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br.s, 1H), 7.27 – 7.23 (m, 1H), 7.05 (d, *J* = 2.5 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.86 (s, 3H), 3.47 – 3.37 (m, 2H), 3.34 – 3.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.31, 131.45, 127.31, 122.81, 115.47, 112.57, 112.14, 100.50, 56.12, 30.52, 6.22. Spectra data are consistent with data previously reported for this compound.[147]

Benzyl 3-(iodomethyl)azetidine-1-carboxylate (iv-11b)

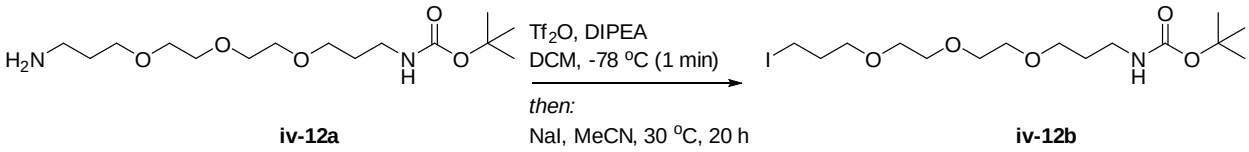


iv-11a **iv-11b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of benzyl 3-(aminomethyl)azetidine-1-carboxylate (0.09 mL, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-30% EtOAc/Hex) to provide iodide **iv-11b** as a clear oil (139 mg, 83%).

R_f = 0.15 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 5.10 (s, 2H), 4.05 (t, *J* = 8.6 Hz, 2H), 3.62 (dd, *J* = 9.0, 5.4 Hz, 2H), 3.33 (d, *J* = 7.8 Hz, 2H), 3.01 – 2.88 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.33, 136.67, 128.63 (2C), 128.23, 128.13 (2C), 66.87, 55.55 (2C), 32.33, 8.50. HRMS (ESI) *m/z*: 332.0142 calcd for $C_{12}H_{15}INO_2^+$; $[M+H]^+$ 332.0153 obsd.

tert-butyl (3-(2-(2-(3-iodopropoxy)ethoxy)ethoxy)propyl)carbamate (iv-12b)



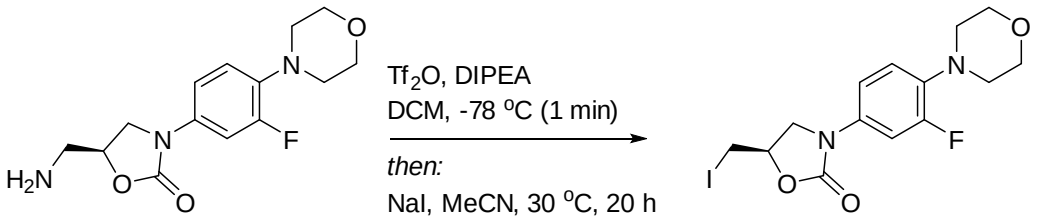
iv-12a **iv-12b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of tert-butyl (3-(2-(2-(3-aminopropoxy)ethoxy)ethoxy)propyl)carbamate HCl (150 mg, 0.50 mmol) and DIPEA (0.35 mL, 2.0 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and

chromatographed (0-30% EtOAc/Hex) to provide iodide **iv-12b** as a yellowish oil (183 mg, 85%).

R_f = 0.30 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (br.s, 1H), 3.71 – 3.57 (m, 8H), 3.57 – 3.49 (m, 4H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.25 – 3.19 (m, 2H), 2.12 – 2.02 (m, 2H), 1.80 – 1.70 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.16, 79.04, 77.48, 70.74, 70.72, 70.67, 70.53, 70.39, 69.79, 38.75, 33.49, 29.76, 28.60 (3C), 3.57. HRMS (ESI) *m/z*: 432.1241 calcd for $C_{15}H_{31}INO_5^+$; $[M+H]^+$ 432.1241 obsd.

(R)-3-(3-fluoro-4-morpholinophenyl)-5-(iodomethyl)oxazolidin-2-one (iv-13b)



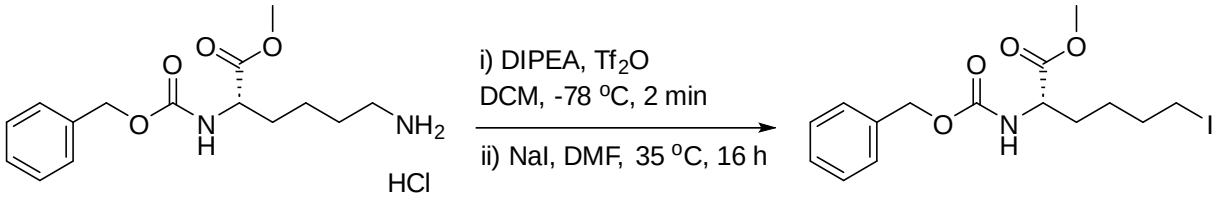
iv-13a **iv-13b**

According to General Procedure A, Tf_2O (0.20 mL, 1.2 mmol) was added to a solution of (S)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (148 mg, 0.50 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s and removed from the acetone bath. At rt, NaI (188 mg, 1.25 mmol) and MeCN (2 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-50% EtOAc/Hex) to provide iodide **iv-13b** as a white powder (41%).

R_f = 0.48 (EtOAc/Hex 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 14.2, 2.6 Hz, 1H), 7.07 (ddd, *J* = 8.8, 2.7, 1.2 Hz, 1H), 6.92 – 6.82 (m, 1H), 4.71 – 4.60 (m, 1H), 4.06 (t, *J* = 8.9 Hz,

1H), 3.82 – 3.78 (m, 4H), 3.68 (dd, *J* = 9.2, 6.1 Hz, 1H), 3.40 (dd, *J* = 10.4, 3.9 Hz, 1H), 3.28 (dd, *J* = 10.4, 8.3 Hz, 1H), 3.01 – 2.97 (m, 4H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -120.63. ^{13}C NMR (101 MHz, $CDCl_3$) δ155.66 (d, $^1J_{CF}$ = 246.5 Hz), 154.06, 136.79 (d, $^3J_{CF}$ = 9.0 Hz), 132.95 (d, $^2J_{CF}$ = 10.4 Hz), 119.00 (d, $^3J_{CF}$ = 4.2 Hz), 114.21 (d, $^4J_{CF}$ = 3.3 Hz), 107.77 (d, $^2J_{CF}$ = 26.3 Hz), 71.36, 67.09 (2C), 51.25, 51.14, 51.11, 6.09. Spectra data are consistent with data previously reported for this compound.[148]

Methyl (S)-2-(((benzyloxy)carbonyl)amino)-6-iodohexanoate (iv-14b)



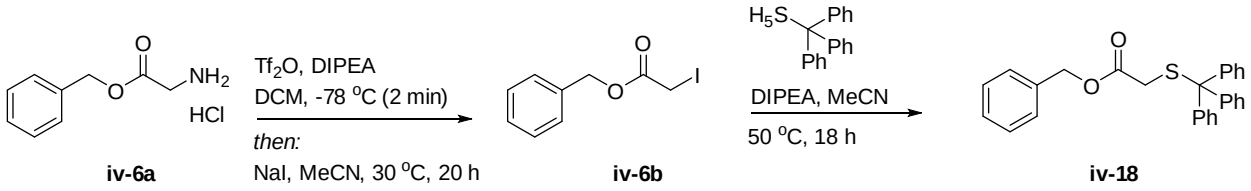
iv-14a **iv-14b**

According to a modified General Procedure A, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl ((benzyloxy)carbonyl)-L-lysinate HCl (165 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 30 s. The solution was stirred at -78 °C for an additional 30 s, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and MeCN (4 mL) were added and heated for 20 h at 40 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15

mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-30% EtOAc/Hex) produced iodide **iv-14b** as a yellowish oil (85 mg, 42%).

R_f = 0.32 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 5H), 5.33 – 5.26 (m, 1H), 5.11 (s, 2H), 4.43 – 4.35 (m, 1H), 3.75 (s, 3H), 3.16 (t, *J* = 6.9 Hz, 2H), 1.92 – 1.77 (m, 3H), 1.73 – 1.63 (m, 1H), 1.53 – 1.37 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.87, 155.96, 136.32, 128.70, 128.38, 128.27, 67.20, 53.70, 52.62, 32.81, 31.70, 26.14, 6.21.Spectra data are consistent with data previously reported for this compound.[149]

Benzyl 2-(tritylthio)acetate (iv-18)



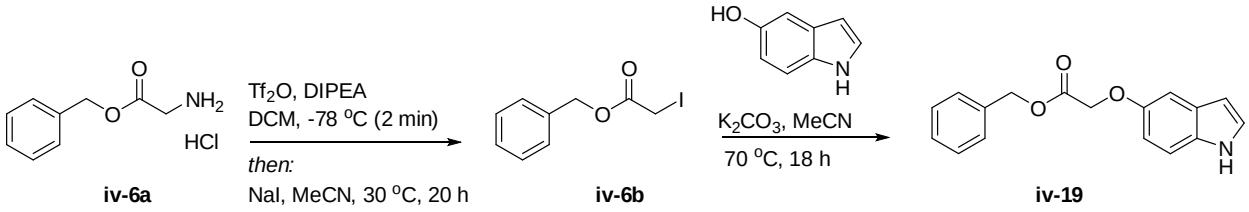
iv-6a **iv-6b** **iv-18**

According to General Procedure A (5x scale), Tf_2O (1.0 mL, 6.0 mmol) was added to a solution of benzyl glycinate HCl (505 mg, 2.5 mmol) and DIPEA (1.75 mL, 10 mmol) in DCM (20 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 60 s and removed from the acetone bath. At rt, NaI (940 mg, 6.25 mmol) and MeCN (10 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (20 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-6b** as a yellowish oil (500 mg, 72%). Tritylthiol (69 mg, 0.25 mmol) and DIPEA (0.09 mL, 0.50 mmol) were stirred in degassed MeCN (2 mL) for 15 min at 50 °C. Then, iodide **iv-6b** (85 mg, 0.30 mmol) in degassed MeCN (0.5 mL) was added to the reaction mixture where it was allowed to react for 18 h. The crude reaction mixture was put on silica and

chromatographed (0-15% EtOAc/Hex) to provide compound **iv-18** as a clear oil (61%).

R_f = 0.40 (EtOAc/Hex 15:85). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 6H), 7.34 – 7.30 (m, 3H), 7.29 – 7.24 (m, 10H), 7.22 – 7.19 (m, 2H), 5.00 (s, 2H), 3.01 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.63, 144.15 (2C), 135.50, 129.69 (5C), 128.67 (2C), 128.47, 128.44 (2C), 128.17 (5C), 128.06 (2C), 127.40, 127.03 (3C), 67.30, 67.24, 34.86. HRMS (ESI) *m/z*: 425.1570 calcd for $C_{28}H_{25}O_2S^+$; $[M+H]^+$ 425.1580 obsd.

Benzyl 2-((1H-indol-5-yl)oxy)acetate (iv-19)

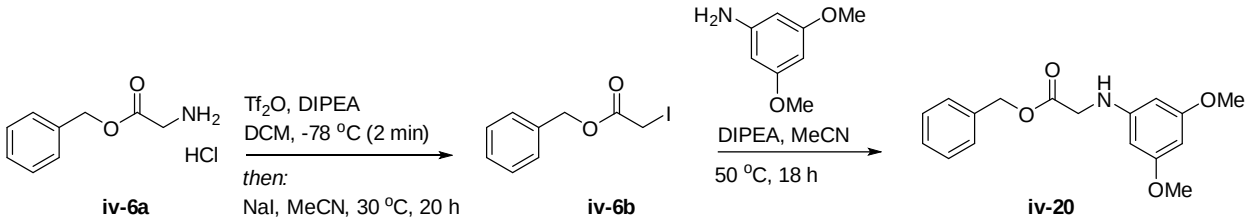


According to General Procedure A (5x scale), Tf_2O (1.0 mL, 6.0 mmol) was added to a solution of benzyl glycinate HCl (505 mg, 2.5 mmol) and DIPEA (1.75 mL, 10 mmol) in DCM (20 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 60 s and removed from the acetone bath. At rt, NaI (940 mg, 6.25 mmol) and MeCN (10 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (20 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-6b** as a yellowish oil (500 mg, 72%). 1*H*-indol-5-ol (33 mg, 0.25 mmol) and K_2CO_3 (86 mg, 0.625 mmol) were stirred in MeCN (2 mL) for 15 min at 70 °C. Then, iodide **iv-6b** (85 mg, 0.30 mmol) in MeCN (0.5 mL) was added to the reaction mixture where it was allowed to react for 18 h. The crude reaction mixture was put on silica and chromatographed (0-40% EtOAc/Hex) to provide compound **iv-19** as a clear oil (60 mg, 86%).

R_f = 0.50 (EtOAc/Hex 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.39 – 7.32 (m,

5H), 7.29 (dt, *J* = 8.8, 0.8 Hz, 1H), 7.19 (t, *J* = 2.8 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.51 – 6.42 (m, 1H), 5.25 (s, 2H), 4.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.60, 152.63, 135.49, 131.73, 128.74 (2C), 128.59, 128.57 (2C), 128.31, 125.23, 113.04, 111.96, 104.36, 102.70, 66.99, 66.84. HRMS (ESI) *m/z*: 282.1125 calcd for $C_{17}H_{16}NO_3^+$; $[M+H]^+$ 282.1134 obsd.

Benzyl (3,5-dimethoxyphenyl)glycinate (iv-20)

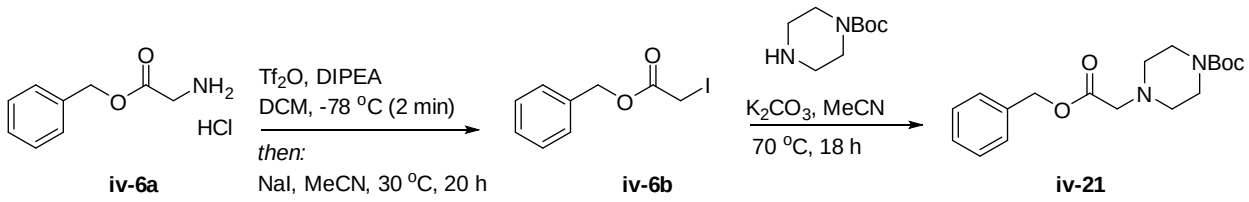


iv-6a **iv-6b** **iv-20**

According to General Procedure A (5x scale), Tf_2O (1.0 mL, 6.0 mmol) was added to a solution of benzyl glycinate HCl (505 mg, 2.5 mmol) and DIPEA (1.75 mL, 10 mmol) in DCM (20 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 60 s and removed from the acetone bath. At rt, NaI (940 mg, 6.25 mmol) and MeCN (10 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (20 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-6b** as a yellowish oil (500 mg, 72%). 3,5-dimethoxyaniline (38 mg, 0.25 mmol) and DIPEA (0.09 mL, 0.50 mmol) were stirred in MeCN (2 mL) for 15 min at 50 °C. Then, iodide **iv-6b** (85 mg, 0.30 mmol) in MeCN (0.5 mL) was added to the reaction mixture where it was allowed to react for 18 h. The crude reaction mixture was put on silica and chromatographed (0-35% EtOAc/Hex) to provide compound **iv-20** as yellow crystals (61 mg, 81%).

R_f = 0.40 (EtOAc/Hex 33:67), Mp: 59-61°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.92 (t, *J* = 2.2 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 2H), 5.22 (s, 2H), 4.31 (br.s, 1H), 3.93 (d, *J* = 5.1 Hz, 2H), 3.74 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.03, 161.90 (2C), 149.02, 135.42, 128.79 (2C), 128.67, 128.56 (2C), 92.04 (2C), 90.79, 67.23, 55.30 (2C), 46.00. HRMS (ESI) *m/z*: 302.1387 calcd for $C_{17}H_{20}NO_4^+$; $[M+H]^+$ 302.1398 obsd.

tert-butyl 4-(2-(benzyloxy)-2-oxoethyl)piperazine-1-carboxylate (iv-21)

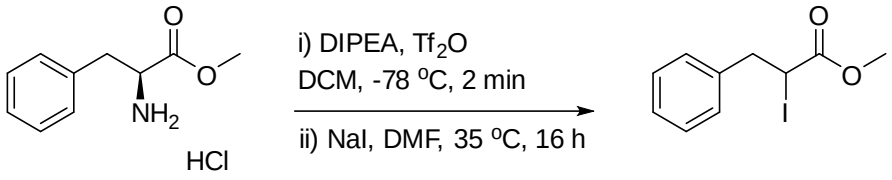


iv-6a **iv-6b** **iv-21**

According to General Procedure A (5x scale), Tf_2O (1.0 mL, 6.0 mmol) was added to a solution of benzyl glycinate HCl (505 mg, 2.5 mmol) and DIPEA (1.75 mL, 10 mmol) in DCM (20 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 60 s and removed from the acetone bath. At rt, NaI (940 mg, 6.25 mmol) and MeCN (10 mL) were added to the reaction mixture and heated for 20 h at 30 °C. The reaction mixture was quenched with the addition of DCM (20 mL) and chromatographed (0-10% EtOAc/Hex) to provide iodide **iv-6b** as a yellowish oil (500 mg, 72%). 1-Boc piperazine (47 mg, 0.25 mmol) and K_2CO_3 (86 mg, 0.625 mmol) were stirred in MeCN (2 mL) for 15 min at 70 °C. Then, iodide **iv-6b** (85 mg, 0.30 mmol) in MeCN (0.5 mL) was added to the reaction mixture where it was allowed to react for 18 h. The crude reaction mixture was put on silica and chromatographed (0-75% EtOAc/Hex) to provide compound **iv-21** as a yellowish oil (65 mg, 77%).

R_f = 0.29 (EtOAc/Hex 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 5H), 5.16 (s, 2H), 3.47 (t, *J* = 5.1 Hz, 4H), 3.28 (s, 2H), 2.53 (t, *J* = 5.0 Hz, 4H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.11, 154.80, 135.72, 128.75 (2C), 128.54, 128.51 (2C), 79.86, 66.58, 59.44, 52.79 (4C), 28.55 (3C). HRMS (ESI) *m/z*: 335.1965 calcd for $C_{18}H_{27}N_2O_4^+$; $[M+H]^+$ 335.1978 obsd

Methyl 2-iodo-3-phenylpropanoate (iv-16b)



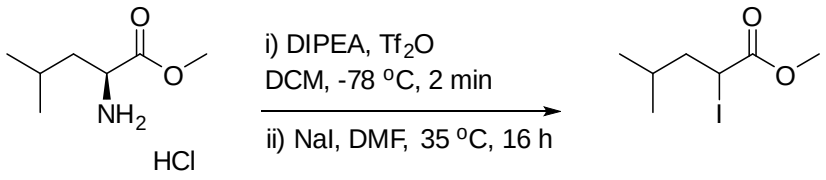
iv-16a **iv-16b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl L-phenylalaninate HCl (108 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-10% EtOAc/Hex) produced iodide **iv-16b** as a colourless oil (112 mg, 77%).

R_f = 0.70 (EtOAc/Hex 5:95), visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, $CDCl_3$) δ

7.33 – 7.25 (m, 3H), 7.21 – 7.17 (m, 2H), 4.52 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.70 (s, 3H), 3.46 (dd, *J* = 14.3, 9.1 Hz, 1H), 3.26 (dd, *J* = 14.3, 6.8 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.61, 138.58, 129.00, 128.84, 127.38, 52.99, 42.53, 20.03. Spectra data are consistent with data previously reported for this compound.[150]

Methyl 2-iodo-4-methylpentanoate (iv-17b)

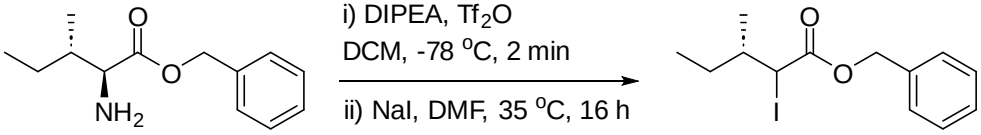


iv-17a **iv-17b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl L-leucinate HCl (91 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-10% EtOAc/Hex) produced iodide **iv-17b** as a colourless oil (102 mg, 80%).

R_f = 0.76 (EtOAc/Hex 5:95), visualized with $KMnO_4$ stain. ^1H NMR (700 MHz, $CDCl_3$) δ 4.38 (t, *J* = 7.9 Hz, 1H), 3.75 (s, 3H), 1.92 (ddd, *J* = 14.5, 8.0, 6.6 Hz, 1H), 1.82 (ddd, *J* = 14.2, 7.8, 7.2 Hz, 1H), 1.65 (dp, *J* = 13.4, 6.7 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.27, 52.98, 44.82, 28.41, 22.19, 21.74, 19.52. HRMS (ESI) *m/z*: 257.0033 calcd for $C_7H_{14}IO_2^+$; $[M+H^+]$ 257.0031 obsd.

Benzyl (3S)-2-iodo-3-methylpentanoate (iv-22b)



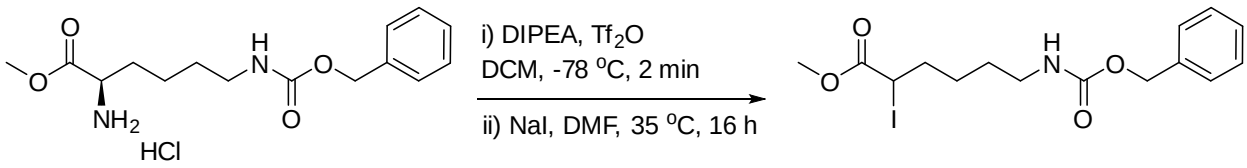
iv-22a **iv-22b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl L-leucinate (111 mg, 0.50 mmol) and DIPEA (0.11 mL, 0.65 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-10%

EtOAc/Hex) produced iodide **iv-22b** as a colourless oil (100 mg, 60%).

R_f = 0.70 (EtOAc/Hex 5:95), visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 4.0, 2.4 Hz, 7H), 7.36 – 7.31 (m, 2H), 5.19 – 5.17 (m, 3H), 4.33 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.22 (dd, *J* = 9.0, 1.2 Hz, 1H), 1.88 (dtdd, *J* = 9.8, 6.5, 3.3, 1.3 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.63 (qdd, *J* = 8.1, 6.3, 3.1 Hz, 1H), 1.41 (dddd, *J* = 12.1, 10.9, 5.5, 2.9 Hz, 1H), 1.29 – 1.21 (m, 2H), 1.07 (dd, *J* = 6.6, 1.3 Hz, 3H), 0.98 (dd, *J* = 6.7, 1.3 Hz, 3H), 0.89 (qd, *J* = 7.4, 1.3 Hz, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.94, 170.86, 135.47, 135.46, 128.73, 128.55, 128.43, 128.41, 67.56, 67.51, 38.37, 38.33, 32.74, 31.17, 28.87, 27.67, 19.44, 16.43, 11.52, 10.68. HRMS (ESI) *m/z*: 205.1223 calcd for $C_{13}H_{17}O_2^+$; $[M\text{-}HI+H]^+$ 205.1223 obsd.

Methyl 6-(((benzyloxy)carbonyl)amino)-2-iodohexanoate (iv-23b)



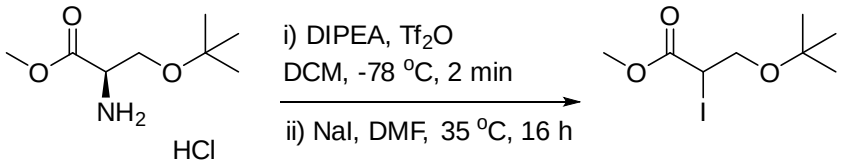
iv-23a **iv-23b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl N^6-((benzyloxy)carbonyl)-D-lysinate HCl (165 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil,

NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-30% EtOAc/Hex) produced iodide **iv-23b** as a colourless oil (103 mg, 51%).

R_f = 0.60 (EtOAc/Hex 40:60), visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 4H), 7.33 – 7.29 (m, 1H), 5.09 (s, 2H), 4.82 (t, *J* = 6.1 Hz, 1H), 4.28 (t, *J* = 7.4 Hz, 1H), 3.74 (s, 3H), 3.19 (q, *J* = 6.7 Hz, 2H), 2.02 – 1.93 (m, 2H), 1.57 – 1.49 (m, 2H), 1.48 – 1.40 (m, 1H), 1.34 – 1.26 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.91, 156.48, 136.67, 128.64 (3C), 128.23 (2C), 77.34, 77.16, 76.98, 66.75, 53.07, 53.00, 40.75, 35.71, 29.18, 26.62, 20.15. HRMS (ESI) *m/z*: 406.0510 calcd for $C_{15}H_{21}INO_4^+$; $[M+H]^+$ 406.0518 obsd.

Methyl 3-(tert-butoxy)-2-iodopropanoate (iv-24b)



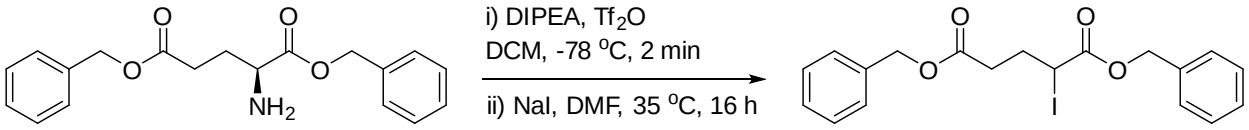
iv-24a **iv-24b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl O-(tert-butyl)-D-serinate HCl (106 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were

washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-15% EtOAc/Hex) produced iodide **iv-24b** as a colourless oil (88 mg, 62%).

R_f = 0.70 (EtOAc/Hex 10:90), visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.29 (dd, *J* = 9.5, 5.6 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.76 (s, 3H), 3.61 (dd, *J* = 9.6, 5.6 Hz, 1H), 1.18 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.02, 74.38, 65.16, 52.95, 27.62, 27.33 (3C), 18.41. HRMS (ESI) *m/z*: 159.1016 calcd for $C_8H_{15}O_3^+$; $[M\text{-}HI+H]^+$ 159.1012 obsd.

Dibenzyl 2-iodopentanedioate (iv-25b)



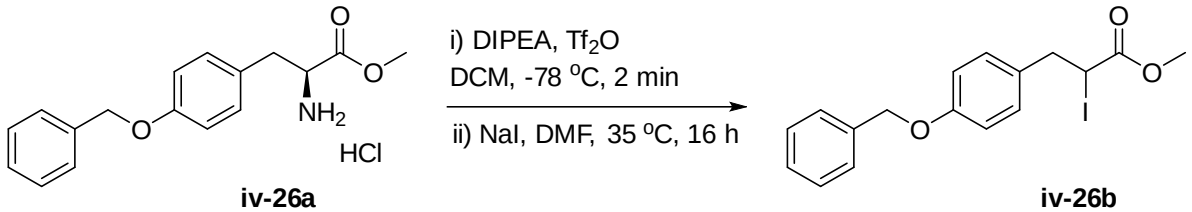
iv-25a **iv-25b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of dibenzyl L-glutamate (164 mg, 0.50 mmol) and DIPEA (0.11 mL, 0.65 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced

pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-10% EtOAc/Hex) produced iodide **iv-25b** as a colourless oil (140 mg, 64%).

R_f = 0.65 (EtOAc/Hex 10:90), visualized with $KMnO_4$ stain.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 10H), 5.18 (d, J = 4.3 Hz, 2H), 5.12 (s, 2H), 4.50 (t, J = 7.4 Hz, 1H), 2.56 – 2.45 (m, 2H), 2.31 (t, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.82, 170.90, 135.79, 135.25, 128.81 (4C), 128.75, 128.61, 128.50, 128.43, 128.40 (2C), 128.38 (2C), 67.72, 66.72, 33.74, 31.04, 19.57. HRMS (ESI) *m/z*: 439.0401 calcd for $C_{19}H_{20}IO_4^+$; $[M+H]^+$ 439.0401 obsd.

Methyl 3-(4-(benzyloxy)phenyl)-2-iodopropanoate (iv-26b)



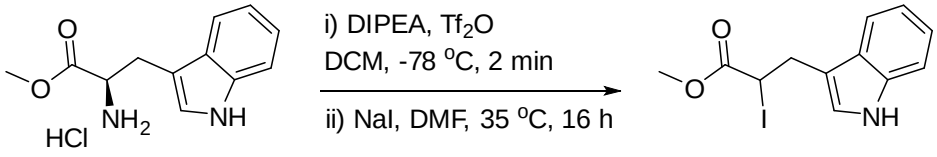
iv-26a **iv-26b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl (S)-2-amino-3-(4-(benzyloxy)phenyl)propanoate HCl (166 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the

combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-30% EtOAc/Hex) produced iodide **iv-26b** as a white solid (135 mg, 68%).

R_f = 0.68 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. Mp: 91-93°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.30 (m, 5H), 7.07 – 7.01 (m, 2H), 6.96 – 6.89 (m, 2H), 5.05 (s, 2H), 4.49 (t, *J* = 5.4 Hz, 1H), 3.78 (s, 3H), 3.16 (dd, *J* = 14.1, 5.1 Hz, 1H), 3.08 (dd, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.35, 158.59, 136.92, 130.66, 128.77, 128.20, 127.63, 126.03, 115.47, 70.20, 57.92, 53.16, 38.92. HRMS (ESI) *m/z*: 269.1172 calcd for $C_{17}H_{17}O_3^+$; $[M\text{-}HI+H]^+$ 269.1172 obsd.

Methyl 3-(1H-indol-3-yl)-2-iodopropanoate (iv-27b)



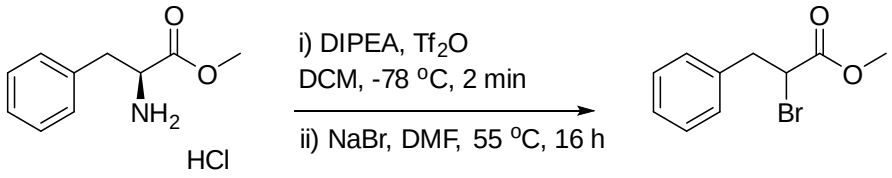
iv-27a **iv-27b**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl D-tryptophanate HCl (127 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The

aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-20% EtOAc/Hex) produced iodide **iv-27b** as a colourless oil (21 mg, 13%).

R_f = 0.68 (EtOAc/Hex 10:90), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 1H), 7.61 – 7.56 (m, 1H), 7.47 – 7.38 (m, 2H), 7.26 (s, 2H), 4.60 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.73 (s, 3H), 3.59 (dd, *J* = 15.2, 8.9, 1.0 Hz, 1H), 3.38 (dd, *J* = 15.3, 6.7, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.41, 135.68, 130.16, 126.44, 125.13, 124.23, 122.38, 119.69, 114.20, 53.21, 32.01, 16.60. HRMS (ESI) *m/z*: 329.9986 calcd for $C_{12}H_{13}INO_2^+$; [M+H$^+$] 329.9987 obsd.

Methyl 2-bromo-3-phenylpropanoate (iv-16c)



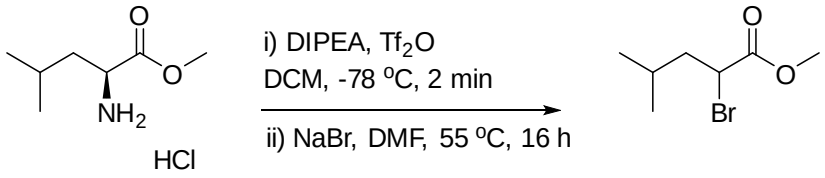
iv-16a **iv-16c**

According to General Procedure C, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution methyl L-phenylalaninate HCl (108 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4

mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting oil, NaBr (129 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-5% EtOAc/Hex) produced bromide **iv-16c** as a colourless oil (28 mg, 23%).

R_f = 0.90 (EtOAc/Hex 10:90), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.11 (m, 5H), 4.41 (dd, *J* = 8.4, 7.1 Hz, 1H), 3.73 (s, 3H), 3.47 (dd, *J* = 14.1, 8.4 Hz, 1H), 3.25 (dd, *J* = 14.1, 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.02, 136.85, 129.30 (2C), 128.82 (2C), 127.49, 53.06, 45.22, 41.27. Spectra data are consistent with data previously reported for this compound.[151]

Methyl 2-bromo-4-methylpentanoate (iv-17c)



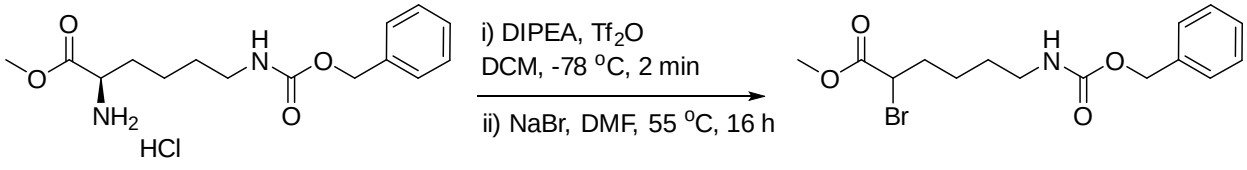
iv-17a **iv-17c**

According to General Procedure C, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution

methyl L-leucinate HCl (91 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting oil, NaBr (129 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-5% EtOAc/Hex) produced bromide **iv-17c** as a colourless oil (30 mg, 29%).

R_f = 0.85 (EtOAc/Hex 10:90), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, *J* = 8.0, 7.4 Hz, 1H), 3.78 (s, 3H), 1.96 – 1.87 (m, 2H), 1.77 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.73, 53.05, 44.48, 43.64, 26.48, 22.49, 21.69. Spectra data are consistent with data previously reported for this compound.[151]

Methyl 6-(((benzyloxy)carbonyl)amino)-2-bromohexanoate (iv-23c)



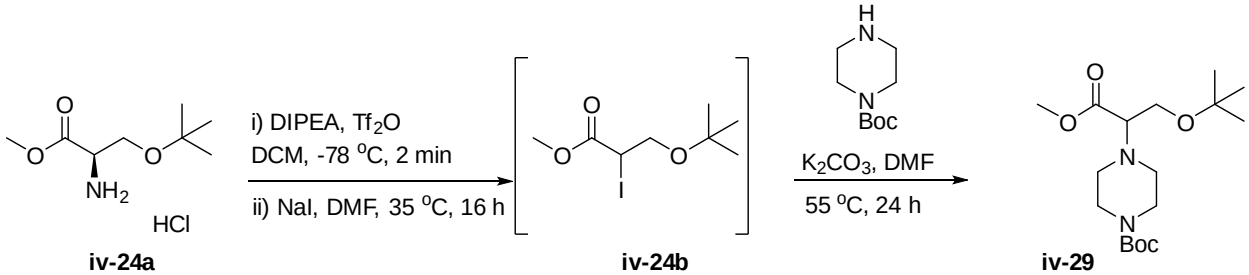
iv-23a **iv-23c**

According to General Procedure C, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution

methyl N^6-((benzyloxy)carbonyl)-D-lysinate HCl (165 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting oil, NaBr (129 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-30% EtOAc/Hex) produced bromide **iv-23c** as a colourless oil (36 mg, 20%).

R_f = 0.48 (EtOAc/Hex 33:67), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 5.10 (s, 2H), 4.75 (s, 1H), 4.21 (t, *J* = 7.4 Hz, 1H), 3.78 (s, 3H), 3.21 (q, *J* = 6.5 Hz, 2H), 2.12 – 1.95 (m, 2H), 1.62 – 1.46 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.34, 156.52, 136.69, 128.69 (3C), 128.28 (2C), 66.83, 53.13, 45.48, 40.80, 34.55, 29.39, 24.56. HRMS (ESI) *m/z*: 358.0648 calcd for $C_{15}H_{21}BrNO_4^+$; $[M+H]^+$ 358.0658 obsd.

***tert*-butyl 4-(3-(tert-butoxy)-1-methoxy-1-oxopropan-2-yl)piperazine-1-carboxylate (iv-29)**

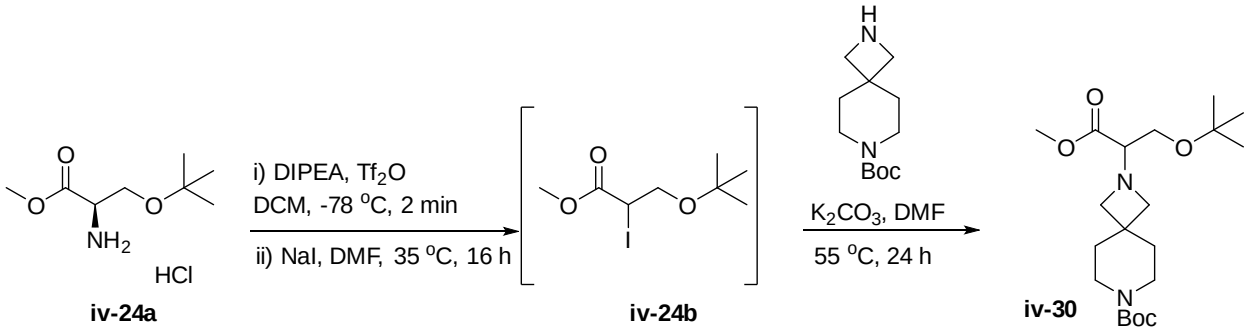


iv-24a **iv-24b** **iv-29**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl O-(tert-butyl)-D-serinate HCl (106 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C to form the iodide **iv-24b** in situ. Then, 1-Boc piperazine (47 mg, 0.25 mmol) and K_2CO_3 (155 mg, 1.13 mmol) in DMF (0.5 mL) were stirred at 55 °C for 10 min and added directly to the iodide-containing reaction mixture to react for 24 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (2 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-50% EtOAc/Hex) provided cyclic amino ester **iv-29** as a clear oil (54 mg, 63%).

R_f = 0.30 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 4H), 3.62 – 3.55 (m, 1H), 3.46 – 3.33 (m, 5H), 2.64 – 2.53 (m, 4H), 1.44 (s, 9H), 1.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.44, 154.82, 79.75, 73.49, 68.30, 60.68, 51.46, 50.43 (2C), 44.28 (2C), 28.56, 27.50. HRMS (ESI) *m/z*: 345.2384 calcd for $C_{17}H_{33}N_2O_5^+$; $[M+H]^+$ 345.2397 obsd.

tert-butyl 2-(3-(tert-butoxy)-1-methoxy-1-oxopropan-2-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (iv-30)

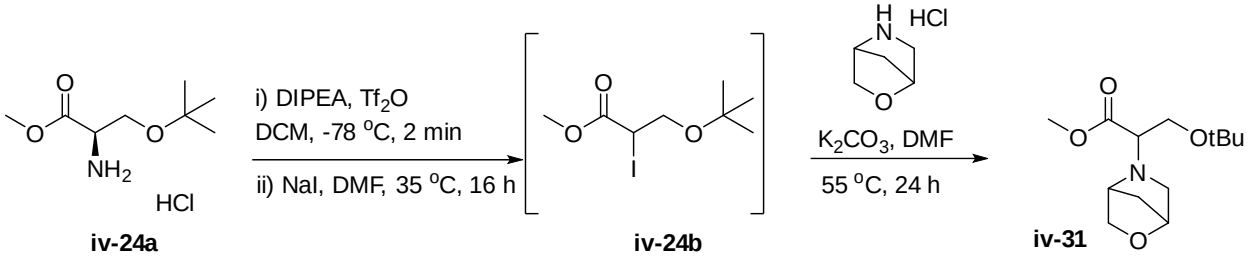


According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl O-(tert-butyl)-D-serinate HCl (106 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C to form the iodide **iv-24b** in situ. Then, *tert*-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (56 mg, 0.25 mmol) and K_2CO_3 (155 mg, 1.13 mmol) in DMF (0.5 mL) were stirred at 55 °C for 10 min and added directly to the iodide-containing reaction mixture to react for 24 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (3 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-40% EtOAc/Hex) provided cyclic amino ester **iv-30** as a clear oil (104 mg, 54%).

R_f = 0.33 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. ^1H NMR (400 MHz, $CDCl_3$) δ

3.71 (s, 3H), 3.58 – 3.43 (m, 2H), 3.35 – 3.26 (m, 4H), 3.27 – 3.22 (m, 1H), 3.19 (s, 4H), 1.75 – 1.62 (m, 4H), 1.44 (s, 9H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.69, 155.03, 79.54, 73.45, 69.97, 62.90 (2C), 61.67, 51.78, 41.03 (2C), 35.94 (2C), 34.84, 28.58 (3C), 27.46 (3C). HRMS (ESI) *m/z*: 385.2697 calcd for $C_{20}H_{37}N_2O_5^+$; $[M+H]^+$ 385.2707 obsd.

Methyl 2-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-(tert-butoxy)propanoate (iv-31)



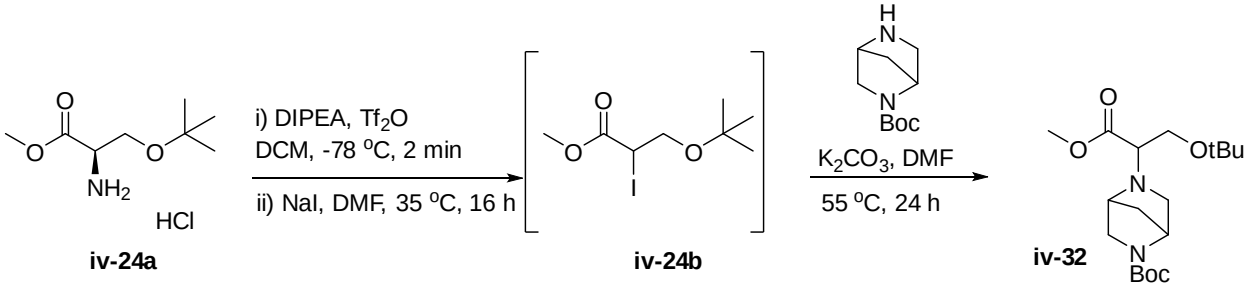
iv-24a **iv-24b** **iv-31**

According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl O-(tert-butyl)-D-serinate HCl (106 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25 mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C to form the iodide **iv-24b** in situ. Then, 2-oxa-5-azabicyclo[2.2.1]heptane HCl (34 mg, 0.25 mmol) and K_2CO_3 (190 mg, 1.38 mmol) in DMF (0.5 mL) were stirred at 55 °C for 10 min and added directly to the iodide-containing reaction mixture to react for 24 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts

were washed with H_2O (3 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-40% EtOAc/Hex) provided cyclic amino ester **iv-31** as a clear oil (37 mg, 57%).

R_f = 0.32 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, *J* = 6.4, 2.1 Hz, 1H), 4.14 – 3.97 (m, 1H), 3.74 (s, 3H), 3.65 – 3.47 (m, 4H), 3.19 – 3.02 (m, 1H), 2.69 – 2.45 (m, 1H), 1.97 – 1.81 (m, 1H), 1.79 – 1.61 (m, 2H), 1.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.62, 172.47, 76.65, 76.51, 73.60, 73.56, 69.49, 69.38, 65.74, 65.66, 63.12, 62.72, 60.45, 60.40, 59.45, 59.03, 52.09, 51.97, 36.07, 35.93, 27.45 (3C). HRMS (ESI) *m/z*: 258.1700 calcd for $C_{13}H_{24}NO_4^+$; $[M+H]^+$ 258.1709 obsd.

tert-butyl 5-(3-(tert-butoxy)-1-methoxy-1-oxopropan-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (iv-32)

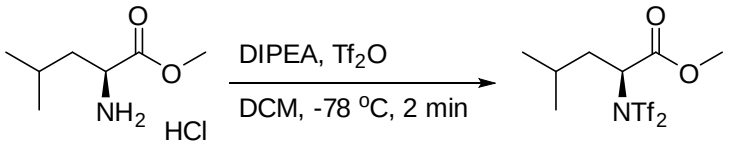


According to General Procedure B, Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl O-(tert-butyl)-D-serinate HCl (106 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. To the resulting crude oil, NaI (188 mg, 1.25

mmol) and DMF (4 mL) were added and heated for 16 h at 35 °C to form the iodide **iv-24b** in situ. Then, tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (50 mg, 0.25 mmol) and K_2CO_3 (155 mg, 1.13 mmol) in DMF (0.5 mL) were stirred at 55 °C for 10 min and added directly to the iodide-containing reaction mixture to react for 24 h at 55 °C. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts were washed with H_2O (3 × 15 mL), 10% LiCl (1 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (0-50% EtOAc/Hex) provided cyclic amino ester **iv-32** as a yellowish oil (63 mg, 71%).

R_f = 0.33 (EtOAc/Hex 50:50), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (dd, *J* = 52.3, 8.2 Hz, 1H), 3.73 (s, 3H), 3.63 – 3.41 (m, 4H), 3.23 – 3.06 (m, 2H), 2.77 – 2.48 (m, 1H), 1.92 – 1.76 (m, 1H), 1.75 – 1.63 (m, 1H), 1.45 (s, 9H), 1.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.68, 172.42, 154.34, 154.20, 79.50, 79.43, 77.48, 77.17, 76.85, 73.57, 73.52, 65.91, 65.58, 62.91, 62.69, 62.59, 60.49, 60.10, 59.56, 59.45, 59.08, 58.94, 58.06, 57.94, 57.59, 57.32, 56.49, 56.31, 52.00, 51.89, 50.38, 50.09, 49.43, 36.86, 36.45, 36.08, 36.03, 28.63 (3C), 27.42 (3C). HRMS (ESI) *m/z*: 357.2384 calcd for $C_{18}H_{33}N_2O_5^+$; $[M+H]^+$ 357.2395 obsd.

Methyl bis((trifluoromethyl)sulfonyl)-L-leucinate (iv-17aa)



iv-17a **iv-17aa**

Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl L-leucinate HCl (91 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s.

The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. Column chromatography (0-5% EtOAc/Hex) provided *N*-ditriflate **iv-17aa** as a colourless oil (166 mg, 81%).

R_f = 0.78 (EtOAc/Hex 5:95), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.85 (s, 3H), 2.25 – 2.15 (m, 1H), 1.89 – 1.76 (m, 2H), 0.99 (t, *J* = 6.2 Hz, 6H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.74 (6F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.76, 119.06 (q, $^1J_{CF}$ = 325.4 Hz, 2C), 65.23, 53.71, 39.72, 24.83, 22.40, 21.74. HRMS (ESI) *m/z*: 278.0668 calcd for $C_8H_{15}F_3NO_4S^+$; $[M\text{-}Tf+2H]^+$ 278.0600 obsd.

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Chapter 5 – Conclusions and Future Work

5.1 Sulfamate and Sulfamide CH Aminations

As exhibited in Chapter 2, our HFIPS sulfamoylation chemistry provides easy access to sulfamates and sulfamides from their corresponding alcohols and amines. This naturally leads to curiosities pertaining to new chemistry that has yet to be explored in this space. Pioneered by Du Bois in the 2000s, the most common type of synthetic chemistry utilizing sulfamates and sulfamides is intramolecular CH aminations (Figure 5-1).[152-154] These aminations were originally achieved via rhodium catalysis, however, recent developments accomplish this transformation with other metals such as palladium, or no transition metal at all (Figure 5-1).[155, 156]

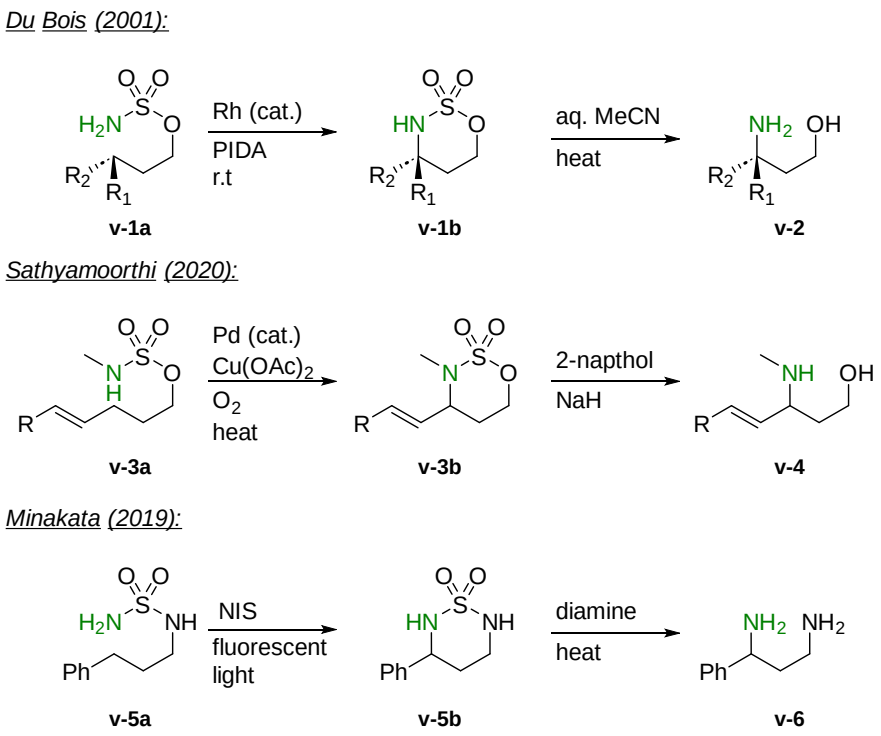


Figure 5-1: Previously reported routes for the CH aminations of sulfamates and sulfamides.

The ability to install a sulfamate or sulfamide amine into a sp^3 hybridized carbon has allowed for the synthesis of several natural products, however, I noticed that there has yet to be a report of CH amination into a sp^2 hybridized carbon.

With the ability to efficiently synthesize sulfamates and sulfamides, I propose future work to investigate the potential of aminating ortho to a phenol or aniline (Figure 5-2).

Proposed Idea:

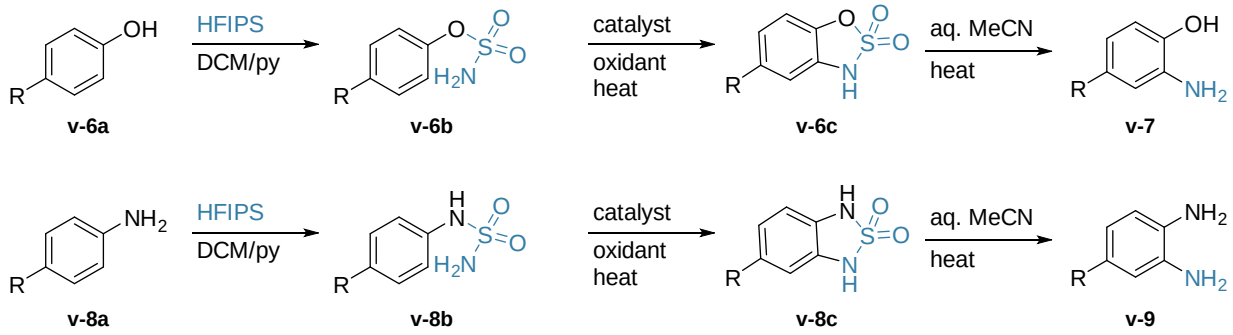


Figure 5-2: Proposed future work for the CH amination of aromatic sulfamates and sulfamides.

There are several issues with my proposal that should be acknowledged. Firstly, it should be noted that Du Bios has done extensive research into the mechanism(s) of their rhodium-catalyzed CH aminations and reports that the rhodium catalysts used prefer a 6-member transition state over a 5-member one (reaction **v-6b** to **v-6c**).[157] However, this is not to say that other transition metals, or a metal-free reaction, would not be able to undergo a mechanism involving a 5-member transition state. Furthermore, simply heating the rhodium-catalyzed chemistry may potentially allow for a 5-member transition state to occur.

Another difference with my proposal is that it requires a new sp^2 carbon bond, instead of the previously disclosed sp^3 carbon bonds. Although a seemingly large change, this may be beneficial to my proposal. The most commonly employed transition metals (such as palladium

and copper) prefer to insert between sp^2 C-H bonds over sp^3 C-H bonds.[158, 159] In fact, sp^3 carbon catalyzed reactions are oftentimes extremely troublesome and difficult to achieve.[160, 161] This may result in conditions similar to Sathyamoorthi's being utilized.[155]

The final difference between my proposal and previous work is that I am suggesting chemistry that involves unstable phenolic sulfamates (**v-6b**). Unlike aliphatic, aromatic sulfamates are known to eliminate under basic or harsh conditions.[162] (Note: aromatic sulfamides do not have these issues). This may be problematic because most known CH aminations involve either basic conditions or heat.[163] However, there are countless examples of CH aminations utilizing acidic conditions, and this is where I would start experimenting.[163, 164]

5.2 Undisclosed Amino Triflimide Chemistry

As demonstrated in Chapter 4, we have achieved the synthesis and subsequent reactions of novel amino triflimides. Although not disclosed in our manuscript, we started to investigate other sorts of chemistry that they may undergo. Our substitution chemistry did not require the isolation of the NTf_2 intermediates, however, we attempted to do so and react them with other nucleophiles to potentially synthesize enantiomerically pure products (Figure 5-3).

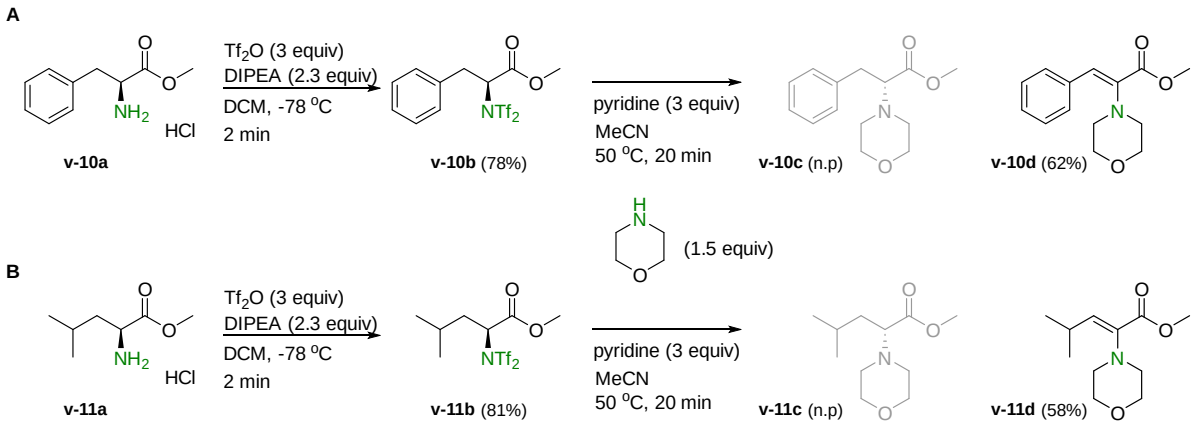


Figure 5-3: Reaction of amino triflate esters with morpholine.

Unfortunately, the desired product **v-10c** with inverted stereochemistry was not detected. Instead, we isolated and characterized the enamino-ester **v-10d** (Figure 5-3A). Interestingly, we were able to oxidize beta to the carbonyl, and suspected that this may have occurred because of our substrate choice, phenylalanine methyl ester **v-10a**. Benzylic protons oftentimes react unpredictably; therefore, we attempted the reaction with leucine methyl ester (Figure 5-3B). Once again, the desired product **v-11c** was not detected, and enamino-ester **v-11d** was isolated. Although unintentional, we hypothesize that this quick route to enamino-esters may have some use.

The first reaction explored was the hydrolysis of the enamino-ester **v-10d** (Figure 5-4). Pleasantly, the reaction proceeded as anticipated to produce compound **v-12** in a 52% yield.

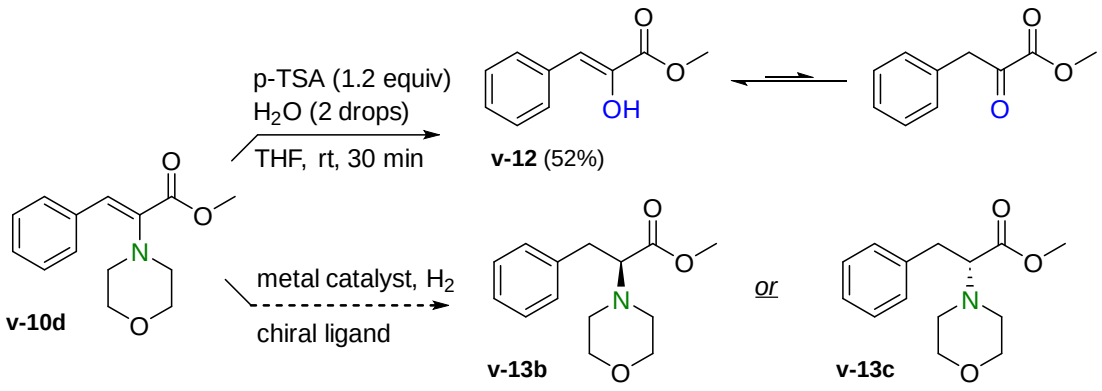


Figure 5-4: Ideas for enamino-ester chemistry.

These α-ketoesters and their corresponding α-oxocarboxylic acids are difficult to access, yet they are prominent in natural products, drugs, metabolism and more.[165] Furthermore, they are known to undergo a plethora of chemical transformations.[166-169] Having access to them from the readily available amino esters is an impactful development and should be further pursued in the Magolan Lab.

Another idea for future work is to asymmetrically hydrogenate the enamino-esters to yield the originally desired enantiomerically pure products (Figure 5-4). This seemingly more difficult reaction has yet to be attempted; however, I have found some relevant literature as a starting point for future work (Figure 5-5).[170-172] Although never performed on the exact substrates we have access to, similar work has previously been reported. Utilizing specific

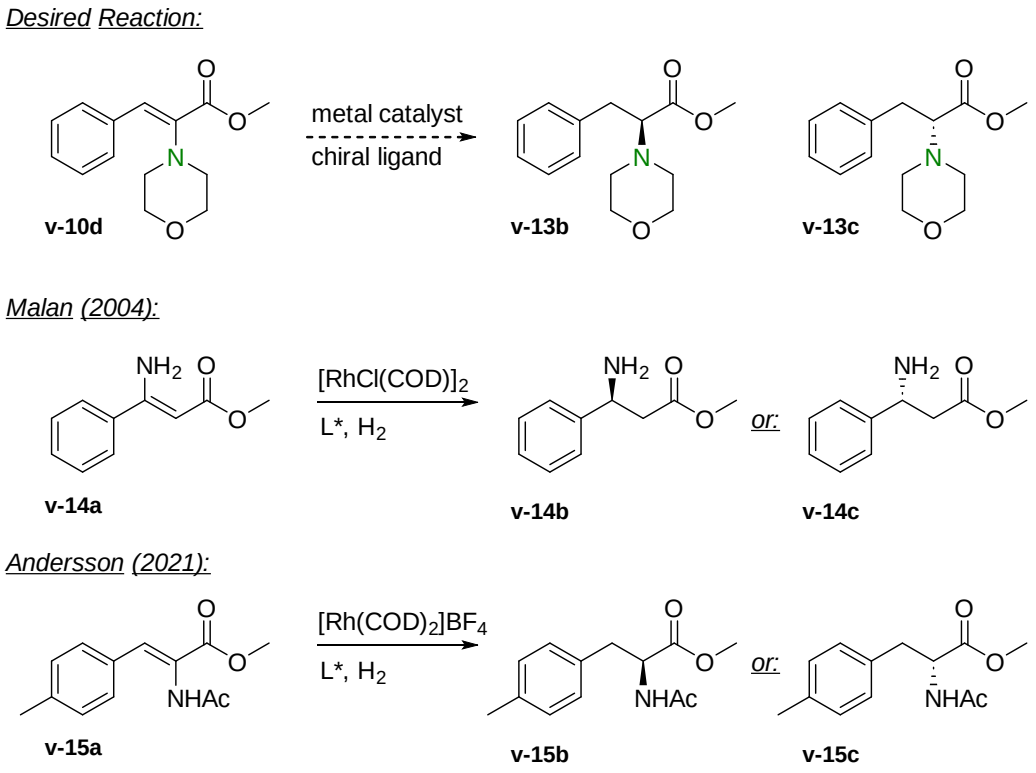


Figure 5-5: Previously reported relevant asymmetric hydrogenations.

rhodium catalysts and chiral iron or phosphine ligands, enantiomerically pure products may potentially be obtained.[171, 172] This is impactful because chiral cyclic amino ester compounds are prominent in drug discovery although challenging to access.[137, 138]

5.3 In Summary

In summary, we have developed an effective and efficient sulfamoylation procedure to synthesize sulfamates and sulfamides from their analogous alcohols and amines. By utilizing HFIPS as a sulfamoylation reagent, the byproducts are volatile, and the desired products can be easily purified and isolated. Furthermore, we have demonstrated that HFIPS can be synthesized on a decagram scale cost-effectively, has a multi-year long benchtop stability, and is compatible with a wide range of alcohol and amine nucleophiles. Since our publication, vendors such as Enamine have added HFIPS to their catalogs, making it commercially available as well.

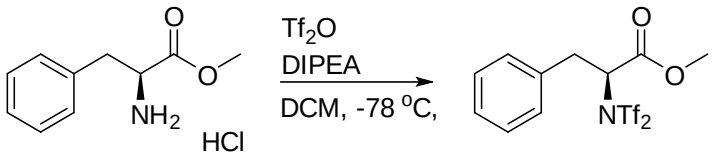
With a robust route to sulfamates and sulfamides in-hand, we have reported their copper-catalyzed *N*-(hetero)arylation. Using a readily available copper catalyst and amine ligand, we can *N*-arylate both sulfamates and sulfamides with the same set of conditions; a first of its kind. Furthermore, we are the first to report the *N*-arylation of sulfamides with a free NH, circumventing the need for protecting groups. This chemistry is impactful because although *N*-aryl sulfamates and sulfamides have biological implications, they have been challenging to access. To make them even more accessible, we have reported a two-step one-pot procedure to synthesize complex *N*-aryl sulfamates and sulfamides from their corresponding alcohol and amine precursors. Due to our sulfamoylation chemistry having volatile byproducts, once concentrated, the crude sulfamates and sulfamides can be subjected to our *N*-arylation chemistry.

Lastly, we have disclosed a practical substitution of amines. Although amines are traditionally known and utilized as nucleophiles, we have discovered that once functionalized into their corresponding *N*-ditriflyl analogues, they can also react as electrophiles. When

subjected to sodium iodide, the NTf_2 intermediates can be displaced to produce their iodinated analogue. This allows for ubiquitous and readily available amines to be transformed into difficult to obtain and expensive alkyl iodides. For example, we have shown that our chemistry is conducive with easily accessible amino esters to form non-commercially available iodo esters. These coveted alkyl iodides can then be reacted with any nucleophile to form a plethora of complex molecules. Moreover, we have proposed future work in this space to further expand the use of this novel class of compounds.

5.4 Supporting Information

Methyl bis((trifluoromethyl)sulfonyl)-L-phenylalaninate (v-10b)

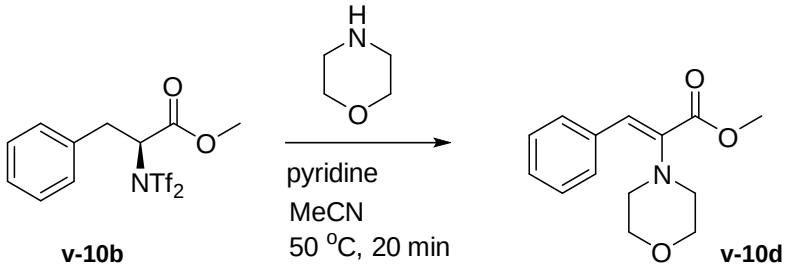


v-10a **v-10b**

Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl L-phenylalaninate HCl (108 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. Column chromatography (0-5% EtOAc/Hex) provided **v-10b** as a colourless oil (173 mg, 78%).

Rf = 0.65 (EtOAc/Hex 5:95), visualized with $KMnO_4$ stain. ^1H NMR (700 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H), 7.30 – 7.27 (m, 1H), 5.03 (dd, J = 9.1, 4.0 Hz, 1H), 3.81 (s, 3H), 3.71 (dd, J = 14.1, 9.1 Hz, 1H), 3.17 (dd, J = 14.1, 4.0 Hz, 1H).

Methyl-2-morpholino-3-phenylacrylate (v-10d)

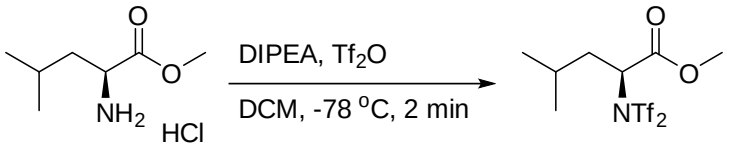


v-10b **v-10d**

Morpholine (39 mg, 0.45 mmol) and pyridine (0.07 mL, 0.9 mmol) were added in MeCN (3 mL) and stirred for 15 min at 50 °C. Then methyl bis((trifluoromethyl)sulfonyl)-L-phenylalaninate **v-10** (133 mg, 0.3 mmol) was added, and the solution was stirred for 20 min at 50 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-30% EtOAc/Hex) to provide **v-10d** as a clear oil (46 mg, 62%).

Rf = 0.48 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. ^1H NMR (700 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 3.82 (s, 3H), 3.77 (t, *J* = 4.6 Hz, 4H), 2.98 (t, *J* = 4.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.02, 139.14, 134.99, 130.24 (2C), 129.00, 128.38 (2C), 127.43, 67.45 (2C), 51.95, 50.36 (2C).

Methyl bis((trifluoromethyl)sulfonyl)-L-leucinate (v-11b)

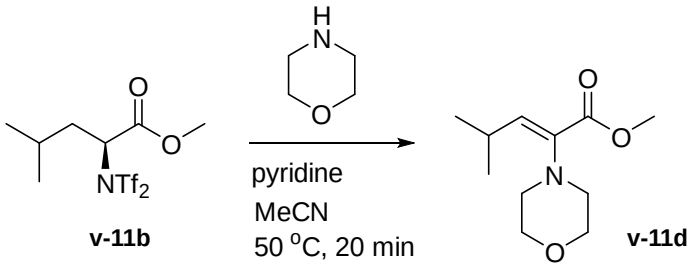


v-11a **v-11b**

Tf_2O (0.30 mL, 1.5 mmol) was added to a solution of methyl L-leucinate HCl (91 mg, 0.50 mmol) and DIPEA (0.20 mL, 1.15 mmol) in DCM (4 mL) at -78 °C dropwise over a period of 60 s. The solution was stirred at -78 °C for an additional 2 min, removed from the acetone bath and immediately quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure at a bath temperature of 40 °C. Column chromatography (0-5% EtOAc/Hex) provided **v-11b** as a colourless oil (166 mg, 81%).

R_f = 0.78 (EtOAc/Hex 5:95), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.85 (s, 3H), 2.25 – 2.15 (m, 1H), 1.89 – 1.76 (m, 2H), 0.99 (t, *J* = 6.2 Hz, 6H). ^{19}F NMR (377 MHz, $CDCl_3$) δ -71.74 (6F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.76, 123.91 - 114.22 (m, 2C), 65.23, 53.71, 39.72, 24.83, 22.40, 21.74. HRMS (ESI) *m/z*: 409.0088 calcd for $C_9H_{13}F_6NO_6S_2$; (M-Tf+2H$^+$) 278.0600 obsd.

Methyl-4-methyl-2-morpholinopent-2-enoate (v-11d)

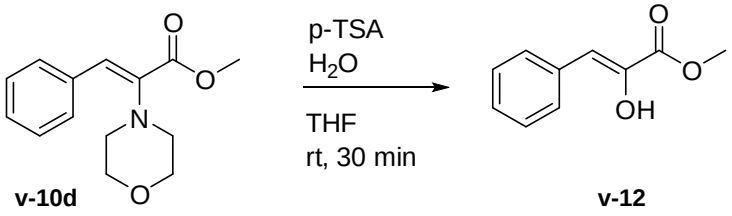


v-11b **v-11d**

Morpholine (39 mg, 0.45 mmol) and pyridine (0.07 mL, 0.9 mmol) were added in MeCN (3 mL) and stirred for 15 min at 50 °C. Then methyl bis((trifluoromethyl)sulfonyl)-L-leucinate **v-11b** (123 mg, 0.3 mmol) was added, and the solution was stirred for 20 min at 50 °C. The reaction mixture was quenched with the addition of DCM (10 mL) and chromatographed (0-30% EtOAc/Hex) to provide **v-10d** as a clear oil (37 mg, 58%).

R_f = 0.56 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, J = 9.9 Hz, 1H), 3.80 (s, 3H), 3.80 – 3.73 (m, 4H), 2.76 – 2.70 (m, 4H), 2.69 – 2.58 (m, 1H), 0.99 (d, J = 6.7 Hz, 6H).

Methyl-2-hydroxy-3-phenylacrylate (v-12)



v-10d **v-12**

p-toluene sulfonic acid:H_2O (37 mg, 0.20 mmol) and H_2O (2 drops) were added to a solution of methyl-2-morpholino-3-phenylacrylate **v-10d** (25 mg, 0.14 mmol) in THF (1.4 mL). The reaction was stirred at room temperature for 30 minutes and then quenched with the

addition of DCM (10 mL). The crude mixture was chromatographed (0-30% EtOAc/Hex) to provide **v-12** as white crystals (13 mg, 52%).

R_f = 0.48 (EtOAc/Hex 25:75), visualized with $KMnO_4$ stain (note: same rf as **v-10c**, but stains a different colour). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.41 – 7.32 (m, 3H), 7.31 – 7.27 (m, 1H), 7.26 – 7.21 (m, 1H), 6.53 (s, 1H), 3.93 (s, 3H).

5.5 References

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