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Regioselective Hydroamination of Unactivated Olefins with Diazirine and Total Synthesis of Nostodione A and Scytonemin

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Regioselective Hydroamination of Unactivated Olefins with Diazirine and Total Synthesis of Nostodione A and Scytonemin

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
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ACKNOWLEDGMENTS

When I was a kid, age 7 or 8, schoolteacher asked the class what you want to be in the future. Most of my classmates said they want to be scientists, astronauts, and all the fancy jobs. I told her I want to be a professional cook, and I announced to my parents I will be a great cook when I got home. Somehow my dream came true, organic chemists are also mixing things up and heating them for certain time.

At that time, my mom showed me how to use a knife, how to cut potatoes, how to pick vegetable and meat from market, etc. And I remembered my dad told me: “You need to understand the different between a professional cook and amateur cook first if you really want to be one; an amateur cook can make shrimp tastes wonderful, but that does not mean he is a great cook, shrimp itself tastes wonderful, no matter who cooks it. However, a professional cook can make anything tastes wonderful, even just a potato.”

I am never a genius or “as tasty as a shrimp” kind of kid, I have always been ordinary like a potato. And now, I am publishing my works, I am finishing up my PhD, working on all these wonderful things.

Dr. Lopchuk, my parents, my committees, and everybody who taught me something, I believe that makes you “professional cooks”.

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ABSTRACT

As an atom-economic way of carbon-nitrogen bond formation, hydroaminations are great tool for make amines, hydrazines, and other nitrogen-containing heterocycles. Specifically, radical hydroamination is a useful approach for functionalization of unactivated olefins, especially in sterically hindered environments. Diversification remains a challenge for radical hydroaminated products, since the nitrogen sources are carefully designed. In the first chapter of this dissertation, we report a highly diversifiable radical hydroamination reaction with diazirine as a nitrogen source and its potential applications in synthesis of several pharmaceutical interested compounds. Cobalt catalyzed regioselective hydroamination with diazirine shows wide function group tolerance, like phenyl thioether, ketones, esters, aldehydes, epoxy, and other function groups. More than 50 alkenes, with 16 from commercially available terpenes, shows possible synthetic application in complex molecules.

Nostodione A and scytonemin are secondary metabolite of cyanobacteria used by as UV screen pigment. After first isolation of scytonemin in 1993 and nostodione A in 1994, research was done in using scytonemin in many applications, like UV screen, radical scavenger, antiparasitic, and possible cell toxin for anti-cancer applications. The former synthetic works reported by Mårtensson and McNulty utilized center five membered ring construction as key steps with pre-set functional groups. In the second chapter of this dissertation, we reported Fisher indole synthesis based synthetic approach to synthetize both nostodione A and scytonemin from a common indole

intermediate. With cyclopentane ring from starting materials, we were able to cut the steps of synthesis of nostodione A from 9 steps to 6 steps and scytonemin, from 11 steps to 7 steps.

CHAPTER ONE: REGIOSELECTIVE HYDROAMINATION OF UNACTIVATED OLEFINS WITH DIAZIRINE

1.1 Nitrogen in Living Systems

Nitrogen is one of the most abundant elements inside the human body. By weight, the human body contains ~3.3% of nitrogen atoms, which is not as remarkable as oxygen (65%) and carbon (18.5%). However, this figure cannot represent the importance of nitrogen in the biological system, because nitrogen-containing functional groups can be found in amino acids, nucleic acids, and some lipids. These biomolecules build up proteins, genes, and membranes, which are responsible for most biotransformation in the living system. Based on the structures of different nitrogen-containing functional groups, they can be either hydrogen bond acceptors or, with a proton attached, hydrogen bond donors. Furthermore, the hydrogen-bonding system is essential for protein folding and DNA base pairing, which are critical for their biofunctions. Additionally, nitrogen-containing functional groups' dipole moment grants stronger ligand to protein binding affinity, at the same time, these functional groups can be basic for ionic interaction. Medicinal chemists take advantage of the extra binding affinities and install these functional groups inside drug molecules, making them more effective toward the target of interest.[1] As reported by Njardarson,[2] 84% of the FDA-approved drugs contain at least one nitrogen atom. Synthetic organic chemists and medicinal chemists have invented many methods to install these functional groups into drug molecules.

1.2 Examples of Amination Reactions in Drugs Synthesis

Fierce Pharma reported the top 20 drugs by worldwide sales in 2023.[2] All drugs in the report contained one or more nitrogen-containing functional groups. Excluding these antibody drugs and analyzing the small-

molecule drugs in the list, we can review the methods used in the medicinally interested molecules and the importance of amination methods in drug discovery.

1.2.1 Synthesis of Apixaban

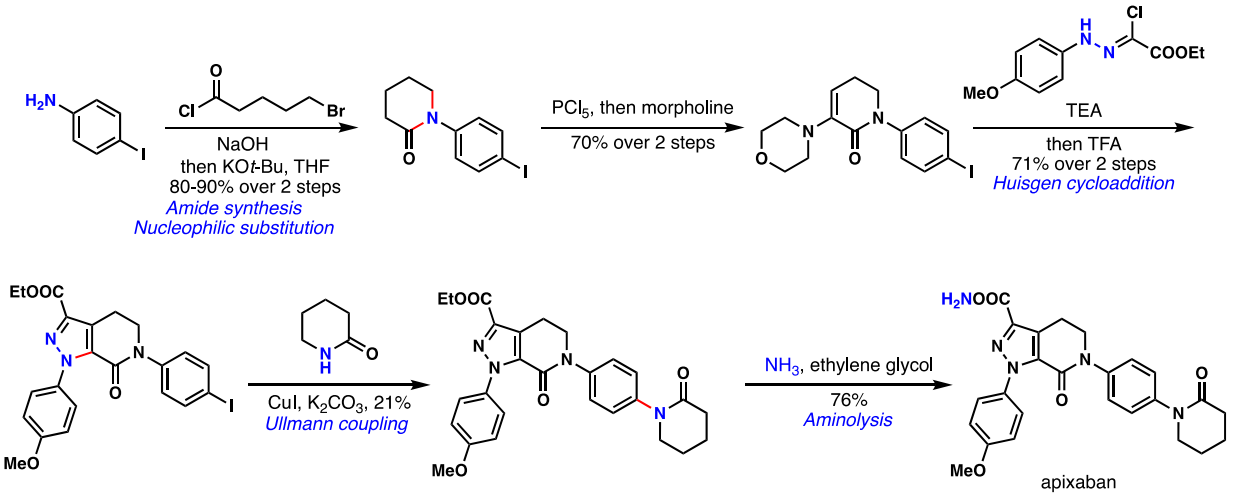


Figure 1. Synthesis of apixaban.

The anticoagulant drug apixaban, or trade name Eliquis, is a drug for the treatment and prevention of blood clots by inhibiting factor Xa.[3] Developed by Pfizer and Bristol-Myers Squibb in 2007, apixaban is listed as an essential medicine by the WHO. The synthesis of apixaban contains multiple carbon-nitrogen bond formations with different methods. The original synthetic route published by Pfizer starting with the reaction of 4-iodoaniline and 5-bromopentanoic acid chloride produced an amide, with the first carbon-nitrogen bond formed. Deprotonation of the corresponding amide by potassium tert-butyl oxide produced the intramolecular cyclization lactam, with the second carbon-nitrogen bond installed in 70% isolated yield over two steps. After transferring the lactam into an enamine, Pfizer scientists used a 1,3-dipolar cycloaddition to produce the diazole and install the fourth carbon-nitrogen bond. After installing the lactam side chain with a copper-catalyzed Ullmann reaction, the fifth carbon-nitrogen bond was made in 21% isolated yield. The ester side chain reacted with ammonia in ethylene glycol to build the last carbon-nitrogen bond. An aminolysis produced apixaban in 76% isolated yield.

Overall, the synthesis of apixaban contains multiple amination reactions, including amide synthesis from acid chloride, nucleophilic substitution, 1,3-dipolar cycloaddition, the Ullmann reaction, and aminolysis. These disconnections facilitate SAR study because many derivatives can be made by different coupling partners. However, the nitrogen-containing groups affect the binding affinity significantly, as shown in Bristol-Myers Squibb's paper.[3]

1.2.2 Synthesis of Ivacaftor

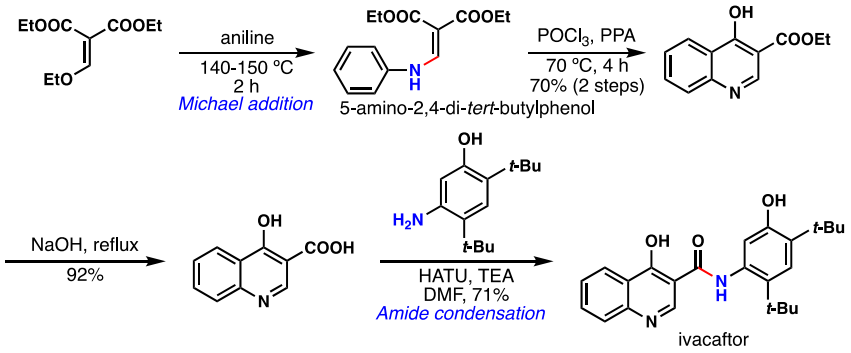


Figure 2. Synthesis of ivacaftor.

Ivacaftor by Vertex is a drug for treating cystic fibrosis caused by gene mutations. Its combination with elexacaftor and tezacaftor is sold under the brand name Trikafta or Kaftrio, which is listed in the top 20 worldwide sales lists.[2] The initial synthetic route by Vertex showed multiple methods for carbon-nitrogen bond formation.[4] The aniline reacted with diethyl ethoxymethylene malonate, which underwent a Michael addition, and the elimination mechanism produced the addition product enamine, with the first carbon-nitrogen bond formed. The corresponding enamine underwent an intramolecular Friedel-Crafts reaction with strong acid as a catalyst, producing a 4-hydroxylquinoline ester with a 70% isolated yield over two steps. After hydrolysis, the resulting acid condensed with 5-amino-2,4-di-*tert*-butylphenol under HATU conditions produced a corresponding amide with another carbon-nitrogen bond installed. Note that the 5-amino-2,4-di-*tert*-butylphenol used in this step was made from a nitration reaction with nitric acid as an electrophilic nitrogen reagent.[4] In this synthesis, multiple carbon-nitrogen bonds were installed by different

reactions, like Michael addition with amine as a nucleophile and nitration reaction with nitric acid as an electrophile. Many versions of the ivacaftor synthesis were reviewed,[5] and the major differences between them were in how the quinoline ring was made, or how to build the first carbon-nitrogen bond.

1.2.3 Synthesis of Elexacaftor

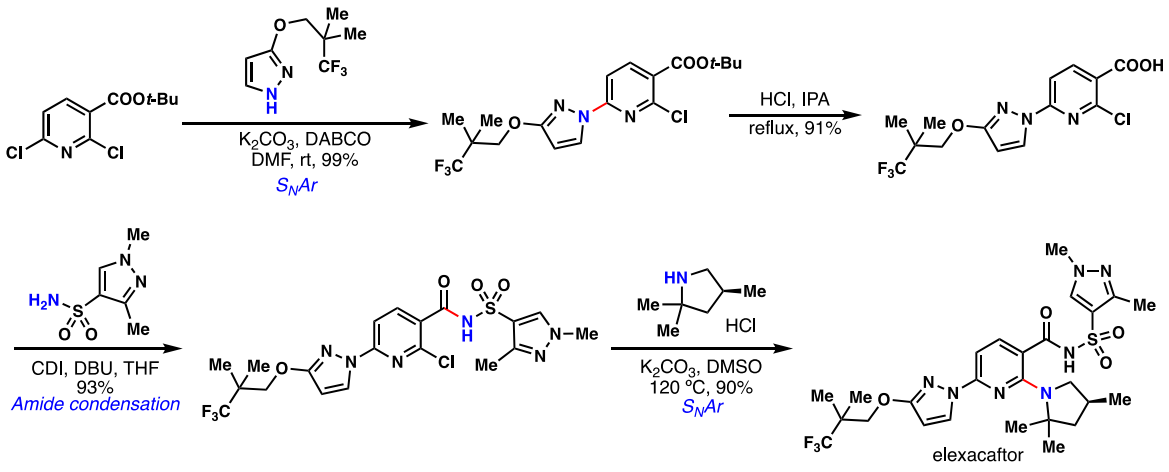


Figure 3. Synthesis of elexacaftor.

Elexacaftor is another component in Trikafta for treating cystic fibrosis. The synthetic route for elexacaftor is well-designed and is achieved with a regioselective S_NAr reaction.[4] The 2,6-di-chloropyridine that reacted with diazole produced the first carbon-nitrogen bond. Interestingly, only the 6-chloride was substituted, and the 2-chloride was blocked by the tert-butyl ester functional group, giving a 6-substitution product in 99% yield. After hydrolysis of the ester, an amide bond was formed from the CDI-mediated condensation reaction, which produced the second carbon-nitrogen bond. The third carbon-nitrogen bond was built from another S_NAr functional group with amide as a directing group. Overall, the synthesis of elexacaftor was achieved by two regioselective S_NAr reactions, and the S_NAr reaction was used in many other medicinal chemistry studies.

1.2.4 Chatterjee's Lead Optimization of the Second-Generation Antimalarial Agent

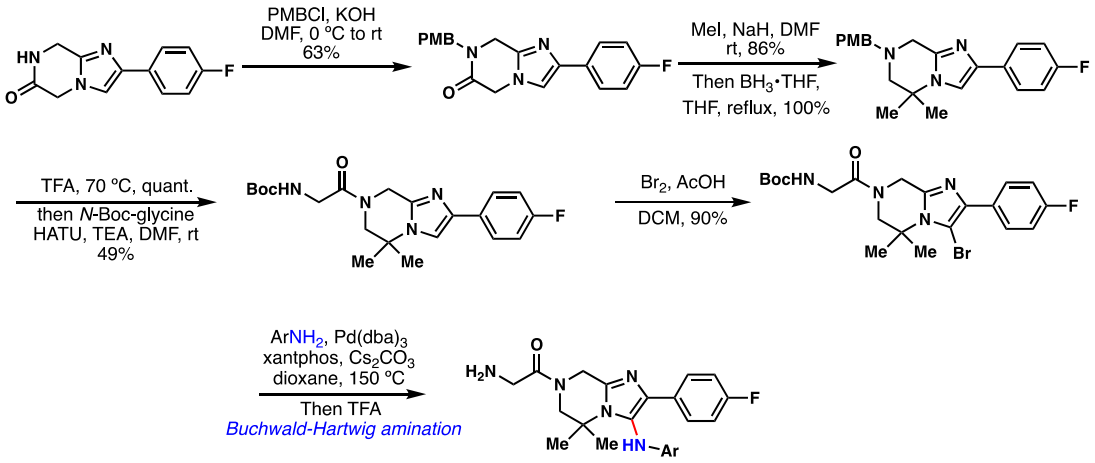


Figure 4. Development of second-generation antimalarial agents by Buchwald-Hartwig amination.

Buchwald-Hartwig amination is the amination reaction with amines and aryl halides, catalyzed by palladium and suitable ligands.[5] The development of the Buchwald-Hartwig amination reaction made it a general approach for the synthesis of multiple amine-containing medicinal derivatives for medicinal chemistry studies. In 2012, Chatterjee's group reported their development of second-generation antimalarial agents through lead optimization.[6] The core heterocycle structure was transferred into an aryl halide and coupled with different amines with the Buchwald-Hartwig amination reaction. This study was possible due to the Buchwald-Hartwig amination reaction, which worked as a general approach for carbon-nitrogen bond-formation to synthesize secondary anilines. To access the 6-position modified imidazolepiperazine core, Chatterjee's group applied an acid-catalyzed hydroamination reaction to build that carbon-nitrogen bond.[6] The imidazole starting material reacted with methylallyl chloride to produce the substitution product in a 55% isolated yield, which was used as a precursor for intramolecular hydroamination reactions.

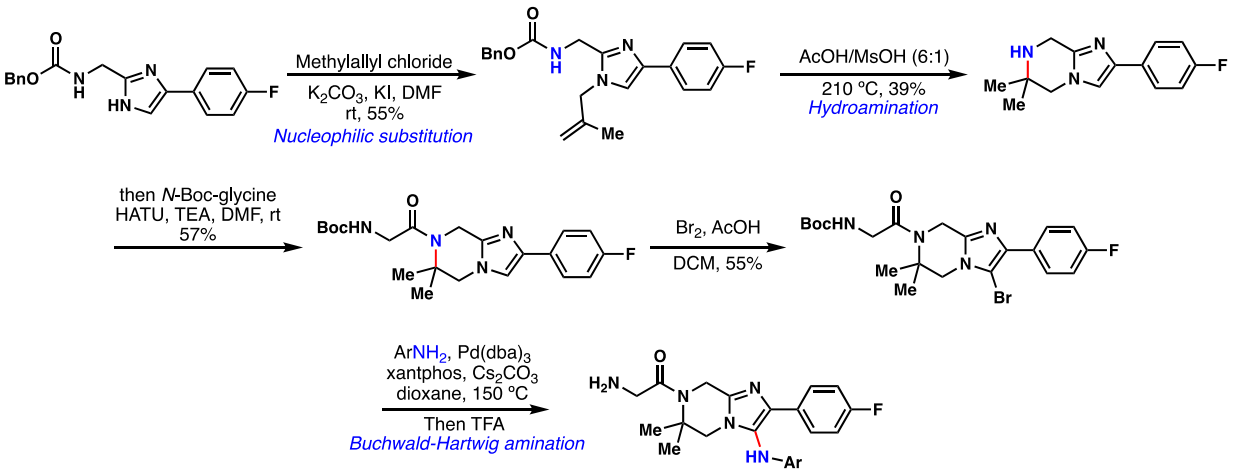


Figure 5. Modification of 6-position via acid-hydroamination reaction.

After extensive optimization, the researchers produced the hydroamination reaction product with a 39% isolated yield. The product from hydroamination underwent amide coupling, bromination, and the Buchwald-Hartwig amination sequences like other imidazolepiperazine cores, producing more derivatives for the SAR study. The hydroamination reaction in the synthesis, even after many optimizations, needed a very high reaction temperature with a moderate yield. Few functional groups can tolerate such high temperatures with acid, which limits the application of hydroamination reactions in medicinal chemistry studies.

1.3: Introduction of Hydroamination Reactions

Hydroamination is an addition reaction wherein nitrogen-hydrogen functional groups add to carbon-carbon multiple bonds.[7-9] Given the possible disconnection that can be made with a hydroamination reaction, its applications in medicinal chemistry are not as common as other amination methods. For example, searching "amination" in the *Journal of Medicinal Chemistry* returned 2,217 articles, whereas searching "hydroamination" returned only 15.

Many new disconnections can be made with hydroamination reactions for more derivatives in SAR studies. Figure 6 shows some pharmaceutical molecule examples, and the bond in red could be built with hydroamination reactions. For example, clobenzorex, which contains a secondary amine, functions as a stimulant; azelastine, an antihistamine, features a phthalazinone core and a tertiary amine. Other notable examples include trilaciclib and labetalol. Despite the potential applications of hydroamination reactions in medicinal chemistry, the lack of attention on them is a result of many practical reasons, like high reaction temperature and excess amount of amines or alkene required.

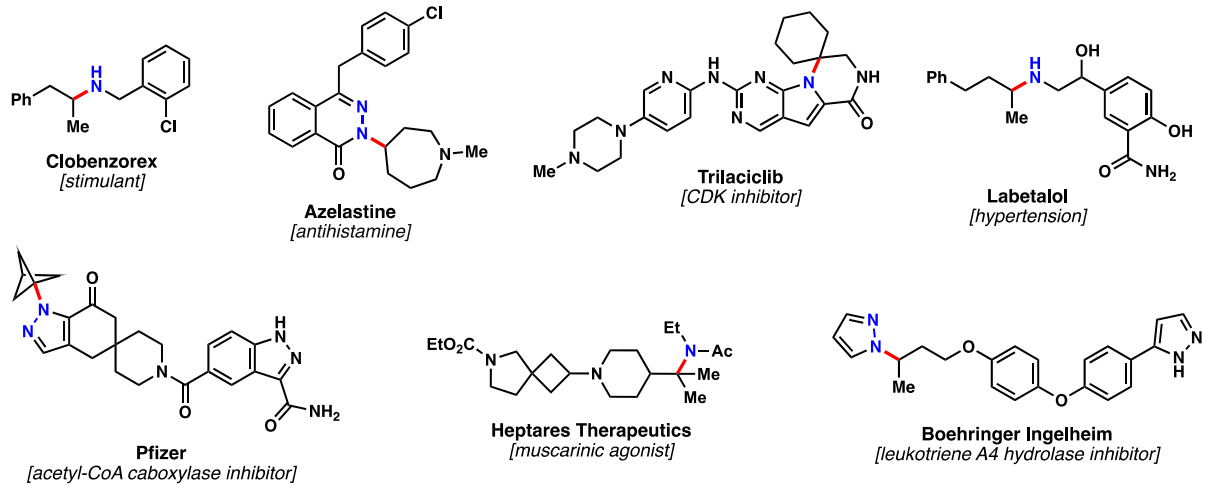


Figure 6. Pharmaceutical molecules containing nitrogen functional groups with possible disconnection from a hydroamination reaction.

Hydroamination reactions can be classified into two types based on reaction intermediates: bis-electron type hydroamination and single-electron type hydroamination. The bis-electron type is the most extensively studied—particularly, with the development of asymmetric transition metal catalysts—which enable some bis-electron hydroaminations to proceed in an enantioselective manner. However, bis-electron hydroamination produces several challenges. Firstly, the

hydroamination reaction is approximately thermoneutral, often necessitating the use of excess amine or alkene or limiting the reaction to intramolecular scenarios. Miura and Buchwald's development of O-benzoylhydroxylamines as an amine source has enabled stoichiometric bis-electron hydroamination, but the phenyl or benzyl substitutions on nitrogen are difficult to remove post-reaction. Additionally, the high activation energy required for hydroamination necessitates an elevated reaction temperature. Furthermore, hydroamination mechanisms can be categorized based on activation types, with two predominant mechanisms: the [2+2] cycloaddition type and metal migratory insertion, followed by the reductive elimination type.

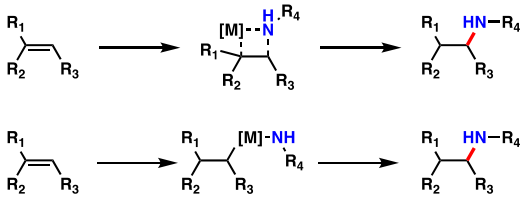


Figure 7. Mechanistic types of bis-electron hydroamination reactions.

Single-electron hydroamination reactions have garnered increasing attention in recent years.[10, 11] With their high-energy radical reactive center, these reactions can overcome the activation-energy barrier at lower temperatures, allowing for the use of stoichiometric amounts of alkenes and amine sources to achieve good yields. Depending on the activation mechanisms, single-electron hydroamination can yield different products. For example, activation at the nitrogen center followed by migratory insertion into the double bond typically produces anti-Markovnikov products, whereas metal-hydride migratory insertion using a suitable electrophilic nitrogen donor results in Markovnikov products (Figure 8).

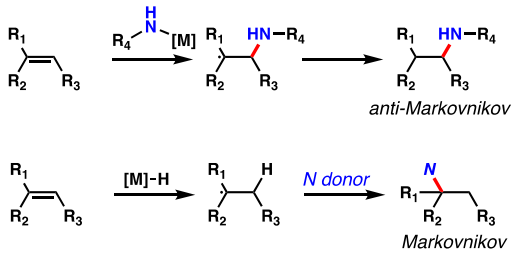


Figure 8. Mechanism for Markovnikov and anti-Markovnikov radical hydroamination reactions.

Like bis-electron hydroamination reactions that use *O*-benzoylhydoxylamines, single-electron hydroamination reactions also depend on the development of suitable nitrogen source reagents. For instance, Baran reported the use of nitroarenes as a nitrogen source in conjunction with an iron hydride intermediate, resulting in the formation of hindered anilines with a high tolerance for various functional groups.[12] Zhu's publication described the use of Ts_2NH with cobalt hydride intermediates to achieve hydroamination products.[13] Similarly, the Shigehisa group reported the application of tosyl amide for intramolecular hydroamination.[14] Zhang's group used NFSI as a nitrogen radical source, leveraging N-X dissociation for radical formation, which could be applied to both intermolecular and intramolecular hydroaminations.[15, 16] These examples, while effective, typically incorporated only a single-nitrogen atom into the substrate, making it challenging to extend the method to different nitrogen-containing functionalities. As a pioneer in the field of metal hydride radical hydroamination, Carreira reported the use of azodicarboxylate for synthesizing protected hydrazine and arylsulfonyl azides for producing azides.[17, 18] The nitrogen sources mentioned previously have significantly expanded synthetic chemist's toolbox by introducing novel methods for forming carbon-nitrogen bonds. However, the products derived from these nitrogen sources often have limited versatility and are challenging to diversify.

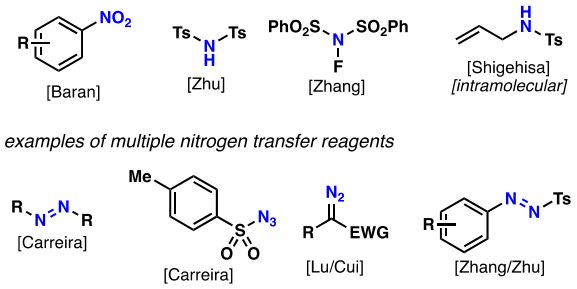


Figure 9. Reported nitrogen sources for radical hydroamination.

For example, Baran's method uses nitrobenzene as nitrogen source, resulting in secondary anilines that are difficult to convert into other nitrogen-containing functional groups; Zhu and Zhang's methods yield tosyl amide,[19, 20] but the aryl sulfonate groups are notoriously difficult to remove; and Carreira's approach, involving cobalt hydride transfer, produces protected hydrazine and azides, which can be converted into amines.[17, 18, 21] Lu and Cui's methods employ diazo compounds as a nitrogen source, resulting in hydrazones that can be further transformed into amines.[22, 23] Additionally, Zhang and Zhu's methods using diazo compounds facilitate the conversion into disubstituted hydrazine.[19]

1.4: Diazirine as Nitrogen Source in Amination Reactions

1.4.1: Introduction of Diazirines

Diazirines are three-membered ring heterocycles containing a nitrogen-nitrogen double bond, while diaziridines have a nitrogen-nitrogen single bond. The highly strained structure of diazirines makes them unstable and capable of releasing nitrogen gas upon exposure to UV light or heat, forming carbon carbene. This carbene can then undergo C-H insertion or cyclization with multiple bonds. In 1981, Moss's group reported synthesis of cyclopropanes using spiro[adamantane-2,3'-diazirine] (**1**) under UV light irradiation.[24] Upon excitation, the diazirine released nitrogen gas,

and the resulting carbene cyclized with alkene double bonds. Later, Brunner's group described the use of 3-aryl-3-trifluoromethyldiazirine (**3**), which, when irradiated with UV light, underwent C-H bond insertion. This reaction has potential applications in photolabeling and cross-linking reagents.[25] More recent research has focused on using diazirine in protein biolabeling, exploiting their ability to form carbon carbene *in situ*.[26-28]

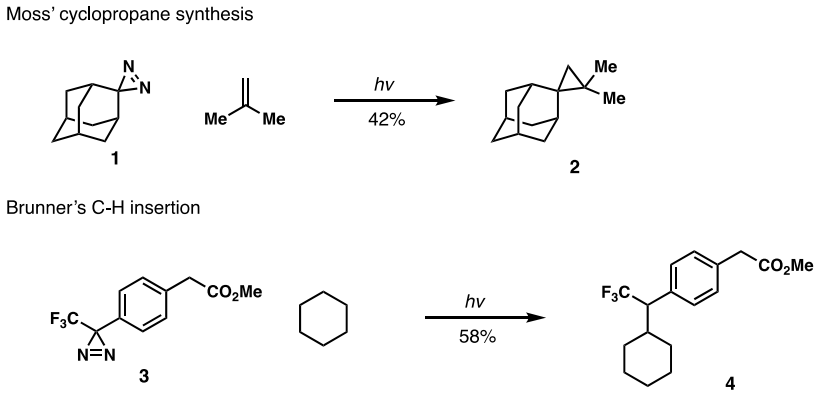
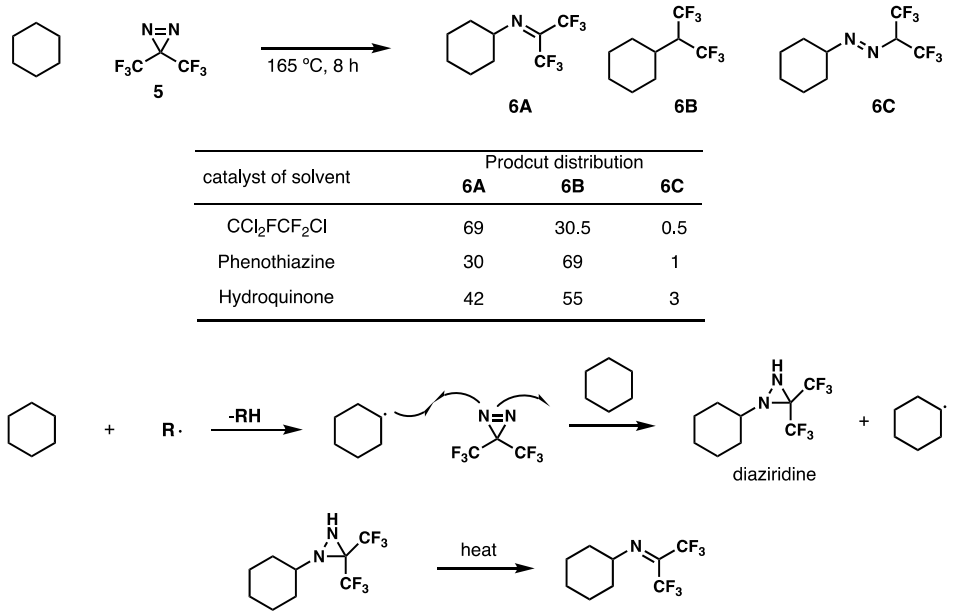


Figure 10. Early application of diazirine in Moss's cyclopropane synthesis and Brunner's carbon-hydrogen insrtion reaction.

Krespan's studies on diazirines have garnered significant attention. In 1966, they reported using bis(trifluoromethyl)diazirine as a carbene precursor under heat, resulting in carbene insertion and cyclization products.[29] Subsequently, in 1968, the same group investigated the reaction between bis(trifluoromethyl)diazirine and cyclohexane under heat with catalysts, producing bis(trifluoromethyl)imine as the major product.[30] Notably, when the reaction was conducted among radical traps, imine formation was suppressed and the insertion product predominated. Based on these findings, Krespan proposed a radical addition mechanism wherein diazirine acted as a radical acceptor, forming diaziridine as an intermediate, which was then rearranged under heat. Later, Barton's group observed the formation of dimerized diaziridine, which explained the detailed mechanism for rearrangement.[31] These intriguing results prompt the following question:

if radicals can be generated at lower temperatures and trapped by hydrogen radicals, could diazirine serve as an effective amination reagent?



catalyst of solvent	Prodcut distribution 6A	6B	6C
CCl_2FCF_2Cl	69	30.5	0.5
Phenothiazine	30	69	1
Hydroquinone	42	55	3

Figure 11. Krespan's report using bis(trifluoromethyl)diazirine for imine synthesis and the proposed mechanism showing diazirine as a carbon radical trap.

1.4.2 Amination Using Diazirine as Nitrogen Source

Inspired by Krespan's pioneering work in 1966, Barton's group in the 1990s explored the use of diazirine as a radical trap for the amination reactions.[31] In the paper, the group employed Barton's decarboxylating method to generate radicals, which were subsequently trapped by 3-phenyl-3-(trifluoromethyl)diazirine (**8**), yielding the corresponding imine (**9**) in great yield. This imine could then be further transferred into an amine using boronic acid as a reagent. Additionally, in 1993, the group discovered that 3-phenyl-3-bromodizirine (**10**) could be used to synthesize amides (**11**) in a single step.[32] In their papers, Barton's group proposed a mechanism wherein the diazirine trapped the resulting radical, leading to dimerization of nitrogen radicals, followed by rearrangement.

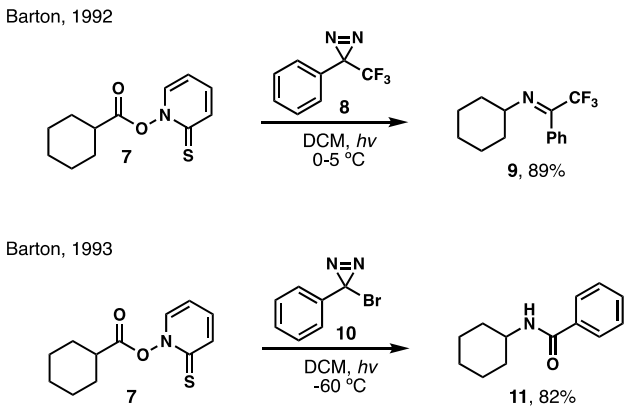


Figure 12. Barton's radical decarboxylative amination with diazirines.

In 2020, Lopchuk's group reported a significant advancement in decarboxylative amination using redox-active esters along with 3–phenyl-3–(trifluoromethyl)diazirine (**8**) as both a single- and double-nitrogen source. This method led to the formation of 3–phenyl-3–(trifluoromethyl)diaziridine (**12**), which is a versatile intermediate for synthesizing amines, hydrazines, and other nitrogen-containing heterocycles.[33]

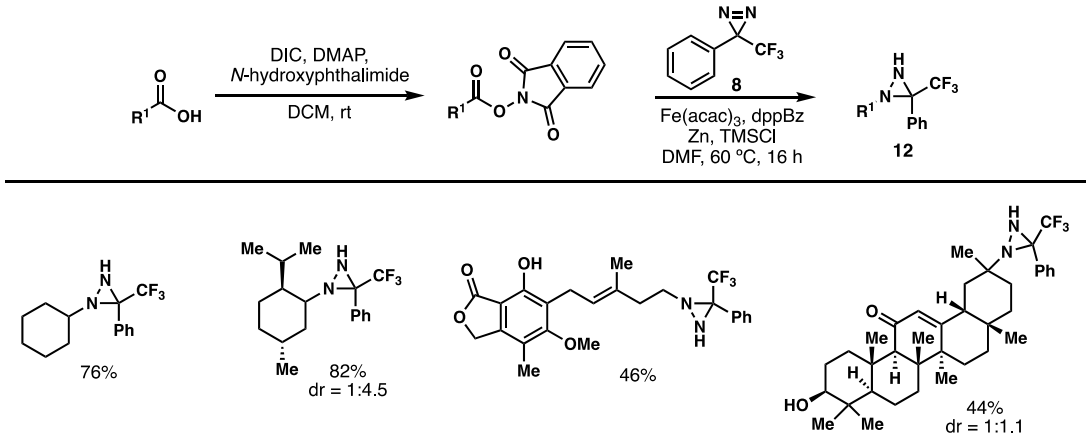


Figure 13. Lopchuk's iron-catalyzed decarboxylative amination reaction.

Lopchuk group's method enables the preservation of both nitrogen atoms in the diazirine, facilitating further exploration of the diversification of the animation reaction. In Barton's method,

nitrogen radical dimerization results in intermediate rearrangement, forming imines, which can subsequently be diversified into amines and amides. In this decarboxylative animation strategy, the resulting diaziridine acts as a masked hydrazine, serving as a precursor to the synthesis of amines, hydrazines, and heterocycles through straightforward transformations. Treatment of diaziridine under halogenated acidic conditions—such as with hydroiodic acid, trimethylsilyl chloride/lithium chloride in DMF, and hydrochloride acid in ethanol—results in a reduction of the nitrogen-nitrogen bond, yielding single-nitrogen functional groups. Conversely, under non-halogenated acid conditions, diaziridine provides access to compounds containing multiple-nitrogen function groups.

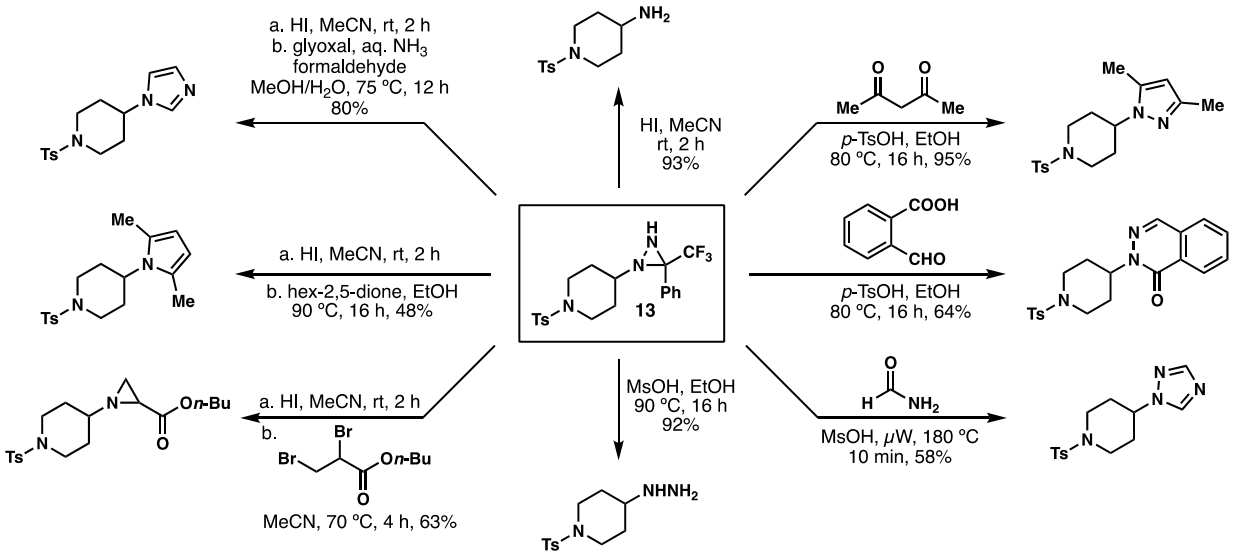


Figure 14. Diversification of diaziridine (**13**) synthesized by Lopchuk's iron-catalyzed decarboxylative amination reaction with diazirine (**8**).

In a subsequent study, Lopchuk's group published another decarboxylative amination with 3-phenyl-3-(trifluoromethyl)diazirine (**8**) under blue LED at a milder temperature, employing a triphenylphosphine-sodium iodide electron donor-acceptor complex as photocatalysts.[34]

Compared to the iron-catalyzed decarboxylative amination reaction, this photochemical method demonstrates enhanced efficacy with primary carboxylic acid in certain scenarios. Furthermore, like the iron approach above, the resulting diaziridine can undergo further diversification.

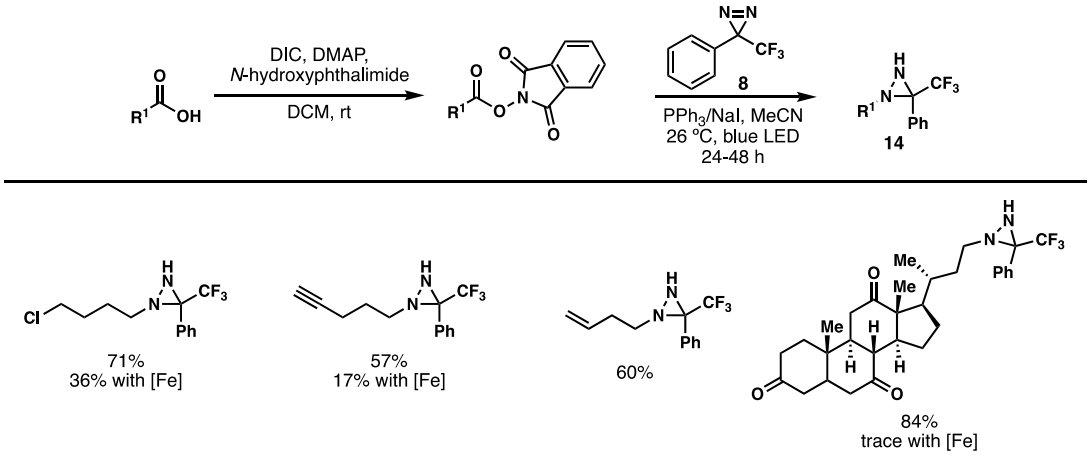


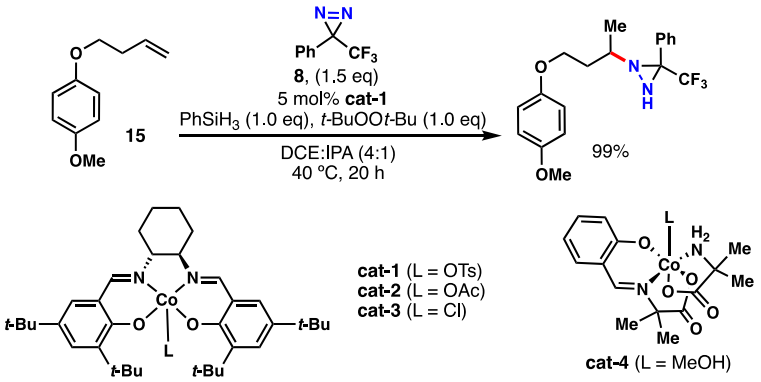
Figure 15. Lopchuk's photo-driven decarboxylative amination with diazirine (**8**).

1.5 Regioselective Hydroamination with Diazirine

Because of their outstanding potential for carbon-nitrogen bond-formation and diversification, decarboxylative amination reactions are a powerful new tool in synthetic chemists' toolbox. However, some reactions need extra steps for redox active ester synthesis, which is its drawback—especially *N*-hydroxyphthalimide, whose large molecular weight makes this reaction not atom-economic. Hydroamination is one type of addition reaction that has very high atom economics; using diazirine in radical-type hydroamination reactions enables achieving carbon-nitrogen bond-formation atom economically and utilizing the widely available alkene sources, both natural and commercial.

1.5.1 The Optimization of Hydroamination Reaction with Diazirine

We first tested Carreira's cobalt catalyst with different silanes as hydride source due to inspiration by Carreira's hydrogen atom transfer hydrohydrazination reaction.[17, 18, 21, 35] Phenylsilane produced the best outcome, and further screen of catalysts showed that salen-Co-OTs provided the best outcome. After further screens, we found peroxide to be crucial for the reaction. The isolated yield was boosted to 99% for the standard substrate with di-*tert*-butylperoxide as an additive. Figure 16 shows some key optimization results: salen-Co-OTs is crucial, and other cobalt catalyst gave much lower yield (Entries 1, 2, 4, 5, and 6); when conducting the reaction with $Mn(dpm)_3$, the reaction gave a 51 to 35 mixture of Markovnikov and anti-Markovnikov product, but the reaction can be run at 0 ℃, which is useful for symmetric alkenes which lack regioselectivity issues (Entry 3); running the reaction for 30 hr with only isopropanol as solvent resulted in 84% of isolated yield, but this condition turned out to be useful for steric hindered alkenes, when the DCE/IPA system produced lower yields (Entry 7); the starting material was difficult to find on TLC after the reaction ran for 3 hr, but decreased yield was obtained, and prolonging the reaction time can elevate the yield (Entries 8 and 9); without di-*tert*-butylperoxide, the reaction produced product with 38% of isolated yield (Entry 10); with *tert*-butylperoxide, the reaction produced Mukaiyama hydration as a major product, along with 36% of desired diaziridine (Entry 11); and other silane produced very low yield (Entries 12 and 13); running the reaction at higher temperature (60 ℃) resulted in 56% isolated yield (Entry 14); and running the reaction with no precautions (no argon protection and no shade of light), the reaction produced 54% of isolated yield (Entry 15).



entry[a]	deviation from above	yield (%)[b]
1	$Co(dpm)_3$	trace
2	Co(TPP)Cl	trace
3	$Mn(dpm)_3$	51/35[c,d]
4	**cat-2**	51
5	**cat-3**	39
6	**cat-4**	57
7	IPA only	84[e]
8	3 h	66
9	16 h	93
10	w/o *t*-BuOO*t*-Bu	38
11	*t*-BuOOH (2.5 eq)[f]	36
12	TES	trace
13	PHMS	trace
14	60 °C	56
15	no precautions[g]	54

Figure 16. Selected optimization conditions for hydroamination reactions with diazirine (**8**). a) Reactions were conducted with **15** (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), **cat-1** (0.005 mmol, 0.05 eq), DCE (400 µL) and IPA (100 µL), 40 °C for 20 hr under argon atmosphere; b) Isolated yields; c) Reaction conducted with **15** (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), $Mn(dpm)_3$ (0.005 mmol, 0.05 eq), DCE (400 µL) and IPA (100 µL), 0 °C for 2 hr under argon atmosphere; d) Markovnikov/anti-Markovnikov ratio; e) Reaction run for 30 h; f) 5.5 M solution in decane (dried over 4Å molecular sieves); g) Reaction run under air atmosphere with no protection from light.

1.5.2 Scope Table for Hydroamination with Diazirine

With the optimized condition in hand, we then investigated the functional group tolerance and scope broadness of our hydroamination reaction. Over 50 examples were reported with wide functional group tolerance.

1.5.2.1 Monosubstituted Terminal Alkene Examples

Fifteen monosubstituted alkenes were produced with our cobalt-catalyzed hydroamination reaction, and they produced great–excellent isolated yields. Functional groups like phenyl ethers (**16a**, **16b**, **16c**, **16f**, **16g**, **16h**, **16n**), nitro group (**16c**), nitrile group (**16k**), primary amine (**16i**), quinoline (**16n**) and phenyl thioether (**16j**) were tolerated. Interestingly, phenyl thioethers are toxic for many transition metal catalysts due to their good chelating abilities, which can quench the reactivity of those catalysts; however, in our hydroamination reaction, an 83% isolated yield was obtained. Many protective groups for primary amine were tolerated during the hydroamination reaction, like Boc (**16f**, **16n**), Ac (**16g**), Cbz (**16h**), and Ts (**16p**). This hydroamination can be adopted in fluorous chemistry by replacing diazirine (**8**) with perfluorodiazirine (**16b**). As shown in the iron-catalyzed decarboxylative amination paper, perfluorodiaziridine can be used in fluorous phase synthesis in drug discovery. To investigate whether the reaction can work on a large scale, we ran the reaction with 1 g of heptene and produced the corresponding diaziridine (**16d**) in comparable yields with other substrates in the table. With suitable alkenes, our reaction can work in the synthesis of some pharmaceutically interested molecules, like clobenzorex (**16l**), labetalol (**16m**), and quinocide (**16n**).

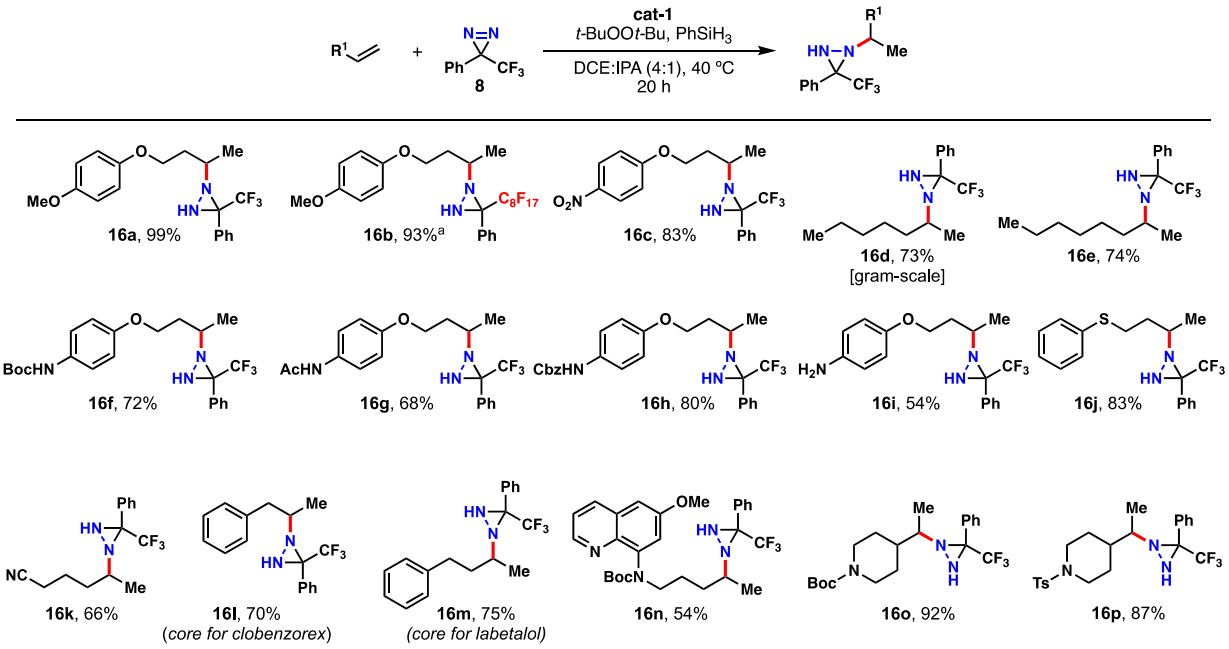


Figure 17. Scope for monosubstituted terminal alkenes. Reactions were conducted with alkene (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), *t*-BuOO*t*-Bu (0.1 mmol, 1 eq), **cat-1** (0.005 mmol, 0.05 eq), DCE (400 μL) and IPA (100 μL), 40 °C for 20 hr under argon atmosphere with shade of light. (a) Reaction was conducted with perfluorodiazirine (0.25 mmol, 2.5 eq).

1.5.2.2 1,1-Disubstituted Terminal Alkene Examples

Thirteen 1,1-disubstituted terminal alkenes were tested, and as the reactive center became more steric-hindered compared to the monosubstituted alkenes, the reaction yields dropped slightly. The reactions produced great yields and showed tolerance for more functional groups. Unprotected hydroxyl groups were tolerated in the reaction (**17a**), and protected hydroxyl groups showed similar yields. Substrates with multiple protection groups for the hydroxyl group—like Ac (**17b**), MOM (**17c**), THP (**17d**), Cbz (**17e**), and Bn (**17f**)—produced great yields.

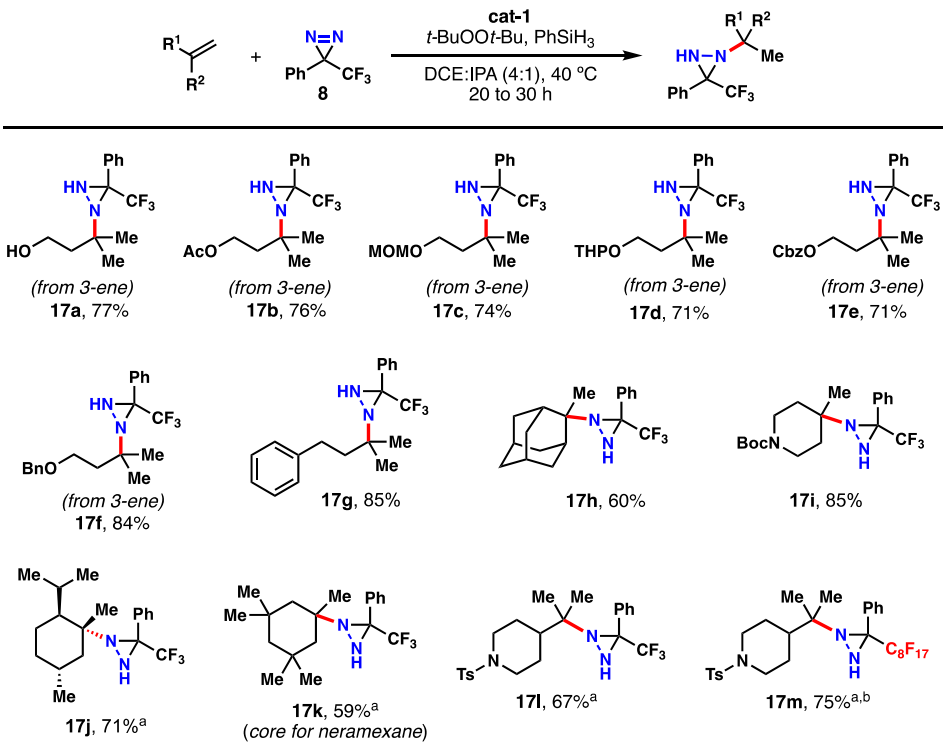


Figure 18. Scope for 1,1-disubstituted terminal alkenes. Reactions were conducted with alkene (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), *t*-BuOO*t*-Bu (0.1 mmol, 1 eq), **cat-1** (0.005 mmol, 0.05 eq), DCE (400 µL) and IPA (100 µL), 40 °C for 20 hr under an argon atmosphere with a shade of light unless noted otherwise. (a) The reaction was conducted with IPA (500 µL), 40 °C for 30 h. (b) The reaction was conducted with perfluorodiazirine (0.25 mmol, 2.5 eq).

Perfluorodiazirine worked with the disubstituted alkene (**17m**), produced hindered diaziridine in a 75% isolated yield. The steric-hindered exocyclic alkenes produced great yields, such as **17h**, **17i**, **17j,** and **17k**. The amine-protecting groups tested, such as Ts (**17l**, **17m**), and Boc (**17i**) survived the reaction conditions. Diaziridine **17K** can be transferred into neramexane with a one-step reaction.

1.5.2.3 Trisubstituted Alkene Examples

Trisubstituted alkenes are not ideal substrates for many transitional metal-catalyzed hydroamination reactions, since coordination between trisubstituted alkenes and transitional metals can be problematic. However, trisubstituted alkenes worked very well with radical-type hydroamination reactions with diazirine (**8**), may be due to radical is a higher-energy intermediate, which can force the insertion to work.

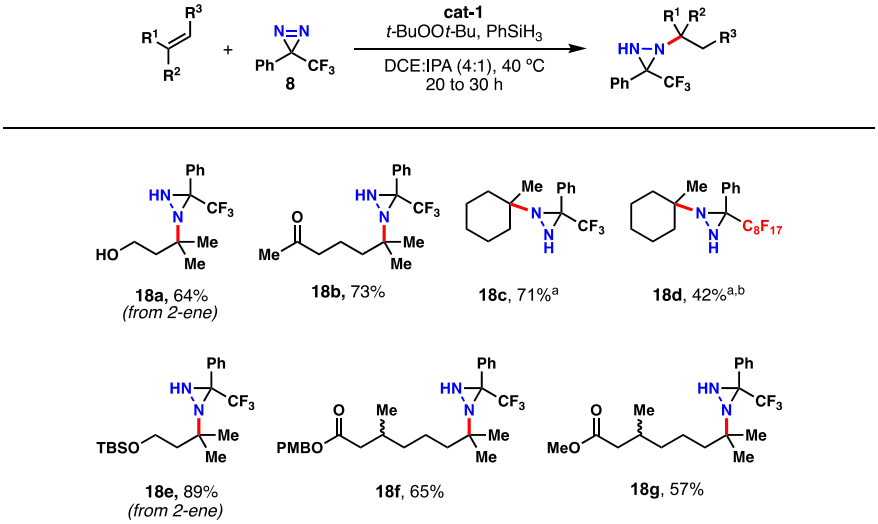


Figure 19. Scope for trisubstituted alkenes. Reactions were conducted with alkene (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), *t*-BuOO*t*-Bu (0.1 mmol, 1 eq), **cat-1** (0.005 mmol, 0.05 eq), DCE (400 µL) and IPA (100 µL), 40 °C for 20 hr under an argon atmosphere with a shade of light unless noted otherwise. (a) The reaction was conducted with IPA (500 µL), 40 °C for 30 h. (b) A reaction was conducted with perfluorodiazirine (0.3 mmol, 3 eq).

More functional groups were tested, such as ketone (**18b**), methyl ester (**18g**), and *p*-methoxybenzyl ester (**18f**), all of which worked well with the hydroamination reaction and produced good to great yields. Another alcohol-protecting group, TBS (**18e**) was tested and gave an 89% isolated yield. Allylic alcohol (**18a**) and endocyclic alkene (**18c**, **18d**) also produced great

yields. Perfluorodiaziridine (**18d**) was synthesized with methylcyclohexene in a 42% isolated yield; the decrease in yield can be a result of a hindered cyclic center.

1.5.2.4 Cyclic alkene examples

Six membered (**18c**, **19b**), seven membered (**19a**) and eight membered (**19c**) cyclic alkenes were run with cobalt hydroamination reaction, especially with the norbornene (**19b**), we did not obvious big drop of yield for this hindered bridged system.

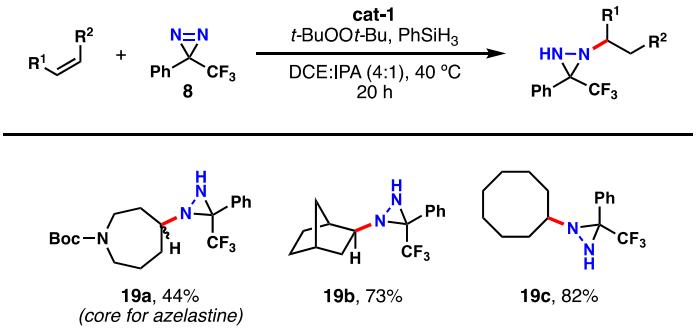


Figure 20. Scope for cyclic alkenes. Reactions were conducted with alkene (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), *t*-BuOO*t*-Bu (0.1 mmol, 1 eq), **cat-1** (0.005 mmol, 0.05 eq), DCE (400 µL) and IPA (100 µL), 40 ºC for 20 h under argon atmosphere with shade of light.

As we mentioned in 1.5.1, the manganese catalyzed condition with mild reaction condition and shorter reaction time can be useful for symmetric alkenes. When we were conducting manganese catalyzed hydroamination reaction for cyclic alkenes in Figure 20 at 0 ºC for 2 h, higher yields were obtained. With *tert*-butyl 2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate, 44% isolated yield was obtained with cobalt condition (**19a**), and 85% isolated yield was obtained with manganese condition (**20a**). On LC-MS, we found major by-product with cobalt condition was the deprotection product. With norbornene, 84% isolated yield was obtained with manganese

condition (**20b**), compared to 73% with cobalt condition (**19b**). Lastly, with cyclooctene, 93% isolated yield was obtained with manganese condition (**20c**), compared to 82% with cobalt condition (**19c**). Surprisingly, [1.1.1]propellane, a highly strained bridged cycloalkane, produced corresponding diaziridine with a 72% isolated yield under manganese catalyzed hydroamination reaction (**20d**). This transformation gave new disconnection for this kind of structure in drug discovery, for example, it has potential to synthetize Pfizer's inhibitor showed in Figure 6 and many other its derivatives.

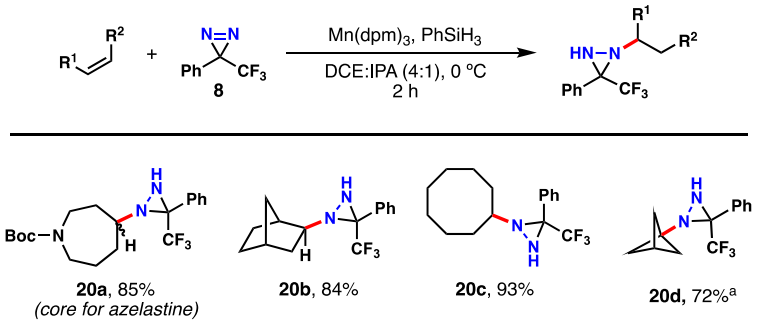


Figure 21. Scope for cyclic alkenes with manganese catalyzed hydroamination reactions. Reactions were conducted with alkene (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), $Mn(dpm)_3$ (0.005 mmol, 0.05 eq), DCE (400 μL) and IPA (100 μL), 0 ºC for 2 h under argon atmosphere with shade of light. a) [1.1.1]Propellane was added as a solution in ether/pentane.

1.5.2.5 Commercial terpene natural product examples

The terpenes are important building blocks in biosynthetic pathways in biology world. Many of them can be obtained in bulk amounts commercially available at a reasonable price, which made them ideal starting materials in synthetic organic chemistry. Amination attempts were made in the past on the terpenes. Some classical examples including Ritter's reaction[36] and mercuriation followed by treated with anilines or azides[37, 38]. Recently, with the development of hydrogen atom transfer reaction, Boger's group[39] reported hydroazidation of citronellol; Carreira's group[35]

reported hydrohydrazination of camphene; Glorius' group[40] reported iminative bisfunctionalization of perillol, limonene, and nootkatone. And with the development of electrochemistry, electrochemically diazidation of limonene oxide and nootkatone were reported by Lin's group[41] and Xu's group[42] separately. Engle's group[43] also reported aminoarylation sclareol.

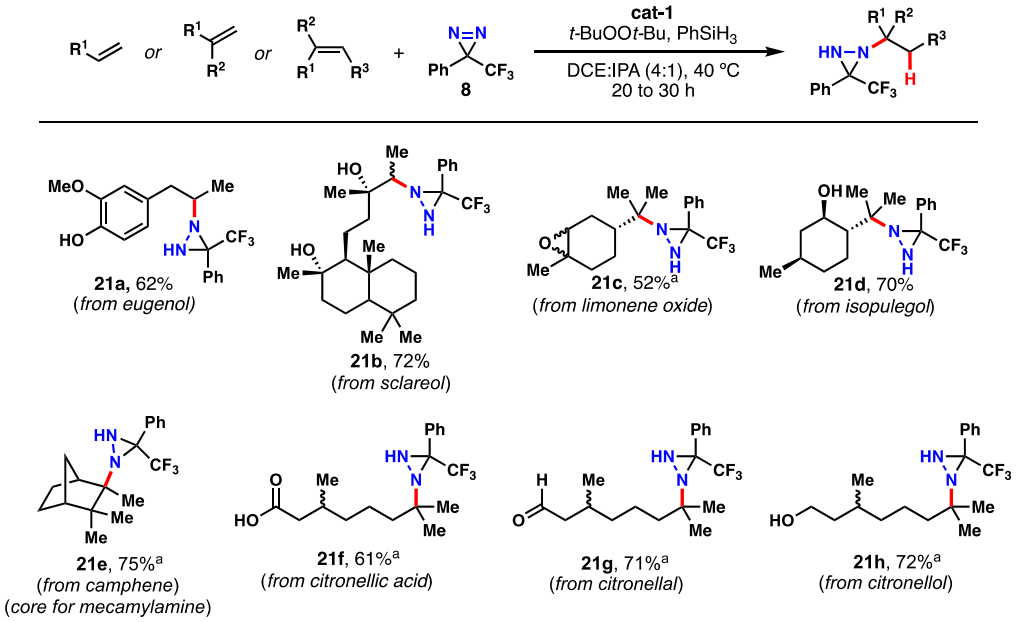


Figure 22. Scope for terpenes with one alkene function group. Reactions were conducted with alkene (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), *t*-BuOO*t*-Bu (0.1 mmol, 1 eq), **cat-1** (0.005 mmol, 0.05 eq), DCE (400 μL) and IPA (100 μL), 40 ºC for 20 h under argon atmosphere with shade of light unless noted otherwise. a) The reaction was conducted with IPA (500 μL), 40 ºC for 30 h.

Our cobalt catalyzed hydroamination can work with commercially available terpenes as a new tool in complex molecule synthesis, produced corresponding diaziridine in moderate to great yield. Eugenol (**21a**) with a phenolic hydroxyl group gave 62% of isolated yield, no oxidative side reaction was observed considering peroxide was used in the reaction system. Other functional

groups like citronellic acid with carboxylic acid group (**21f**), citronellal with aldehyde group (**21g**), and citronellol (**21h**), sclareol (**21b**) and isopulegol (**21d**) with hydroxyl group, produced corresponding diaziridine in good isolated yields. To our delight, limonene oxide (**21c**) with an epoxy group gave 52% isolated yield with the epoxy ring unopened. Terpenes with steric hindered double bonds, like sclareol (**21b** and **21e**) and camphene, produced corresponding diaziridines in great isolated yields.

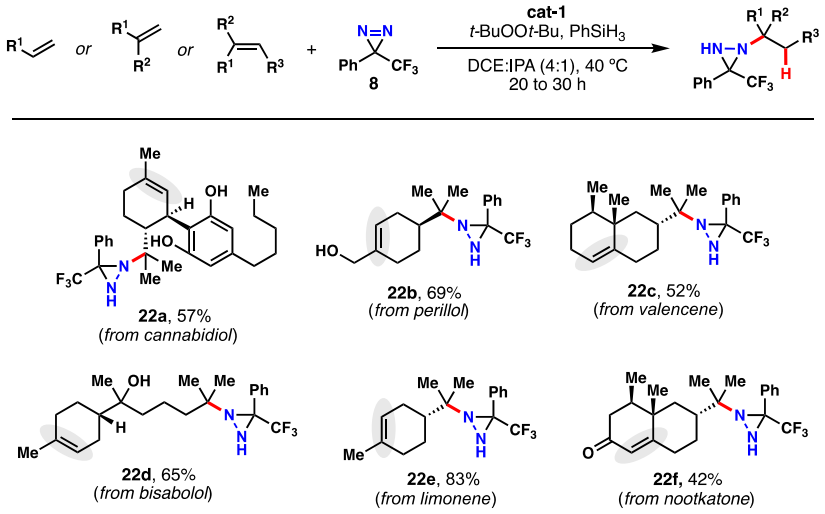


Figure 23. Scope for terpenes with multiple alkene function groups. Reactions were conducted with alkene (0.1 mmol), **8** (0.15 mmol, 1.5 eq), $PhSiH_3$ (0.1 mmol, 1 eq), *t*-BuOO*t*-Bu (0.1 mmol, 1 eq), **cat-1** (0.005 mmol, 0.05 eq), DCE (400 µL) and IPA (100 µL), 40 ºC for 20 h under argon atmosphere with shade of light.

When we ran the hydroamination with limonene, which contains two double bonds, we found the cobalt catalyzed hydroamination reaction can selectively hydroaminate less hindered alkene on the limonene. Reaction produced corresponding diaziridine in 83% isolated yield with limonene (**22e**), and only the double bond on the "fish tail" reacted. The double bond inside of the ring did not undergo the reaction, due to kinetic selectivity. However, when we treated limonene with 3

equivalents of **8**, and double other reagents, double hydroaminated product started to become major product. Similar selectivity was observed with cannabidiol (**22a**), perillol (**22b**), valencene (**22c**), and bisabolol (**22d**); α,β-unsaturated double bond will not react under hydroamination, 42% isolated yield was observed with nootkatone (**22f**).

1.5.2.6 Unsuccessful examples

Despite 54 different alkenes were transformed into corresponding diaziridines with our radical hydroamination with diazirine (**8**), several kinds of alkenes did not produce good yields. Both electron-rich and electron-poor styrenes were tested, gave very low yields, with formation of oligomers as major side reactions. As we mentioned in 1.3.2.5, α,β-unsaturated alkenes did not work under our hydroamination conditions, gave no conversion. A control experiment indicated with adding 1 equivalent of carvone into another hydroamination reaction, the reaction yield will drop dramatically. The low yields may be due to the chelation between carvone and cobalt center. However, nootkatone, with a methyl on β-position, was able to produce corresponding diaziridine. Pinenes, both α-pinene and β-pinene produced ring opening products with same structure as **22e**. Very hindered double bond, like endo cyclic double bond in tetrahydrocannabinol, results in no conversion. Substrates with poor solubility produced no conversion as well, such as cinchonidin, methyl betulinate, protected mycophenolic acid. Quinine and osthole produced no conversion, and this may be due to chelation of substrate on the cobalt center, which quenched the reactive center. Special substrates with double bonds oriented in right manner for radical cascade cyclization reactions produced low yields, like vitamin D_2 and caryophyllene. Interestingly, when ran the reaction with cyclosporin A, we observed right product MS, but was not able to isolate the product.

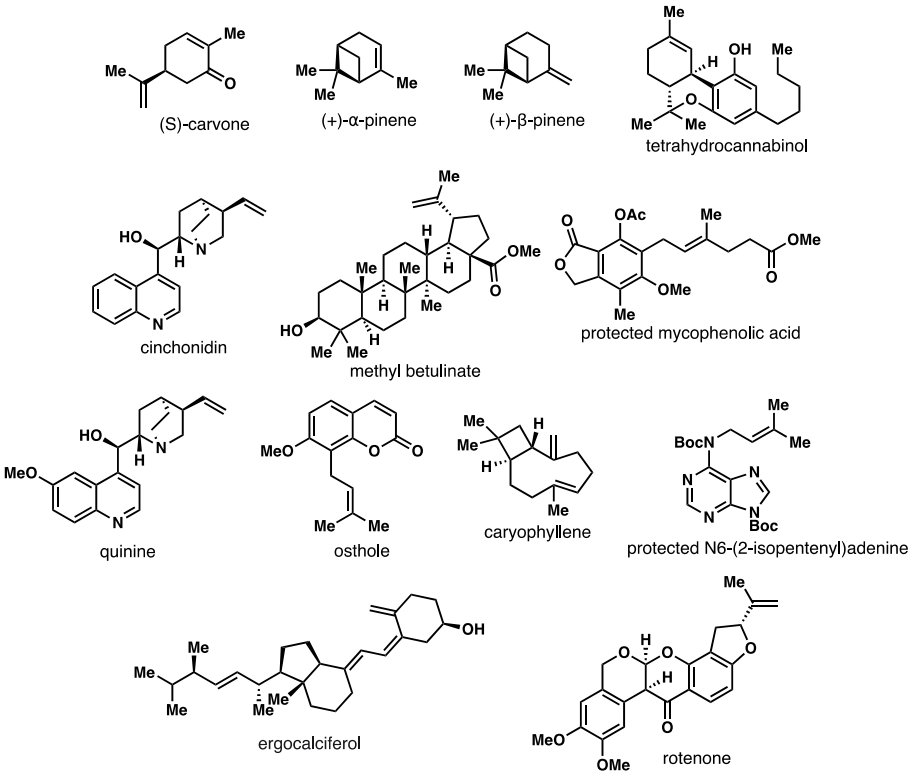
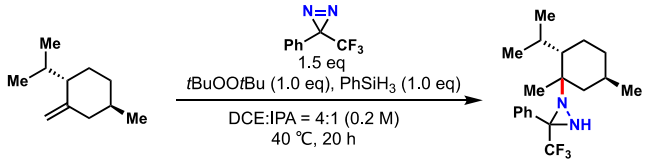


Figure 24. Unsuccessful examples in hydroamination reaction with diazirine (**8**).

1.5.3 Proposed mechanism

Control experiments were conducted to take a glance of possible cobalt catalyzed hydroamination reaction mechanism. First, we treated **16m** with hydroiodic acid, produce primary amine and protected it with benzoic anhydride. The resulting amide was analyzed with chiral-HPLC, and no enantioselectivity was detected, which supported the assumption that carbon radical was the reactive center when carbon bond was formed. If the cobalt complex was oxidized into Co(IV) and acted as an electrophile, there would be enantioselectivity since the catalyst is asymmetric. We then ran hydroamination reactions with chiral alkene catalyzed by both enantiomer of catalyst and similar outcomes were obtained from both catalyst enantiomer. This result suggested that

during the carbon-nitrogen bond formation, the cobalt catalyst may not coordinate with the carbon radical.



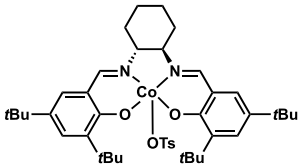
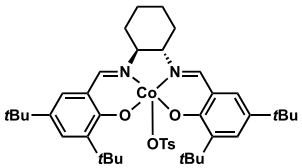
entry	catalyst	yield (%)
1	 (*R*,*R*)-**cat-1**	42
2	 (*S*,*S*)-**cat-1**	41

Figure 25. Enantiomer of Salen-Co-OTs was used in the hydroamination of chiral alkene gave same outcome.

The hydroamination reaction with deuterated isopropanol (*i*PrOD) produced little deuterium, as detected by crude NMR. This result suggested newly formed carbon-hydrogen bond and nitrogen-hydrogen bond may be from cobalt hydride. Based on our optimization reactions with (99%) and without (38%) peroxide, we hypothesize that peroxide was crucial for cobalt hydride complex formation, and the formed byproduct ($PhSiH_2Ot$-Bu) was detected by LC-MS for multiple reactions.

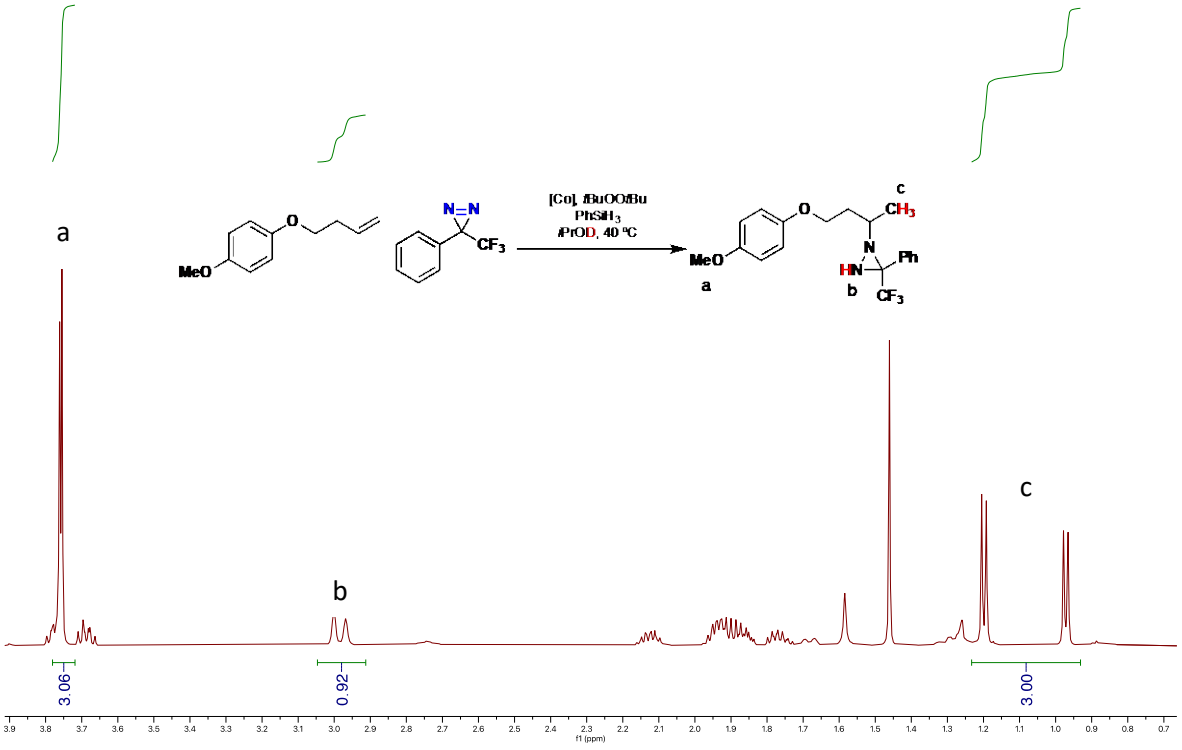


Figure 26. Crude ^{1}H NMR for product from hydroamination reaction with *i*PrOD.

Last, we ran the hydroamination with 1 equivalent of TEMPO, we were able to detect the trapped product by LC-MS, which suggest our hydroamination reaction may go through a radical mechanism instead of bis-electron mechanism.

A plausible mechanism was proposed based on our observations and literature reports. The original Co(III)-Salen-OTs was reduced to Co(II) after the addition of $PhSiH_3$. This can be supported by the reddish mixture after addition of $PhSiH_3$ and a similar hydroamination result can be obtained with the Co(II) complex as a catalyst. The catalytic cycle is proposed as follows:

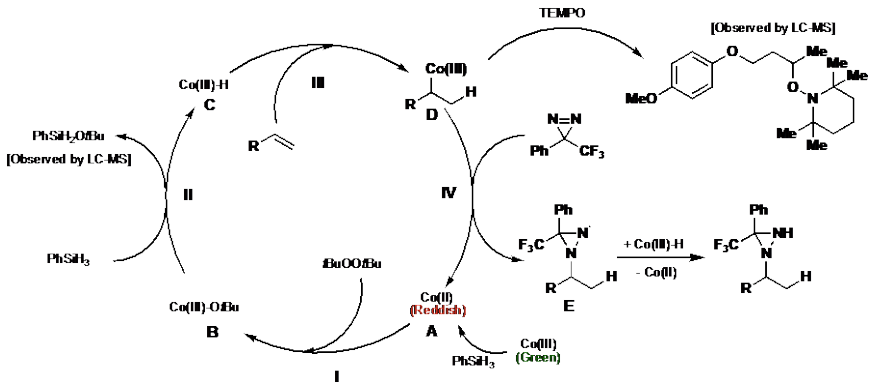


Figure 27. Proposed mechanism for cobalt catalyzed hydroamination reaction.

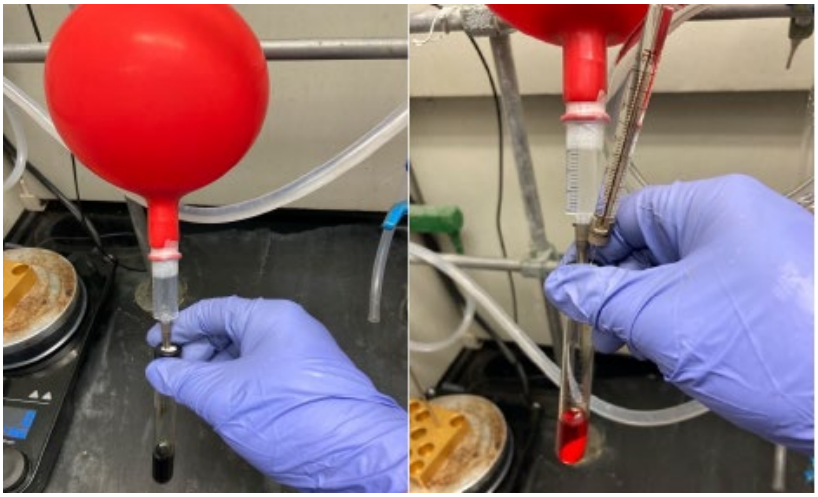


Figure 28: Reaction mixture color change before and after adding $PhSiH_3$. **Left**: Before addition of $PhSiH_3$, the Co(III) complex showed a dark green color. **Right:** After addition of $PhSiH_3$, the system became a reddish Co(II) color .

I: Co(II) complex A was oxidized by *t*-BuOO*t*-Bu produce complex **B**. This process was reported in Nojima's research[44] that cobalt oxygen bond can facilitate formation of cobalt-hydride complex, which agreed with our observation that lower yields were obtained without *t*-BuOO*t*-Bu.

II: The oxidized cobalt species then exchanged ligands with $PhSiH_3$ to afford cobalt hydride complex **C**. $PhSiH_2O$*t*Bu was detected by LC-MS (calculated 181.1 [$M+H^+$], found 181.0) within the crude reaction mixtures, which supports the proposed ligand exchange.

III: Cobalt hydride complex **C** underwent migratory insertion into the double bond of the substrate, with cobalt bonded to the more substituted side due to the stability of the radical and produced **D**.

IV: The carbon-cobalt complex **D** cleaved into complex **A** and the corresponding carbon radical, which was supported by our observation of TEMPO trapped product (observed by LC-MS, calculated 336.3 [$M+H^+$], found 336.2). The carbon radical is presumably quenched by the diazirine and forms diaziridinyl radical **E**, which was then quenched by a hydrogen radical source to deliver the product. This can be supported by our *i*PrOD experiment.

1.5.4 Synthetic applications

With more understanding of our cobalt catalyzed hydroamination reactions, we then investigated possible synthetic applications.

1.5.4.1 Synthesis of quinocide

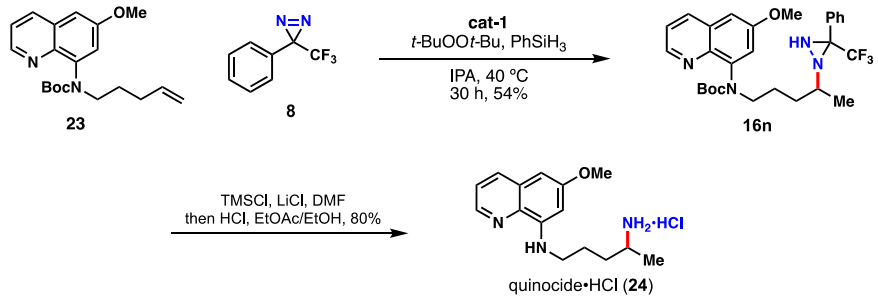


Figure 29. Synthesis of quinocide hydrochloride with cobalt catalyzed hydroamination reaction.

Primaquine is one of the 8-aminoquinoline class of drugs works for prevention and treatment of malaria.[45] For industry scale of primaquine synthesis, quinocide is one of key contaminate in quality control process. However, access to quinocide is limited and costly.[46] Reacted alkene **23** with diazirine **8** under cobalt condition produced **16n** at 54% isolated yield, then treated the resulting **16n** with TMSCl and LiCl in DMF at 60 ºC to reduce it into primary amine followed by salt formation process produced quinocide hydrochloride salt in 80% isolated yield.

1.5.4.2 Synthesis of mecamylamine hydrochloride

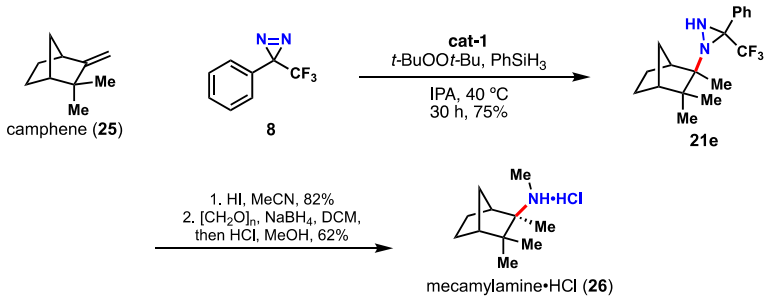


Figure 30. Synthesis of mecamylamine hydrochloride with cobalt catalyzed hydroamination reaction.

Reacted camphene (**25**) with diazirine (**8**) under cobalt catalyzed hydroamination reaction gave **21e** in 75% of isolated yield. Then treated the resulting **21e** with hydroiodic acid produced primary amine, followed by reductive amination with paraformaldehyde produced mecamylamine. After salt formation for purification, gave mecamylamine hydrochloride at 62% isolated yield. Previous pathways need to use highly toxic hydrocyanic acid for the carbon-nitrogen bond formation.[47] Our route offered more potential in making more derivatives for drug discovery purposes.

1.5.4.3 Synthesis of Neramexane hydrochloride

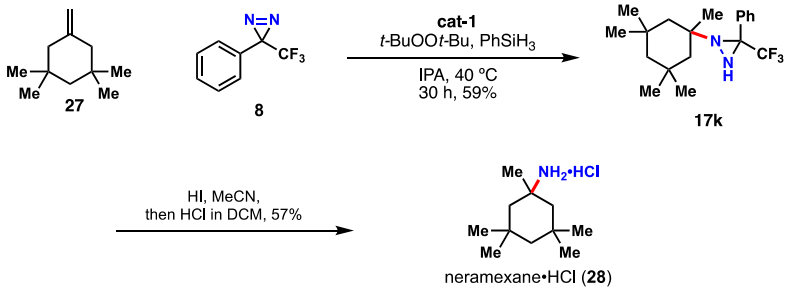


Figure 31. Synthesis of Neramexane hydrochloride with cobalt catalyzed hydroamination reaction.

The alkene (**27**) reacted with diazirine (**8**) under cobalt catalyzed hydroamination reaction produced **17k** in 59% of isolated yield. After treating the resulting **17k** with hydroiodic acid produced primary amine, followed by salt formation produced Neramexane hydrochloride in 57% of isolated yield. Neramexane is an NMDA antagonist, and previous way for making it was to go with target oriented Ritter's reaction.[48] Additionally, with diaziridine **17k**, more derivatives with nitrogen containing functional groups can be achieved.

1.5.4.4 Diversity-oriented synthesis

Diversifiable synthesis is very important in medicinal chemistry for generating as many derivatives as possible for high throughput screen after a lead was found. Compound **29** is a drug candidate for muscarinic M1 receptor, and in the original patent, the nitrogen in blue color was installed with S_N1 reaction in low yield.[49] Common intermediate **16p** and **17l** can be obtained with cobalt catalyzed hydroamination reaction, then we can either achieve amine synthesis or diazole synthesis with one step transformation with good yields. More importantly, **34**-like structure cannot be accessed with the patent route and was missing from screening.

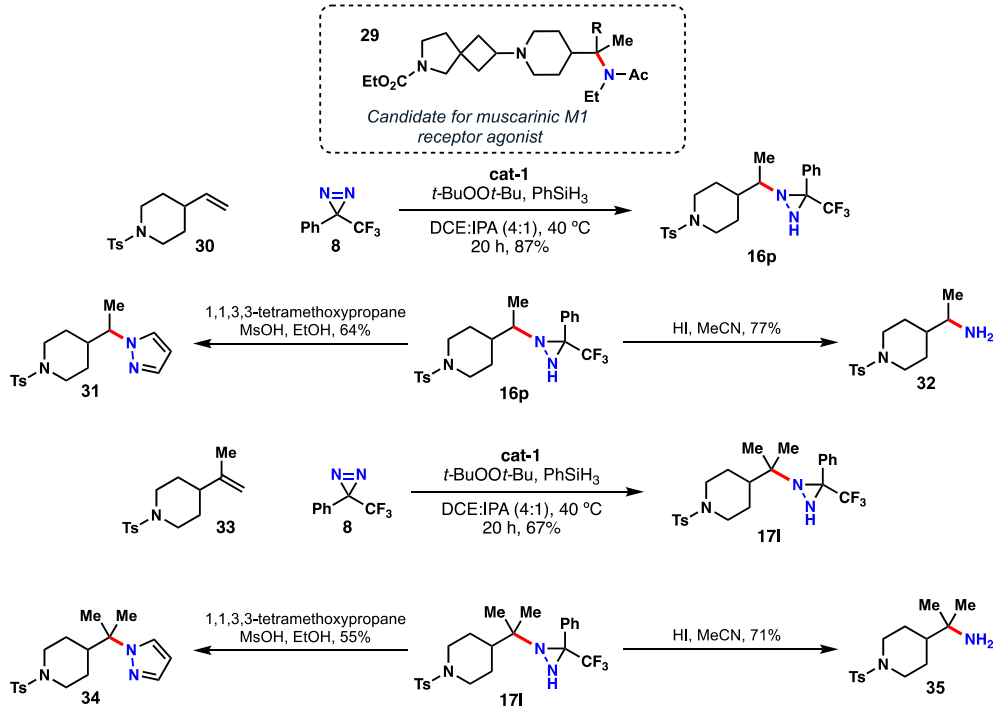


Figure 32. Diversifiable synthesis of candidates for muscarinic M1 receptor agonist with cobalt catalyzed hydroamination reaction.

1.5.4.5 Synthesis of splicing modulator candidate

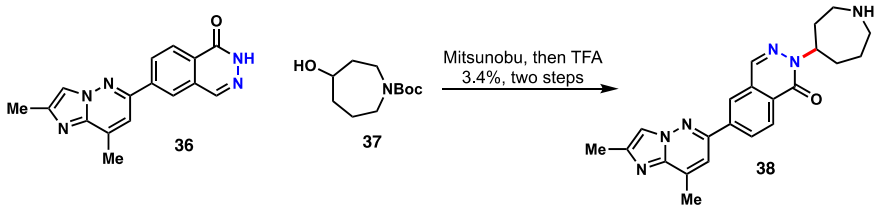


Figure 33. Patent route for splicing modulator candidate **38** synthesis.

Splicing modulator **38** is a drug candidate developed by Remix Therapeutics for potential RNA targeting activity.[50] In the patent route, intermediate **36** was obtained by Suzuki coupling, carbon nitrogen bond was formed by Mitsunobu reaction produced **37**. After deprotection with trifluoroacetic acid, they obtained **38** in 3.4% isolated yield over two steps. In medicinal chemistry,

this is a good synthetic approach to accumulating more derivatives quickly. However, come to synthetic molecule in demand, a high yielding route is in need.

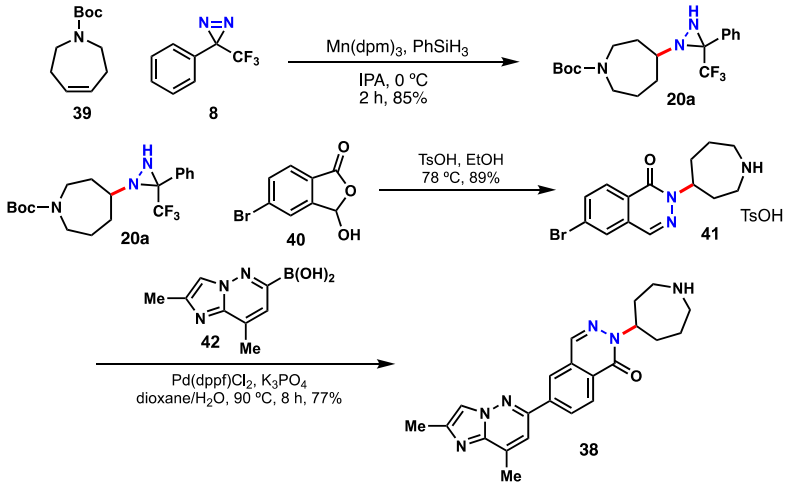


Figure 34. Diversifiable route for splicing modulator candidate **38** synthesis.

The alkene **39** reacted with diazirine **8** under our manganese hydroamination condition, resulted in diaziridine **20a**, which then reacted with **40** under acidic condition gave phthalazinone **41** in 89% isolated yield. Phthalazinone **41** bearing a bromo group on the aromatic ring underwent Suzuki coupling reaction with boronic acid **42** produced compound **38** in 77% isolated yield. Additionally, phthalazinone **41** has a bromo group on its aromatic ring, allows it to undergo multiple types of coupling reaction generated great number of compounds in short synthesis.

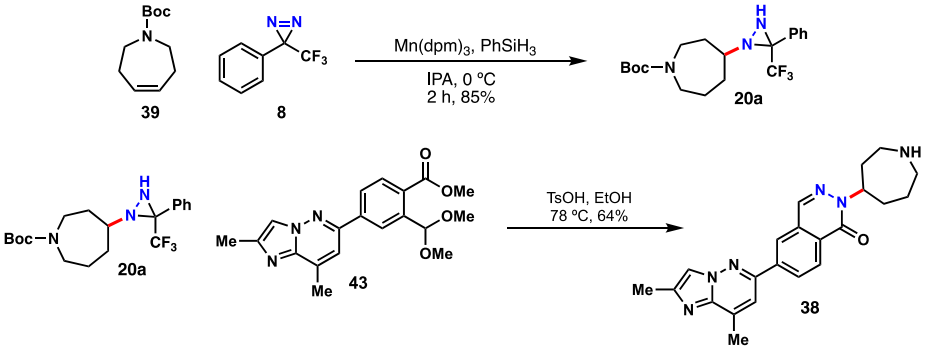


Figure 35. Late-stage orientated route for splicing modulator candidate **38** synthesis.

Another approach used ester **43** to synthetize **38**. React diaziridine **20a** with ester **43** under an acidic condition gave **38** in one step with 64% of isolated yield. Compared to the diversifiable route, this route has the potential of installing nitrogen containing part at the late stage, which worked especially for some precious building block.

1.5.5 Isotopic labeling with diazirine **8**

Isotopic labeling is a useful method in analytic chemistry, due to isotopes share very similar chemical properties, but differ in some physic properties, isotopes can act as a traceless label. Nitrogen-15 is an isotope of nitrogen with one more neutron than nitrogen-14. It makes up 0.4% in nitrogen atoms, and because of its non-radioactive property and single number of nucleus, nitrogen-15 is useful in use NMR,[51, 52] MRI,[53] and MS[54] to track biological transformations,[54, 55] protein packing,[56] drug binding,[57] and some reaction mechanisms.[58, 59] Consider its potential applications, the methods for installing nitrogen-15 into molecule is very limited. The starting materials for nitrogen-15 containing molecules are limited, such as ^{15}N-ammonia,[60] ^{15}N-hydroxylamine,[61] ^{15}N-hydrazine monohydrate,[57] and ^{15}N-urea,[62] made them harder to install into molecules.

1.5.5.1 Decagram synthesis of diazirine **8**

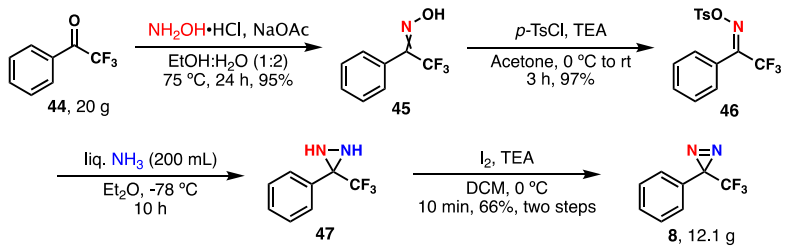


Figure 36. Decagram synthesis of diazirine **8**.

For development of cobalt catalyzed hydroamination reaction, we developed the pathway for decagram synthesis of diazirine **8**.[33] Starting from ketone **44**, it reacted with hydroxylamine hydrochloride in water and ethanol, produced oxime **45** in 95% of isolated yield. Tosylation of **45** with tosyl chloride in acetone at room temperature produced tosylate **46** in 97% isolated yield, which was then cyclized with liquid ammonia at -78 ºC. Resulting diaziridine **47** collected by extraction and oxidated with diiodine, gave diazirine **8** in 66% isolated yield over two steps. This is a very efficient synthetic route, gave over 10 g of product with one column chromatography, but is not suitable for expensive isotopic synthesis. During the cyclization step, over 100 eq of liquid ammonia needs to be used as solvent, this would be a huge waste for isotope like ^{15}N-ammonia.

1.5.5.2 Synthesis of ^{15}N-diazirine **8**

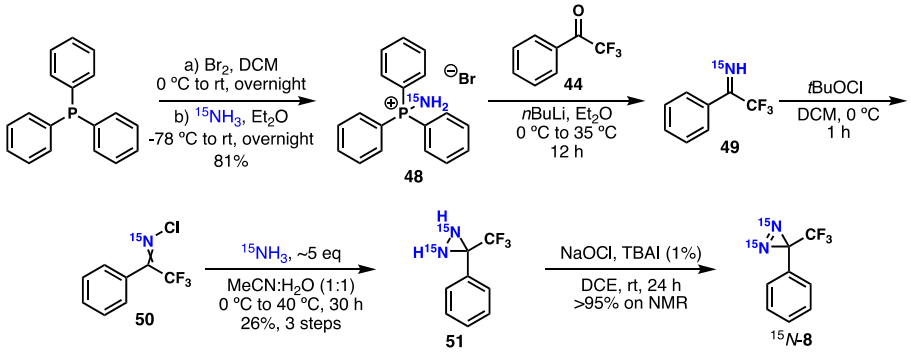


Figure 37. Synthetic route of ^{15}N-diazirine **8**.

The attempts via imine synthesis with ammonium chloride combined with strong base or acid was unsuccessful. And other diazirine synthesis with ammonia and hypochlorite or PIDA did not give desired product.[63] To our delight, we successfully built the first carbon nitrogen bond with a phosphorus-nitrogen ylide, went through a Wittig-like rection, produced imine **49** with only 7 eq

of ^{15}N-ammonia. Then oxidize it with *t*-BuOCl in DCM, we were able to produce chloride **50** and reacted it with 5 eq of ^{15}N-ammonia, we were able to synthetize ^{15}N-diaziridine **51**. However, the attempt of isolating of ^{15}N-diazirine **8** was unsuccessful due to the volatility of the compound. To our delight, we were about to oxidize the diaziridine *in situ* produced ^{15}N-diazirine **8** as a DCE solution for directly usage in the hydroamination reaction.

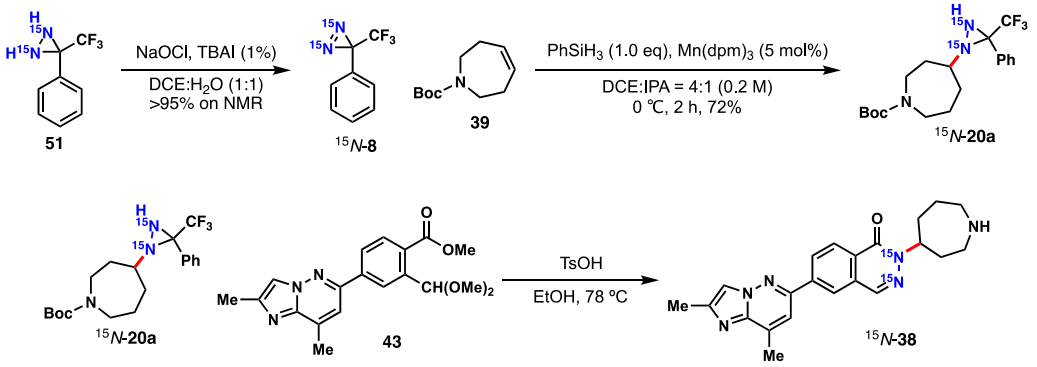


Figure 38. Synthetic route of ^{15}N-**38**.

After we oxidized ^{15}N-diaziridine **51** into ^{15}N-dizirine **8** as a DCE solution, we were able to utilize it in a manganese catalyzed hydroamination with alkene **39**, produced ^{15}N-diaziridine ^{15}N-**20a**, which can then be condensed with ester **43** to give nitrogen-15 version of splicing modulator candidate ^{15}N-**38**.

CHAPTER TWO: TOTAL SYNTHESISI OF NOTODIONE A AND SCYTONEMIN

2.1 Introduction

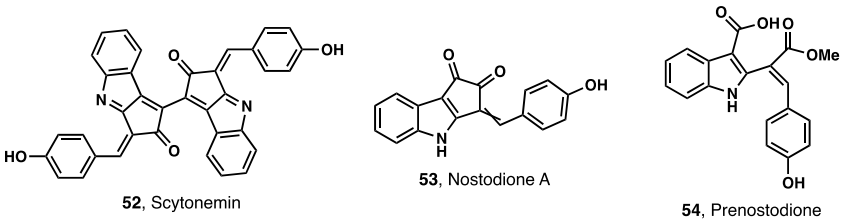


Figure 39. Secondary metabolite of cyanobacteria scytonemin, nostodione A, and prenostodione.

Cyanobacteria is a great source for isolation of natural products, there are reports on hundreds of different natural products with potential medicinal applications.[64, 65] Nostodione A, scytonemin, and prenostodione are three examples of secondary metabolite isolated from cyanobacteria. They share a similar indole core in their structures, and it is suggested they might be synthetized in similar biosynthetic pathways, specifically, prenostodione is believed to be precursor of nostodione A. In 1993, scytonemin was first isolated and characterized by Gerwick's group.[66] The first report of scytonemin can be tracked to the 19th century, as it was believed to be the first identified sunscreen pigment produced by prokaryote to protect cyanobacteria from sunlight.[66] Later in 2009, Walsh's group discovered the enzymatic synthesis approach to scytonemin and proposed its possible biosynthesis pathway.[67] Interestingly, nostodione A was not discovered yet in 1993, Gerwick's group synthetized nostodione A accidentally without knowing it is another natural product, when they tried to identify the structure of scytonemin by fragmentation. One year

later in 1994, Kawazu's group isolated nostodione A from *Nostoc commune* and characterized its structure. In the paper, Kawazu's group published its potential mitotic spindle toxicity as a possible anti-cancer drug.[68] In 2014, Jones-Brando's synthetic paper of nostodione A found an analog that showed good antiparasitic activity against *Toxoplasma gondii* after SAR studies.[69] Later in 2001, Carmeli's group reported isolation of prenostodione, another natural product bearing the similar indole core structure, the name was given due to its role as a precursor of nostodione A in biosynthesis.[70]

2.2 Synthetic Work towards Nostodione A and Scytonemin in Literature

2.2.1 Mårtensson's synthesis of nostodione A

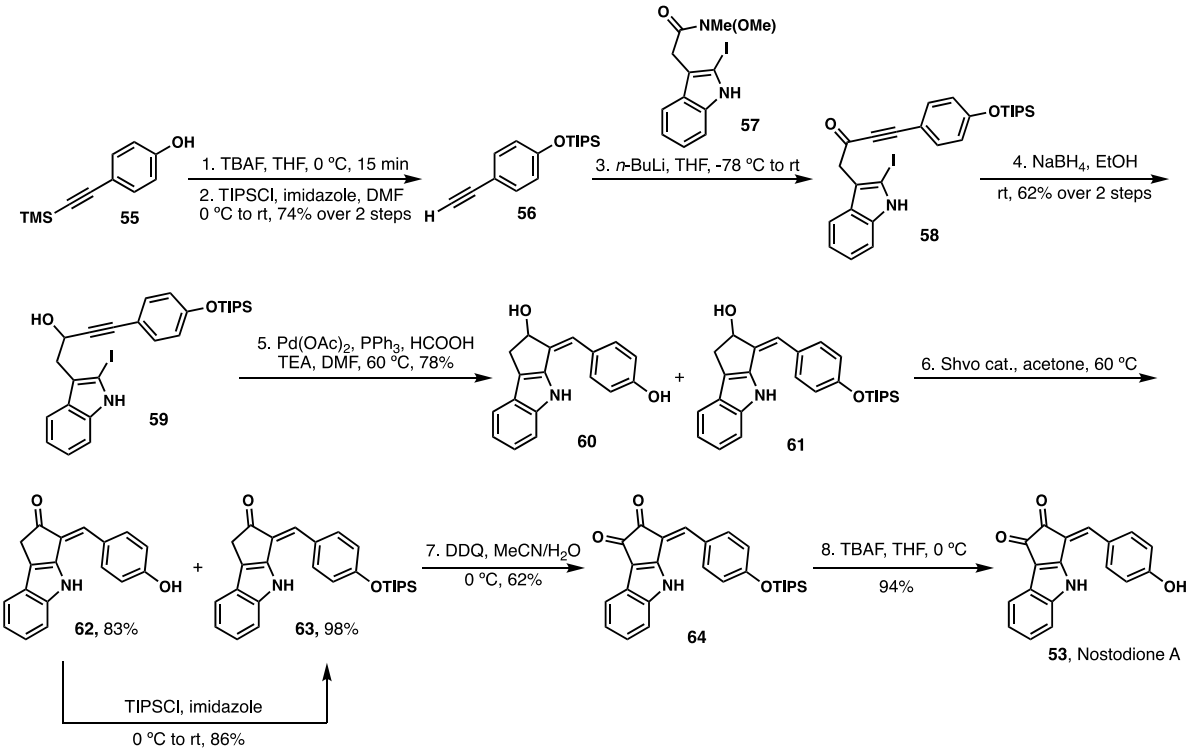


Figure 40. Mårtensson's synthesis of nostodione A.

The first synthesis of nostodione A was done by Mårtensson's group in 2012.[71] This synthesis adopted a palladium catalyzed 5-exo-dig cyclization for center five membered ring closing in its key step. Starting from silyl alkyne **55**, which was prepared by Sonogashira reaction, after deprotected by TBAF and reprotected the phenol hydroxy by TIPSCl and imidazole condition, terminal alkyne **56** was obtained. Deprotonation of **56** by *n*-butyl lithium, then treatment with Weinreb amide **57** gave substitution product **58** to set the alkyne and iodide in the right geometry to be ready for Heck-like cyclization reaction. However, Mårtensson indicated the cyclization reaction with **58** cannot be achieved. After reducing the ketone **58** into **59** with sodium borohydride, they were able to get the cyclization reaction working under a unique Heck-like reaction, and got the major core of nostodione A set. The palladium-catalyzed reaction gave both protected **61** and deprotected **60** products, which was oxidized separately into ketone **62** and **63**, and **62** was reprotected into **63** with TIPSCl. After benzyl oxidation with DDQ and deprotection with TBAF, nostodione A was made in 8 or 9 steps (as seen in Fig 35).

2.2.2 Mårtensson's synthesis of scytonemin

First synthesis of scytonemin was accomplished by Mårtensson's group in 2011.[72] Starting from indoleacetic acid **65**, Weinreb amide installed with mixed anhydride approach produced **66**. The iodide group was then installed with diiodide in THF and to ready it for palladium cyclization. An alkyne side chain was then installed with deprotected trimethylsilylacetylene to produce ketone **68**. Like their synthesis of nostodione A, the ketone needs to be protected for the cyclization reaction to work. Alkyne **69** and boronic **70** were treated with a palladium catalyst and underwent a Suzuki-Heck cascade reaction which cyclized the five-membered ring, then produced **71** in 47% of isolated yield.

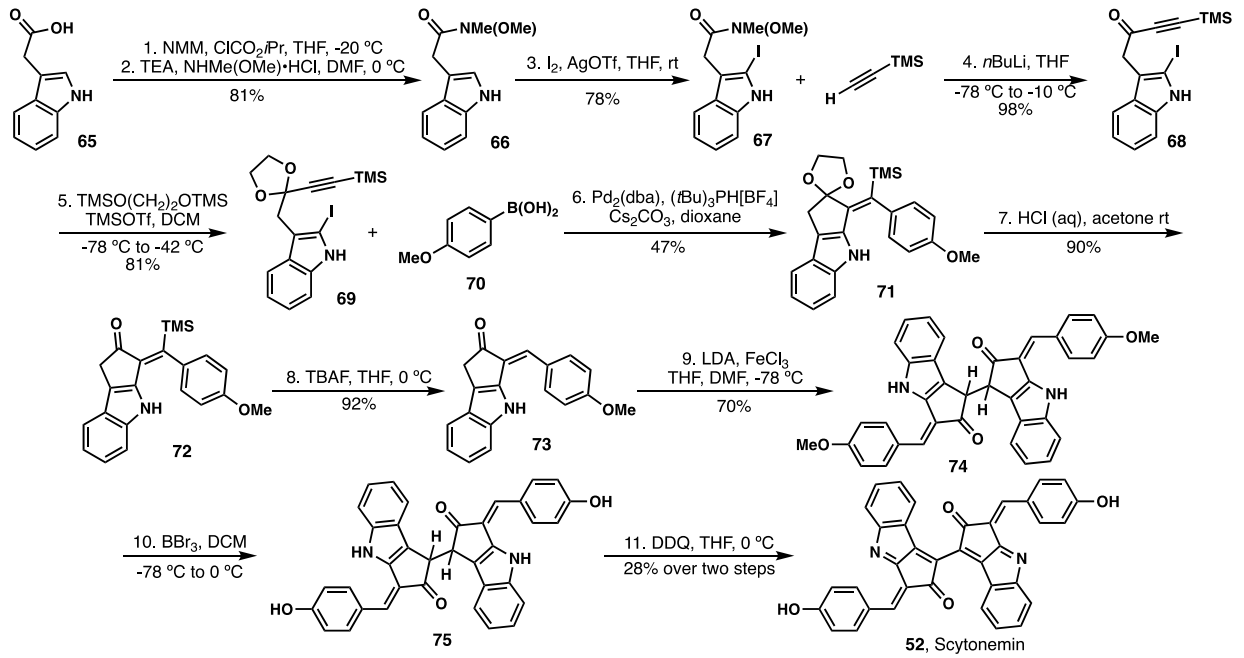


Figure 41. Mårtensson's synthesis of scytonemin.

Compound **71** underwent global deprotection to give **72** and was set up for the radical type oxidative coupling reaction. The key steps involved using LDA deprotonated α-position of ketone **72** and oxidized resulting anion with iron chloride produced carbon radical which dimerized at low temperature. After deprotection and oxidation with DDQ, they were able to synthetize scytonemin **52** in 11 steps.

2.2.3 McNulty's synthesis of nostodione A

In 2014, McNulty synthetized nostodione A through a different pathway to construct diketone 5-membered ring.[69] Their synthesis started from ethyl ester **76**, deprotonated the N-H bond and protected with tosyl chloride, gave ester **77**. It was transferred into chloride through a two-step sequence and treated with methyl phosphite at 100 ºC gave compound **80**, then deprotected with TBAF gave **81**.

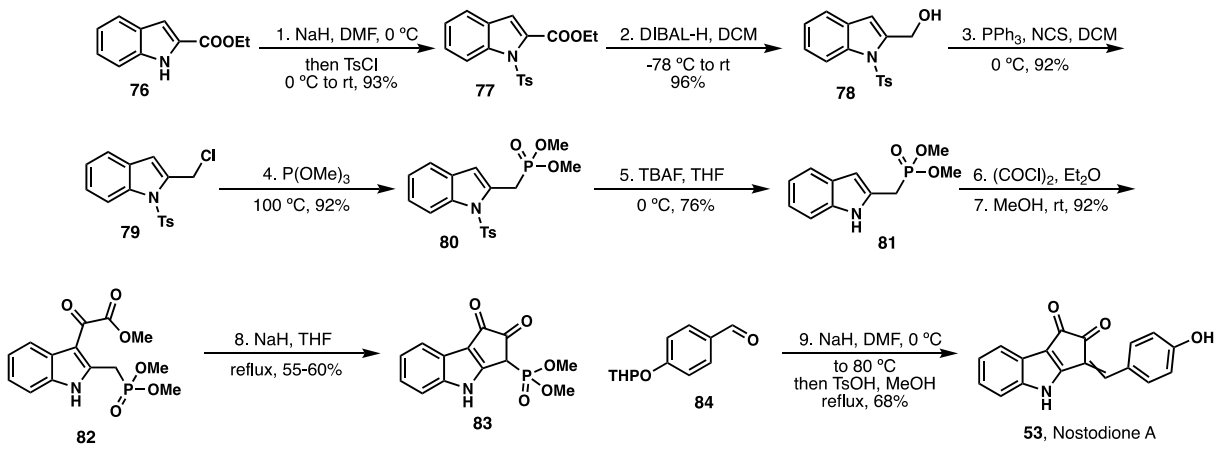


Figure 42. McNulty's synthesis of nostodione A.

Compound **81** reacted with oxalyl chloride, then esterified with methanol gave methyl ester **82**, which was then cyclized with sodium hydride closed diketone ring, followed by Horner-Wadsworth-Emmons reaction and deprotection gave nostodione A in 9 steps. Compound **84** in last synthetic step can be switched with other aldehyde and diversified into 7 derivatives and tested their antiparasitic activities.

2.3 Synthesis of Nostodione A and Scytonemin

2.3.1 Retrosynthetic analysis of nostodione A

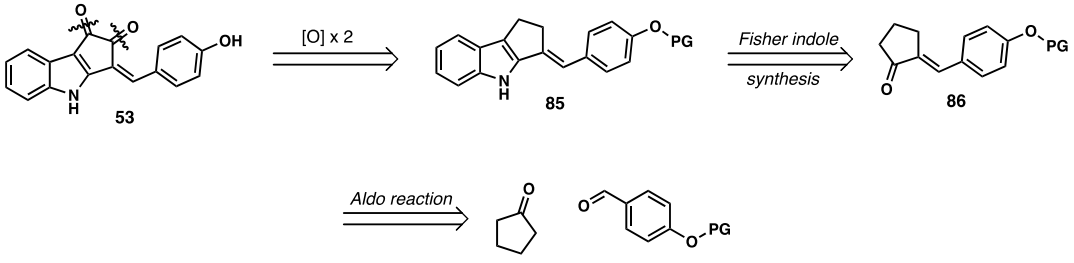


Figure 43. Retrosynthetic analysis of nostodione A.

In both Mårtensson's and McNulty's synthesis, they started from indole derivatives and closed the diketone ring with different cyclization strategies. To do so, all function groups in precursors have to be pre-set for cyclization reactions. For example, in Mårtensson's synthesis, alkyne side chain and iodide group are essential for palladium catalyzed cyclization reaction; and in McNulty's synthesis, ester part and phosphate part need to be installed separately. Steps taking to install those function groups can be saved if starting material with 5-membered ring was used. In our retrosynthetic analysis, two carbonyl groups in diketone can be installed separately with chemoselective oxidation reactions. Indole **85** can be obtained from Fisher's indole synthesis from ketone **86** and it can come from aldol condensation with cyclopentone and corresponding benzaldehyde. The 5-membered ring is coming from cyclopentone and the indole **85** can be used as a common intermediate for scytonemin synthesis.

2.3.2 Retrosynthetic analysis of scytonemin

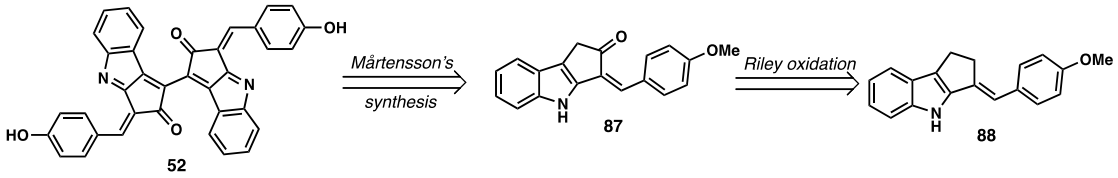


Figure 44. Retrosynthetic analysis of scytonemin.

As we discussed in 2.3.1, the indole intermediate can act as a common intermediate for both nostodione A and scytonemin. After Riley oxidation reaction, compound **87** is Mårtensson's key intermediate towards scytonemin **52**.

2.3.3 Synthesis of nostodione A

Our synthesis of nostodione A started from aldol condensation of cyclopentone and *p*-methoxybenzaldehyde heterogeneously in sodium hydroxide solution produced ketone **89** in 97% isolated yield at decagram scale. Ketone **89** refluxed with phenylhydrazine, and the resulting hydrazone collected from filtration was heated under acidic condition in acetonitrile gave indole **90** at decagram scale.

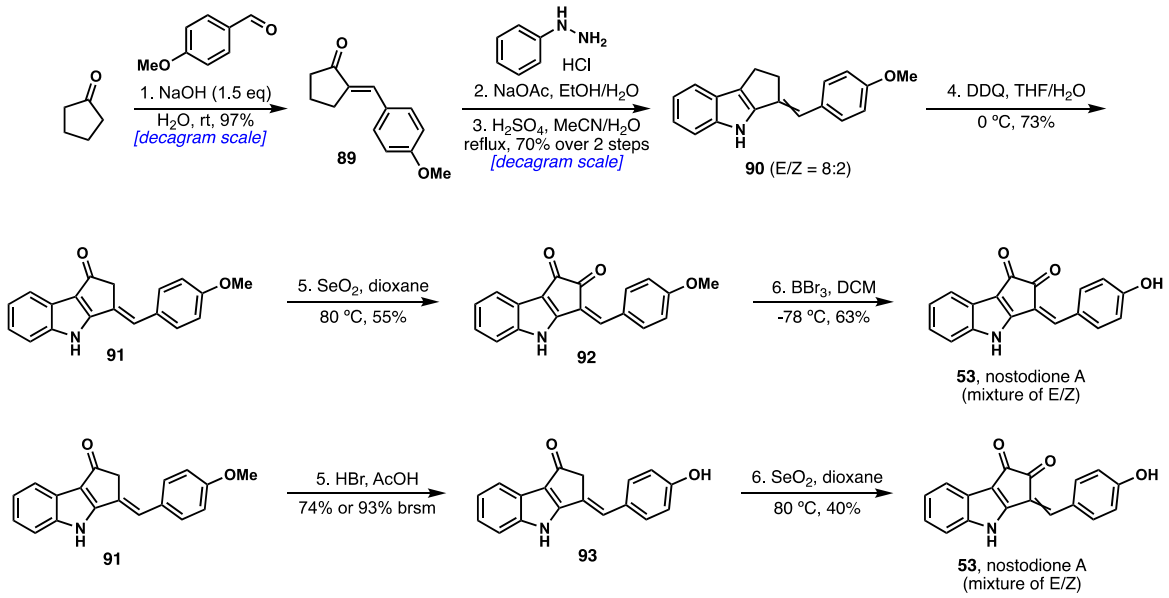


Figure 45. Synthesis of nostodione A with Fisher indole synthesis as key step.

Indole **90** is very unstable under acidic condition; the column chromatography needs to be fast or resulting in lower yield. DDQ oxidation on the benzyl position turned out to be a very efficient reaction, resulting ketone **91** was obtained within 1 h at 73% of isolated yield. Second carbonyl was installed by Riley oxidation in dioxane with selenium dioxide at 55% of isolated yield. After deprotected methoxy group with BBr_3 at low temperature gave nostodione A in 63% of isolated yield. In an alternative route, ketone **91** can be deprotected with a mixture of hydrobromide acid and acetic acid at 74% yield and 93% based on recovery of starting materials, followed by Riley

oxidation, nostodione A can be obtained at 40% isolated yield. Nostodione A can be made through two different route with six steps at 17% overall yield with deoxidation then deprotection sequence or 15% overall yield with oxidation deprotection oxidation sequence.

2.3.4 Synthesis of scytonemin

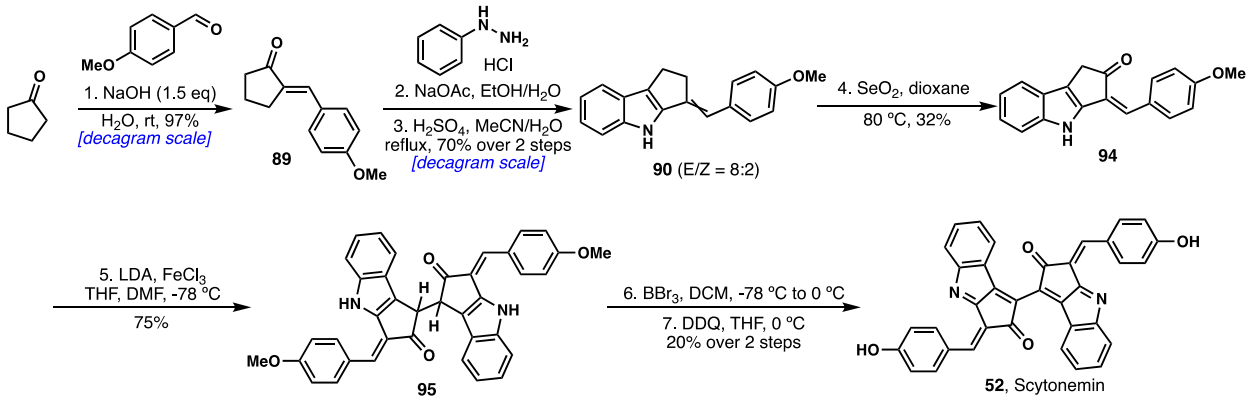


Figure 46. Synthesis of scytonemin with radical oxidative coupling as key step.

As we described in 2.3.2, the synthesis of scytonemin can be done with common intermediate indole **90**. The Riley oxidation of **90** was problematic, after an extensive screen, we were able to produce **94** in a 32% of isolated yield with the major side rection as formation of elimination product or retro-Aldo reaction. The radical type of allylic oxidation attempts was unsuccessful. Moved on with 32% isolated yield, and followed Mårtensson's approach, we were able to synthetize scytonemin for 7 steps in 3% overall yield.

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APPENDIX A: SUPPLEMENTARY INFORMATION FOR CHAPTER ONE

General Experimental:

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Anhydrous methylene chloride (DCM) and ether (Et_2O) were obtained by passing the previously degassed solvent through an activated alumina column (PPT Glass Contour Solvent Purification System) unless otherwise stated. Tetrahydrofuran (THF) was dried over a sodium/benzophenone system and stored over 4 Å MS under argon. Dichloroethane (DCE) was dried over distillation from CaH_2 and stored over 4 Å MS under argon. Isopropanol (IPA) was purchased at the highest commercial quality and further dried over 4 Å MS and stored under argon. Methanol (MeOH) and Ethanol (EtOH) were purchased as highest quality and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by Liquid Chromatography Mass spectrometry (LC/MS) or Thin Layer Chromatography (TLC) carried out on 250 μm SiliCycle SiliaPlates (TLC Glass-Backed TLC Extra Hard Layer, 60 Å), using visualizing agents such as shortwave UV light, iodine, $KMnO_4$, CAM, PMA, ninhydrin or *p*-anisaldehyde with heat as the developing agent. Flash column chromatography was performed with a Biotage Isolera One (ZIP or SNAP Ultra cartridges) or with traditional glass flash columns using SiliCycle SiliaFlash® P60 (particle size 40 - 63 μm). NMR spectra were recorded on a Bruker Ascend^{TM} 500 MHz instrument and were calibrated using residual undeuterated solvent as an internal reference (Chloroform-*d*:

7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; DMSO-*d6*: 2.50 ppm ^{1}H NMR, 39.5 ppm ^{13}CNMR). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, tt = triplet of triplet, ddt = doublet of doublet of triplet, m = multiplet. High resolution mass spectra (HRMS) were recorded on an Agilent 6230 LC–MS TOF mass spectrometer.

Handling of Reagents:

All diazirines were stored in a vial at -20 °C under argon (although the diazirines are moisture stable, this prevented water from being introduced into subsequent reactions). The vials containing diazirines were covered with aluminum foil to avoid prolonged exposure to direct light. (R,R)SalenCo^{III}OTs, tris(2,2,6,6-tetramethyl-3,5-heptanedionato)Mn^{III} [Mn(dpm)$_3$], and phenylsilane ($PhSiH_3$) were stored in a desiccator. *t*-Butyl hydroperoxide solution (*t*BuOOH) and di-*t*-butyl peroxide (*t*BuOO*t*Bu) were stored at 0-4 °C.

Synthesis of Diazirine 8:

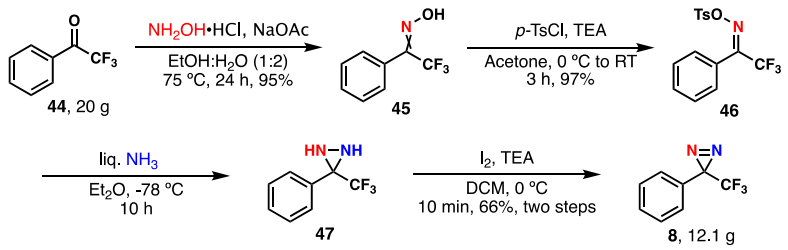
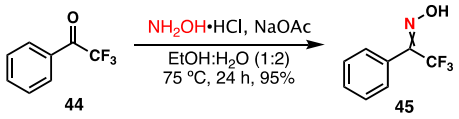


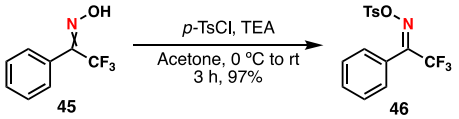
Figure S1: 3-(trifluoromethyl)-3-phenyldiazirine (**8**) was synthesized as previously reported with minor modifications.[33]

2,2,2-trifluoro-1-phenylethan-1-one oxime



Followed previously reported protocol.[73] To a 100 mL round-bottom flask equipped with magnetic stir bar, 2,2,2-trifluoro-1-phenylethan-1-one (10.0 g, 57.4 mmol, 1 eq) was added followed by 30 mL water and 15 mL ethanol. Hydrochloride hydroxylamine (8.0 g, 114 mmol, 2 eq) and sodium acetate (10.8 g, 132 mmol, 2.3 eq) were added, and the mixture heated at 75 ºC for 24 h. After TLC indicating the disappearance of starting materials, ethanol was removed *in vacuo* and the solid was collected by filtration, washed with water (2 x 50 mL) and dried under reduced pressure offered **45** as white solid (10.3 g, 95%) and used without further purification.

2,2,2-trifluoro-1-phenylethan-1-one *O*-tosyl oxime



2,2,2-trifluoro-1-phenylethan-1-one *O*-tosyl oxime (**46**) was made following our published procedure with minor modifications. To a 500 mL round-bottom flask equipped with magnetic stir bar, **45** (10.0 g, 52.9 mmol, 1 eq.) was added, followed by 250 mL acetone then cooled to 0 °C with an ice bath. 4-Toluenesulfonyl chloride (12.1 g, 63.5 mmol, 1.2 eq) was added, followed by addition of triethyl amine (22.3 ml, 16.1 g, 159 mmol, 3 eq) dropwise then stirred at room

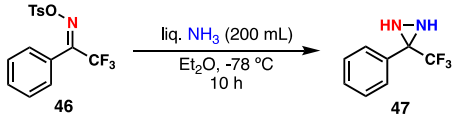
temperature for 3 h until TLC monitoring indicated total consumption of starting material **45**. The reaction mixture slowly transitioned from white to an orange color and solid formation was observed. The suspension was filtered, and the cake washed with acetone (2 x 50 mL). Filtrate was concentrated *in vacuo*, giving a light orange solid, to which ethanol (75 mL) and water (25 mL) were added, then refluxed for 1 h and stirred at room temperature overnight. Another portion of water (100 mL) added and solid was collected by filtration, washed with water (2 x 25 mL), then dried under reduced pressure to afford **46** as a white solid (17.6 g, 97%) in mostly (>95%) the E form.

The ^{1}H NMR spectrum matched with previously reported spectra.[33]

Physical state: White solid. $\mathbf{R_f}$ = 0.5 (20 % EA in hexanes, vis. UV and iodine).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.57 – 7.51 (m, 1H), 7.47 (ddd, J = 8.5, 7.2, 1.1 Hz, 2H), 7.41 – 7.35 (m, 4H), 2.48 (s, 3H).

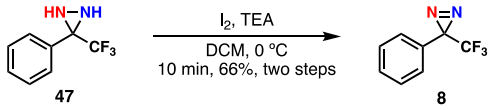
3-phenyl-3-(trifluoromethyl)diaziridine



To a flame-dried 1000 mL round-bottom flask equipped with a magnetic stir bar at -78 ºC, liq. NH_3 (approx. 200 mL) was added under argon atmosphere, followed by addition of anhydrous ether (140 mL). **46** (33.5 g, 97.6 mmol, 1 eq.) was added then stirred for 10 hours at -78 ºC. The

septum was removed, the reaction slowly warmed to room temperature overnight, and ammonia was evaporated slowly. To the residue was added water (100 mL) and extracted with Et_2O (3 x 100 mL), then washed with brine (100 mL), dried over anhydrous sodium sulfate (Na_2SO_4), filtered and concentrated *in vacuo*, yielding diaziridine **47** (19.0 g, >99% yield). **47** was used in the next step without further purification.

3-phenyl-3-(trifluoromethyl)-3*H*-diazirine



To a flame-dried 1000 mL round-bottom flask equipped with a magnetic stir bar under argon was added diaziridine **47** (18.4 g, 97.8 mmol, 1 eq.), followed by anhydrous dichloromethane (500 mL) then cooled to 0 °C. The round-bottom flask was covered with aluminum foil, then triethyl amine (21.6 g, 30.0 mL, 213 mmol, 2.2 eq.) was added dropwise and stirred for 10 min before iodine (13.4 g, 52.7 mmol, 1.1 eq.) was added portion-wise. With each addition, a dark yellow/brown color developed and then vanished shortly after. Upon completion of the reaction, the brown color persisted for more than 10 minutes at room temperature. The reaction mixture was poured into separatory funnel then was washed with saturated sodium thiosulphate (100 mL) and water (100 mL). The aqueous phases were combined, then extracted with dichloromethane (3 x 50 mL). Then organic phases were combined, dried over anhydrous magnesium sulfate, concentrated *in vacuo* then purified with column chromatography (silica gel, 100% pentane) to afford **8** (12.1 g, 66% yield over two steps) as a colorless oil.

Note: a) extraction must be quickly and protected from light. b) **8** is volatile (high vacuum drying not recommended).

Physical state: colorless oil. $\mathbf{R_f}$ = 0.8 (10 % EA in hexanes, vis. UV).

^{1}H NMR: (500 MHz, Chloroform-*d*) δ 7.45 - 7.37 (m, 3H), 7.23 - 7.18 (m, 2H).

^{13}C NMR: (126 MHz, Chloroform-*d*) δ 129.8, 129.3, 128.9, 126.6, 122.3 (q, J_{C-F} = 274.7 Hz), 28.6 (q, J_{C-F} = 40.4 Hz).

^{19}F NMR: (471 MHz, Chloroform-*d*) δ -65.25.

Synthesis of (*R*,*R*)-SalenCo^{III}OTs:

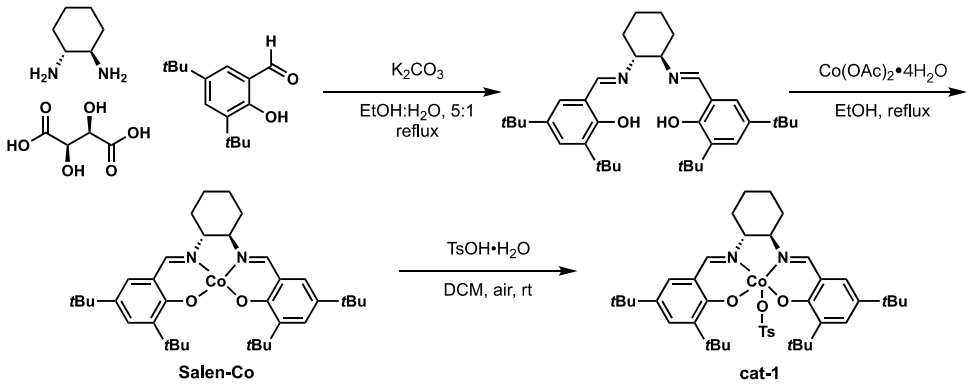
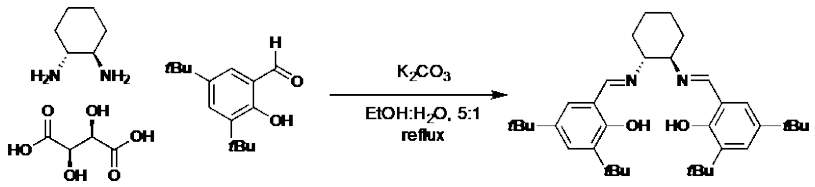
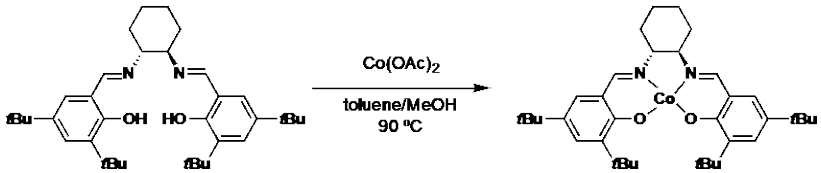


Figure S2: Synthesis of **cat-1**.

6,6'-((1*E*,1'*E*)-(((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(azaneylylidene))bis(methaneylylidene)) bis(2,4-di-*tert*-butylphenol)

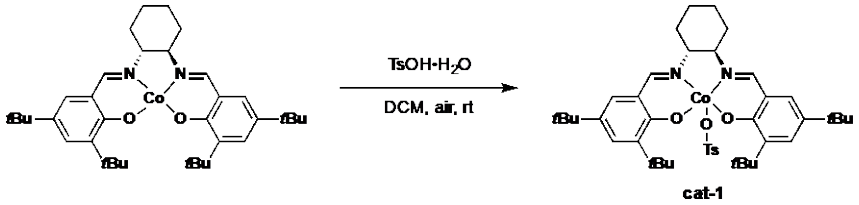


Step 1: Followed previously reported protocol.[74] To a flame-dried 1000 mL round-bottom flask equipped with a magnetic stir bar was added (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate (2.00 g, 7.57 mmol, 1 eq) followed by ethanol (50 mL) and water (10 mL). 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (3.51 g, 15.0 mmol, 1.98 eq) and potassium carbonate (2.09 g, 15.1 mmol, 2 eq) were added. The reaction mixture was stirred at reflux for 2 h until TLC monitoring indicated the disappearance of 3,5-di-*tert*-butyl-2-hydroxy benzaldehyde. The reaction mixture was cooled to room temperature with stirring and filtered with a Büchner funnel. The yellow solid was washed with a small amount of chilled ethanol and dried on vacuum, yielding (*R,R*)-salenH_2 (3.99 g , 97% yield).



Step 2: Followed previously reported protocol.[74] To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar under argon was added (*R,R*)-salenH_2 (1.30 g, 2.40 mmol, 1 eq) followed by dry toluene (10 mL). A solution of $Co(OAc)_2$ (0.42 g, 2.40 mmol, 1 eq) in dry

methanol (20 mL) was then added via syringe to afford a red precipitate. The reaction mixture was stirred at 90 ºC for 1 h. The reaction mixture was cooled and the red precipitate was collected by filtration and washed with methanol until the filtrate turned colorless. The final product was dried at 40 ºC under vacuum to a constant weight, yielding the product as a red powder (1.20 g, 83% yield).



cat-1

Step 3: Followed previously reported protocol.[74] To a 500 mL round-bottom flask equipped with a magnetic stir bar under argon was added (*R,R*)-salenCo^{II} complex (6.00 g, 9.95 mmol, 1 eq) followed by *p*-toluenesulfonic acid monohydrate (1.90 g, 9.95 mmol, 1 eq) and dichloromethane (200 mL). The reaction mixture was stirred under air atmosphere at room temperature for 3 h. The volatiles were removed *in vacuo* and the remaining solid was suspended in hexane (50 mL), re-collected by filtration, washed with a dichloromethane/hexanes (1:3) mixture (40 mL), and dried at 40 ºC under vacuum to a constant weight (6.61 g, 86 % yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[74]

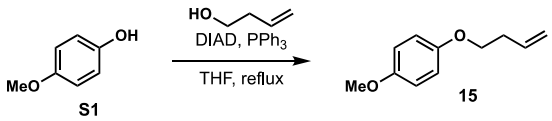
Physical state: dark green solid.

^{1}H NMR (500 MHz, DMSO) δ 7.81 (s, 2H), 7.51 – 7.42 (m, 6H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.62 (dd, *J* = 7.1, 2.8 Hz, 2H), 3.07 (d, *J* = 11.8 Hz, 2H), 2.29 (s, 3H), 2.06 – 1.97 (m, 2H), 1.97 – 1.86 (m, 2H), 1.75 (s, 18H), 1.63 – 1.54 (m, 2H), 1.31 (s, 18H).

The following catalysts were synthesized by slight modifications to **step 3** of the above procedure: (*R,R*)-SalenCo^{III} (OAc) was synthesized via reaction of **Salen-Co** with acetic acid (AcOH), (*R,R*)-(*R,R*)-SalenCo^{III} (Cl) via reaction of **Salen-Co** with sodium chloride. ^{1}H NMR matched previously reported spectra.

Characterization Data for Alkenes

1-(But-3-en-1-yloxy)-4-methoxybenzene



Followed previously reported protocol.[75] To a 50 mL round-bottom flask equipped with a magnetic stir bar under argon was added 3-buten-1-ol (642 mg, 8.91 mmol, 1.05 eq) and anhydrous tetrahydrofuran (25 mL). 4-Methoxyphenol (1.06 g, 8.50 mmol, 1 eq) and triphenylphosphine (2.90 g, 11.1 mmol, 1.3 eq) were added then the reaction mixture was stirred for 5 min at 0 ºC, followed by addition of diisopropyl azodicarboxylate (DIAD) (2.41 g, 2.34 mL, 11.9 mmol, 1.4 eq) via syringe slowly. The mixture was then refluxed for 15 min until TLC monitoring indicated total consumption of the starting material. The crude mixture was concentrated *in vacuo* and

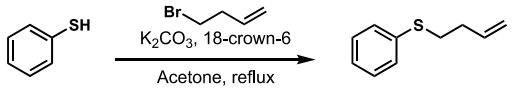
purified via flash column chromatography (silica gel, 10% EA in hexanes) yielding **15** (1.42 g, 93% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[75]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.5 (10% EA in hexanes, vis. UV and $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 – 6.81 (m, 4H), 5.91 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.17 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.13 – 5.08 (m, 1H), 3.97 (t, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 2.52 (qt, *J* = 6.7, 1.4 Hz, 2H).

But-3-en-1-yl(phenyl)sulfane



Followed previously reported protocol.[76] To a 50 mL round-bottom flask equipped with a magnetic stir bar under argon was added thiophenol (648 mg, 5.88 mmol, 1 eq), acetone (40 ml), potassium carbonate (1.21 g, 8.82 mmol, 1.5 eq) and 18-crown-6 (155 mg, 0.588 mmol, 0.1 eq). The reaction mixture was stirred for 5 min followed by addition of 4-bromobut-1-ene (795 mg, 5.88 mmol, 1.0 eq). The reaction mixture was stirred under reflux overnight until TLC monitoring indicated total consumption of the starting material (SM and TM have a very close R_f, but stain differently with $KMnO_4$). The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (50 mL x 3). The organic layers were combined and washed with 10% sodium hydroxide (50 mL),

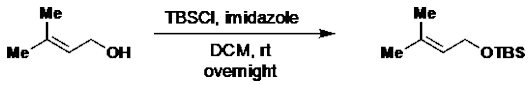
brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 100% hexanes) yielding but-3-en-1-yl(phenyl)sulfane (716 mg, 74% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[76]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.3 (100% hexanes, vis. UV and $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 1H), 5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.15 – 4.95 (m, 2H), 2.99 (dd, *J* = 7.9, 7.0 Hz, 2H), 2.40 (dtt, *J* = 9.4, 6.7, 1.4 Hz, 2H).

***tert*-Butyldimethyl((3-methylbut-2-en-1-yl)oxy)silane**



Followed previously reported protocol.[77] To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 3-methylbut-3-en-1-ol (1.00 g, 11.6 mmol, 1 eq) followed by anhydrous dichloromethane (10 mL) and imidazole (1.58 g, 23.2 mmol, 2.0 eq). *tert*-Butyldimethylsilyl chloride (2.62 g, 17.4 mmol, 1.5 eq) was added in one portion then stirred overnight under room temperature until TLC monitoring indicated total consumption of starting material. The reaction mixture was concentrated *in vacuo*, and the residue purified via flash column chromatography

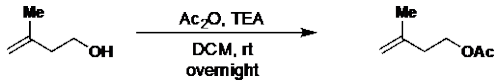
(silica gel, 100% hexanes) yielding *tert*-butyldimethyl((3-methylbut-2-en-1-yl)oxy)silane (1.11 g, 48% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[77]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.3, (100% hexanes, vis. PMA and $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.38 – 5.20 (m, 1H), 4.17 (dt, *J* = 6.5, 1.1 Hz, 2H), 1.71 (q, *J* = 1.4 Hz, 3H), 1.63 (d, *J* = 1.3 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

3-Methylbut-3-en-1-yl acetate



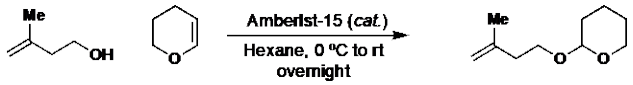
To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 3-methylbut-3-en-1-ol (860 mg, 10.0 mmol, 1 eq) followed by anhydrous dichloromethane (10 mL). Acetic anhydride (1.13 g, 1.05 ml, 11.1 mmol, 1.1 eq) was added in one portion and the reaction mixture was stirred for 10 min at room temperature, then triethylamine (1.19 g, 1.66 ml, 11.8 mmol, 1.2 eq) was added dropwise. The mixture was stirred at room temperature overnight until TLC monitoring indicated total consumption of starting material. The reaction mixture was concentrated *in vacuo*, and the residue purified via flash column chromatography (silica gel, 2% ethyl actate in hexanes) yielding 3-methylbut-3-en-1-yl acetate (430 mg, 34% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[78]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.8 (10% EA in hexanes vis. PMA and $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.89 – 4.63 (m, 2H), 4.18 (t, J = 6.9 Hz, 2H), 2.45 – 2.18 (m, 2H), 2.04 (s, 3H), 1.87 – 1.68 (m, 3H)**.**

2-((3-Methylbut-3-en-1-yl)oxy)tetrahydro-2*H*-pyran



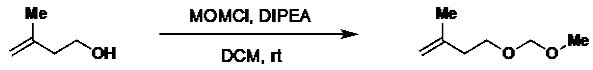
Followed previously reported protocol.[79] To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 3-methylbut-3-en-1-ol (860 mg, 10.0 mmol, 1 eq) and hexane (10 mL), followed by 3,4-dihydro-2*H*-pyran (1.29 g, 1.40 mL, 15.4 mmol, 1.5 eq). The reaction mixture was stirred at 0 ºC then several pellets of Amberlyst-15 was added. The reaction mixture was warmed to room temperature and stirred overnight until TLC monitoring indicated total consumption of the starting material. Amberlyst-15 was removed by filtration and the filtrate was washed with *sat.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with dichloromethane (25 mL x 3), the organic layers combined, then washed with brine, dried over *anhydrous* Na_2SO_4 then concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 14% acetone in hexanes) yielding 2-((3-methylbut-3-en-1-yl)oxy)tetrahydro-2H-pyran (1.30 g, 76% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[79]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.7 (10% ethyl actate in hexanes, vis. PMA and $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.80 – 4.69 (m, 2H), 4.59 (dd, *J* = 4.4, 2.9 Hz, 1H), 3.85 (ddd, *J* = 14.3, 10.5, 7.8 Hz, 2H), 3.56 – 3.44 (m, 2H), 2.32 (t, *J* = 7.1 Hz, 2H), 1.83 (td, *J* = 8.7, 3.6 Hz, 1H), 1.77 – 1.74 (m, 3H), 1.68 (t, *J* = 4.4 Hz, 1H), 1.61 – 1.49 (m, 4H).

4-(Methoxymethoxy)-2-methylbut-1-ene



To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 3-methylbut-3-en-1-ol (200 mg, 2.32 mmol, 1 eq) and anhydrous dichloromethane (5 mL), followed by chloro(methoxymethoxy)methane (747 mg, 0.71 mL, 9.28 mmol, 4.0 eq). The reaction mixture was stirred for 10 min under room temperature then *N*-ethyl-*N*-isopropylpropan-2-amine (1.40 g, 1.94 mL, 13.8 mmol, 6.0 eq) was added. The reaction mixture was stirred at room temperature overnight until TLC monitoring indicated total consumption of the starting materials, then the reaction mixture was concentrated *in vacuo*, and the residue purified via flash column chromatography (silica gel, 2% ethyl acetate in hexanes) yielding 4-(methoxymethoxy)-2-methylbut-1-ene (34.2 mg, 11% yield).

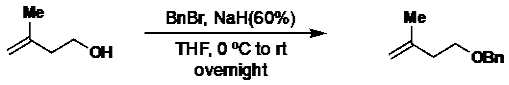
Physical state: colorless oil. $\mathbf{R_f}$ = 0.7 (10% ethyl acetate in hexanes, vis. PMA and $KMnO_4$).

^{1}H NMR: (500 MHz, CDCl3) δ 4.87 – 4.70 (m, 2H), 4.63 (s, 2H), 3.65 (t, J = 6.8 Hz, 2H), 3.36 (s, 3H), 2.37 – 2.23 (m, 2H), 1.76 (t, J = 1.2 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.86, 111.71, 96.57, 66.15, 55.35, 37.94, 22.68.

HRMS: Calculated for $C_7H_{15}O_2^+$ 131.1067 [M+H$^+$]; found 131.1071.

(((3-Methylbut-3-en-1-yl)oxy)methyl)benzene



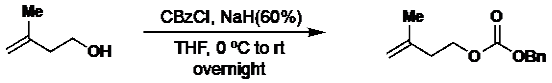
To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 3-methylbut-3-en-1-ol (500 mg, 5.80 mmol, 1 eq) and anhydrous tetrahydrofuran (5 mL). The resulting mixture was cooled to 0 ºC. Sodium hydride (60% in mineral oil, 280 mg, 7.00 mmol, 1.2 eq) was added portion-wise with stirring. After addition, argon was replaced and benzyl bromide (1.09 g, 0.76 mL, 6.39 mmol, 1.1 eq) was added via syringe. The reaction mixture was warmed to room temperature and stirred overnight, until TLC indicated total consumption of starting material. Water (10 mL) was added slowly to quench the reaction, and the mixture was poured into a separatory funnel, followed by addition of water (50 mL) and extracted with ethyl acetate (30 mL x 3). The organic phases were combined, washed with brine (50 mL), dried over *anhyd.* Na_2SO_4, then concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 2% ethyl acetate in hexanes) yielding (((3-methylbut-3-en-1-yl)oxy)methyl)benzene (1.02 g, 99% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[80]

Physical state: colorless oil. **R_f** = 0.9 (10% ethyl acetate in hexanes, vis. PMA and $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 4.85 – 4.70 (m, 2H), 4.53 (s, 2H), 3.59 (t, *J* = 6.9 Hz, 2H), 2.35 (tt, *J* = 6.9, 0.9 Hz, 2H), 1.75 (t, *J* = 1.2 Hz, 3H).

Benzyl (3-methylbut-3-en-1-yl) carbonate



To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 3-methylbut-3-en-1-ol (500 mg, 5.80 mmol, 1 eq) and anhydrous tetrahydrofuran (5 mL). The resulting mixture was cooled to 0 ºC. Sodium hydride (60% in mineral oil, 280 mg, 7.00 mmol, 1.2 eq) was added portion-wise with stirring. After addition, argon was replaced and benzyl chloroformate (1.20 g, 1.00 mL, 7.03 mmol, 1.2 eq) was added via syringe. The reaction mixture was warmed to room temperature and stirred overnight, until TLC indicated total consumption of starting material. Water (10 mL) was added slowly to quench the reaction, and the mixture was poured into a separatory funnel, followed by addition of water (50 mL) and extracted with ethyl acetate (30 mL x 3). The organic phases were combined, washed with brine (50 mL), dried over *anhyd.* Na_2SO_4, then concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel,

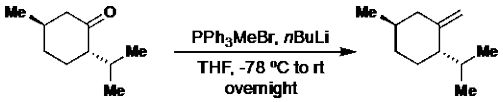
2% ethyl acetate in hexanes) yielding benzyl (3-methylbut-3-en-1-yl) carbonate (854 mg, 67% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[81]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.7 (10% ethyl acetate in hexanes, vis. PMA and $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.47 – 7.31 (m, 5H), 5.18 (s, 2H), 4.88 – 4.74 (m, 2H), 4.29 (t, *J* = 7.0 Hz, 2H), 2.41 (td, *J* = 6.9, 1.3 Hz, 2H), 1.78 (t, *J* = 1.2 Hz, 3H).

(1S,4R)-1-isopropyl-4-methyl-2-methylenecyclohexane



To a 250 mL round-bottom flask equipped with a magnetic stir bar was added triphenylphosphine methyl bromide (6.00 g, 16.8 mmol, 1.3 eq) then the placed under argon. Anhydrous tetrahydrofuran (45 mL) added, followed by slow addition of *n*BuLi (2.5 M, 6.8 mL, 16.8 mmol, 1.3 eq) under -78 ºC with stirring. The reaction mixture was stirred under -78 ºC for 1 h and a yellow solution was formed. Menthone (2.01 g, 13.0 mmol, 1 eq) was added in one portion via a syringe and the reaction mixture warmed to room temperature slowly and stirred overnight. Water (25 mL) was added slowly to quench the reaction, and the mixture was poured into a separatory funnel, followed by addition of water (200 mL) and extracted with ether (100 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue purified via

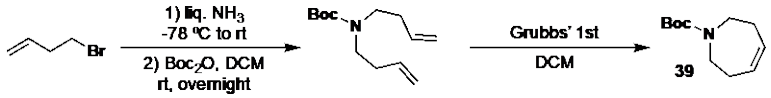
flash column chromatography (silica gel, 100% hexanes) yielding **(**1S,4R)-1-isopropyl-4-methyl-2-methylenecyclohexane (883 mg, 45% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[81]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.9, (10% ethyl acetate in hexanes, vis. PMA and $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.70 (dd, *J* = 2.2, 1.1 Hz, 1H), 4.58 (t, *J* = 1.4 Hz, 1H), 2.28 (dddd, *J* = 12.7, 4.1, 1.8, 1.0 Hz, 1H), 1.96 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.84 – 1.72 (m, 2H), 1.70 – 1.63 (m, 2H), 1.62 – 1.51 (m, 1H), 1.21 – 1.03 (m, 2H), 0.93 – 0.87 (m, 9H).

***tert*-butyl 2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate** (**39**)



To a flame-dried 25 mL sealed tube equipped with a magnetic stir bar, a rubber stopper was fitted, and liq. ammonia (~6 mL) added under -78 ºC, followed by addition of 1-bromobut-3-ene (5.00 g, 37.04 mmol, 1 eq). The reaction mixture was sealed and stirred at 40 ºC overnight then the tube was cooled to -78 ºC, carefully opened and warmed to room temperature until the ammonia evaporated. Water (20 mL) was added, the pH was adjusted to 1 with 3 M HCl and extracted with ether (50 mL x 3). The organic phase was discarded. To the aqueous layer was added a 5% sodium hydroxide solution until pH 14, then extracted with ether (50 mL x 3). The organic layers were

combined, dried over *anhyd.* Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was used in the next step without further purification.

To a 50 mL round-bottom flask equipped with a magnetic stir bar was added the residue (0.96 g) from the previous step and dichloromethane (10 mL). Boc_2O (2.85 g, 3.00 mL, 13.05 mmol, 0.5 eq based on 1-bromobut-3-ene) was added slowly, and the reaction mixture stirred at room temperature overnight, until TLC monitoring confirmed the disappearance of the starting material. The reaction mixture was concentrated *in vacuo* and the residue purified via flash column chromatography (silica gel, 5% ethyl acetate in hexanes) yielding *tert*-butyl di(but-3-en-1-yl)carbamate (1.26 g , 31% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[82]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.5 (10% ethyl acetate in hexanes, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.91 – 5.57 (m, 2H), 5.15 – 4.91 (m, 4H), 3.28 – 3.18 (m, 4H), 2.27 (q, J = 7.2 Hz, 4H), 1.46 (s, 9H).

To a 500 mL round-bottom flask equipped with a magnetic stir bar was added *tert*-butyl di(but-3-en-1-yl)carbamate (380 mg, 1.68 mmol, 1 eq) and dichloromethane (200 mL). Grubbs' 1st generation catalyst (93 mg, 0.11 mmol, 6.5 %) was added, and the reaction placed under argon. The reaction mixture was stirred under reflux for 2 h until TLC monitoring indicated the disappearance of the starting material. The reaction mixture was concentrated on silica gel and

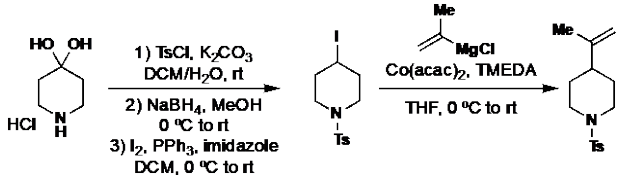
purified via flash column chromatography (silica gel, 4% ethyl acetate in hexanes) affording *tert*-butyl 2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (**39**) (240 mg, 72% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[82]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.4 (10% ethyl acetate in hexane, vis. $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.72 (d, *J* = 2.6 Hz, 2H), 3.55 – 3.36 (m, 4H), 2.37 – 2.16 (m, 4H), 1.46 (s, 9H).

4-(prop-1-en-2-yl)-1-tosylpiperidine



Followed previously reported procedure.[83] To a 250 mL round-bottom flask equipped with a magnetic stir bar was added 4-piperidone monohydrate hydrochloride (5.00 g, 32.5 mmol, 1 eq), dichloromethane (30 mL), water (30 mL) and potassium carbonate (10.8 g, 78.0 mmol, 2.4 eq). The reaction mixture was stirred until all the solid disappeared, followed by addition of 4-toluenesulfonyl chloride (6.50 g, 34.1 mmol, 1.05 eq) portion-wise, then the reaction mixture was stirred overnight at room temperature, until LC-MS indicated disappearance of the starting materials. The reaction mixture poured into a separatory funnel and extracted with

dichloromethane (50 mL x 3), washed with brine (50 mL) and concentrated *in vacuo*. A white solid (9.49 g, over 100%) was collected and used without further purification.

The tosylated compound from the previous step was dissolved in methanol (20 mL) in a 50 mL round bottom flask. The mixture was cooled to 0 ºC followed by addition of $NaBH_4$ (1.40 g, 35.0 mmol, 1.1 eq based on 4-piperidone monohydrate hydrochloride) portion-wise. The reaction mixture warmed to room temperature and stirred overnight until LC-MS indicated the disappearance of the starting materials. Most of the methanol (not to dryness) was removed *in vacuo*, then water (100 mL) was added. The resulting suspension was stirred for 1 h and the solid collected by filtration. The yellow solid (7.48 g) was collected and used without further purification.

Followed previously reported protocol. To a 100 mL round bottom flask equipped with a magnetic stir bar was added imidazole (800 mg, 11.8 mmol, 1.5 eq), PPh_3 (3.08 g, 11.8 mmol, 1.5 eq) and dichloromethane (20 mL). Iodine (2.98 g, 11.8 mmol, 1.5 eq) was added portion-wise, then the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0ºC, followed by slow addition of the alcohol from the last step (2.00 g, 7.83 mmol, as a solution in 8 mL dichloromethane), then warmed to room temperature and stirred overnight. After LC-MS indicated disappearance of starting materials, the reaction mixture was concentrated *in vacuo* and purified via flash column chromatography (silica gel, 5% to 10% ethyl acetate in hexane), to afford a white solid (1.68 g, 59% over three steps). The product slowly turned yellow under light.
(Note: changing the order of addition will give no desired product.)

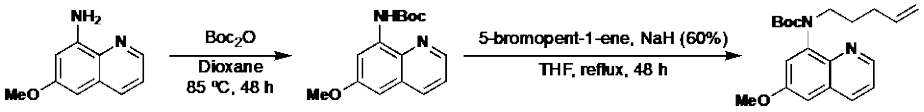
The coupling reaction followed Cossy's reported procedure.[84] To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added 4-iodo-1-tosylpiperidine (1.00 g, 2.74 mmol, 1 eq) and anhydrous tetrahydrofuran (5 mL). $Co(acac)_2$ (24.7 mg, 0.095 mmol, 3.5 mol%) and dried TMEDA (318 mg, 410 μL, 2.74 mmol, 1 eq) were added sequentially, then the reaction placed under argon. The reaction mixture was cooled to 0 ºC, followed by the addition of prop-1-en-2-ylmagnesium chloride (6.85 mL, 0.5 M in THF, 3.42 mmol, 1.25 eq) with a syringe pump at a rate of 1 mL/h with stiring at 0 ºC. After the addition was complete, the reaction mixture was warmed to room temperature and stirred at room temperature for 7 h until TLC indicated the disappearance of starting materials. The reaction mixture was concentrated *in vacuo* and the residue purified via flash column chromatography (silica gel, 5% ethyl acetate in hexane), yielding the product as a white solid (488 mg, 64%).

The ^{1}H NMR spectrum matched with previously reported spectra.[85]

Physical state: white solid. $\mathbf{R_f}$ = 0.3 (10% ethyl acetate in hexane, vis. UV).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 4.83 – 4.61 (m, 2H), 3.87 (dt, *J* = 11.6, 2.5 Hz, 2H), 2.46 (s, 3H), 2.25 (td, *J* = 12.0, 2.5 Hz, 2H), 1.84 – 1.73 (m, 3H), 1.70 (t, *J* = 1.1 Hz, 3H), 1.64 – 1.53 (m, 2H).

***tert*-butyl (6-methoxyquinolin-8-yl)(pent-4-en-1-yl)carbamate**



To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was added 8-amino-6-methoxyquinoline (305 mg, 1.75 mmol, 1 eq) and dioxane (6 mL). Boc_2O (764 mg, 804 µL, 3.50 mmol, 2 eq) was added and the reaction mixture was stirred at 85 ºC for 48 h until LC-MS indicated disappearance of the starting materials. The reaction mixture was concentrated *in vacuo* and the residue was purified via flash column chromatography (silica gel, 40% dichloromethane in hexanes), yielding *tert*-butyl (6-methoxyquinolin-8-yl)(pent-4-en-1-yl)carbamate (446 mg, 93% yield) as a white foam.

The ^{1}H NMR spectrum matched with previously reported spectra.[86]

Physical state: white foam. $\mathbf{R_f}$ = 0.4 (20% ethyl acetate in hexanes, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.62 (dd, J = 4.3, 1.7 Hz, 1H), 8.22 – 8.06 (m, 1H), 8.00 (dd, J = 8.2, 1.7 Hz, 1H), 7.37 (dd, J = 8.2, 4.1 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 3.91 (s, 3H), 1.57 (s, 9H).

To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was added *tert*-butyl (6-methoxyquinolin-8-yl) carbamate (160 mg, 0.583 mmol, 1 eq) and anhydrous tetrahydrofuran

(5 mL). Sodium hydride (34.8 mg, 60% in mineral oil, 0.875 mmol, 1.5 eq) was added portion-wise at 0 ºC. After addition, the reaction was placed under argon, and the reaction mixture stirred for 1 h at 0 ºC, followed by addition of 5-bromopent-1-ene (869 mg, 691 µL, 5.80 mmol, 10 eq). The mixture was then stirred under reflux for 48 h, until TLC indicated the disappearance of starting materials. The reaction mixture was cooled to room temperature, quenched with aq. NH_4Cl (5 mL), the resulting mixture poured into a separatory funnel. Water (50 mL) was added, and the mixture extracted with ethyl acetate (20 mL x 3), washed with brine (25 mL), dried over *anhyd.* Na_2SO_4, and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 2% to 10% ethyl acetate in hexanes), affording *tert*-butyl (6-methoxyquinolin-8-yl)(pent-4-en-1-yl) carbamate (146 mg, 73% yield) as a light brown gum-like solid.

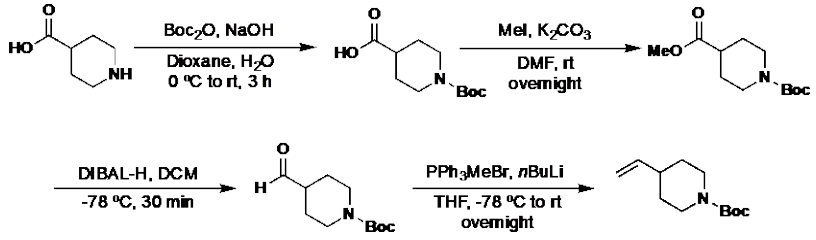
Physical state: light brown gum-like solid. $\mathbf{R_f}$ = 0.2 (10% ethyl acetate in hexanes, vis. UV, blue under UV light).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.35 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.23 (s, 1H), 7.01 (d, *J* = 2.7 Hz, 1H), 5.90 – 5.59 (m, 1H), 5.07 – 4.79 (m, 2H), 3.93 (s, 3H), 3.50-4.17 (br, m, 2H), 2.21 – 2.03 (m, 2H), 1.72 – 1.59 (m, 2H), 1.30 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.16, 155.55, 147.50, 140.98, 138.24, 134.90, 129.94, 121.63, 114.69, 104.43, 79.73, 55.60, 49.87, 31.13, 28.21, 27.99.

HRMS: Calculated for $C_{20}H_{27}N_2O_3^+$ 343.2016 [M+H$^+$]; found 343.2023.

***tert*-butyl 4-vinylpiperidine-1-carboxylate**



Step 1: Followed previously reported protocol. To a 250 mL round-bottom flask equipped with a magnetic stir bar was added isonipecotic acid (3.00 g, 23.2 mmol, 1 eq), dioxane (46 mL), water (46 mL) and sodium hydroxide (920 mg, 23.0 mmol, 1 eq) sequentially. The reaction mixture was cooled to 0 ºC, followed by addition of Boc_2O (5.32 g, 5.60 mL, 24.39 mmol, 1.05 eq), then warmed up to room temperature and stirred for 3 h at room temperature. Dioxane was removed *in vacuo* and the residue was acidified with 3 N HCl to pH 3. The precipitate was collected by filtration, washed with cold water and dried on vacuum overnight. Obtained 1-(*tert*-butoxycarbonyl) piperidine-4-carboxylic acid (4.45 g, 84% yield) as a white solid.

The ^{1}H NMR spectrum matched with previously reported spectra.[87]

Physical state: white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 2H), 2.86 (t, J = 12.2 Hz, 2H), 2.49 (tt, J = 10.9, 3.9 Hz, 1H), 1.98 – 1.86 (m, 2H), 1.64 (dtd, J = 13.4, 11.2, 4.3 Hz, 2H), 1.46 (s, 9H).

Step 2: Followed previously reported protocol.[88] To a 100 mL round-bottom flask equipped with a magnetic stir bar was added 1-(*tert*-butoxycarbonyl) piperidine-4-carboxylic acid (1.00 g, 4.36 mmol, 1 eq) and dimethylformamide (20 mL). Potassium carbonate (662 mg, 4.80 mmol, 1.1 eq) was added, followed by methyl iodide (325 μL, 5.23 mmol, 1.2 eq), then the reaction mixture was stirred at room temperature overnight. Water (100 mL) was added and extracted with ethyl acetate (30 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 2% to 10% ethyl acetate in hexanes), affording 1-(*tert*-butyl) 4-methyl piperidine-1,4-dicarboxylate (1.12 g, 106% yield, contain solvents) as a light brown oil.

The ^{1}H NMR spectrum matched with previously reported spectra.[88]

Physical state: light brown oil. $\mathbf{R_f}$ = 0.5 (25% ethyl acetate in hexane, vis. PMA).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 2H), 3.68 (s, 3H), 2.82 (t, *J* = 12.5 Hz, 2H), 2.44 (tt, *J* = 11.0, 3.9 Hz, 1H), 1.86 (dd, *J* = 12.9, 4.3 Hz, 2H), 1.62 (dtd, *J* = 13.4, 11.4, 4.3 Hz, 2H), 1.45 (s, 9H).

Step 3: To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added 1-(*tert*-butyl) 4-methyl piperidine-1,4-dicarboxylate (1.04 g, 4.27 mmol, 1 eq) and anhydrous dichloromethane (20 mL) at -78 ºC. DIBAL-H (1.0 M in heptane, 4.27 mL, 4.27 mmol, 1 eq) was added slowly, then the reaction mixture stirred at -78 ºC for 30 min followed by addition of 3 N HCl (20 mL) to quench the reaction. The reaction mixture was poured into a separatory funnel,

extracted with dichloromethane (20 mL x 2), washed with *sat*. $NaHCO_3$ (50 mL), brine (25 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo.* The residue was purified by flash column chromatography (silica gel, 15% ethyl acetate in hexanes), affording *tert*-butyl 4-formylpiperidine-1-carboxylate (456 mg, 51% yield) as a white solid.

The ^{1}H NMR spectrum matched with previously reported spectra.[89]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.2 (25% ethyl acetate in hexane, vis. PMA).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.0 Hz, 1H), 3.98 (s, 2H), 2.92 (ddd, *J* = 13.9, 10.8, 3.0 Hz, 2H), 2.41 (ttd, *J* = 10.7, 4.0, 1.1 Hz, 1H), 1.89 (dd, *J* = 12.5, 4.9 Hz, 2H), 1.56 (tdd, *J* = 10.8, 7.5, 5.4 Hz, 2H), 1.45 (s, 9H).

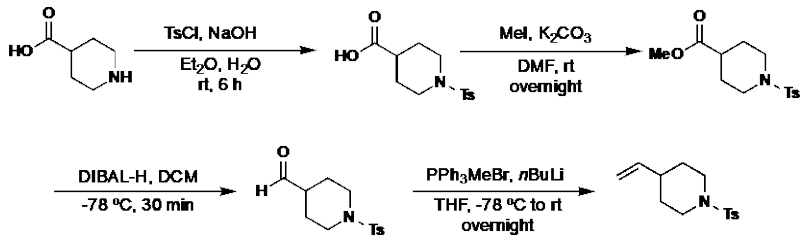
Step 4: To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added triphenylphosphine methyl bromide (1.66 g, 4.64 mmol, 2.2 eq) and anhydrous tetrahydrofuran (20 mL). After cooling to -78 ºC, *n*BuLi (1.06 M, 3.98 mL, 4.22 mmol, 2 eq) was added, followed by stirring at -78 ºC for 1 h to afford a yellow solution. *t*-Butyl 4-formylpiperidine-1-carboxylate (450 mg, 2.11 mmol, 1 eq) was added slowly as a solution in tetrahydrofuran (5 mL), then the reaction mixture warmed room temperature slowly and stirred overnight. Water (100 mL) was added then extracted with dichloromethane (30 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4, concentrated *in vacuo*, and the residue purified via flash column chromatography (silica gel, 5% ethyl acetate in hexanes) yielding *tert*-butyl 4-vinylpiperidine-1-carboxylate (290 mg, 65% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[85]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.6 (10% ethyl acetate in hexanes, vis. PMA or $KMnO_4$).

^{1}H NMR: (600 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 17.1, 10.4, 6.4 Hz, 1H), 5.14 – 4.86 (m, 2H), 4.08 (d, *J* = 12.8 Hz, 2H), 2.81 – 2.62 (m, 2H), 2.20 – 2.01 (m, 1H), 1.71 – 1.64 (m, 2H), 1.45 (d, *J* = 1.1 Hz, 9H), 1.32 – 1.21 (m, 2H).

1-tosyl-4-vinylpiperidine



Step 1: Hu's protocol was followed with modifications.[90] To a 250 mL round-bottom flask equipped with a magnetic stir bar was added isonipecotic acid (6.45 g, 49.9 mmol, 1 eq), ether (50 mL), water (50 mL) and sodium hydroxide (4.00 g, 100 mmol, 2 eq) sequentially. Tosyl chloride (9.55 g, 49.9 mmol, 1 eq) was added portion-wise, then the mixture stirred for 6 h. More ether (50 mL) and H_2O (50 mL) added until the system became clear. The layers were separated, the aqueous layer acidified to pH 3 with 3 M HCl, the white precipitate collected by filtration and dried on vacuum overnight to afford a white solid (5.94 g, 42% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[90]

Physical state: white solid.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.69 – 7.57 (m, 2H), 7.41 – 7.29 (m, 2H), 3.64 (dt, *J* = 12.1, 4.0 Hz, 2H), 2.52 – 2.40 (m, 5H), 2.29 (tt, *J* = 10.7, 4.0 Hz, 1H), 2.04 – 1.95 (m, 2H), 1.90 – 1.76 (m, 2H).

Step 2: To a 250 mL round-bottom flask equipped with a magnetic stir bar was added 1-tosylpiperidine-4-carboxylic acid (2.49 g, 8.79 mmol, 1 eq), dimethylformamide (50 mL) and potassium carbonate (1.33 g, 9.64 mmol, 1.1 eq). Methyl iodide (1.50 g, 657 μL, 10.6 mmol, 1.2 eq) was added and the reaction stirred at room temperature overnight. The reaction mixture was poured into water (400 mL), the precipitate was collected by filtration and dried on vacuum, affording a white solid (2.77 g, 105% yield, contains a little water).

The ^{1}H NMR spectrum matched with previously reported spectra.[91]

Physical state: White solid. $\mathbf{R_f}$ = 0.2 (17% ethyl acetate in hexanes, vis. PMA and UV).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.70 – 7.55 (m, 2H), 7.36 – 7.28 (m, 2H), 3.69 – 3.58 (m, 5H), 2.52 – 2.39 (m, 5H), 2.25 (tt, *J* = 10.7, 4.0 Hz, 1H), 2.02 – 1.91 (m, 2H), 1.90 – 1.74 (m, 2H).

Step 3: To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added methyl 1-tosylpiperidine-4-carboxylate (2.00 g, 6.72 mmol, 1 eq) and anhydrous dichloromethane (40 mL). The reaction mixture was cooled to -78 ºC, then DIBAL-H (1 M in heptane, 7.06 mL, 7.06 mmol, 1 eq) was added slowly. The reaction mixture was stirred at -78 ºC for 30 min then quenched with 3 N HCl (20 mL). The reaction mixture was poured into separatory funnel, extracted with dichloromethane (20 mL x 2), washed with *sat*. $NaHCO_3$ (50 mL), brine (25 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo.* The residue was purified by flash column chromatography (silica gel, 17% to 25% ethyl acetate in hexanes), affording (1.08 g, 60% yield) as a colorless oil, which solidified slowly on standing.

The ^{1}H NMR spectrum matched with previously reported spectra.[92]

Physical state: white solid. $\mathbf{R_f}$ = 0.2 (25% ethyl acetate in hexanes, vis. PMA and UV).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.51 – 3.42 (m, 2H), 2.55 (ddd, *J* = 11.9, 10.1, 3.1 Hz, 2H), 2.38 (s, 3H), 2.22 – 2.13 (m, 1H), 2.00 – 1.89 (m, 2H), 1.71 (dtd, *J* = 13.9, 10.1, 4.0 Hz, 2H).

Step 4: To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added triphenylphosphine methyl bromide (2.52 g, 7.05 mmol, 2.2eq) and anhydrous tetrahydrofuran (40 mL). After cooling to -78 ºC, *n*BuLi (1.06 M, 6.05 mL, 6.41 mmol, 2 eq) was added, followed by stirring at -78 ºC for 1 h to afford a yellow solution. 1-Tosylpiperidine-4-carbaldehyde (857 mg, 3.20 mmol, 1 eq) was added slowly as a solution in tetrahydrofuran (5 mL), then the reaction

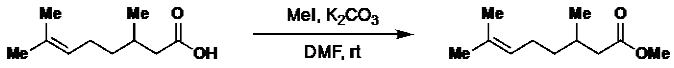
mixture warmed room temperature slowly and stirred overnight. Water (100 mL) was added then extracted with dichloromethane (30 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4, concentrated *in vacuo*, and the residue purified via flash column chromatography (silica gel, 5% ethyl acetate in hexanes) yielding 1-tosyl-4-vinylpiperidine (590 mg, 67% yield) as a white solid.

The ^{1}H NMR spectrum matched with previously reported spectra.[85]

Physical state: colorless oil. $\mathbf{R_f}$ = 0.5 (17% ethyl acetate in hexanes, vis. UV, PMA or $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 2H), 7.32 – 7.24 (m, 2H), 5.66 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.02 – 4.73 (m, 2H), 3.84 – 3.60 (m, 2H), 2.38 (s, 3H), 2.23 (td, *J* = 11.9, 2.7 Hz, 2H), 1.90 – 1.78 (m, 1H), 1.73 – 1.65 (m, 2H), 1.43 (dtd, *J* = 13.4, 11.8, 4.1 Hz, 2H).

Methyl 3,7-dimethyloct-6-enoate



To a 50 mL round bottom flask equipped with a magnetic stir bar was added citronellic acid (1.00 g, 5.87 mmol, 1 eq), dimethylformamide (10 mL) and potassium carbonate (1.62 g, 11.8 mmol, 2 eq). The mixture was stirred for 10 min before methyl iodide (1.67 g, 731 μL, 11.8 mmol, 2 eq) was added slowly and stirred for 2 h until LC-MS indicated the disappearance of starting materials. Water (100 mL) was added and extracted with ethyl acetate (20 mL x 3), washed with 5% sodium

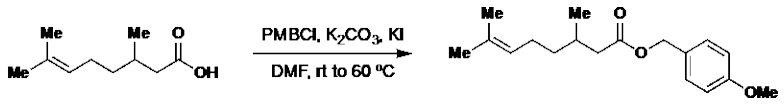
hydroxide (25 mL) and brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 3% ethyl acetate in hexanes) yielding methyl 3,7-dimethyloct-6-enoate (674 mg, 62% yield) as a colorless oil.

The ^{1}H NMR spectrum matched with previously reported spectra.[93]

Physical state: colorless oil; $\mathbf{R_f}$ = 0.5 (20% ethyl acetate in hexanes, vis iodine).

^{1}HNMR: (600 MHz, Chloroform-*d*) δ 5.08 (t, J = 5.7 Hz, 1H), 3.66, (s, 3H), 2.32 (dd, J = 5.7, 14.9 Hz, 1H), 2.12 (dd, J = 8.6, 14.9 Hz, 1H), 2.01-1.94 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.37-1.18 (m, 2H), 0.94 (d, J = 6.3 Hz, 3H).

4-Methoxybenzyl 3,7-dimethyloct-6-enoate



To a 50 mL round bottom flask equipped with a magnetic stir bar was added citronellic acid (1.00 g, 5.87 mmol, 1 eq), dimethylformamide (10 mL) and potassium carbonate (1.62 g, 11.8 mmol, 2 eq). The reaction mixture was stirred for 10 min, followed by addition of 4-methoxybenzyl chloride (1.84 g, 11.8 mmol, 2 eq) and potassium iodide (cat.). The reaction mixture was then stirred at 60 ºC for 2 h until TLC indicated disappearance of starting materials. Water (100 mL) was added and extracted with ethyl acetate (20 mL x 3), washed with 5% sodium hydroxide (25 mL) and brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was

purified via flash column chromatography (silica gel, 1% to 3% ethyl acetate in hexanes) yielding 4-methoxybenzyl 3,7-dimethyloct-6-enoate (1.29 g, 76% yield) as a colorless oil.

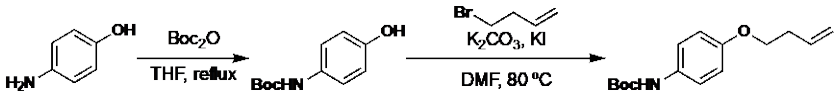
Physical state: colorless oil; $\mathbf{R_f}$ = 0.4 (10% ethyl acetate in hexanes, vis UV and CAM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.13 – 4.97 (m, 3H), 3.81 (s, 3H), 2.33 (dd, *J* = 14.6, 6.0 Hz, 1H), 2.14 (dd, *J* = 14.6, 8.2 Hz, 1H), 2.03 – 1.90 (m, 3H), 1.67 (t, *J* = 1.3 Hz, 3H), 1.58 (d, *J* = 1.1 Hz, 4H), 1.33 (ddt, *J* = 13.4, 9.5, 6.3 Hz, 1H), 1.20 (dddd, *J* = 13.6, 9.3, 7.8, 6.0 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.31, 159.70, 131.65, 130.19, 128.43, 124.41, 114.05, 65.97, 55.42, 41.97, 36.89, 30.20, 25.83, 25.53, 19.74, 17.76.

HRMS: Calculated for $C_{18}H_{27}O_3^+$ 291.1960 [M+H$^+$]; found 291.1958.

***tert*-Butyl (4-(but-3-en-1-yloxy)phenyl)carbamate**



Step 1: To a 500 mL round bottom flask equipped with a magnetic stir bar was added 4-aminophenol (5.00 g, 45.8 mmol, 1 eq) and anhydrous tetrahydrofuran (100 mL). Boc_2O (11.0 g, 50.4 mmol, 1.1 eq) in anhydrous tetrahydrofuran (50 mL) was added dropwise. The reaction mixture was stirred vigorously at room temperature for 24 h and concentrated *in vacuo*, affording

tert-butyl (4-(but-3-en-1-yloxy)phenyl)carbamate in quantitative yield and was used without further purification.

The ^{1}H NMR spectrum matched with previously reported spectra.[94]

^{1}H NMR: (500 MHz, DMSO) δ 9.04 (s, 1H), 8.97 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.65 – 6.58 (m, 2H), 1.43 (s, 9H).

Step 2: To a 25 mL round-bottom flask equipped with a magnetic stir bar was added *tert*-butyl (4-hydroxyphenyl)carbamate (1.20 g, 5.73 mmol, 1 eq) and dimethylformamide (6 mL). 1-Bromobut-3-ene (1.70 g, 1.28 mL, 12.6 mmol, 2.2 eq) and potassium iodide (cat.) were added, then the reaction mixture was stirred at 80 ºC for 24 h. Water (50 mL) was added and extracted with ethyl acetate (50 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified via flash column chromatography (silica gel, 5% to 10% ethyl acetate in hexanes) yielding *tert*-butyl (4-(but-3-en-1-yloxy)phenyl)carbamate (490 mg, 32% yield) as a white solid.

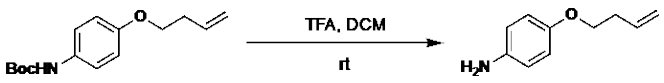
Physical state: white solid; $\mathbf{R_f}$ = 0.3 (10% ethyl acetate in hexanes, vis UV and CAM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H), 6.89 – 6.82 (m, 2H), 6.34 (s, 1H), 5.92 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.23 – 5.05 (m, 2H), 4.00 (t, *J* = 6.7 Hz, 2H), 2.54 (qt, *J* = 6.7, 1.4 Hz, 2H), 1.53 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.13, 153.29, 134.62, 131.59, 120.63, 117.13, 115.15, 80.37, 67.72, 33.82, 28.52.

HRMS: Calculated for de-*tert*-butyl compound $C_{11}H_{14}NO_3^+$ 208.0968 [$M+H^+$]; found 208.0973.

4-(But-3-en-1-yloxy)aniline



To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 1-(4-*N*-Boc-aminophenoxy)-3-butene (788 mg, 2.99 mmol, 1 eq) and dichloromethane (8 mL). Trifluoroacetic acid (2 ml) was added, and the reaction mixture stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with dichloromethane, basified with *sat.* $NaHCO_3$, extracted with dichloromethane (20 mL x 3), dried over *anhyd.* $MgSO_4$ and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 0 – 5% methanol in DCM) to afford 4-(but-3-en-1-yloxy)aniline (447 mg, 92% yield) as a yellow oil.

The ^{1}H NMR spectrum matched with previously reported spectra.[95]

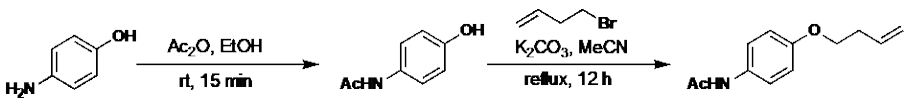
Physical state: yellow oil; $\mathbf{R_f}$ = 0.5 (3% methanol in DCM, vis UV and CAM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 – 6.71 (m, 2H), 6.68 – 6.54 (m, 2H), 5.90 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.30 – 4.98 (m, 2H), 3.94 (t, *J* = 6.8 Hz, 2H), 3.41 (s, 2H), 2.50 (qt, *J* = 6.7, 1.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.22, 140.15, 134.83, 116.95, 116.56, 116.53, 116.00, 68.14, 33.95.

HRMS: Calculated for $C_{10}H_{14}NO^+$ 164.1070 [$M+H^+$]; found 164.1071.

***N*-(4-(But-3-en-1-yloxy)phenyl)acetamide**



Step 1: To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 4-aminophenol (500 mg, 4.58 mmol, 1 eq), absolute ethanol (5 mL) and acetic anhydride (467 mg, 433 μL, 4.58 mmol, 1 eq). The solution was stirred for 15 min at room temperature, then evaporated to dryness. The residue was purified via flash column chromatography (silica gel, 5% methanol in DCM) affording *N*-(4-hydroxyphenyl)acetamide (463 mg, 67% yield) as a white solid.

The ^{1}H NMR spectrum matched with previously reported spectra.[96]

Physical state: white solid; **R_f** = 0.1 (50% EA in hexane, vis UV and CAM)

^{1}H NMR: (600 MHz, DMSO) δ 9.67 (s, 1H), 9.15 (s, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 2.01 (s, 3H).

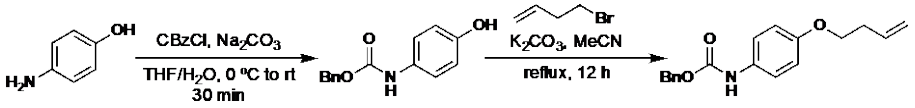
Step 2: To a 25 mL round bottom flask equipped with a magnetic stir bar was added *N*-(4-hydroxyphenyl)acetamide (290 mg, 1.92 mmol, 1 eq), potassium carbonate (398 mg, 2.88 mmol, 1.5 eq) and acetonitrile (10 mL). 1-Bromobut-3-ene (518 mg, 390 µL, 3.84 mmol, 2 eq) was added, and the reaction mixture stirred under reflux for 12 h, concentrated *in vacuo*, diluted with water (10 mL), extracted with ethyl acetate (25 mL x 3), washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 15 – 100% ethyl acetate in hexanes) affording *N*-(4-(but-3-en-1-yloxy)phenyl)-acetamide (148 mg, 38% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[97]

Physical state: off white solid. **R_f** = 0.20 (50 % ethyl acetate in hexanes, vis iodine)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 2H), 7.15 (s, 1H), 6.90 – 6.82 (m, 2H), 5.89 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.19-5.09 (m, 2H), 3.99 (t, *J* = 6.7 Hz, 2H), 2.53 (qt, *J* = 6.7, 1.4 Hz, 2H), 2.15 (s, 3H).

Benzyl (4-hydroxyphenyl) carbamate



Step 1: To a 25 mL round-bottom flask equipped with a magnetic stir bar was added 4-aminophenol (250 mg, 2.29 mmol, 1 eq), water (2 mL), tetrahydrofuran (2 mL) and sodium carbonate (486 mg, 4.59 mmol, 2 eq). The reaction mixture was cooled to 0 °C, followed by the addition of benzyl chloroformate (406 mg, 340 µL, 2.38 mmol, 1.04 eq) in tetrahydrofuran (1 mL) dropwise over 15 min. The brown suspension was then stirred for 30 min at room temperature and concentrated *in vacuo*. The residue was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3), washed with brine (10 mL x 2), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The crude product was recrystallized from ethyl acetate to yield benzyl (4-hydroxyphenyl)carbamate (347 mg, 62% yield).

The ^{1}H NMR spectrum matched with previously reported spectra.[98]

Physical state: off white solid **R_f**= 0.3 (25% ethyl acetate in hexanes, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 5H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.81 – 6.75 (m, 2H), 6.51 (s, 1H), 5.19 (s, 2H), 4.70 (s, 1H).

Step 2: Followed the same procedure as above from benzyl (4-hydroxyphenyl)carbamate on a 0.740 mmol scale. Purification via flash column chromatography (silica gel, 5 – 20% ethyl acetate in hexanes) afforded benzyl (4-(but-3-en-1-yloxy)phenyl)carbamate (93.1 mg, 42% yield).

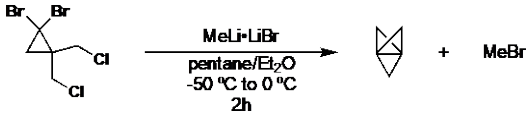
Physical state: off white solid. $\mathbf{R_f}$ = 0.7 (25 % ethyl acetate in hexanes, vis. UV and CAM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.12 (m, 8H), 6.95 – 6.78 (m, 2H), 6.53 (s, 1H), 5.90 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.27 – 5.07 (m, 4H), 3.99 (t, *J* = 6.7 Hz, 2H), 2.62 – 2.33 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.49, 153.80, 136.32, 134.57, 130.98, 128.75, 128.46, 120.74, 117.16, 115.20, 67.70, 67.09, 33.80.

HRMS: calculated for $C_{18}H_{20}NO_3$ 298.1438 [M+H$^+$]; found 298.1431.

[1.1.1]Propellane solution in pentane/ether



Followed previously reported protocol.[99] To a 50 mL 3 neck-round-bottom flask equipped with a magnetic stir bar and a thermometer under argon was added 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (2.96 g, 9.97 mmol, 1 eq), followed by anhydrous ether (0.36 mL) and pentane (2.4 mL). The reaction mixture was cooled to -50 ºC with an isopropanol/dry ice bath,

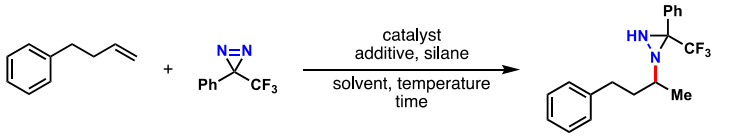
then methyllithium-lithium bromide complex (1.5 M, 16.0 mL, 24.0 mmol, 2.4 eq) was added slowly with a syringe. (Keep the temperature inside between -40 ºC to -50 ºC.) Isopropanol/dry ice bath was removed after addition and the reaction mixture warmed to 0 ºC and stirred for 2 h with an ice bath. A short path distilling head was attached, with a 25 mL round-bottom flask as a receiving flask (cooling with an acetone/dry ice bath). A vacuum was slowly applied, collected [1.1.1]propellane as a solution in ether and pentane (~15 mL, 0.452 M), which was stored at -80 ºC before use. (The concentration of [1.1.1]propellane was determined by titration with thiophenol.)

The ^{1}H NMR spectrum matched with previously reported spectra.[99]

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (s, 6H).

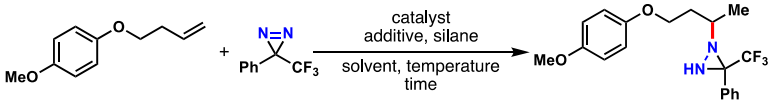
Optimization Experiments:

Table S1: Hydroamination reaction optimization with 4-phenylbut-1-ene



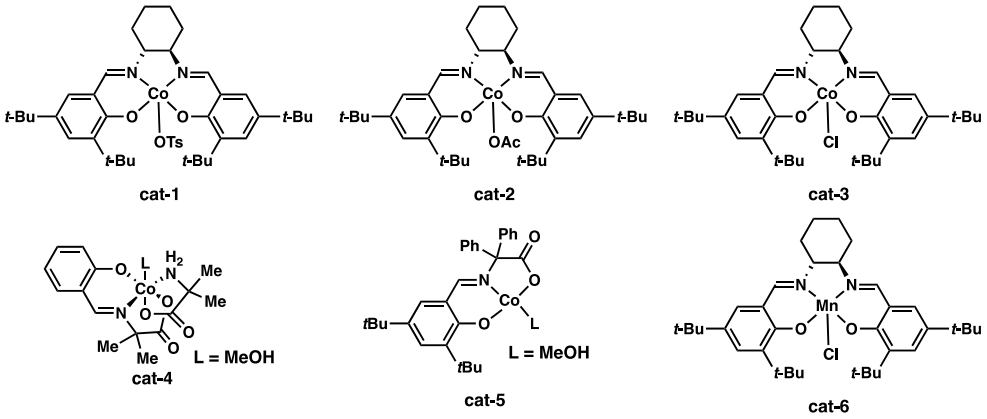
entry	diazirine (equiv)	catalyst (mol%)	additive (equiv)	silane (equiv)	solvent temp (°C), time (h)	yield (%)
1	1.5	cat-4, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 40 °C, 16 h	35
2	1.5	cat-4, (5)	none	$(SiMe_2H)_2O$, (0.5)	DCM/IPA 4:1 40 °C, 16 h	24
3	1.5	cat-4, (5)	none	TTMS, (0.5)	DCM/IPA 4:1 40 °C, 16 h	ND
4	1.5	cat-4, (5)	none	PMHS, (0.1)	DCM/IPA 4:1 40 °C, 16 h	ND
5	1.5	$Mn(dpm)_3$, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 2 h	44/39
6	1.5	$Co(dpm)_3$, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 16 h	11
7	1.5	$Mn(acac)_2$, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 16 h	ND
8	1.5	$Co(acac)_2$, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 16 h	trace
9	1.5	$Fe(acac)_2$, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 16 h	trace
10	1.5	Co(TPP)Cl, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 16 h	trace
11	1.5	Mn(TPP)Cl, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 16 h	trace
12	1.5	$Co(OAc)_2$, (5)	none	$PhSiH_3$ (0.5)	DCM/IPA 4:1 0 °C, 48 h	trace
13	1.5	cat-4, (5)	none	$PhSiH_3$ (0.5)	DCE/IPA 4:1 40 °C, 16 h	54
14	2	cat-4, (10)	none	$PhSiH_3$ (0.5)	DCE/IPA 4:1 40 °C, 16 h	67
15	1.5	cat-5, (10)	none	$PhSiH_3$ (0.5)	DCE/IPA 4:1 40 °C, 16 h	trace
16	1.5	cat-1, (5)	none	$PhSiH_3$ (0.33)	DCE/IPA 4:1 40 °C, 16 h	47
17	1.5	cat-1, (5)	none	$(SiMe_2H)_2O$, (0.5)	DCE/IPA 4:1 40 °C, 16 h	35
18	1.5	cat-6, (5)	none	$PhSiH_3$ (0.5)	DCE/IPA 4:1 40 °C, 16 h	ND

Table S2: Hydroamination reaction optimization with **15**

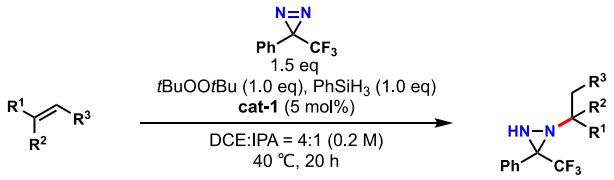


entry	diazirine (equiv)	catalyst (mol%)	additive (equiv)	silane (equiv)	solvent temp (°C), time (h)	yield (%)
1	1.5	cat-4, (5)	none	$PhSiH_3$ (0.3)	DCE/IPA 4:1 40 °C, 16 h	27
2	1.5	cat-5, (5)	none	$PhSiH_3$ (0.3)	DCE/IPA 4:1 40 °C, 16 h	trace
3	1.5	cat-1, (5)	none	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 20 h	38
4	1.5	cat-1, (5)	*t*-BuOOH	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 20 h	36
5	1.5	cat-1, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 20 h	99
6	1.5	cat-1, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	IPA 40 °C, 30 h	84
7	1.5	cat-2, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 20 h	51
8	1.5	cat-3, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 20 h	39
9	1.5	cat-4, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 20 h	57
10	1.5	cat-1, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	DCE/IPA 4:1 60 °C, 20 h	56
11	1.5	cat-1, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 3 h	66
12	1.5	cat-1, (5)	*t*-BuOO*t*-Bu	$PhSiH_3$, (1)	DCE/IPA 4:1 40 °C, 16 h	93
13	1.5	cat-1, (5)	*t*-BuOO*t*-Bu	TES, (1)	DCE/IPA 4:1 40 °C, 20 h	trace
14	1.5	cat-1, (5)	*t*-BuOO*t*-Bu	PHMS, (1)	DCE/IPA 4:1 40 °C, 20 h	trace
15	1.5	$Mn(dpm)_3$, (5)	none	$PhSiH_3$, (1)	DCE/IPA 4:1 0 °C, 2 h	51/35
16	1.5	$Co(dpm)_3$, (5)	none	$PhSiH_3$, (1)	DCE/IPA 4:1 0 °C, 16 h	trace
17	1.5	Co(TPP)Cl, (5)	none	$PhSiH_3$, (1)	DCE/IPA 4:1 0 °C, 16 h	trace

Table S3: List of catalysts



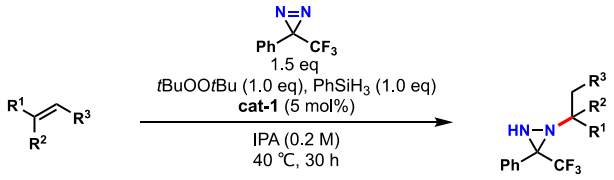
General Procedure A: Cobalt Catalyzed Markovnikov-Type Hydroamination



To a flame-dried reaction vial equipped with a magnetic stir-bar and rubber-lined cap under argon atmosphere was added catalyst **cat-1** (3.9 mg, 0.005 mmol, 0.05 eq) and the vial back-flushed with argon twice, followed by addition of a mixture of *anhydrous* DCE: IPA (4:1, 500 µL) via syringe, resulting in a dark green solution. To this solution, alkene (0.100 mmol, 1 eq.), diazirine **1** (28.0 mg, 0.150 mmol, 1.5 eq), *t*-BuOO*t*-Bu (14.6 mg, 18.4 µL, 0.100 mmol, 1 eq) and phenylsilane (10.8 mg, 12.3 µL, 0.100 mmol, 1 eq) were added sequentially via syringe. The vial was covered with aluminum foil and stirred at 40 °C for 20 h. The crude reaction mixture was dried *in vacuo*, adsorbed onto silica gel, and purified via flash column chromatography on silica gel.

(Note: Alternatively, the reaction mixture may also be quenched with water (10 mL), extracted with either dichloromethane or ethyl acetate (15 mL x 3), dried over anhydrous $MgSO_4$, concentrated *in vacuo,* and stored at -20 °C for later purification.)

General Procedure B: Cobalt Catalyzed Markovnikov-Type Hydroamination with IPA



To a flame-dried reaction vial equipped with a magnetic stir-bar and rubber-lined cap under argon atmosphere was added catalyst **cat-1** (3.9 mg, 0.005 mmol, 0.05 eq) and the vial back-flushed with argon twice, followed by addition of *anhydrous* IPA (500 µL) via syringe, resulting in a dark green solution. To this solution, alkene (0.100 mmol, 1 eq.), diazirine **1** (28.0 mg, 0.150 mmol, 1.5 eq), *t*-BuOO*t*-Bu (14.6 mg, 18.4 µL, 0.100 mmol, 1 eq) and phenylsilane (10.8 mg, 12.3 µL, 0.100 mmol, 1 eq) were added sequentially via syringe. The vial was covered with aluminum foil and stirred at 40 °C for 20 h. The crude reaction mixture was dried *in vacuo*, adsorbed onto silica gel, and purified via flash column chromatography on silica gel.

(Note: Alternatively, the reaction mixture may also be quenched with water (10 mL), extracted with either dichloromethane or ethyl acetate (15 mL x 3), dried over anhydrous $MgSO_4$, concentrated *in vacuo,* and stored at -20 °C for later purification.)

Graphical Procedure for Co-catalyzed Synthesis of Substituted Diaziridines:

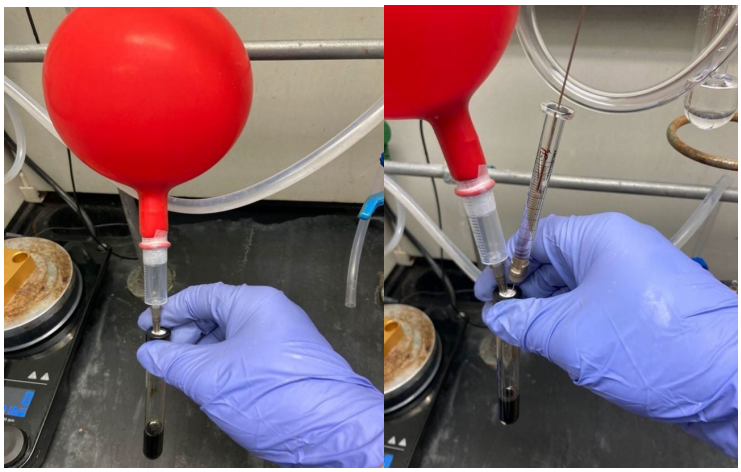


Figure S3: Graphical procedure for Co-catalyzed hydroamination (part A). **Left**: Addition of catalyst, alkene, and solvent to reaction vial. **Right**: Addition of diazirine **2** to reaction mixture.

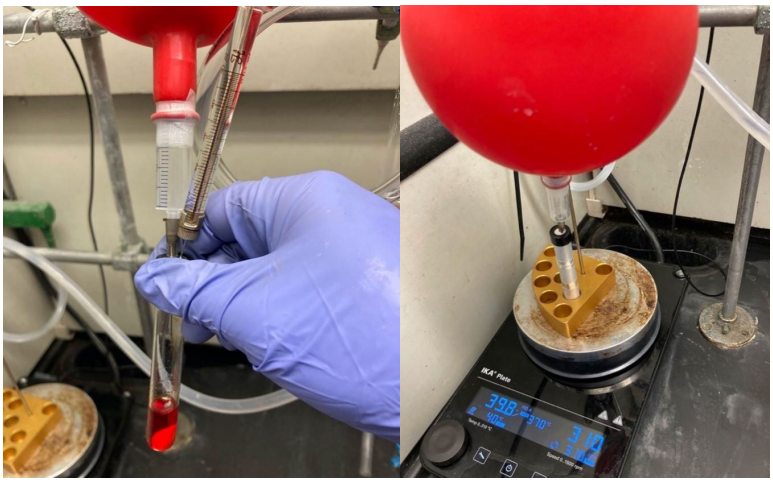
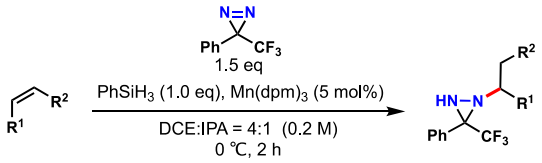


Figure S4: Graphical procedure for Co-catalyzed hydroamination (part B). **Left**: Addition of *t*-BuOO*t*-Bu and silane to reaction mixture; the color changed to red after silane addition. **Right:** Vial was covered with aluminum foil and heated with stirring.

Figure S5: Reaction mixture after stirring for 20 h at 40 ºC

General Procedure C: Mn-Catalyzed Hydroamination



To a flame-dried reaction vial equipped with a magnetic stir-bar and rubber-lined cap under argon atmosphere was added $Mn(dpm)_3$ (3.0 mg, 0.005 mmol, 0.05 eq) and the vial back-flushed with argon, followed by addition of a mixture of anhydrous DCE: IPA (4:1, 500 µL) via syringe, resulting in a black suspension. To this mixture, alkene (0.100 mmol, 1 eq.), diazirine **1** (28.0 mg, 0.150 mmol, 1.5 eq), and phenylsilane (10.8 mg, 12.3 µL, 0.100 mmol, 1 eq) were added sequentially via syringe. The reaction vial was then cooled to 0 ºC in an ice bath and covered with aluminum foil and stirred for two hours until TLC monitoring indicated total consumption of the starting material. A color change from black to yellow or brown (substrate dependent) also

indicated reaction completion. The crude reaction mixture was dried *in vacuo*, adsorbed onto silica gel, and purified via flash column chromatography on silica gel.

(Note: Alternatively, the reaction mixture may also be quenched with water (10 mL), extracted with either dichloromethane or ethyl acetate (15 mL x 3), dried over anhydrous $MgSO_4$, concentrated *in vacuo,* and stored at -20 °C for later purification.)

Graphical Procedure for Mn-Catalyzed Synthesis of Substituted Diaziridines:

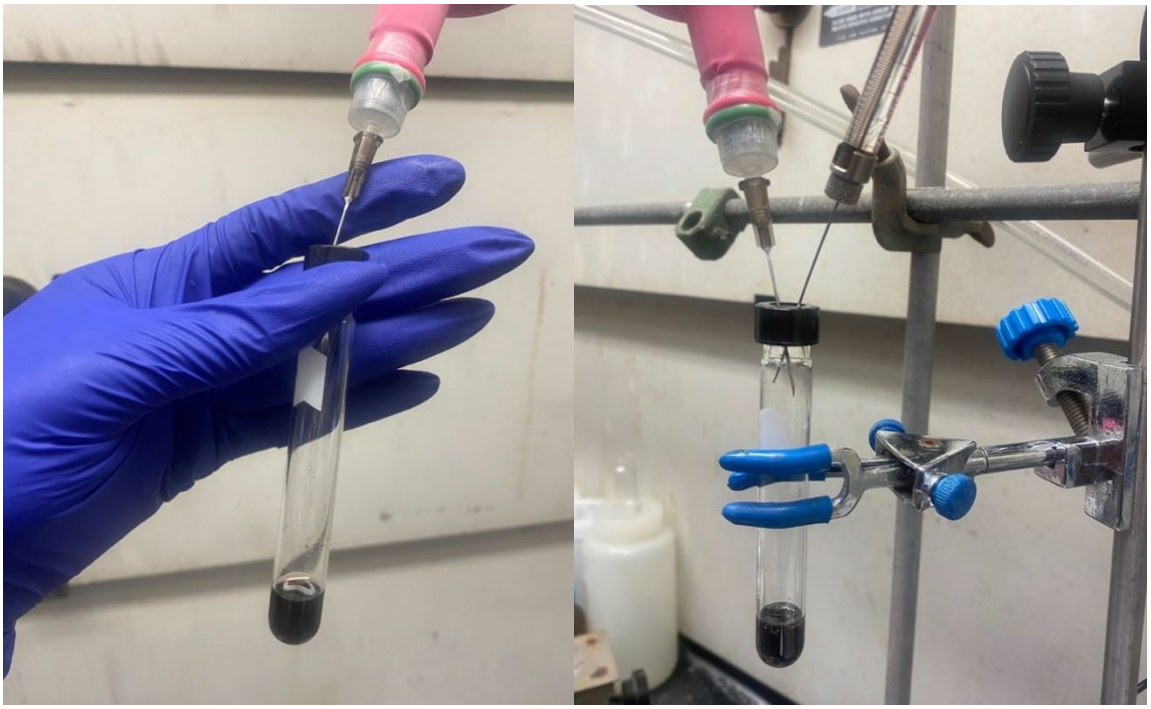


Figure S6: Graphical procedure for Mn-catalyzed hydroamination (part A). **Left**: Addition of catalyst, alkene, and solvent to reaction vial. **Right:** Addition of diazirine **2** to reaction mixture.

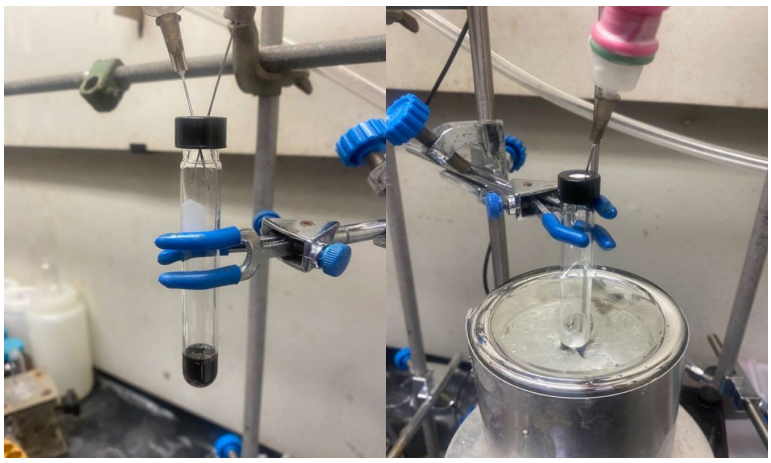


Figure S7: Graphical procedure for Mn-catalyzed hydroamination (part B). **Left:** Addition of silane to reaction mixture. **Right:** Reaction mixture cooled to 0 ºC in an ice bath with stirring.

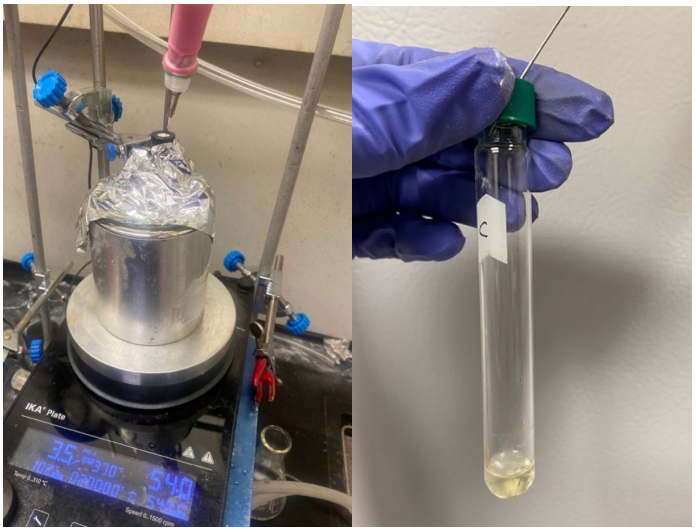
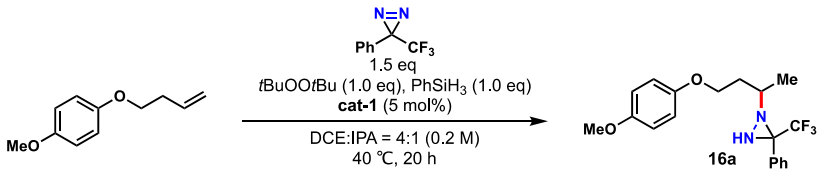


Figure S8: Graphical procedure for Mn-catalyzed hydroamination (part C). **Right:** Vial covered with aluminum foil **Left:** Reaction mixture after stirring at 0 ºC for 2 h (light brown or yellow color change typically observed).

Synthesis of Substituted Diaziridine Substrates:

1-(4-(4-methoxyphenoxy)butan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (16a)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 10 % ethyl acetate in hexanes) afforded **16a** (36.2 mg, 99 % yield).

Physical state: dark yellow oil. $\mathbf{R_f}$ = 0.6 (10 % ethyl acetate in hexanes, vis. UV, iodine, and CAM).

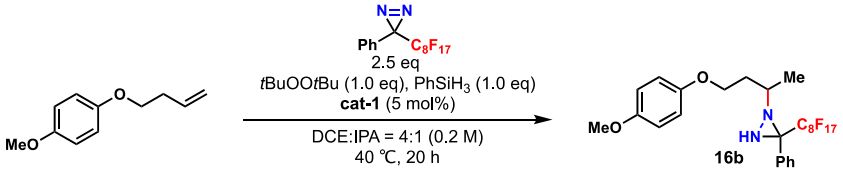
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.50 – 7.38 (m, 3H), 6.84 – 6.73 (m, 3H), 6.66 – 6.57 (m, 1H), 4.05 – 3.93 (m, 1H), 3.80 – 3.66 (m, 4H), 3.05 – 2.91 (m, 1H), 2.21 – 1.72 (m, 3H), 1.23 – 0.94 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.89, 153.83, 153.19, 152.94, 130.30, 130.15, 130.10, 128.90, 128.50, 128.43, 128.27, 128.06, 128.02, 123.88 (q, J = 278.8 Hz), 123.82 (q, J = 278.8 Hz), 115.64, 115.26, 114.72, 114.69, 65.79, 64.82, 64.09 (q, J = 34.3 Hz), 63.18 (q, J = 34.3 Hz), 55.87, 54.40, 54.03, 36.00, 33.96, 19.33, 17.75.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.95.

HRMS: *m/z* calculated for $C_{19}H_{22}F_3N_3O_2^+$: 367.1628 [M+H$^+$]; found: 367.1624.

1-(4-(4-methoxyphenoxy)butan-2-yl)-3-(perfluorooctyl)-3-phenyldiaziridine (16b)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 5% ethyl acetate in hexanes, isocratic) afforded **16b** (66.5 mg, 93% yield).

Physical state: brown solid. $\mathbf{R_f}$ = 0.5 (30% ethyl acetate in hexanes, vis. UV, iodine, and CAM).

^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 7.72 – 7.61 (m, 2H, merged with minor isomer), 7.49 – 7.34 (m, 3H, merged with minor isomer), 6.84 – 6.57 (m, 4H, merged with minor isomer), 3.82 (ddd, *J* = 9.5, 7.0, 5.3 Hz, 1H), 3.76 (s, 3H, merged with minor isomer), 3.71 (ddd, *J* = 9.3, 7.5, 6.4 Hz, 1H), 2.97 (t, *J* = 3.1 Hz, 1H), 2.00 – 1.74 (m, 3H, merged with minor isomer), 1.19 (d, *J* = 6.1 Hz, 3H).

^{1}H NMR (500 MHz, $CDCl_3$, minor isomer) δ 7.72 – 7.61 (m, 2H, merged with major isomer), 7.49 – 7.34 (m, 3H, merged with major isomer), 6.84 – 6.61 (m, 4H, merged with major isomer),

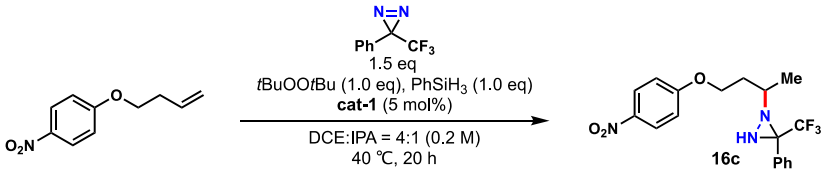
4.02 – 3.92 (m, 2H), 3.76 (s, 3H, merged with major isomer), 2.94 (d, J = 3.4 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.00 – 1.74 (m, 2H, merged with major isomer), 1.03 (d, J = 6.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of isomers) δ 153.76, 153.72, 153.04, 152.85, 130.60, 130.04, 129.97, 128.23, 128.17, 118.11 (d, J = 33.6 Hz), 115.95, 115.52, 115.13, 114.62, 114.57, 112.83, 110.53 (dd, J = 63.6, 31.8 Hz), 109.52 – 107.81 (m), 65.67, 64.76, 63.80 (t, J = 22.5 Hz), 63.06 (t, J = 22.9 Hz), 55.73, 53.87, 53.50, 35.88, 33.76, 28.45, 19.14, 17.60.

^{19}F NMR (471 MHz, $CDCl_3$, mixture of isomers) δ -80.79 (t, J = 9.5 Hz), -114.32 (q, J = 9.1 Hz), -114.81 – -115.05 (m), -118.22 (ddt, J = 36.4, 24.3, 12.6 Hz), -118.86 (ddt, J = 36.4, 19.1, 12.1 Hz), -119.75 (q, J = 11.3 Hz), -120.27 – -120.51 (m), -120.53 – -120.79 (m), -120.93 – -121.45 (m), -121.53 – -122.22 (m), -122.45 – -123.03 (m), -125.35 (ddt, J = 48.6, 40.7, 13.4 Hz), -125.80 – -126.15 (m), -126.32 (dt, J = 19.1, 10.8 Hz).

HRMS: *m/z* calculated for $C_{26}H_{22}F_{17}N_2O_2^+$: 717.1404 [M+H$^+$]; found: 717.1405.

1-(4-(4-Nitrophenoxy)butan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (16c)



General procedure A was followed on a 0.140 mmol scale. Purification via column chromatography (silica gel, 0 – 30% EA in hexanes) afforded **16c** (42.8 mg, 83 % yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.3 (10% ethyl acetate in hexanes, vis. UV and iodine).

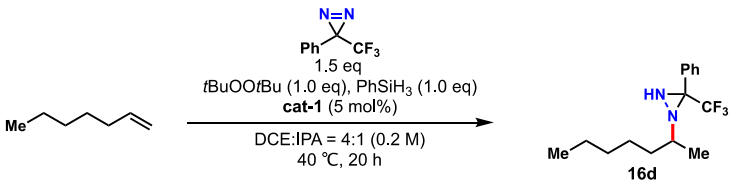
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 – 8.13 (m, 2H), 7.76 – 7.63 (m, 2H), 7.53 – 7.38 (m, 3H), 6.95 – 6.71 (m, 2H), 4.28 – 3.84 (m, 2H), 3.11 – 2.91 (m, 1H), 2.06 – 1.80 (m, 3H), 1.26 – 0.99 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.97, 163.64, 141.40, 130.17, 130.09, 128.44, 128.39, 127.80, 126.96, 125.93, 125.87, 123.64 (q, J = 278.8 Hz), 114.41, 114.24, 65.86, 64.98, 63.90 (q, J = 34.5 Hz), 63.02 (d, J = 34.5 Hz), 53.97, 53.49, 35.50, 33.33, 19.07, 17.70.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.78.

HRMS: *m/z* calculated for $C_{18}H_{19}F_3N_3O_3^+$: 382.1373 [M+H$^+$]; found:382.1362.

1-(Heptan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (16d)



General procedure A was followed on a 10.0 mmol scale. Purification via column chromatography (silica gel, 100% hexanes) afforded **16d** (2.09 g, 73 % yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.2, (100% hexanes, vis. iodine).

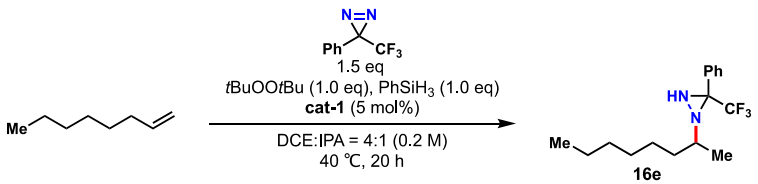
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.80 – 7.59 (m, 2H), 7.52 – 7.32 (m, 3H), 2.93 (s, 1H), 1.62 (tt, *J* = 8.5, 4.6 Hz, 2H), 1.42 (qt, *J* = 9.3, 4.6 Hz, 1H), 1.33 – 1.09 (m, 6H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 130.05, 129.88, 128.23, 128.19, 123.80 (q, *J* = 278.8 Hz), 63.10 (q, *J* = 34.5 Hz), 56.85, 36.17, 32.03, 29.73, 25.25, 22.59, 17.14, 14.06.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -74.06.

HRMS: *m/z* calculated for $C_{15}H_{22}F_3N_2^+$: 287.1730 [M+H$^+$]; found 287.1736.

1-(Octan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (16e)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 6 % ethyl acetate in hexanes) afforded **16e** (22.2 mg, 74 % yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.8, 0.7 (5% ethyl acetate in hexanes, vis. UV, iodine and CAM).

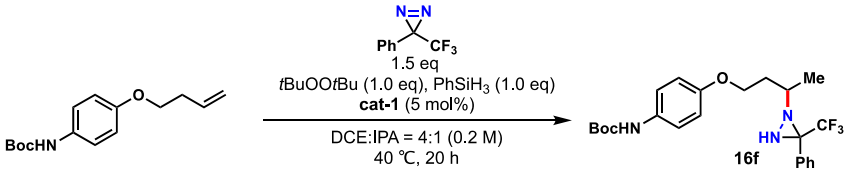
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.62 (m, 2H), 7.52 – 7.36 (m, 3H), 2.94 (d, *J* = 6.1 Hz, 1H), 1.74 – 1.52 (m, 2H), 1.49 – 1.17 (m, 7H), 1.15 – 1.06 (m, 3H), 1.06 – 0.97 (m, 1H), 0.95 – 0.78 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.06, 129.86, 128.27, 128.21, 123.94 (q, *J* = 278.8 Hz), 123.90 (q, *J* = 278.8 Hz), 120.44, 63.95 (q, *J* = 34.5 Hz), 63.23 (q, *J* = 34.3 Hz), 56.81, 56.67, 36.20, 33.88, 31.77, 31.56, 29.47, 29.04, 25.52, 25.22, 22.61, 22.49, 18.98, 17.14, 14.08, 14.01.

^{19}F NMR (471 MHz, $CDCl_3$) δ -74.02, -74.06.

HRMS: Calculated for $C_{16}H_{25}F_3N_2^+$ 301.1886 [M+H$^+$]; found 301.1880.

***tert*-butyl (4-(3-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)butoxy)phenyl)carbamate (16f)**



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 10 % ethyl acetate in hexanes) afforded **16f** (32.5 mg, 72% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.4 (25% ethyl acetate in hexanes, vis. UV, iodine, and CAM).

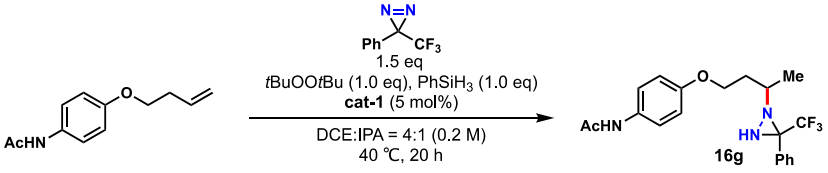
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, *J* = 8.0 Hz, 2H), 7.54 – 7.35 (m, 3H), 7.22 (dd, *J* = 15.5, 8.6 Hz, 2H), 6.83 – 6.57 (m, 2H), 6.47 – 6.24 (m, 1H), 3.99 (qt, *J* = 9.3, 6.5 Hz, 1H), 3.85 – 3.58 (m, 1H), 3.11 – 2.91 (m, 1H), 2.21 – 1.71 (m, 3H), 1.51 (s, 9H), 1.23 – 0.93 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.99, 154.73, 153.18, 131.40, 131.36, 130.04, 130.01, 128.39, 128.31, 127.89, 127.87, 123.75 (d, *J* = 278.8 Hz), 123.69 (d, *J* = 278.8 Hz), 120.43, 114.93, 114.61, 80.24, 65.32, 63.97 (q, *J* = 34.3 Hz), 63.05 (q, *J* = 34.5 Hz),54.21, 53.84, 35.79, 33.78, 28.38, 19.20, 17.63.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.91, -73.93.

HRMS: *m/z* calculated for $C_{23}H_{29}F_3N_3O_3^+$: 452.2156 [$M+H^+$]; found:452.2156.

***N*-(4-(3-(3-Phenyl-3-(trifluoromethyl)diaziridin-1-yl)butoxy)phenyl)acetamide (16g)**



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 30% ethyl acetate in hexanes) afforded **16g** (26.9 mg, 68 % yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.3 (50 % ethyl acetate in hexanes, vis. UV and iodine).

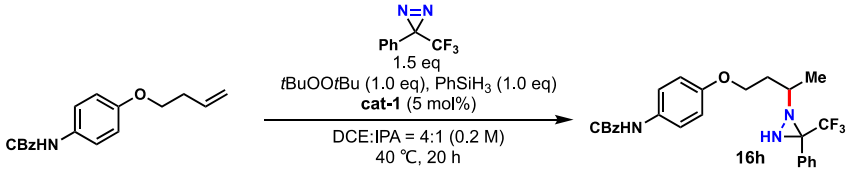
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (t, *J* = 7.9 Hz, 2H), 7.51 – 7.27 (m, 6H), 6.81 – 6.53 (m, 2H), 4.11 – 3.93 (m, 1H), 3.85 – 3.64 (m, 1H), 2.99 (d, *J* = 16.6 Hz, 1H), 2.13 (s, 3H), 1.98 – 1.67 (m, 4H), 1.23 – 0.93 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.41, 155.89, 155.62, 131.03, 131.01, 130.16, 130.13, 128.50, 128.43, 127.98, 127.95, 123.84 (d, *J* = 278.8 Hz), 123.79 (q, *J* = 278.8 Hz), 121.99, 121.92, 114.93, 114.62, 65.38, 64.49, 64.06 (d, *J* = 34.5 Hz), 63.15 (d, *J* = 34.5 Hz), 54.31, 53.93, 35.87, 33.82, 24.44, 19.28, 17.74.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.91, -73.94.

HRMS: *m/z* calculated for $C_{20}H_{23}F_3N_3O_2^+$: 394.1737 [M+H$^+$]; found: 394.1739.

Benzyl (4-(3-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)butoxy)phenyl)carbamate (16h)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 30% ethyl acetate in hexanes) afforded **16h** (18.1 mg, 80% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.7 (30% ethyl acetate in hexanes, vis. UV, iodine and CAM).

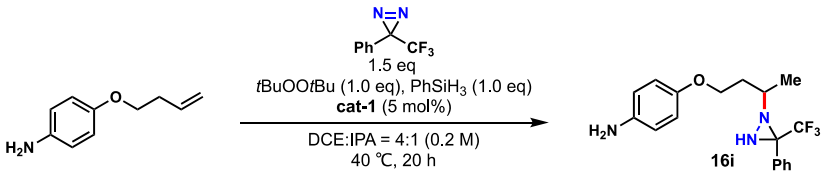
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, *J* = 8.1 Hz, 2H), 7.40 – 7.18 (m, 8H), 7.12 (q, *J* = 9.2 Hz, 2H), 6.71 – 6.62 (m, 1H), 6.50 (dq, *J* = 10.2, 4.0 Hz, 2H), 5.06 (s, 2H), 3.87 (qt, *J* = 9.3, 6.6 Hz, 1H), 3.77 – 3.43 (m, 1H), 3.04 – 2.80 (m, 1H), 2.08 – 1.60 (m, 3H), 1.12 – 0.79 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.42, 155.16, 153.83, 136.30, 136.28, 130.91, 130.86, 130.14, 130.11, 128.71, 128.58, 128.49, 128.41, 127.97, 127.95, 123.84 (d, *J* = 278.4 Hz), 123.79 (d, *J* = 278.8 Hz), 120.67, 115.07, 114.76, 67.03, 65.40, 64.50, 64.06 (q, *J* = 34.5 Hz), 63.14 (q, *J* = 34.5 Hz), 54.30, 53.92, 35.86, 33.82, 19.28, 17.73.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.87, -73.89.

HRMS: Calculated for $C_{26}H_{24}F_3N_3O_2Na^+$ 508.1818 [M+Na^+]; found 508.1826.

4-(3-(3-Phenyl-3-(trifluoromethyl)diaziridin-1-yl)butoxy)aniline (16i)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 5% methanol in DCM) afforded **16i** (18.1 mg, 54 % yield).

Physical state: dark yellow oil. $\mathbf{R_f}$ = 0.5 (3 % methanol in DCM, vis. UV and iodine).

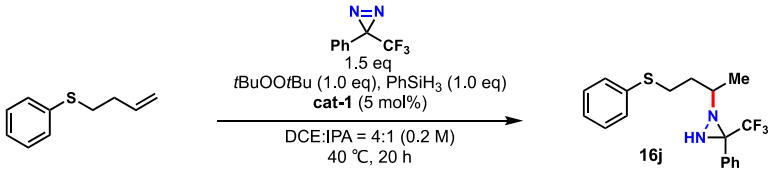
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (ddd, *J* = 10.0, 8.0, 1.5 Hz, 2H), 7.55 – 7.34 (m, 3H), 6.71 – 6.66 (m, 1H), 6.64 – 6.57 (m, 2H), 6.53 (d, *J* = 8.8 Hz, 1H), 4.02 – 3.88 (m, 1H), 3.82 – 3.60 (m, 1H), 3.40 (s, 2H), 2.98 (dd, *J* = 15.2, 2.1 Hz, 1H), 2.20 – 2.07 (m, 1H), 1.98 – 1.80 (m, 2H), 1.75 (dddd, *J* = 14.0, 8.7, 6.7, 5.6 Hz, 1H), 1.21 – 0.92 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.19, 151.95, 139.72, 139.64, 130.00, 129.96, 128.37, 126.36, 123.68 (d, *J* = 279.0 Hz), 116.47, 116.43, 115.75, 115.34, 65.69, 64.72, 63.05 (d, *J* = 34.6 Hz), 54.30, 53.96, 35.89, 33.86, 29.98, 29.72, 19.22, 17.61, 14.14.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.95, -73.99.

HRMS: *m/z* calculated for $C_{18}H_{21}F_3N_3O^+$: 352.1631 [$M+H^+$]; found: 352.1629.

3-phenyl-1-(4-(phenylthio)butan-2-yl)-3-(trifluoromethyl)diaziridine (16j)



General procedure A was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 3 – 5% ethyl acetate in hexanes) afforded **16j** (57.6 mg, 83% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.4 (10% ethyl acetate in hexanes, vis. iodine and CAM).

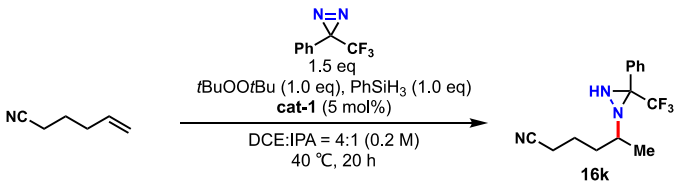
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.52 (m, 2H), 7.51 – 7.39 (m, 2H), 7.38 – 7.26 (m, 4H), 7.25 – 7.14 (m, 2H), 3.05 – 2.76 (m, 2H), 2.04 – 1.62 (m, 3H), 1.19 – 0.85 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.66, 136.30, 130.17, 130.13, 129.75, 129.42, 129.40, 129.02, 128.98, 128.87, 128.55, 128.46, 127.98, 126.15, 126.06, 123.79 (d, J = 266.6 Hz), 123.79 (d, J = 266.6 Hz), 55.92, 55.80, 35.87, 33.93, 30.17, 29.38, 18.86, 17.24.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.99, -74.00.

HRMS: Calculated for $C_{18}H_{20}F_3N_2S^+$ 353.1294 [M+H$^+$]; found 353.1297.

5-(3-Phenyl-3-(trifluoromethyl)diaziridin-1-yl)hexanenitrile (16k)



General procedure A was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 0 – 20% ethyl acetate in hexanes) afforded **16k** (37.4 mg, 66 % yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.3 (10 % ethyl acetate in hexanes, vis. iodine and CAM).

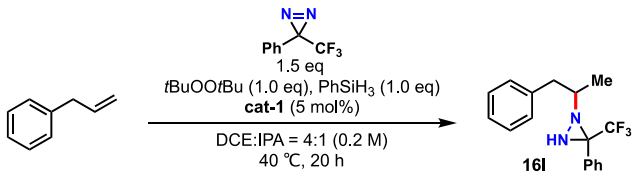
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (t, *J* = 5.9 Hz, 2H), 7.52 – 7.38 (m, 3H), 3.10 – 2.89 (m, 1H), 2.33 (t, *J* = 6.9 Hz, 1H), 2.11 (td, *J* = 7.1, 3.3 Hz, 1H), 1.83 – 1.54 (m, 4H), 1.52 – 1.40 (m, 1H), 1.37 – 1.23 (m, 1H), 1.13 (d, *J* = 6.4 Hz, 3H, major isomer), 0.91 (d, *J* = 6.3 Hz, 3H, minor isomer).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.27, 130.23, 129.81, 128.64, 128.49, 128.01, 127.92, 123.66 (d, *J* = 278.8 Hz), 123.61 (q, *J* = 279.1 Hz), 63.79 (d, *J* = 34.5 Hz), 62.96 (d, *J* = 35.0 Hz), 55.84, 55.66, 35.24, 33.02, 21.71, 21.33, 18.93, 17.43, 17.28.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.86, -74.10.

HRMS: Calculated for $C_{14}H_{18}F_3N_2^+$ 284.1369 [M+H$^+$]; found 284.1382.

3-phenyl-1-(1-phenylpropan-2-yl)-3-(trifluoromethyl)diaziridine (16l)



General procedure A was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 3 – 5% ethyl acetate in hexanes) afforded **16l** (43.1 mg, 70% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.5 (10% ethyl acetate in hexanes, vis. iodine and CAM).

^{1}H NMR (major isomer): (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 5.8, 3.6 Hz, 2H, merged with minor isomer), 7.58 – 7.37 (m, 2H, merged with minor isomer), 7.24 – 7.10 (m, 3H, merged with minor isomer), 7.07 (dd, *J* = 7.0, 1.7 Hz, 1H, merged with minor isomer), 6.66 – 6.59 (m, 1H, merged with minor isomer), 3.02 (s, 1H, merged with minor isomer), 2.75 (dd, *J* = 13.2, 3.8 Hz, 1H), 2.48 (dd, *J* = 13.2, 9.7 Hz, 1H), 1.90 (tdd, *J* = 9.5, 6.5, 3.8 Hz, 1H, merged with minor isomer), 1.05 (d, *J* = 6.2 Hz, 3H).

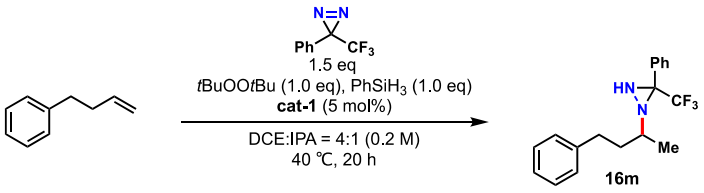
Minor isomer: (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 5.8, 3.6 Hz, 2H, merged with major isomer), 7.58 – 7.37 (m, 3H, merged with major isomer), 7.24 – 7.10 (m, 3H, merged with major isomer), 7.09 – 7.03 (m, 1H, merged with major isomer), 6.66 – 6.59 (m, 1H, merged with major isomer), 3.07 (dd, *J* = 13.1, 4.1 Hz, 1H), 3.02 (s, 1H, merged with major isomer), 2.65 (dd, *J* = 13.1, 9.5 Hz, 1H), 1.91 (dtt, *J* = 13.0, 6.5, 3.2 Hz, 1H, merged with major isomer), 0.83 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diastereomers) δ 138.83, 138.15, 133.02, 130.21, 130.14, 129.67, 129.37, 128.70, 128.53, 128.45, 128.32, 128.31, 128.19, 128.13, 128.09, 126.27, 126.22, 127.42 – 120.37 (m, merged both major and minor), 64.52 – 63.33 (m, merged both major and minor), 58.96, 58.62, 42.74, 40.62, 18.73, 16.72.

^{19}F NMR: (471 MHz, $CDCl_3$) Major isomer: δ -73.68, minor isomer: δ -74.06.

HRMS: Calculated for $C_{17}H_{18}F_3N_2^+$ 307.1417 [M+H$^+$]; found 307.1423.

3-Phenyl-1-(4-phenylbutan-2-yl)-3-(trifluoromethyl)diaziridine (16m)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 10 % ethyl acetate in hexanes) afforded **16m** (24.0 mg, 75% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.6 (10 % ethyl acetate in hexanes, vis. UV, iodine, and CAM).

^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 7.59 – 7.46 (m, 2H, merged with minor isomer), 7.34 – 7.22 (m, 3H, merged with minor isomer), 7.17 – 6.97 (m, 4H, merged with minor isomer), 6.88 – 6.74 (m, 1H, merged with minor isomer), 2.92 – 2.82 (m, 1H), 2.46 – 2.28 (m, 1H, merged with minor isomer), 2.04 (ddd, J = 13.7, 10.1, 6.7 Hz, 1H), 1.70 – 1.55 (m, 3H), 1.05 (d, J = 6.3 Hz, 3H).

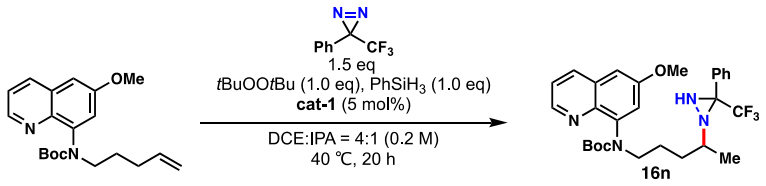
^{1}H NMR (500 MHz, $CDCl_3$, minor isomer) δ 7.59 – 7.46 (m, 2H, merged with major isomer), 7.34 – 7.22 (m, 3H, merged with major isomer), 7.17 – 6.97 (m, 4H, merged with major isomer), 6.88 – 6.74 (m, 1H, merged with major isomer), 2.82 – 2.75 (m, 1H), 2.52 (ddd, J = 14.0, 11.1, 5.1 Hz, 1H), 2.46 – 2.28 (m, 1H, merged with major isomer), 1.93 – 1.78 (m, 1H), 1.51 (dtd, J = 10.4, 7.7, 4.3 Hz, 2H), 0.82 (d, J = 6.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.27, 141.73, 129.96, 129.92, 128.38, 128.36, 128.34, 128.32, 128.29, 128.26, 128.14, 128.10, 128.06, 125.76, 125.71, 123.80 (d, *J* = 278.8 Hz), 123.75 (d, *J* = 278.8 Hz), 63.82 (q, *J* = 34.5 Hz), 63.03 (q, *J* = 34.3 Hz), 56.39, 56.31, 37.84, 35.65, 31.83, 31.67, 18.86, 17.25.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.91, -73.94.

HRMS: *m/z* calculated for $C_{18}H_{20}F_3N_2^+$: 321.1573 [$M+H^+$]; found: 321.1574.

***tert*-butyl (6-methoxyquinolin-8-yl)(4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)pentyl)carbamate (16n)**



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 20 – 50% ethyl acetate in hexanes) afforded **16n** (28.4 mg, 54% yield).

Physical state: pale yellow gum like. **R_f** = 0.4 (35% ethyl acetate in hexanes, UV and iodine).

^{1}H NMR (major isomer): (500 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H, merged with minor), 8.03 (ddd, *J* = 8.3, 4.0, 1.7 Hz, 1H, merged with minor), 7.61 (dd, *J* = 16.4, 7.5 Hz, 2H, merged

with minor), 7.47 – 7.29 (m, 4H, merged with minor), 7.23 – 7.08 (m, 1H, merged with minor), 7.00 (t, J = 3.3 Hz, 1H, merged with minor), 3.93 (s, 3H), 3.59 (s, br, 2H), 2.90 (s, 1H), 1.79 – 1.56 (m, 3H, merged with minor), 1.50 – 1.14 (m, 11H, merged with minor), 1.06 (d, J = 6.3 Hz, 3H).

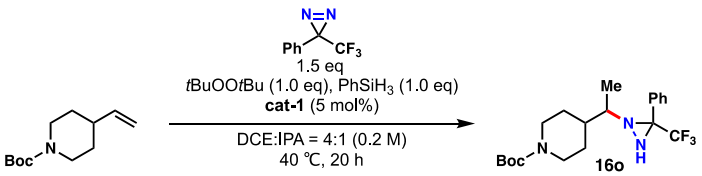
Minor isomer: (500 MHz, $CDCl_3$) δ 8.76 (dd, J = 4.2, 1.7 Hz, 1H, merged with major), 8.03 (ddd, J = 8.3, 4.0, 1.7 Hz, 1H, merged with minor), 7.61 (dd, J = 16.4, 7.5 Hz, 2H, merged with minor), 7.47 – 7.29 (m, 4H, merged with minor), 7.23 – 7.08 (m, 1H, merged with minor), 7.00 (t, J = 3.3 Hz, 1H, merged with minor), 3.93 (s, 3H), 3.59 (s, br, 2H, merged with minor), 1.79 – 1.56 (m, 3H, merged with minor), 1.50 – 1.14 (m, 11H, merged with minor), 0.84 (d, J = 6.1 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diastereomers) δ 157.25, 155.68, 155.58, 147.67, 141.03, 134.94, 130.01, 129.98, 128.40, 128.34, 128.26, 128.20, 123.83 (d, J = 266.6 Hz), 121.75, 104.51, 79.78, 63.95 (d, J = 34.5 Hz), 56.65, 56.51, 55.71, 50.32, 33.35, 31.61, 28.32, 24.81, 19.22, 17.22.

^{19}F NMR: Major: (471 MHz, $CDCl_3$) δ -74.07. Minor: δ -74.05.

HRMS: Calculated for $C_{28}H_{34}F_3N_4O_3^+$ 531.2578 [M+H$^+$]; found 531.2583.

***tert*-butyl 4-(1-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)ethyl)piperidine-1-carboxylate (16o)**



General procedure A was followed on a 0.961 mmol scale. Purification via column chromatography (silica gel, 5 – 10% ethyl acetate in hexanes) afforded **16o** (355 mg, 92% yield).

Physical state: white solid. $\mathbf{R_f}$ = 0.5 (17% ethyl acetate in hexanes, vis. iodine).

^{1}H NMR major isomer (spectrum contaminated with minor isomer): (500 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.47 – 7.37 (m, 3H), 4.26 – 4.00 (m, 2H), 2.92 (d, *J* = 1.7 Hz, 1H), 2.64 (s, 2H), 1.79 (dt, *J* = 12.8, 2.7 Hz, 1H), 1.76 – 1.66 (m, 1H), 1.63 – 1.54 (m, 1H), 1.44 (s, 9H), 1.33 – 1.13 (m, 2H), 0.79 (d, *J* = 6.6 Hz, 3H).

minor isomer: (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.52 – 7.36 (m, 3H), 4.39 – 3.81 (m, 2H), 2.95 (d, *J* = 1.8 Hz, 1H), 2.74 – 2.40 (m, 2H), 1.83 – 1.71 (m, 1H), 1.69 – 1.60 (m, 1H), 1.43 (s, 9H), 1.24 – 1.12 (m, 1H), 1.07 – 0.92 (m, 5H).

^{13}C NMR major isomer (spectrum contaminated with minor isomer): (126 MHz, $CDCl_3$) δ 154.97, 130.21 (br), 130.09, 128.37, 128.07, 123.92 (q, *J* = 278.8 Hz), 79.40, 62.76 (d, *J* = 34.5 Hz), 60.15, 44.22, 41.23, 28.61, 26.74, 13.49.

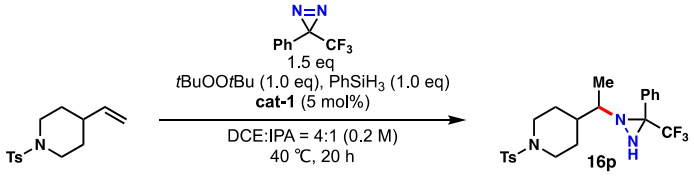
minor isomer: (126 MHz, $CDCl_3$) δ 154.82, 129.97, 129.81, 128.32, 128.20, 123.73 (q, *J* = 278.8 Hz), 79.31, 63.85 (q, *J* = 34.1 Hz), 59.18, 44.12, 40.01, 28.82, 28.46, 26.33, 15.00.

^{19}F NMR major isomer (spectrum contaminated with minor isomer): (471 MHz, $CDCl_3$) δ -73.92.

minor isomer: (471 MHz, $CDCl_3$) δ -73.65.

HRMS: *m/z* calculated for $C_{20}H_{28}F_3N_3NaO_2^+$: 422.2026 [M+H$^+$]; found: 422.2032. Also found minus *t*Bu form *m/z* calculated for $C_{16}H_{21}F_3N_3O_2^+$: 344.1580 [M+H$^+$]; found: 344.1577.

4-(1-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)ethyl)-1-tosylpiperidine (16p)



General procedure A was followed on a 1.02 mmol scale. Purification via column chromatography (silica gel, 7 – 12% ethyl acetate in hexanes) afforded **16p** (400 mg, 87% yield).

Physical state: colorless oil. **R_f** = 0.6 (17% ethyl acetate in hexanes, vis. iodine and UV).

^{1}H NMR major isomer: (500 MHz, $CDCl_3$) δ 7.68 – 7.55 (m, 4H, merged with minor isomer), 7.49 – 7.29 (m, 5H, merged in minor isomer), 3.91 – 3.66 (m, 2H, merged in minor isomer), 2.93 (s, 1H), 2.45 (s, 3H), 2.24 – 2.11 (m, 2H, merged in minor isomer), 1.66 – 1.52 (m, 2H), 1.52 –

1.34 (m, 1H, merged in minor isomer), 1.28 – 1.15 (m, 2H, merged in minor isomer), 0.99 (d, J = 6.6 Hz, 3H).

minor isomer: (500 MHz, $CDCl_3$) δ 7.70 – 7.55 (m, 4H, merged with major isomer), 7.50 – 7.29 (m, 5H, merged with major isomer), 3.96 – 3.59 (m, 2H, merged with major isomer), 2.89 – 2.73 (s, 1H), 2.43 (s, 3H), 2.28 – 1.98 (m, 2H, merged with major isomer), 1.83 (tt, J = 13.1, 2.7 Hz, 2H), 1.68 – 1.51 (m, 2H, merged with major isomer), 1.51 – 1.33 (m, 1H, merged with major isomer), 1.28 – 1.07 (m, 2H, merged with major isomer), 0.76 (d, J = 6.4 Hz, 3H).

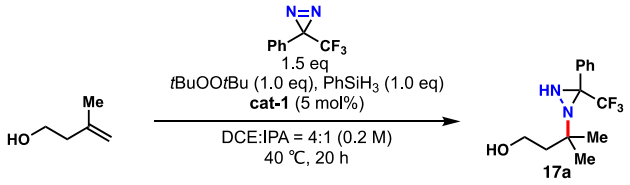
^{13}C NMR mixture of both isomers: (126 MHz, $CDCl_3$) δ 143.55, 143.51, 133.43, 133.30, 130.15, 130.13, 129.77, 129.67, 128.50, 128.39, 128.17, 127.87, 127.84, 123.76 (q, J = 279.1 Hz, major isomer), 123.81 (d, J = 278.8 Hz), 63.99 (q, J = 34.3 Hz, major isomer), 62.83 (q, J = 34.5 Hz), 59.73, 58.78, 46.76, 46.74, 46.71, 46.68, 40.33, 39.34, 28.36, 28.26, 26.05, 25.94, 21.69, 21.63, 15.12, 13.37.

^{19}F NMR major isomer: (471 MHz, $CDCl_3$) δ -73.67.

minor isomer: (471 MHz, $CDCl_3$) δ -73.99.

HRMS: *m/z* calculated for $C_{22}H_{27}F_3N_3O_2S^+$: 454.1771 [$M+H^+$]; found: 454.1763.

3-methyl-3-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)butan-1-ol (17a)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 10% ethyl acetate in hexanes) afforded **17a** (21.1 mg, 77% yield).

Physical state: light yellow oil. $\mathbf{R_f}$ = 0.1 (10% ethyl acetate in hexanes, vis. iodine).

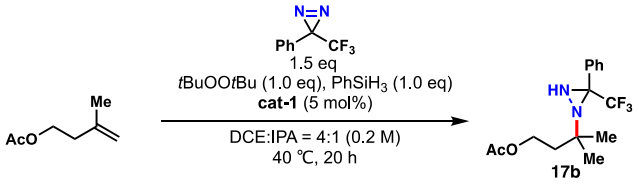
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dt, *J* = 6.6, 1.5 Hz, 2H), 7.52 – 7.35 (m, 3H), 3.95 (ddd, *J* = 11.5, 9.1, 4.0 Hz, 1H), 3.77 (dt, *J* = 11.5, 5.1 Hz, 1H), 2.90 (s, 1H), 1.87 (ddd, *J* = 14.1, 9.1, 4.8 Hz, 1H), 1.47 (ddd, *J* = 14.6, 5.4, 4.0 Hz, 1H), 1.01 (s, 3H), 0.57 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.30, 130.14, 129.50, 129.18, 128.92, 128.19, 123.60 (d, *J* = 279.9 Hz), 62.62 (d, *J* = 34.5 Hz), 61.03, 59.95, 44.57, 24.47, 23.32.

^{19}F NMR (471 MHz, $CDCl_3$) δ -76.23.

HRMS Calculated for $C_{13}H_{18}F_3N_2O^+$ 275.1366 [$M+H^+$]; found 275.1367.

3-methyl-3-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)butyl acetate (17b)



General procedure A was followed on a 0.130 mmol scale. Purification via column chromatography (silica gel, 3% ethyl acetate in hexanes) afforded **17b** (31.3 mg, 76% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.3 (10% ethyl acetate in hexanes, iodine)

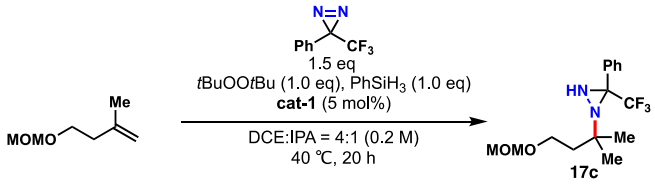
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.5 Hz, 2H), 7.41 (ddq, *J* = 14.7, 7.6, 4.3 Hz, 3H), 4.26 (ddd, *J* = 8.2, 7.0, 1.7 Hz, 2H), 2.78 (s, 1H), 2.03 (s, 3H), 1.76 (td, *J* = 7.2, 1.4 Hz, 2H), 0.86 (s, 3H), 0.65 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.28, 131.32, 129.90, 129.42, 128.81, 128.15, 123.80 (q, *J* = 279.9 Hz), 62.14 (q, *J* = 34.2 Hz), 61.38, 58.91, 41.42, 24.29, 21.19.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.79.

HRMS: Calculated for $C_{15}H_{20}F_3N_2O_2^+$ 317.1471 [M+H$^+$]; found 317.1472.

1-(4-(methoxymethoxy)-2-methylbutan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (17c)



General procedure A was followed on a 0.130 mmol scale. Purification via column chromatography (silica gel, 2% ethyl acetate in hexanes) afforded **17c** (30.5 mg, 74% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.4 (10% ethyl acetate in hexanes, vis. iodine).

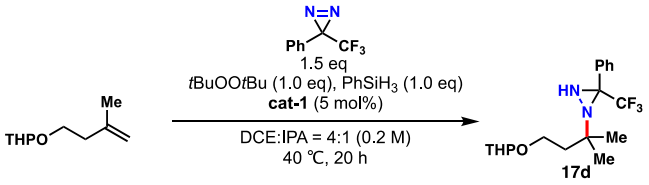
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 2H), 7.43 – 7.33 (m, 3H), 4.61 (s, 2H), 3.78 – 3.60 (m, 2H), 3.36 (s, 3H), 2.76 (s, 1H), 1.83 – 1.68 (m, 2H), 0.82 (s, 3H), 0.69 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.34, 129.92, 129.83, 129.47, 128.77, 128.10, 123.87 (q, J = 279.7 Hz), 96.62, 64.34, 62.12 (q, J = 34.2 Hz), 58.98, 55.31, 42.34, 24.87, 24.32.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.75.

HRMS: Calculated for $C_{15}H_{22}F_3N_2O_2^+$ 319.1628 [M+H$^+$]; found 319.1631.

1-(2-methyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)butan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (17d)



General procedure A was followed on a 0.150 mmol scale. Purification via column chromatography (silica gel, 2% ethyl acetate in hexanes) afforded **17d** (39.0 mg, 71% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.5 (10% ethyl acetate in hexanes, vis. iodine).

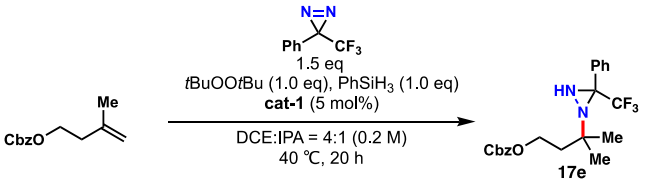
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.60 (m, 2H), 7.44 – 7.33 (m, 3H), 4.58 (dd, *J* = 4.7, 2.6 Hz, 1H), 3.99 – 3.77 (m, 2H), 3.65 – 3.42 (m, 2H), 2.74 (s, 1H), 1.86 – 1.66 (m, 4H), 1.59 – 1.46 (m, 4H), 0.82 (d, *J* = 7.8 Hz, 3H), 0.68 (d, *J* = 5.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.33, 129.99, 129.77, 129.48, 128.73, 128.08, 123.88 (q, *J* = 279.8 Hz), 99.15, 64.08, 62.61, 62.48, 62.12 (q, *J* = 34.1 Hz), 59.05, 42.41, 30.96, 25.62, 24.81, 24.27, 19.79.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.72, -75.74.

HRMS: Calculated for $C_{18}H_{26}F_3N_2O_2^+$ 359.1941 [M+H$^+$]; found 359.1943.

2-(3-methyl-3-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)butoxy)-1-phenyl-2□^{2}-ethan-1-one (17e)



General procedure A was followed on a 0.143 mmol scale. Purification via column chromatography (silica gel, 2 – 5% ethyl acetate in hexanes) afforded **17e** (41.4 mg, 71% yield).

Physical state: pale yellow foam. $\mathbf{R_f}$ = 0.4 (10% ethyl acetate in hexanes, vis. iodine and CAM).

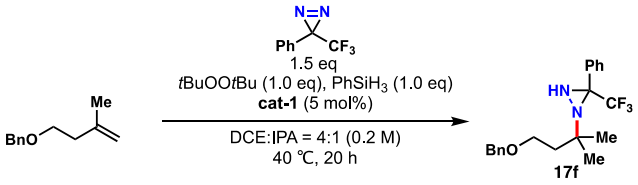
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.78 – 7.63 (m, 2H), 7.44 – 7.33 (m, 5H), 5.34 – 5.11 (m, 1H), 4.43 – 4.28 (m, 2H), 2.88 – 2.68 (m, 1H), 1.80 (dd, *J* = 8.2, 6.7 Hz, 2H), 0.89 (d, *J* = 2.0 Hz, 3H), 0.64 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 155.26, 155.19, 135.37, 131.18, 129.79, 129.62, 129.59, 129.29, 128.77, 128.70, 128.60, 128.51, 128.32, 128.04, 123.66 (d, *J* = 280.2 Hz), 69.49, 64.95, 64.66, 62.05 (q, *J* = 34.1 Hz), 58.67, 41.36, 41.33, 24.32, 24.29, 24.24, 24.21.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.77.

HRMS: Calculated for $C_{21}H_{22}F_3N_2O_2^+$ 391.1628. [M+H$^+$]; found 391.1635.

1-(4-(benzyloxy)-2-methylbutan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (17f)



General procedure A was followed on a 0.155 mmol scale. Purification via column chromatography (silica gel, 2% ethyl acetate in hexanes) afforded **17f** (47.2 mg, 84% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.6 (10% ethyl acetate in hexanes, iodine).

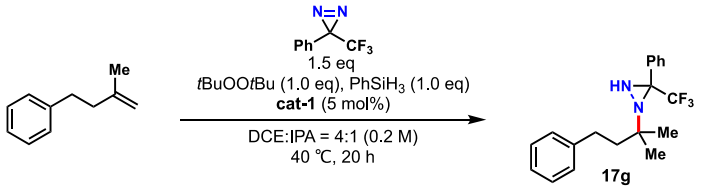
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.68 (t, *J* = 7.7 Hz, 2H), 7.50 – 7.27 (m, 8H), 4.51 (s, 2H), 3.79 – 3.54 (m, 2H), 2.74 (s, 1H), 1.95 – 1.71 (m, 2H), 0.82 (s, 3H), 0.70 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 138.60, 131.21, 129.83, 129.69, 129.36, 128.63, 128.37, 127.99, 127.62, 127.51, 123.77 (q, *J* = 279.9 Hz), 72.97, 66.80, 62.02 (q, *J* = 34.2 Hz), 58.96, 42.18, 24.86, 24.17.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.80.

HRMS: Calculated for $C_{20}H_{24}F_3N_2O^+$ 365.1835 [M+H$^+$]; found 365.1838.

1-(2-Methyl-4-phenylbutan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (17g)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 5% ethyl acetate in hexanes) afforded **17g** (28.4 mg, 85% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.6 (10 % ethyl acetate in hexanes, vis. UV, iodine and CAM).

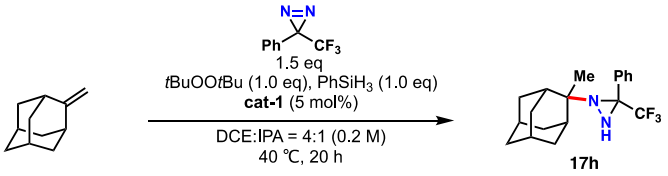
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 2H), 7.46 – 7.36 (m, 3H), 7.32 – 7.27 (m, 2H), 7.19 (ddt, *J* = 7.3, 3.5, 1.5 Hz, 3H), 2.85 – 2.64 (m, 3H), 1.84 – 1.66 (m, 2H), 0.82 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.06, 131.40, 130.07, 129.79, 129.48, 128.76, 128.51, 128.48, 128.09, 125.80, 123.97 (q, *J* = 279.7 Hz), 62.05 (q, *J* = 34.1 Hz), 59.69, 45.14, 30.63, 24.63, 23.91.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.62.

HRMS: Calculated for $C_{19}H_{22}F_3N_2^+$ 335.1730 [M+H$^+$]; found 335.1727.

1-(2-methyladamantan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (17h)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 1% ethyl acetate in hexanes) afforded **17h** (20.1 mg, 60% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.4 (100% hexanes, vis. iodine).

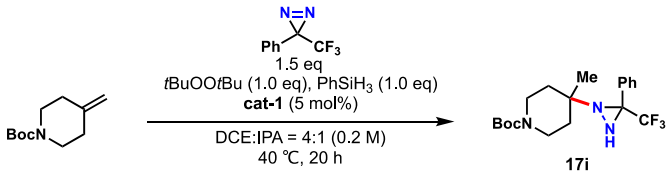
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.81 – 7.49 (m, 2H), 7.49 – 7.28 (m, 3H), 2.77 – 2.71 (m, 1H), 2.69 (d, J = 14.0 Hz, 2H), 1.91 – 1.83 (m, 2H), 1.78 – 1.69 (m, 4H), 1.66 – 1.54 (m, 5H), 1.51 (dd, J = 12.1, 2.6 Hz, 1H), 0.38 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 131.16, 130.42, 129.39, 128.47, 124.06 (d, J = 280.3 Hz), 61.58 (q, J = 34.0 Hz), 39.21, 38.13, 36.45, 34.06, 33.84, 32.80, 32.59, 29.72, 27.53, 27.50, 17.48.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.50.

HRMS: Calculated for $C_{19}H_{24}F_3N_2^+$ 337.1886 [M+H$^+$]; found 337.1895.

***tert*-Butyl 4-methyl-4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)piperidine-1-carboxylate (17i)**



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 15% ethyl acetate in hexanes) afforded **17i** (32.7 mg, 85% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.4 (10% ethyl acetate in hexanes, vis. iodine and CAM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.57 (m, 2H), 7.46 – 7.33 (m, 3H), 3.64 (ddd, *J* = 12.7, 8.2, 3.9 Hz, 1H), 3.56 (ddd, *J* = 12.5, 8.1, 4.0 Hz, 1H), 3.42 – 3.29 (m, 1H), 3.22 (ddd, *J* = 13.4, 7.5, 4.0 Hz, 1H), 2.76 (d, *J* = 1.7 Hz, 1H), 1.79 – 1.64 (m, 1H), 1.60 (ddd, *J* = 12.2, 7.6, 4.0 Hz, 1H), 1.44 (s, 10H), 0.94 – 0.82 (m, 1H), 0.56 (s, 3H).

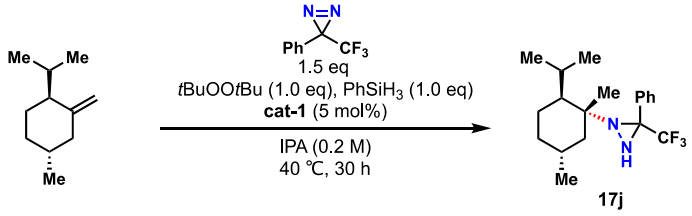
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.80, 131.09, 129.82, 129.79, 129.19, 128.80, 128.06, 123.71 (q, *J* = 280.0 Hz), 79.30, 62.14 (q, *J* = 34.5 Hz), 57.30, 40.26, 39.45, 36.34, 28.46, 21.17.

^{13}C NMR (126 MHz, $CDCl_3$) δ 123.71 (q, *J* = 280.0 Hz), 62.14 (q, *J* = 34.5 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.73.

HRMS: *m/z* calculated for $C_{19}H_{26}F_3N_3NaO_2^+$: 408.1869 [M+Na$^+$]; found 408.1865.

1-((2*S*,5*R*)-2-isopropyl-1,5-dimethylcyclohexyl)-3-phenyl-3-(trifluoromethyl)diaziridine (17j)



General procedure B was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 0 – 5% ethyl acetate in hexanes) afforded **17j** (47.8 mg, 71% yield, over 20:1 dr).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.3 (5% ethyl acetate in hexanes, vis. iodine).

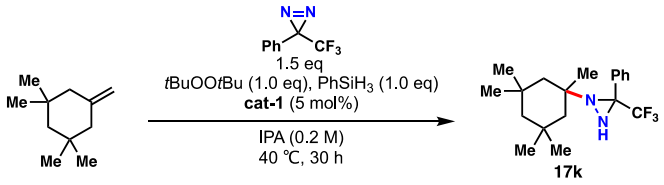
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.79 – 7.60 (m, 2H), 7.43 – 7.30 (m, 3H), 2.84 – 2.44 (m, 2H), 1.53 (ddq, *J* = 16.5, 10.1, 3.4 Hz, 2H), 1.33 – 1.21 (m, 2H), 1.16 – 1.05 (m, 2H), 1.03 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.70 (qd, *J* = 13.0, 4.0 Hz, 1H), 0.50 (d, *J* = 6.4 Hz, 3H), 0.09 (ddd, *J* = 12.8, 3.6, 1.9 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 131.04, 130.71, 129.53, 129.44, 129.28, 128.44, 127.84, 127.29, 123.95 (q, *J* = 280.2 Hz), 120.61, 63.29, 62.74, 62.34 (q, *J* = 34.1 Hz), 61.93, 50.86, 43.24, 34.69, 29.17, 24.86, 24.59, 22.74, 22.60, 18.71, 18.33.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.87.

HRMS: *m/z* calculated for $C_{19}H_{28}F_3N_2^+$: 341.2199 [M+H$^+$]; found: 341.2193.

1-(1,3,3,5,5-pentamethylcyclohexyl)-3-phenyl-3-(trifluoromethyl)diaziridine (17k)



General procedure B was followed on a 0.130 mmol scale. Purification via column chromatography (silica gel, 0 – 3% ethyl acetate in hexanes) afforded **17k** (26.4 mg, 59% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.3 (100% hexanes, vis. iodine).

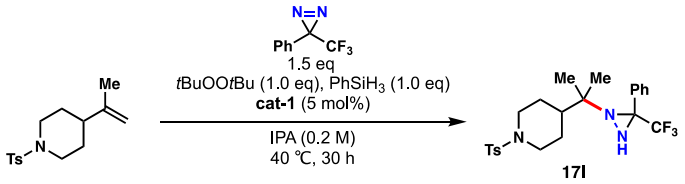
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.67 (t, *J* = 7.5 Hz, 2H), 7.48 – 7.32 (m, 3H), 2.58 (s, 1H), 1.68 (ddd, *J* = 14.7, 9.6, 2.2 Hz, 2H), 1.45 – 1.36 (m, 1H), 1.31 (d, *J* = 2.5 Hz, 3H), 1.23 (d, *J* = 2.5 Hz, 3H), 1.07 (ddd, *J* = 14.7, 7.7, 2.4 Hz, 2H), 0.92 (d, *J* = 2.4 Hz, 3H), 0.87 (d, *J* = 2.5 Hz, 3H), 0.80 (dd, *J* = 14.2, 2.5 Hz, 1H), 0.18 (d, *J* = 2.5 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 131.20, 130.53, 129.54, 128.65, 127.87, 123.90 (d, *J* = 280.3 Hz), 63.47 (d, *J* = 34.1 Hz), 60.92, 51.78, 51.61, 48.53, 36.28, 36.11, 31.49, 31.37, 29.85, 28.78, 25.12.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.81.

HRMS: Calculated for $C_{19}H_{28}F_3N_2^+$ 341.2199 [M+H$^+$]; found 341.2210.

4-(2-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)propan-2-yl)-1-tosylpiperidine (17l)



General procedure B was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 10 – 20% ethyl acetate in hexanes) afforded **17l** (62.3 mg, 67% yield).

Physical state: pale yellow foam. $\mathbf{R_f}$ = 0.40 (20% ethyl acetate in hexanes, vis. UV and iodine).

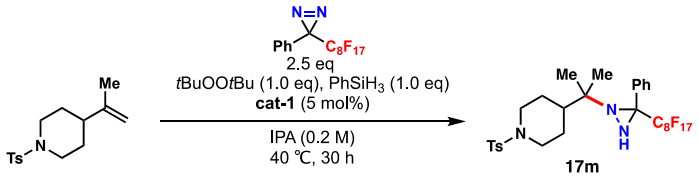
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.68 – 7.58 (m, 4H), 7.40 – 7.30 (m, 5H), 3.87 (ddq, *J* = 13.7, 11.4, 2.1 Hz, 2H), 2.68 (d, *J* = 1.5 Hz, 1H), 2.43 (s, 3H), 2.25 – 2.09 (m, 2H), 1.89 (dt, *J* = 13.3, 2.7 Hz, 1H), 1.76 (dt, *J* = 13.1, 2.8 Hz, 1H), 1.58 (qd, *J* = 11.8, 3.4 Hz, 1H), 1.48 – 1.39 (m, 1H), 1.24 – 1.16 (m, 1H), 0.77 (d, *J* = 1.7 Hz, 3H), 0.45 (d, *J* = 1.7 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 143.39, 133.25, 131.30, 129.71, 129.69, 129.57, 129.55, 129.35, 128.64, 128.14, 128.11, 127.92, 127.80, 127.78, 123.73 (d, *J* = 279.7 Hz), 60.95 (q, *J* = 34.1 Hz), 60.89, 47.42, 46.99, 46.89, 26.26, 25.94, 22.09, 21.53, 20.65.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.57.

HRMS: Calculated for $C_{23}H_{29}F_3N_3O_2S^+$ 468.1927 [M+H$^+$]; found 468.1931.

4-(2-(3-(perfluorooctyl)-3-phenyldiaziridin-1-yl)propan-2-yl)-1-tosylpiperidine (17m)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 30% ethyl acetate in hexanes) afforded **17m** (61.1 mg, 75% yield).

Physical state: brown oil. **R_f** = 0.5 (15% ethyl acetate in hexanes, vis. UV, iodine and CAM).

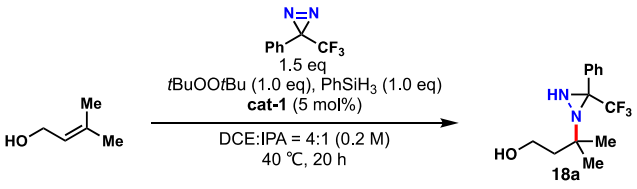
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.58 (m, 4H), 7.41 – 7.31 (m, 5H), 3.98 – 3.82 (m, 2H), 2.65 (t, *J* = 3.0 Hz, 1H), 2.44 (s, 3H), 2.26 – 2.11 (m, 2H), 1.95 – 1.87 (m, 1H), 1.77 (dt, *J* = 13.3, 2.9 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.45 (td, *J* = 12.7, 4.1 Hz, 1H), 1.20 (tt, *J* = 12.2, 3.3 Hz, 1H), 0.79 (s, 3H), 0.40 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.36, 133.29, 131.53, 130.45, 129.79, 129.56, 129.54, 128.58, 128.08, 127.80, 127.75, 127.56, 60.91, 47.65, 47.01, 46.90, 26.26, 25.95, 22.02, 21.51, 20.69.

^{19}F NMR (471 MHz, $CDCl_3$) δ -80.75 (t, *J* = 10.0 Hz), -111.36 – -111.55 (m), -114.35 (q, *J* = 13.4 Hz), -114.81 – -115.07 (m), -117.29 – -117.50 (m), -118.03 (dt, *J* = 21.7, 13.9 Hz), -120.18 (dd, *J* = 17.3, 10.4 Hz), -120.71 – -120.94 (m), -121.18 – -121.48 (m), -121.52 – -122.35 (m), -122.39 – -123.07 (m), -124.91 (dt, *J* = 26.9, 13.9 Hz), -125.39 – -125.61 (m), -125.77 – -126.17 (m), -126.31 (dd, *J* = 17.3, 10.4 Hz).

HRMS: *m/z* calculated for $C_{30}H_{29}F_{17}N_2O_2S^+$: 818.1704 [M+H$^+$]; found: 818.1709.

3-methyl-3-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)butan-1-ol (18a)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 10% ethyl acetate in hexanes) afforded **18a** (17.5 mg, 64% yield).

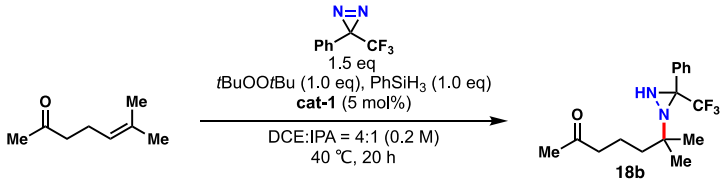
Physical state: light yellow oil. **R_f** = 0.1 (10% ethyl acetate in hexanes, vis. iodine).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 2H), 7.49 – 7.34 (m, 3H), 3.95 (ddd, *J* = 11.4, 8.9, 4.2 Hz, 1H), 3.78 (dt, *J* = 11.1, 5.2 Hz, 1H), 3.53 – 3.31 (m, 1H), 2.89 (s, 1H), 1.87 (ddd, *J* = 14.0, 8.9, 4.9 Hz, 1H), 1.48 (ddd, *J* = 14.5, 5.5, 4.1 Hz, 1H), 1.00 (s, 3H), 0.58 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.31, 130.13, 129.51, 129.23, 128.91, 128.18, 123.62 (q, J = 280.0 Hz), 62.63 (q, J = 34.1 Hz), 60.98, 59.94, 44.64, 24.50, 23.36.

^{19}F NMR (471 MHz, $CDCl_3$) δ -76.22.

6-methyl-6-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)heptan-2-one (18b)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 5 – 10% ethyl acetate in hexanes) afforded **18b** (23.0 mg, 73% yield).

Physical state: pale yellow oil. **R_f** = 0.4 (20% ethyl acetate in hexanes, iodine).

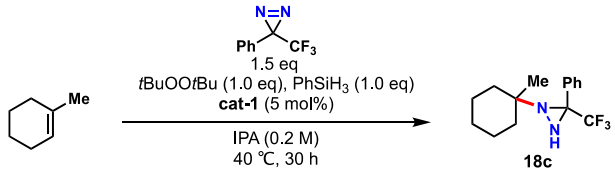
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.67 (t, J = 7.2 Hz, 2H), 7.52 – 7.31 (m, 3H), 2.74 (s, 1H), 2.41 (t, J = 7.3 Hz, 2H), 2.13 (s, 3H), 1.73 – 1.60 (m, 2H), 1.45 – 1.29 (m, 2H), 0.79 (s, 3H), 0.63 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 209.12, 131.36, 130.06, 129.77, 129.49, 128.73, 128.08, 123.93 (d, J = 279.9 Hz), 61.95 (d, J = 34.1 Hz), 59.67, 44.34, 42.54, 30.02, 24.17, 23.87, 18.60.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.71.

HRMS: Calculated for $C_{16}H_{22}F_3N_2O^+$ 315.1679 [M+H$^+$]; found 315.1687.

1-(1-methylcyclohexyl)-3-phenyl-3-(trifluoromethyl)diaziridine (18c)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 2% ethyl acetate in hexanes) afforded **18c** (19.9 mg, 71% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.6 (10% ethyl acetate in hexanes, vis. iodine).

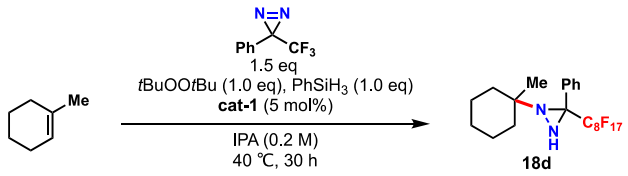
^{1}H NMR (500 MHz, CDCl3) δ 7.70 – 7.63 (m, 2H), 7.41 – 7.34 (m, 3H), 2.69 (s, 1H), 1.71 (ddt, *J* = 12.7, 9.7, 5.2 Hz, 1H), 1.65 – 1.57 (m, 2H), 1.52 – 1.28 (m, 6H), 0.92 – 0.86 (m, 1H), 0.54 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.20, 130.53, 129.65, 129.52, 128.71, 128.01, 124.04 (d, *J* = 280.0 Hz), 62.15 (d, *J* = 34.0 Hz), 59.32, 37.21, 37.06, 29.85, 25.93, 22.38, 21.17.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.76.

HRMS: Calculated for $C_{15}H_{20}F_3N_2^+$ 285.1573 [M+H$^+$]; found 285.1582.

1-(1-methylcyclohexyl)-3-(perfluorooctyl)-3-phenyldiaziridine (18d)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 3% ethyl acetate in hexanes) afforded **18d** (15.1 mg, 42% yield).

Physical state: yellow amorphous solid. $\mathbf{R_f}$ = 0.7 (15% ethyl acetate in hexanes, vis. UV, iodine, and CAM).

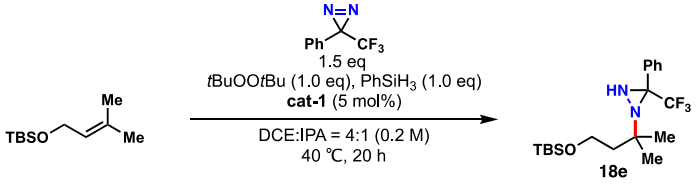
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.60 (t, *J* = 9.6 Hz, 2H), 7.35 – 7.26 (m, 3H), 2.60 (s, 1H), 1.65 (q, *J* = 8.2 Hz, 1H), 1.55 (tt, *J* = 8.6, 4.2 Hz, 2H), 1.46 – 1.34 (m, 2H), 1.33 – 1.25 (m, 3H), 1.27 – 1.22 (m, 2H), 0.93 – 0.78 (m, 1H), 0.42 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$) δ 131.31, 130.45, 130.21, 129.57, 128.49, 127.50, 62.06, 59.26, 37.41, 36.82, 36.50, 25.80, 22.24, 22.21, 21.00.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -80.59 – -80.97 (m), -114.36 (t, *J* = 14.5 Hz), -114.94 (d, *J* = 14.7 Hz), -117.25 – -117.54 (m), -117.86 – -118.20 (m), -120.18 (dd, *J* = 17.8, 10.0 Hz), -120.82 (p, *J* = 13.1, 10.4 Hz), -121.14 – -122.27 (m), -122.36 – -123.12 (m), -124.90 (d, *J* = 19.6 Hz), -125.20 – -125.64 (m), -125.74 – -126.48 (m), -126.89 – -127.03 (m).

HRMS: *m/z* calculated for $C_{22}H_{19}F_{17}N_2^+$: 635.1350 [M+H$^+$]; found: 635.1365.

1-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylbutan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (18e)



General procedure A was followed on a 0.110 mmol scale. Purification via column chromatography (silica gel, 1% ethyl acetate in hexanes) afforded **18e** (38.0 mg, 89% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.1 (100% hexanes, vis. iodine).

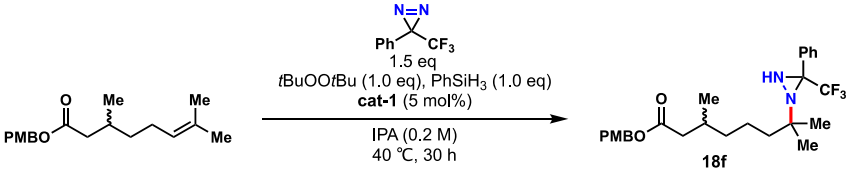
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 2H), 7.49 – 7.33 (m, 3H), 3.86 – 3.70 (m, 2H), 2.72 (d, *J* = 2.2 Hz, 1H), 1.68 (t, *J* = 7.5 Hz, 2H), 0.89 (s, 9H), 0.78 (s, 3H), 0.70 (s, 3H), 0.05 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.34, 130.03, 129.78, 129.49, 128.75, 128.09, 123.91 (q, *J* = 279.7 Hz), 62.19 (q, *J* = 34.1 Hz), 59.66, 59.16, 45.33, 26.10, 25.11, 24.19, 18.43, -5.14, -5.16.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.78.

HRMS Calculated for $C_{19}H_{32}F_3N_2OSi^+$ 389.2231 [M+H$^+$]; found 389.2241.

4-Methoxybenzyl 3,7-dimethyl-7-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)octanoate (18f)



General procedure B was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 0 – 20% ethyl acetate in hexanes) afforded **18f** (61.9 mg, 65% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.4 (20 % ethyl acetate in hexanes, vis. UV, iodine and CAM).

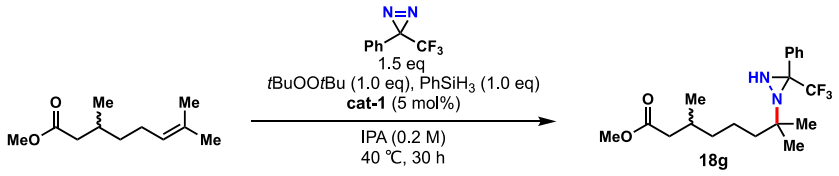
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.61 (m, 2H), 7.44 – 7.34 (m, 3H), 7.33 – 7.27 (m, 2H), 6.94 – 6.81 (m, 2H), 5.06 (s, 2H), 3.80 (s, 3H), 2.81 – 2.63 (m, 1H), 2.33 (ddd, J = 14.6, 6.1, 2.2 Hz, 1H), 2.14 (ddd, J = 14.6, 8.1, 5.3 Hz, 1H), 2.03 – 1.90 (m, 1H), 1.44 – 1.20 (m, 5H), 1.21 – 1.08 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 5.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.34, 173.31, 159.72, 131.37, 130.21, 130.20, 130.16, 130.14, 129.70, 129.47, 128.68, 128.41, 128.02, 123.96 (q, J = 280.0 Hz), 114.05, 65.98, 65.97, 61.89 (q, J = 34.3 Hz), 59.73, 55.39, 43.08, 43.06, 42.06, 41.98, 37.43, 37.41, 30.43, 30.40, 24.47, 24.39, 23.87, 21.31, 21.29, 19.87, 19.81.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.65.

HRMS: Calculated for $C_{26}H_{34}F_3N_2O_3^+$ 479.2522. [M+H$^+$]; found 479.2525.

Methyl 3,7-dimethyl-7-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)octanoate (18g)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 5% ethyl acetate in hexanes) afforded **18g** (21.2 mg, 57% yield).

Physical state: colorless oil. $\mathbf{R_f}$ = 0.5 (10 % ethyl acetate in hexanes, vis. iodine and CAM).

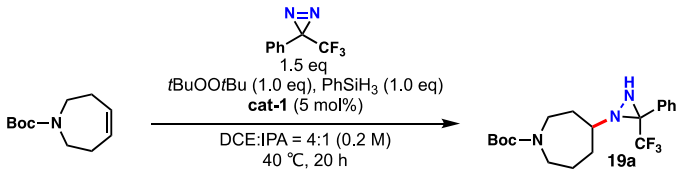
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 14.8, 7.6 Hz, 2H), 7.39 (tq, *J* = 7.8, 3.6 Hz, 3H), 3.67 (s, 3H), 2.82 – 2.65 (m, 1H), 2.31 (ddd, *J* = 14.6, 6.0, 1.6 Hz, 1H), 2.12 (ddd, *J* = 14.6, 8.2, 4.1 Hz, 1H), 2.04 – 1.88 (m, 1H), 1.46 – 1.22 (m, 5H), 1.16 (ddd, *J* = 15.1, 10.8, 7.1 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.3 Hz, 3H), 0.64 (d, *J* = 4.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.92, 173.90, 131.38, 130.16, 130.14, 129.71, 129.48, 128.69, 128.02, 123.96 (q, *J* = 279.7 Hz), 61.92 (q, *J* = 34.1 Hz), 59.75, 51.50, 43.07, 43.05, 41.81, 41.74, 37.46, 30.40, 30.37, 24.51, 24.44, 23.88, 21.33, 19.90, 19.84.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.69.

HRMS: Calculated for $C_{19}H_{28}F_3N_2O_2^+$ 373.2097 [M^+H^+]; found 373.2096.

***tert*-butyl 4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)azepane-1-carboxylate (19a)**



General procedure A was followed on a 0.450 mmol scale. Purification via column chromatography (silica gel, 5% to 10% ethyl acetate in hexanes) afforded **19a** (75.7 mg, 44% yield).

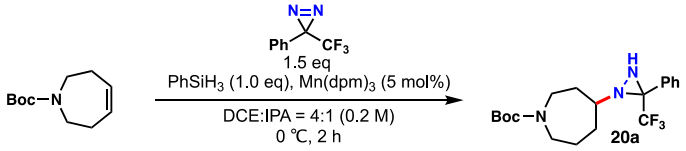
Physical state: pale yellow foam. $\mathbf{R_f}$ = 0.3 (10% ethyl acetate in hexanes, vis. iodine).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.3 Hz, 2H), 7.53 – 7.32 (m, 3H), 3.55 – 2.87 (m, 5H), 2.06 – 1.55 (m, 6H), 1.53 – 1.44 (m, 1H, major isomer), 1.41 – 1.30 (m, 9H), 1.00 (dddt, J = 12.8, 9.2, 6.0, 3.1 Hz, 1H, minor isomer).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 155.25, 155.16, 130.12, 129.95, 128.38, 127.97, 127.78, 123.64 (q, J = 278.4 Hz), 79.07, 63.92 (d, J = 38.1 Hz), 61.03, 60.93, 60.77, 60.56, 46.81, 46.56, 46.24, 45.68, 44.16, 43.55, 43.04, 42.49, 34.21, 33.85, 32.50, 32.37, 31.79, 31.69, 30.58, 30.19, 28.45, 28.41, 28.36, 24.94, 24.73, 24.13, 23.73.

^{19}F NMR (471 MHz, $CDCl_3$) δ -74.03, -74.09, -74.19.

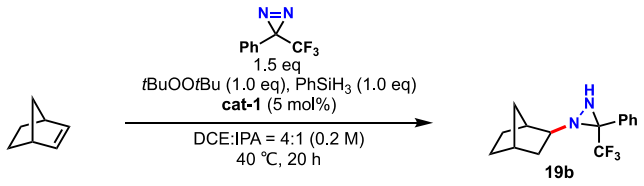
HRMS: Calculated for $C_{19}H_{27}F_3N_3O_2^+$ 386.2050. [M+H$^+$]; found 386.2058.



General procedure C was followed on a 0.270 mmol scale. Purification via column chromatography (silica gel, 5% to 10% ethyl acetate in hexanes) afforded **20a** (89.3 mg, 85% yield).

Characterization data matched with **19a**.

1-(Bicyclo[2.2.1]heptan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (19b)



General procedure A was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 5 – 10 % ethyl acetate in hexanes) afforded **19b** (41.3 mg, 73 % yield).

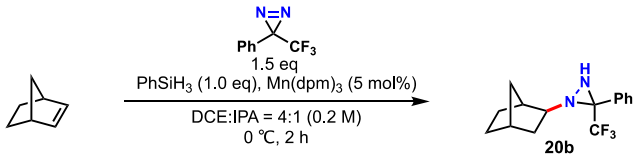
Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.5 (10 % ethyl acetate in hexanes, vis. iodine).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.51 (m, 2H), 7.53 – 7.33 (m, 3H), 3.09 – 2.79 (m, 1H), 2.31 – 2.03 (m, 2H), 1.89 – 1.74 (m, 1H), 1.60 (ddt, *J* = 12.6, 10.9, 3.4 Hz, 2H), 1.49 – 1.24 (m, 4H), 1.14 (dddd, *J* = 9.5, 4.0, 2.6, 1.4 Hz, 1H), 1.03 (ddd, *J* = 12.6, 7.5, 2.5 Hz, 1H, major isomer), 0.93 – 0.80 (m, 2H), 0.58 – 0.45 (m, 1H, minor isomer).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.29, 129.90, 129.88, 128.99, 128.96, 128.48, 128.33, 123.82 (q, *J* = 278.6 Hz), 123.78 (q, *J* = 278.6 Hz), 66.36, 65.02, 64.64 (d, *J* = 34.4 Hz), 63.41 (q, *J* = 34.5 Hz), 42.19, 41.17, 37.94, 36.58, 36.33, 36.03, 35.63, 35.58, 28.72, 28.57, 26.29.

^{19}F NMR (471 MHz, $CDCl_3$) δ -74.90, -75.03.

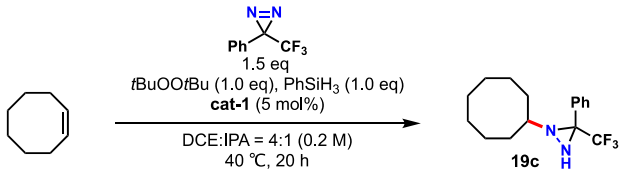
HRMS: *m/z* calculated for $C_{15}H_{19}F_3N_2^+$: 283.1417 [M+H$^+$]; found 282.1416.



General procedure C was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 5% to 10% ethyl acetate in hexanes) afforded **20b** (47.3 mg, 84% yield).

Characterization data matched with **5c**.

1-cyclooctyl-3-phenyl-3-(trifluoromethyl)diaziridine (19c)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 5% ethyl acetate in hexanes) afforded **19c** (24.5 mg, 82 % yield).

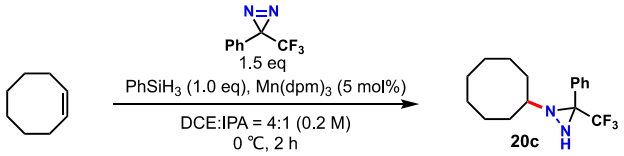
Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.6 (5 % ethyl acetate in hexanes, vis. iodine).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.54 – 7.37 (m, 3H), 2.94 (s, 1H), 1.89 – 1.73 (m, 1H), 1.68 (qd, *J* = 7.9, 3.2 Hz, 3H), 1.62 – 1.46 (m, 4H), 1.46 – 1.36 (m, 3H), 1.36 – 1.30 (m, 1H), 1.26 (ddt, *J* = 11.7, 8.5, 3.2 Hz, 1H), 1.17 (tdd, *J* = 14.2, 7.6, 3.9 Hz, 1H), 1.05 (dddd, *J* = 15.6, 13.3, 6.6, 2.9 Hz, 1H), 0.91 – 0.77 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.21, 129.98, 128.49, 128.34, 123.94 (q, *J* = 278.6 Hz), 63.88 (q, *J* = 34.1 Hz), 61.26, 33.10, 30.31, 27.03, 26.24, 26.10, 24.85, 23.69.

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.91.

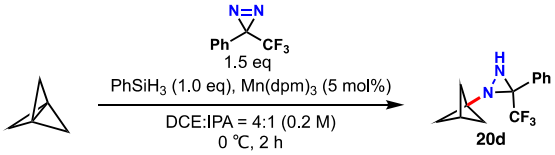
HRMS: *m/z* calculated for $C_{16}H_{23}F_3N_2^+$: 299.1730 [$M+H^+$]; found: 299.1726.



General procedure C was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 to 5% ethyl acetate in hexanes) afforded **20c** (27.6 mg, 93% yield).

Characterization data matched with **5f**.

1-(bicyclo[1.1.1]pentan-1-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (20d)



General procedure C was followed on a 0.200 mmol scale. [1.1.1]Propellane was added as a solution in ether/pentane. Purification via column chromatography (silica gel, 2% ethyl acetate in hexanes) afforded **20d** (35.8 mg, 72% yield).

Physical state: colorless oil. $\mathbf{R_f}$ = 0.7 (10% ethyl acetate in hexanes, vis. iodine).

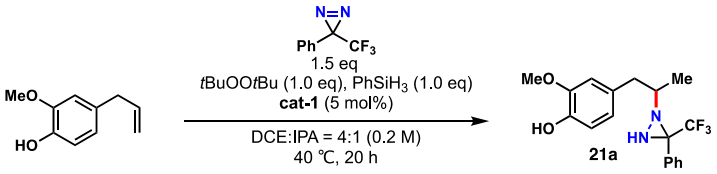
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.3 Hz, 2H), 7.49 – 7.36 (m, 3H), 3.11 – 2.85 (m, 1H), 2.16 (s, 1H), 1.60 (dd, *J* = 9.3, 1.8 Hz, 3H), 1.29 (dd, *J* = 9.3, 1.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.93, 130.14, 128.70, 127.94, 123.48 (d, *J* = 278.8 Hz), 63.44 (q, *J* = 34.5 Hz), 57.25, 51.18, 24.22.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.70.

HRMS: *m/z* calculated for $C_{13}H_{14}F_3N_2^+$: 255.1104 [$M+H^+$]; found: 255.1106.

2-methoxy-4-(2-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)propyl)phenol (21a)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 5 – 10% ethyl acetate in hexanes) afforded **21a** (21.9 mg, 62% yield).

Physical state: pale yellow oil. **R_f** = 0.3 (35% ethyl acetate in hexanes, vis. UV and iodine).

^{1}H NMR: Major isomer: (500 MHz, $CDCl_3$) δ 7.71 (ddd, *J* = 7.4, 5.1, 1.7 Hz, 2H), 7.55 – 7.35 (m, 3H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.26 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.96 (d, *J* = 1.9 Hz, 1H), 5.40 (s, 1H), 3.66 (s, 3H), 3.01 (d, *J* = 2.4 Hz, 1H), 2.66 (dd, *J* = 13.3, 3.7 Hz, 1H), 2.40 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.85 (dtt, *J* = 13.4, 6.6, 3.2 Hz, 1H), 1.05 (d, *J* = 6.2 Hz, 3H).

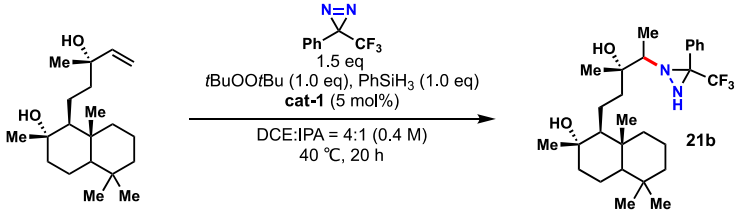
Minor isomer: (500 MHz, $CDCl_3$) δ 7.71 (ddd, *J* = 7.4, 5.1, 1.8 Hz, 2H), 7.55 – 7.35 (m, 3H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.59 – 6.49 (m, 2H), 5.43 (s, 1H), 3.82 (s, 3H), 3.01 (d, *J* = 2.4 Hz, 1H), 2.98 (dd, *J* = 13.3, 4.1 Hz, 1H), 2.56 (dd, *J* = 13.3, 9.4 Hz, 1H), 1.85 (tdd, *J* = 9.8, 6.5, 3.7 Hz, 1H), 0.83 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diasteromers) δ 146.13, 143.94, 130.55, 130.02, 129.93, 129.84, 128.30, 128.23, 127.98, 123.76 (d, *J* = 279.3 Hz), 122.19, 122.02, 114.04, 113.90, 111.99, 111.35, 63.75 (dd, *J* = 34.5, 19.4 Hz), 58.97, 58.77, 55.85, 55.73, 42.24, 40.20, 18.64, 16.61.

^{19}F NMR: (471 MHz, $CDCl_3$) major isomer: δ -73.57, minor isomer: δ -74.10.

HRMS: Calculated for $C_{18}H_{20}F_3N_2O_2^+$ 353.1471 [M+H$^+$]; found 353.1475.

(1R,2R,8R)-1-((3R)-3-hydroxy-3-methyl-4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)pentyl)-2,5,5,8-tetramethyldecahydronaphthalen-2-ol (21b)



General procedure A was followed on a 0.105 mmol scale on 0.4 M concentration. Purification via column chromatography (silica gel, 10 – 20% ethyl acetate in hexanes) afforded **21b** (37.5 mg, 72% yield).

Physical state: yellow oil. $\mathbf{R_f}$ = 0.4 (30% ethyl acetate in hexanes, vis. iodine and CAM).

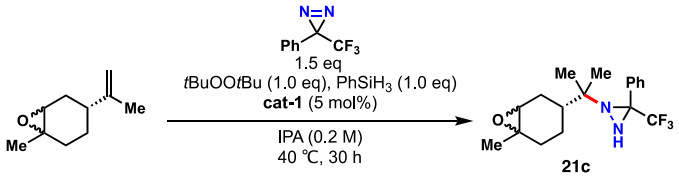
^{1}H NMR: (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.66 (ddd, *J* = 16.2, 7.6, 3.2 Hz, 2H), 7.55 – 7.34 (m, 3H), 3.21 – 2.64 (m, 2H), 1.96 – 1.71 (m, 3H), 1.71 – 1.29 (m, 10H), 1.29 – 1.18 (m, 4H), 1.18 – 1.00 (m, 7H), 1.00 – 0.91 (m, 2H), 0.91 – 0.80 (m, 7H), 0.80 – 0.71 (m, 6H).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diastereomers) δ 130.41, 130.39, 130.32, 130.06, 128.68, 128.65, 128.61, 128.57, 128.54, 128.47, 128.44, 127.35, 127.28, 123.81 (d, *J* = 278.8 Hz, three different sets), 76.38, 75.77, 74.99, 74.74, 74.59, 74.44, 64.04 (d, *J* = 34.1 Hz), 63.06, 62.45, 62.41, 62.31, 62.13, 61.71, 56.29, 56.24, 56.17, 44.22, 44.03, 43.31, 42.39, 42.16, 42.11, 41.00, 40.45, 39.81, 39.76, 39.68, 39.24, 39.22, 33.53, 33.50, 33.37, 33.35, 24.61, 24.35, 24.32, 23.49, 21.60, 21.50, 20.60, 20.52, 20.49, 18.60, 18.56, 18.39, 18.30, 17.86, 15.62, 15.52, 15.50, 14.23, 14.18, 13.60.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -73.43, -73.93, -74.02.

HRMS: Calculated for $C_{28}H_{44}F_3N_2O_2^+$ 497.3349. [$M+H^+$]; found 497.3355.

1-(2-(6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)propan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (21c)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 10% ethyl acetate in hexanes) afforded **21c** (17.6 mg, 52% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.3 (20% ethyl acetate in hexanes, iodine).

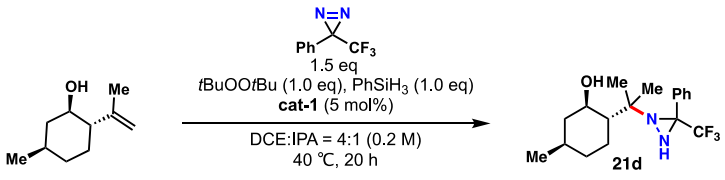
^{1}H NMR: (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.67 (dd, *J* = 13.7, 6.9 Hz, 2H), 7.49 – 7.31 (m, 3H), 3.06 – 2.93 (m, 1H), 2.80 – 2.63 (m, 1H), 2.15 – 1.83 (m, 2H), 1.66 (dtd, *J* = 17.2, 13.8, 11.2 Hz, 2H), 1.49 – 1.33 (m, 1H), 1.32 (t, *J* = 2.8 Hz, 3H), 1.30 – 1.09 (m, 2H), 0.85 – 0.38 (m, 6H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 131.37, 129.97, 129.63, 129.61, 128.60, 127.94, 123.85 (d, *J* = 279.5 Hz), 61.37, 61.26, 61.20, 59.56, 59.47, 57.71, 45.02, 44.24, 31.24, 31.15, 25.93, 25.45, 23.02, 22.99, 22.16, 21.57, 20.87, 20.31, 20.18, 19.91.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.48.

HRMS: Calculated for $C_{18}H_{24}F_3N_2O^+$ 341.1835 [M+H$^+$]; found 341.1834.

(1*R*,2*S*,5*R*)-5-Methyl-2-(2-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)propan-2-yl)cyclohexan-1-ol (21d)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 5 – 40% ethyl acetate in hexanes) afforded **21d** (24.0 mg, 70% yield).

Physical state: yellow oil. $\mathbf{R_f}$=0.5 (30% ethyl acetate in hexanes, vis. iodine and CAM).

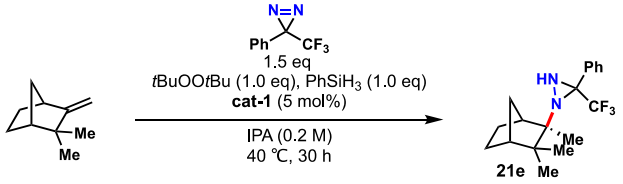
^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereomers) δ 7.61 – 7.48 (m, 2H), 7.33 – 7.24 (m, 3H), 5.41 (s, 1H), 3.59 (tdd, J = 10.3, 6.3, 4.2 Hz, 1H), 2.78 (s, 1H), 1.95 – 1.88 (m, 1H), 1.84 (dq, J = 12.6, 3.5 Hz, 1H), 1.55 – 1.21 (m, 5H), 1.14 – 1.00 (m, 4H), 1.00 – 0.84 (m, 2H), 0.84 – 0.65 (m, 6H), 0.23 – -0.02 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, mixture of diastereomers) δ 131.12, 131.04, 130.14, 129.98, 129.51, 129.37, 129.01, 128.95, 128.80, 128.20, 128.14, 123.26 (qd, J_{C-F} = 280.7, 57.9 Hz), 62.62 (qd, J_{C-F} = 34.5, 18.8z Hz), 77.24, 77.02, 76.81, 72.17, 72.04, 64.93, 64.83, 52.47, 51.78, 44.26, 44.03, 34.79, 34.73, 30.90, 25.94, 25.42, 23.66, 21.99, 21.11, 20.51, 19.19.

^{19}F NMR: (564 MHz, $CDCl_3$, mixture of diastereomers) δ -76.35, -76.39.

HRMS: *m/z* calculated for $C_{18}H_{26}F_3N_2O^+$ 343.1992 [M+H$^+$]; found 343.1988.

3-phenyl-3-(trifluoromethyl)-1-((1*S*,2*R*,4*R*)-2,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)diaziridine (21e)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 2% ethyl acetate in hexanes) afforded **21e** (24.1 mg, 75% yield).

Physical state: Colorless oil. **R$_f$** = 0.7 (10% ethyl acetate in hexanes, vis. iodine).

^{1}H NMR (major isomer): (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.44 – 7.33 (m, 3H, merged with minor isomer), 2.69 (s, 1H, merged with minor isomer), 2.43 (dtd, *J* = 9.8, 2.5, 1.3 Hz, 1H), 1.80 (dd, *J* = 4.4, 1.8 Hz, 1H), 1.72 – 1.67 (m, 1H), 1.28 – 1.10 (m, 7H, merged with minor isomer), 1.00 (dt, *J* = 9.7, 1.5 Hz, 1H), 0.80 (s, 3H), 0.49 (s, 3H).

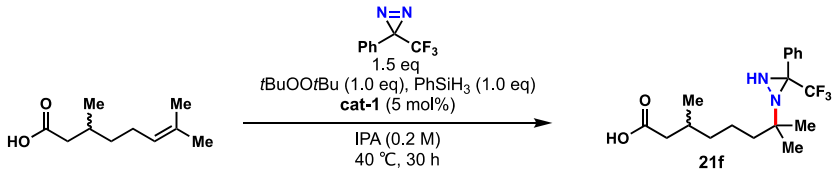
Minor isomer (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.43 – 7.33 (m, 3H, merged with major isomer), 2.67 (s, 1H, merged with major isomer), 2.59 – 2.53 (m, 1H), 2.16 (dd, *J* = 4.4, 1.7 Hz, 1H), 1.76 (dt, *J* = 2.8, 1.6 Hz, 1H), 1.30 – 1.09 (m, 8H, merged with major isomer), 0.82 (s, 3H), 0.20 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 130.80, 130.65, 129.59, 129.46, 128.39, 125.21, 122.98, 69.52, 69.07, 62.81, 60.83, 50.44, 50.39, 48.98, 48.79, 45.98, 45.12, 35.03, 34.73, 29.86, 26.78, 24.15, 23.86, 23.76, 23.54, 23.30, 23.21, 16.10, 13.84.

^{19}F NMR (471 MHz, $CDCl_3$) **major isomer:** δ -75.75. **Minor isomer:** δ -75.71

HRMS Calculated for $C_{18}H_{24}F_3N_2^+$ 325.1886 [M+H$^+$]; found 325.1892.

3,7-Dimethyl-7-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)octanoic acid (21f)



General procedure B was followed on a 0.200 mmol scale. Purification via column chromatography (silica gel, 0 – 5% MeOH in DCM) afforded **21f** (43.5 mg, 61% yield).

Physical state: yellow oil. **R_f** = 0.3 (10% ethyl acetate in hexanes, vis. iodine and CAM).

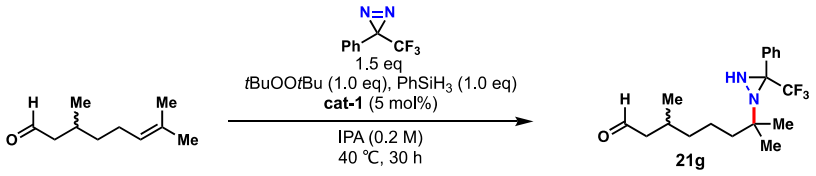
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.56 (m, 2H), 7.40 (ddt, *J* = 11.4, 7.9, 3.5 Hz, 3H), 2.75 (s, 1H), 2.36 (ddd, *J* = 15.1, 6.0, 1.4 Hz, 1H), 2.16 (ddd, *J* = 15.1, 8.2, 4.8 Hz, 1H), 1.97 (hept, *J* = 6.1 Hz, 1H), 1.52 – 1.27 (m, 6H), 1.20 (td, *J* = 8.2, 5.4 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 5.8 Hz, 3H), 0.65 (d, *J* = 4.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.44, 178.42, 131.25, 130.01, 129.99, 129.60, 129.35, 128.58, 127.91, 123.83 (d, J = 280.2 Hz), 61.81 (d, J = 36.3 Hz), 59.64, 42.87, 42.85, 41.39, 41.32, 37.25, 30.06, 30.05, 24.38, 24.32, 23.78, 21.18, 19.71, 19.66.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.66, -75.67.

HRMS: *m/z* calculated for $C_{18}H_{26}F_3N_2O_2^+$: 359.1941 [M+H$^+$]; found: 359.1944.

3,7-Dimethyl-7-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)octanal (21g)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 3 – 10% ethyl acetate in hexanes) afforded **21g** (24.3 mg, 71% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.4 (10% ethyl acetate in hexanes, vis. iodine and CAM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, J = 2.7 Hz, 1H), 7.80 – 7.59 (m, 2H), 7.40 (ddt, J = 11.6, 7.9, 3.5 Hz, 3H), 2.81 – 2.66 (m, 1H), 2.40 (ddd, J = 16.0, 5.7, 2.1 Hz, 1H), 2.29 – 2.19 (m, 1H),

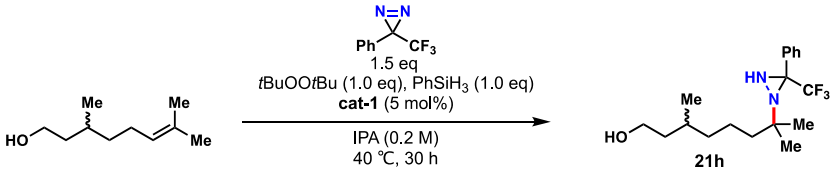
2.12 – 2.00 (m, 1H), 1.47 – 1.17 (m, 6H), 0.96 (d, J = 6.7 Hz, 3H), 0.75 (d, J = 3.8 Hz, 3H), 0.65 (d, J = 2.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.19, 131.38, 130.13, 130.11, 129.75, 129.45, 128.72, 128.04, 123.95 (q, J = 279.7 Hz), 61.92 (q, J = 34.1 Hz), 59.73, 51.24, 51.18, 43.02, 37.65, 28.19, 24.50, 24.46, 23.94, 21.38, 20.11, 20.06.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.68.

HRMS: *m/z* calculated for $C_{18}H_{26}F_3N_2O^+$: 343.1992 [$M+H^+$]; found: 343.1990.

3,7-Dimethyl-7-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)octan-1-ol (21h)



General procedure B was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 10% ethyl acetate in hexanes) afforded **21h** (24.6 mg, 72% yield).

Physical state: pale yellow oil. **R_f** = 0.3 (20% ethyl acetate in hexanes, vis. iodine and CAM).

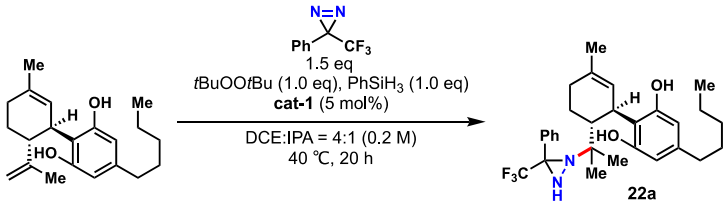
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.58 (m, 2H), 7.45 – 7.32 (m, 3H), 3.79 – 3.56 (m, 2H), 2.85 – 2.58 (m, 1H), 1.73 – 1.06 (m, 12H), 0.95 – 0.84 (m, 3H), 0.74 (d, *J* = 4.6 Hz, 3H), 0.66 (d, *J* = 2.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.39, 130.19, 130.18, 129.71, 129.49, 128.69, 128.02, 123.97 (q, *J* = 279.7 Hz), 61.94 (q, *J* = 33.8 Hz), 61.35, 59.84, 43.19, 43.17, 40.14, 40.06, 37.92, 29.53, 29.51, 24.56, 24.51, 23.87, 21.37, 19.75, 19.72.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.67, -75.68.

HRMS: Calculated for $C_{18}H_{28}F_3N_2O^+C_{18}H_{27}F_3N_2NaO$ 367.1968 [$M+Na^+$]; found 367.1972.

(1'*R*,2'*R*)-5'-methyl-4-pentyl-2'-(2-((1*R*)-3-phenyl-3-(trifluoromethyl)-1□^{4}-diaziridin-1-yl)propan-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol (22a)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 2 – 5% ethyl acetate in hexanes) afforded **22a** (28.6 mg, 57% yield, dr = 6:4).

Physical state: pale yellow foam. $\mathbf{R_f}$ = 0.5 (10% ethyl acetate in hexanes, vis. UV and iodine).

^{1}H NMR major isomer (500 MHz, $CDCl_3$) δ 7.71 (t, *J* = 9.1 Hz, 2H), 7.50 – 7.35 (m, 4H), 6.85 (s, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 5.84 (d, *J* = 4.7 Hz, 1H), 4.06 – 3.82 (m, 1H), 3.04 (s, 1H), 2.46 (dd, *J* = 8.8, 6.6 Hz, 2H), 2.12 – 2.02 (m, 1H), 1.98 (dd, *J* = 9.8, 3.4 Hz, 2H), 1.86 (d, *J* = 4.7 Hz, 1H), 1.81 (d, *J* = 2.1 Hz, 3H), 1.59 (d, *J* = 7.6 Hz, 2H), 1.31 (ddt, *J* = 10.1, 6.7, 5.0 Hz, 5H), 1.08 (s, 3H), 0.91 – 0.87 (m, 3H), 0.42 (s, 3H).

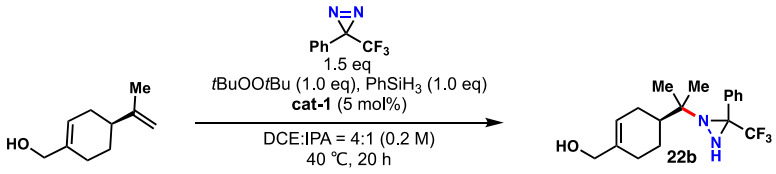
Minor isomer (500 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 2H), 7.50 – 7.31 (m, 4H), 6.42 (s, 1H), 6.29 (s, 1H), 5.80 (s, 1H), 5.52 – 5.37 (m, 1H), 4.10 (dq, *J* = 9.3, 2.7 Hz, 1H), 3.05 (s, 1H), 2.48 (td, *J* = 7.6, 4.0 Hz, 2H), 2.08 (qd, *J* = 4.7, 2.3 Hz, 4H), 1.76 (t, *J* = 1.8 Hz, 5H), 1.31 (dt, *J* = 7.6, 3.1 Hz, 4H), 0.95 – 0.83 (m, 8H), 0.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.37, 154.70, 143.77, 143.73, 140.79, 139.55, 131.50, 131.19, 130.30, 130.24, 130.19, 129.70, 129.55, 129.41, 129.35, 129.13, 129.00, 128.92, 128.90, 128.83, 128.23, 128.16, 128.07, 125.27, 124.00, 123.59 (d, *J* = 280.7 Hz), 116.16, 113.23, 110.04, 109.32, 108.83, 64.06, 63.27 (d, *J* = 34.1 Hz), 62.63, 60.69 (d, *J* = 35.0 Hz), 50.85, 48.41, 35.70, 35.64, 34.77, 33.77, 31.66, 30.96, 30.76, 27.97, 26.16, 24.91, 23.81, 23.69, 23.28, 22.69, 22.37, 22.00, 20.73, 14.19, 14.17.

^{19}F NMR (471 MHz, $CDCl_3$) Major isomer: δ -74.77. Minor isomer: δ -75.31.

HRMS: Calculated for $C_{29}H_{38}F_3N_2O_2^+$ 503.2880. [M+H$^+$]; found 503.2888.

((4*S*)-4-(2-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)propan-2-yl)cyclohex-1-en-1-yl)methanol (22b)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 10% ethyl acetate in hexanes) afforded **22b** (23.5 mg, 69% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.3 (20% ethyl acetate in hexanes, vis. UV and iodine).

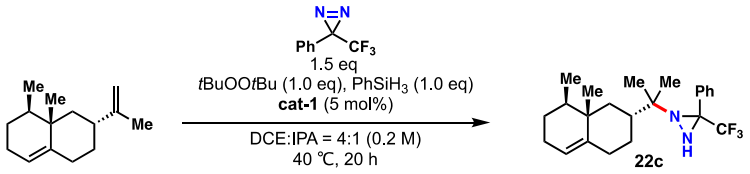
^{1}H NMR: (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.82 – 7.60 (m, 2H), 7.44 – 7.36 (m, 3H), 5.82 – 5.59 (m, 1H), 4.08 – 3.92 (m, 2H), 2.83 – 2.64 (m, 1H), 2.30 – 1.83 (m, 5H), 1.67 – 1.58 (m, 1H), 1.30 – 1.22 (m, 2H), 0.85 – 0.52 (m, 6H).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diastereomers) δ 137.54, 137.17, 131.35, 130.03, 129.60, 129.57, 128.56, 127.95, 123.14, 123.90 (d, J = 273.4 Hz), 122.64, 67.28, 67.22, 61.41 (d, J = 16.2 Hz), 45.71, 45.00, 26.77, 26.75, 26.62, 26.19, 23.91, 23.45, 22.26, 21.81, 21.28, 20.78.

^{19}F NMR (471 MHz, $CDCl_3$) major isomer: δ -75.54, minor isomer: δ -75.52.

HRMS: Calculated for $C_{18}H_{24}F_3N_2O^+$ 341.1835 [M+H$^+$]; found 341.1843.

1-(2-((2*R*,8*R*,8a*S*)-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)propan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (22c)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 2% ethyl acetate in hexanes) afforded **22c** (20.4 mg, 52% yield).

Physical state: pale yellow oil. $\mathbf{R_f}$ = 0.7 (10% ethyl acetate in hexanes, vis. iodine).

^{1}H NMR: (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.70 (td, *J* = 9.4, 4.1 Hz, 2H), 7.49 – 7.31 (m, 3H), 5.40 – 5.19 (m, 1H), 2.72 (d, *J* = 10.7 Hz, 1H), 2.35 – 1.79 (m, 5H), 1.78 – 1.63 (m, 2H), 1.49 – 1.24 (m, 4H), 1.21 (d, *J* = 6.0 Hz, 1H), 1.20 – 0.90 (m, 4H), 0.88 (s, 2H), 0.83 (dd, *J* = 11.5, 6.5 Hz, 2H), 0.79 – 0.49 (m, 6H).

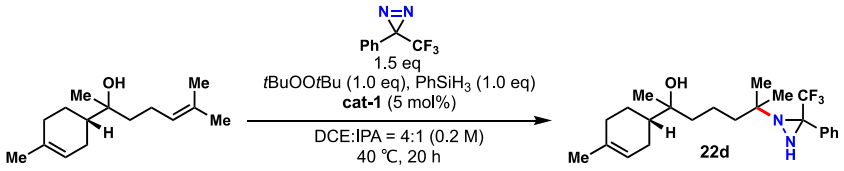
^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diastereomers) δ 144.87, 144.32, 143.60, 143.53, 134.92, 131.41, 130.11, 129.93, 129.57, 129.54, 129.50, 129.37, 128.51, 127.88, 127.76, 127.63, 123.91 (d, *J* = 279.7 Hz), 119.67, 119.17, 118.69, 65.40, 61.91, 61.80, 61.62, 61.43, 61.20 (d, *J* = 34.1 Hz), 44.22, 44.20, 44.15, 43.95, 43.53, 41.84, 41.51, 41.06, 41.03, 41.00, 40.69, 40.32, 39.92, 39.21, 38.72, 38.67, 38.52, 37.79, 37.73, 37.71, 32.81, 32.78, 32.54, 32.49, 31.16, 29.72, 29.32,

29.18, 28.70, 27.80, 27.57, 27.21, 27.19, 27.07, 25.90, 25.87, 25.51, 24.76, 22.23, 22.10, 22.06, 22.03, 21.82, 21.78, 21.54, 21.45, 21.20, 18.49, 18.05, 17.84, 15.81, 15.79, 15.77, 15.72.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.28, -75.39, -75.40, -75.49.

HRMS: Calculated for $C_{23}H_{32}F_3N_2^+$ 393.2512. [M+H$^+$]; found 393.2516.

6-methyl-2-((*S*)-4-methylcyclohex-3-en-1-yl)-6-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)heptan-2-ol (22d)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 5 – 10% ethyl acetate in hexanes) afforded **22d** (26.6 mg, 65% yield).

Physical state: pale yellow foam. **R_f** = 0.3 (20% ethyl acetate in hexanes, vis. iodine).

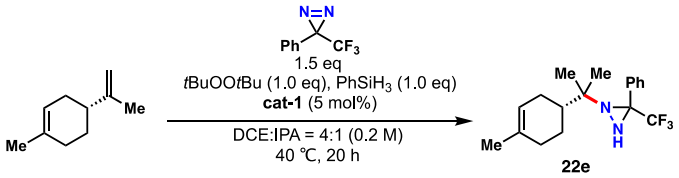
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 14.3, 8.2 Hz, 2H), 7.47 – 7.35 (m, 3H), 5.49 – 5.27 (m, 1H), 2.74 (s, 1H), 2.06 – 1.93 (m, 3H), 1.90 (ddt, *J* = 12.4, 5.2, 2.3 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.56 (tdt, *J* = 11.4, 4.7, 2.2 Hz, 2H), 1.50 – 1.34 (m, 6H), 1.34 – 1.20 (m, 2H), 1.17 – 1.12 (m, 1H), 1.11 (d, *J* = 2.9 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diastereomers) δ 134.18, 134.16, 133.93, 133.91, 131.26, 130.01, 130.00, 129.60, 129.34, 128.58, 127.91, 123.83 (d, J = 279.7 Hz), 120.56, 74.34, 74.33, 74.32, 61.81 (d, J = 34.1 Hz), 59.73, 43.56, 43.53, 43.51, 43.36, 43.10, 42.92, 42.85, 41.00, 40.96, 40.27, 40.12, 31.05, 31.01, 26.93, 26.88, 26.12, 26.08, 24.46, 24.43, 24.22, 24.20, 23.97, 23.92, 23.82, 23.80, 23.77, 23.48, 23.44, 23.38, 23.35, 23.32, 17.94, 17.91, 17.70, 17.65.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.64, -75.65.

HRMS: Calculated for $C_{23}H_{34}F_3N_2O^+$ 411.2618. [M+H$^+$]; found 411.2618.

1-(2-((*R*)-4-methylcyclohex-3-en-1-yl)propan-2-yl)-3-phenyl-3-(trifluoromethyl)diaziridine (22e)



General procedure A was followed on a 0.100 mmol scale. Purification via column chromatography (silica gel, 0 – 2% ethyl acetate in hexanes) afforded **22e** (27.0 mg, 83% yield).

Physical state: pale yellow oil. **R$_f$** = 0.2 (100% hexanes, vis. iodine).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.75 – 7.50 (m, 2H), 7.37 – 7.16 (m, 3H), 5.38 – 5.21 (m, 1H), 2.69 – 2.56 (m, 1H), 2.04 (ddt, J = 12.5, 5.3, 2.3 Hz, 1H), 1.99 – 1.64 (m, 4H), 1.55 (s, 3H), 1.52

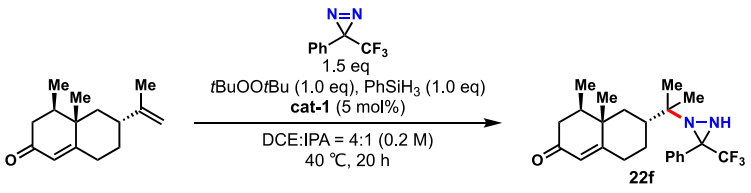
– 1.42 (m, 1H), 1.09-1.32 (m, 1H, mixture of diastereomers), 0.77 – 0.37 (m, 6H, mixture of diastereomers).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of diastereomers) δ 134.28, 133.83, 131.49, 130.26, 129.68, 129.65, 128.64, 128.06, 127.98, 124.05 (d, J = 279.8 Hz), 121.28, 120.92, 61.69, 61.56, 61.39 (d, J = 20.3 Hz), 61.12 (d, J = 20.0 Hz), 45.65, 44.93, 31.38, 31.34, 27.06, 26.60, 25.65, 24.44, 23.96, 23.54, 23.51, 22.33, 21.93, 21.48, 20.94.

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.51, -75.54.

HRMS: Calculated for $C_{18}H_{24}F_3N_2^+$ 325.1886 [M+H$^+$]; found 325.1892.

(4*R*,4a*S*,6*R*)-4,4a-dimethyl-6-(2-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)propan-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (22f)



General procedure A was followed on a 0.115 mmol scale. Purification via column chromatography (silica gel, 10% – 17% ethyl acetate in hexanes) afforded **22f** (19.4 mg, 42% yield).

Physical state: pale yellow oil. R_f = 0.3 (17% ethyl acetate in hexanes, vis. iodine).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.62 (m, 2H), 7.48 – 7.36 (m, 3H), 2.86 – 2.70 (m, 1H), 2.60 – 2.11 (m, 5H), 2.11 – 1.71 (m, 3H), 1.40 – 1.28 (m, 1H), 1.24 – 1.17 (m, 1H), 1.17 – 1.09 (m, 2H), 1.05 (s, 2H), 1.03 – 0.81 (m, 5H), 0.80 – 0.56 (m, 6H).

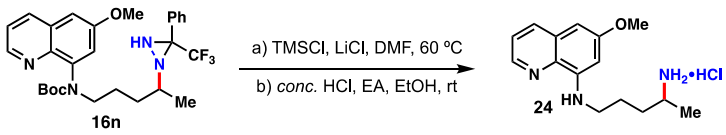
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.76, 199.66, 170.94, 131.42, 129.82, 129.76, 129.73, 129.40, 129.21, 128.71, 128.66, 127.97, 127.86, 127.80, 124.38, 124.36, 123.82 (d, J = 279.3 Hz), 113.93, 61.57, 61.47 (d, J = 34.1 Hz), 61.42, 61.11 (d, J = 34.1 Hz), 44.14, 43.42, 42.10, 40.55, 40.54, 39.82, 39.28, 39.22, 39.20, 33.14, 28.02, 27.44, 22.15, 21.94, 21.92, 21.23, 16.91, 16.87, 14.99.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.27, -75.44.

HRMS: Calculated for $C_{23}H_{30}F_3N_2O^+$ 407.2305. [M+H$^+$]; found 407.2309.

Applications:

Quinocide hydrochloride (24)



Followed our previously reported procedure.[33] To a septum capped vial equipped with a magnetic stir bar was added **16n** (24.6 mg, 0.046 mmol, 1 eq) and dimethylformamide (0.2 mL). Lithium chloride (5.9 mg, 0.138 mmol, 3 eq) and trimethylsilyl chloride (60.0 mg, 70.1 μL, 0.552 mmol, 12 eq) were added, then the vial was sealed and stirred at 60 ºC for 24 h. To the reaction mixture, 10% NaOH (20 mL) was added, and the mixture was extracted with dichloromethane (20 mL x 3), washed with water (50 mL), and brine (20 mL), dried with *anhyd.* Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (basic alumina, 5% MeOH in DCM to 20% MeOH in DCM) to afford the crude product. It was was dissolved in ethyl acetate (1 mL) and ethanol (1 mL). Conc. HCl (200 μL) was added, the reaction mixture stirred for 1 h and concentrated. The residue was washed with several drops of dichloromethane, which gave 11.0 mg (80%) of **24** as a brown solid.

The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[45]

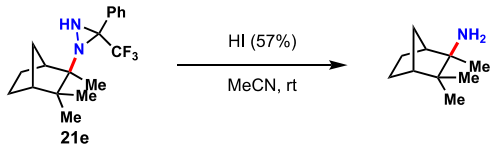
Physical state: brown solid. $\mathbf{R_f}$ = 0.3 (20% MeOH in DCM, vis. UV and PMA).

^{1}H NMR (500 MHz, DMSO) δ 8.66 – 8.56 (m, 1H), 8.35 – 8.17 (m, 1H), 7.87 (s, 3H), 7.62 – 7.44 (m, 1H), 6.59 (d, *J* = 9.0 Hz, 1H), 6.34 (d, *J* = 4.7 Hz, 1H), 3.84 (s, 3H), 3.26 (t, *J* = 6.5 Hz, 2H), 1.79 – 1.52 (m, 4H), 1.19 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, DMSO) δ 159.67, 143.65, 142.37, 138.52, 130.41, 122.21, 98.34, 92.90, 55.32, 46.64, 42.47, 31.87, 24.00, 18.24.

HRMS: Calculated for $C_{15}H_{22}N_3O^+$: 260.1757 [M+H$^+$]; found: 260.1752.

(1*S*,2*R*,4*R*)-2,3,3-trimethylbicyclo[2.2.1]heptan-2-amine



Followed our previously reported procedure.[33] To a 25 mL round bottom flask equipped with a magnetic stir bar was added **21e** (109 mg, 0.336 mmol, 1 eq) and acetonitrile (3 mL). The mixture was cooled with an ice bath, followed by slow addition of addition of hydroiodic acid (57%, 310 µL, 7 eq). Then the reaction mixture was stirred at room temperature for 1 h until TLC indicating disappearance of starting material. Sat. Na_2SO_3 (10 mL) and 1 M NaOH (5 mL) was added and stirred until the color of iodine disappeared. The mixture was then extracted with dichloromethane (20 mL x 3), washed with brine (20 mL), dried with *anhyd.* Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (basic alumina, 10% MeOH in DCM) to afford a white solid (42.2 mg, 82% yield).

The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[47]

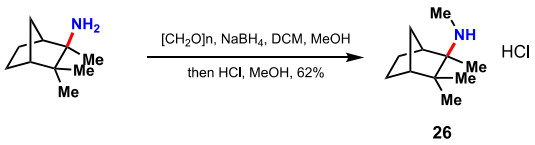
Physical state: white solid. **R$_f$** = 0.3 (20% MeOH in DCM, vis. PMA).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92 (dt, *J* = 10.4, 2.4 Hz, 1H), 1.83 – 1.78 (m, 1H), 1.71 (dd, *J* = 4.0, 1.8 Hz, 1H), 1.58 (ddt, *J* = 12.1, 9.0, 2.7 Hz, 1H), 1.51 (dddd, *J* = 11.1, 8.7, 4.4, 2.4 Hz, 1H), 1.40 – 1.31 (m, 1H), 1.31 – 1.16 (m, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 59.78, 52.49, 50.27, 42.89, 34.44, 26.30, 24.01, 23.55, 23.52, 23.16.

HRMS: Calculated for $C_{10}H_{20}N^+$: 154.1590 [M+H$^+$]; found 154.1588.

Mecamylamine HCl (26)



26

To a 10 mL round bottom flask equipped with a magnetic stir bar under argon was added (1*S*,2*R*,4*R*)-2,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (31.0 mg, 0.202 mmol, 1 eq) and anhydrous dichloromethane (2.5 mL). Paraformaldehyde (60.5 mg, 2.02 mmol, 10 eq) and activated 4 Å MS (70 mg) was added sequentially, followed by back-flush with argon and the reaction mixture stirred under reflux overnight until crude NMR indicated the disappearance of starting materials. The reaction mixture was then cooled to 0 ºC and anhydrous methanol (1 mL) was added, followed by sodium borohydride (38.0 mg, 0.950 mmol, 5 eq) portion-wise. The reaction was then stirred at room temperature overnight before acetone (~2 mL) was added to quench the reaction. The reaction mixture was concentrated *in vacuo* and the residue purified by

flash column chromatography (silica gel, ethyl acetate to 50% MeOH in ethyl acetate). To the obtained white solid was added methanol (5 mL), followed by *conc.* HCl (1 mL). The mixture was shaken for 5 min and concentrated *in vacuo*, offering mecamylamine HCl as a white solid (25.7 mg, 62% yield).

The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[47]

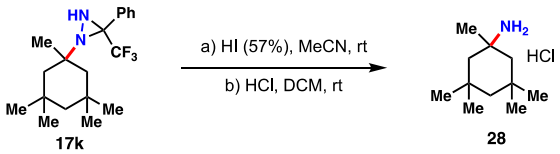
Physical state: white solid. **R_f** = 0.2 (50% MeOH in ethyl acetate, vis. PMA).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.14 (s, 1H), 2.65 (s, 3H), 2.39 (s, 2H), 1.91 – 1.82 (m, 1H), 1.60 (d, *J* = 4.3 Hz, 1H), 1.44 (d, *J* = 17.1 Hz, 5H), 1.36 – 1.20 (m, 5H), 1.02 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 70.21, 50.72, 45.19, 44.78, 35.31, 27.23, 23.72, 23.54, 23.08, 16.85.

HRMS: Calculated for $C_{11}H_{22}N^{+}$: 168.1747 [M+H^{+}]; found 168.1751.

Neramexane hydrochloride (**28**)



Followed our previously reported procedure.[33] (*29*) To a septum capped vial equipped with a magnetic stir bar was added **17k** (11.0 mg, 0.032 mmol, 1 eq) and acetonitrile (0.35 mL). The mixture cooled with an ice bath, followed by addition of hydroiodic acid (57%, 30 μL, 7 eq). Then the reaction mixture was stirred at room temperature for 1 h until TLC indicated disappearance of starting material. Sat. Na_2SO_3 (~10 mL) and 10% NaOH (~5 mL) were added, and the reaction stirred until the color of iodine disappeared. The mixture was then extracted with dichloromethane (20 mL x 3), washed with brine (20 mL), dried with *anhyd.* Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 10% MeOH in DCM to 20% MeOH in DCM) to afford the crude product. It was redissolved in dichloromethane (~1 mL), and HCl gas was bubbled for several minutes. The mixture was concentrated *in vacuo*, washed with several drops of dichloromethane, affording neramexane hydrochloride (3.8 mg, 57% yield) as a white solid.

The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[36]

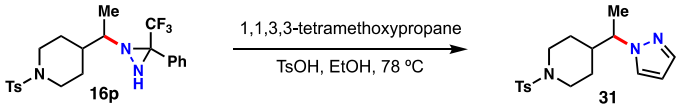
Physical state: white solid. $\mathbf{R_f}$ = 0.4 (20% MeOH in DCM, vis. PMA).

^{1}H NMR (500 MHz, DMSO) δ 8.00 (s, 3H), 1.62 – 1.53 (m, 2H), 1.46 – 1.37 (m, 5H), 1.34 – 1.27 (m, 1H), 1.01-1.07 (m, 7H), 0.93 (s, 6H).

^{13}C NMR (126 MHz, DMSO) δ 54.49, 49.94, 46.80, 35.54, 31.13, 28.94, 26.54.

HRMS: Calculated for $C_{11}H_{24}N^+$: 170.1903 [M+H$^+$]; found 170.1905.

4-(1-(1*H*-pyrazol-1-yl)ethyl)-1-tosylpiperidine (31)



Followed our previously reported procedure.[33] To a 10 mL round bottom flask equipped with a magnetic stir bar was added **16p** (199 mg, 0.439 mmol, 1 eq) and ethanol (4 mL). 1,1,3,3-Tetramethoxypropane (210 µL, 0.878 mmol, 2 eq) was added followed by *p*-toluenesulfonic acid monohydrate (417 mg, 2.20 mmol, 5 eq). The reaction mixture was stirred for 48 h at 78 ºC. To the reaction mixture, 10% NaOH (10 mL) was added, and the mixture extracted with ethyl acetate (10 mL x 3), washed with brine (20 mL), dried over *anhyd.* Na_2SO_4, concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in DCM to 5% ethyl acetate in DCM) affording the product (94.2 mg, 64% yield) as a white solid.

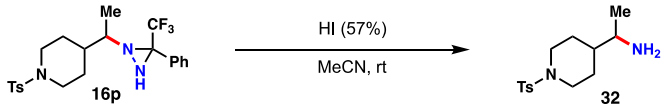
Physical state: white solid. $\mathbf{R_f}$ = 0.6 (10% ethyl acetate in DCM, vis. UV and I_2).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 2H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.34 – 7.27 (m, 3H), 6.19 (t, *J* = 2.1 Hz, 1H), 4.00 (dq, *J* = 8.4, 6.9 Hz, 1H), 3.83 (ddt, *J* = 11.6, 4.7, 2.5 Hz, 1H), 3.71 (ddt, *J* = 11.6, 4.6, 2.7 Hz, 1H), 2.42 (s, 3H), 2.19 (td, *J* = 12.1, 2.7 Hz, 1H), 2.11 (td, *J* = 11.9, 3.0 Hz, 1H), 1.84 – 1.65 (m, 3H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.38 (qd, *J* = 12.3, 4.3 Hz, 1H), 1.32 – 1.21 (m, 1H), 1.21 – 1.12 (m, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 143.65, 139.27, 132.96, 129.70, 128.31, 127.83, 104.86, 62.02, 46.29, 41.69, 28.39, 28.25, 21.63, 18.14.

HRMS: Calculated for $C_{17}H_{24}N_3O_2S^+$: 334.1584 [M+H$^+$]; found: 334.1578.

1-(1-tosylpiperidin-4-yl)ethan-1-amine (**32**)



Followed our previously reported procedure.[33] To a septum capped vial equipped with a magnetic stir bar was added **16p** (31.0 mg, 0.068 mmol, 1 eq) and acetonitrile (0.7 mL). The mixture was cooled with an ice bath, followed by the addition of hydroiodic acid (57%, 65 μL, 7 eq). The reaction mixture was stirred at room temperature for 1 h until TLC indicated the disappearance of starting material. Sat. Na_2SO_3 (~10 mL) and 10% NaOH (~5 mL) were added and stirred until the color of iodine disappeared. The mixture was then extracted with dichloromethane (20 mL x 3), washed with brine (20 mL), dried with *anhyd.* Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (basic alumina, 3% MeOH in DCM to 20% MeOH in DCM) to afford the product (14.8 mg, 77% yield) as a white solid.

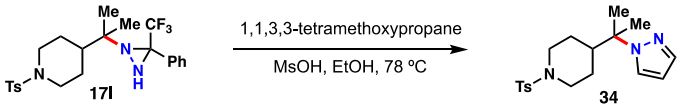
Physical state: white solid. **R_f** = 0.6 (20% MeOH in DCM, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.58 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.91 – 3.74 (m, 2H), 2.69 (t, *J* = 6.5 Hz, 1H), 2.43 (s, 3H), 2.28 – 2.12 (m, 2H), 1.87 – 1.66 (m, 2H), 1.42 – 1.14 (m, 5H), 1.01 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.53, 133.28, 129.70, 127.86, 50.74, 46.61, 46.57, 43.02, 29.83, 27.88, 27.80, 21.65, 20.92.

HRMS: Calculated for $C_{14}H_{23}N_2O_2S^+$: 283.1475 [M+H$^+$]; found: 283.1471.

4-(2-(1*H*-pyrazol-1-yl)propan-2-yl)-1-tosylpiperidine (34)



Followed our previously reported procedure.[33] To a septum capped vial equipped with a magnetic stir bar was added **17l** (39.7 mg, 0.085 mmol, 1 eq) and ethanol (1 mL). 1,1,3,3-Tetramethoxypropane (180 mg, 180 µL, 1.10 mmol, 12.9 eq) was added, followed by methanesulfonic acid (80 µL). The reaction mixture was stirred for 48 h at 78 ºC. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (silica, 20% ethyl acetate in hexane) affording the product (16.1 mg, 55% yield) as a white foam.

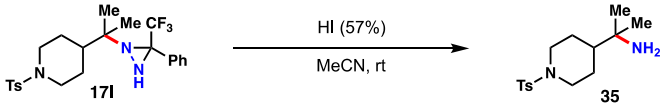
Physical state: white foam. **R_f** = 0.3 (30% ethyl acetate in hexanes, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.14 (d, *J* = 2.0 Hz, 1H), 3.79 – 3.68 (m, 2H), 2.38 (s, 3H), 2.07 (td, *J* = 11.9, 2.7 Hz, 2H), 1.85 (tt, *J* = 12.2, 3.4 Hz, 1H), 1.46 (s, 6H), 1.33 (qd, *J* = 12.5, 4.1 Hz, 2H), 1.26 – 1.16 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.54, 139.02, 132.66, 129.56, 127.74, 126.65, 104.35, 62.71, 46.68, 45.99, 26.12, 24.37, 21.51.

HRMS: Calculated for $C_{18}H_{26}N_3O_2S^+$: 348.1740 [$M+H^+$]; found 348.1744.

2-(1-tosylpiperidin-4-yl)propan-2-amine (35)



Followed our previously reported procedure.[33] To a septum capped vial equipped with a magnetic stir bar was added **17l** (39.6 mg, 0.085 mmol, 1 eq) and acetonitrile (1 mL). The mixture was cooled with an ice bath, followed by addition of hydroiodic acid (57%, 133 μL, 7 eq). Then the reaction mixture was stirred at room temperature for 1 h until TLC indicated disappearance of starting material. Sat. Na_2SO_3 (10 mL) and 10% NaOH (5 mL) were added and stirred until the color of iodine disappeared. The mixture was then extracted with dichloromethane (20 mL x 3), washed with brine (20 mL), dried with *anhyd.* Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (silica gel, 10% MeOH in DCM, with 1% NH_4OH) to afford the product (17.9 mg, 71% yield) as a white foam.

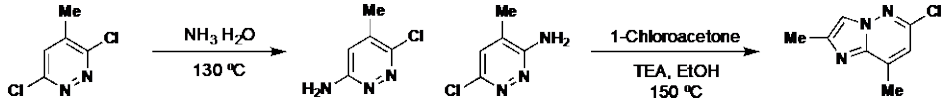
Physical state: white foam. $\mathbf{R_f}$ = 0.2 (10% MeOH in DCM plus 1% NH_4OH, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.52 (m, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 3.81 (dq, *J* = 11.6, 2.4 Hz, 2H), 2.37 (s, 3H), 2.11 (td, *J* = 12.0, 2.4 Hz, 2H), 1.77 – 1.67 (m, 2H), 1.37 (qd, *J* = 12.5, 4.3 Hz, 2H), 1.23 – 1.08 (m, 2H), 1.04 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.55, 132.99, 129.66, 127.75, 52.90, 46.56, 45.91, 26.53, 26.13, 21.53.

HRMS: Calculated for $C_{15}H_{24}N_2O_2S$+ 297.1637. [M+H$^+$]; found 297.1634.

6-chloro-2,8-dimethylimidazo[1,2-*b*]pyridazine



Followed a reported procedure.[100] To a 150 mL sealed tube equipped with a magnetic stir bar was added 3,6-dichloro-4-methylpyridazine (4.00 g, 36.8 mmol, 1 eq) and 25% aqueous ammonia (40 mL). The tube was sealed and stirred at 130 ºC for 24 h. The sealed tube was cooled to room temperature where a cloudy mixture formed. The precipitate was collected by filtration, washed thoroughly with water, and dried on vacuum to give a mixture of 6-chloro-5-methylpyridazin-3-amine and 6-chloro-4-methylpyridazin-3-amine (2.13 g, 61% yield in total, 1:0.85 by NMR) as white solid that was used without further purification.

The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[100]

Physical state: white solid. **R$_f$** = 0.6 (ethyl acetate, vis. UV).

^{1}H NMR: major isomer (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 0.9 Hz, 1H), 4.76 (d, *J* = 6.3 Hz, 2H), 2.17 (d, *J* = 1.2 Hz, 3H).

minor isomer (500 MHz, $CDCl_3$) δ 6.63 (q, *J* = 1.1 Hz, 1H), 4.68 (s, 2H), 2.30 (d, *J* = 1.2 Hz, 3H).

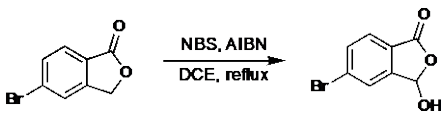
Followed a reported procedure.[101] To a 150 mL sealed tube equipped with a magnetic stir bar was added mixture of 6-chloro-5-methylpyridazin-3-amine and 6-chloro-4-methylpyridazin-3-amine (2.13 g, 13.1 mmol, 1 eq), 1-chloroacetone (2.42 g, 2.10 mL, 2 eq), triethylamine (3.97 g, 5.51 mL, 3 eq) and ethanol (24 mL). The reaction mixture was stirred in a sealed tube at 150 ºC overnight. The sealed tube was cooled to room temperature, the reaction concentrated *in vacuo* and the residue purified by flash column chromatography (silica, 50% ethyl acetate in hexanes to 80% ethyl acetate in hexanes) to give 6-chloro-2,8-dimethylimidazo[1,2-*b*]pyridazine (607 mg, 49% yield based on 6-chloro-4-methylpyridazin-3-amine) as a white solid.

The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[101]

Physical state: white solid. $\mathbf{R_f}$ = 0.7 (ethyl acetate, vis. UV).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 0.9 Hz, 1H), 6.84 (q, *J* = 1.1 Hz, 1H), 2.63 (d, *J* = 1.1 Hz, 3H), 2.49 (d, *J* = 0.9 Hz, 3H).

5-bromo-3-hydroxyisobenzofuran-1(3*H*)-one



Followed a reported procedure.[102] To a 100 mL round bottom flask equipped with a magnetic stir bar under argon was added 5-bromophthalide (2.00 g, 9.4 mmol, 1 eq) and dichloroethane (45 mL). *N*-Bromosuccinimide (1.84 g, 10.3 mmol, 1.1 eq) was added, followed by AIBN (77.2 mg, 0.47 mmol, 0.05 eq). Argon was back-flushed, and the reaction mixture stirred under reflux for 2 h. The reaction mixture was cooled to -20 ºC overnight, the white precipitate removed by filtration, and the filtrate was concentrated *in vacuo*. Water (20 mL) was added, and the suspension stirred under reflux for 2 h, followed by cooling to 4 ºC overnight. The white precipitate was collected by filtration, washed with cold water (5 mL x 2) and dried *in vacuo* overnight affording a white solid (1.86 g, 83% yield).

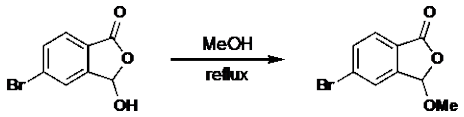
The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[102]

Physical state: white solid.

^{1}H NMR: lactone form (500 MHz, DMSO) δ 8.29 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.86 (dd, J = 8.1, 1.7 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 7.3 Hz, 1H).

aldehyde form (500 MHz, DMSO) δ 10.43 (s, 1H), 7.96 (d, J = 1.1 Hz, 1H), 7.88 (s, 1H), 7.78 (d, J = 1.2 Hz, 1H), 5.40 (d, J = 0.9 Hz, 1H).

5-bromo-3-methoxyisobenzofuran-1(3*H*)-one



To a 10 mL round bottom flask equipped with a magnetic stir bar was added 5-bromo-3-hydroxyisobenzofuran-1(3*H*)-one (700 mg, 3.06 mmol, 1 eq) and methanol (5 mL). The reaction mixture was stirred under reflux overnight, then concentrated *in vacuo.* To the residue was added hexane (10 mL). The mixture was stirred overnight and the solid collected by filtration to afford a white solid (613 mg, 83% yield) that was used without further purification.

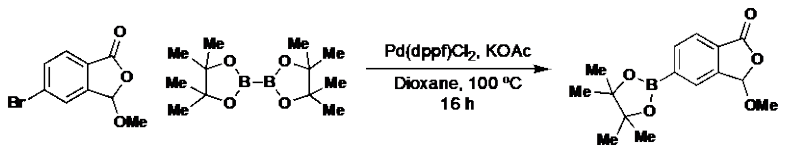
Physical state: white solid. $\mathbf{R_f}$ = 0.6 (25% ethyl acetate in hexane, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 3H), 6.26 (s, 1H), 3.65 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.74, 146.54, 134.63, 129.79, 127.17, 126.93, 126.29, 102.48, 57.29.

HRMS: Calculated for $C_9H_7BrNaO_3^+$: 264.9471 [M+Na^+]; found: 264.9473.

3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isobenzofuran-1(3*H*)-one



To a 50 mL round bottom flask equipped with a magnetic stir bar under argon was added 5-bromo-3-methoxyisobenzofuran-1(3*H*)-one (360 mg, 1.48 mmol, 1 eq) and dioxane (15 mL). Bis(pinacolato)diboron (451 mg, 1.78 mmol, 1.2 eq) and potassium acetate (450 mg, 4.58 mmol, 3 eq) were added and the mixture degassed with argon for 10 minutes, followed by addition of $Pd(dppf)Cl_2$ (100 mg, 0.148 mmol, 10 mol%). The reaction mixture was back-flushed with argon and stirred for 16 h at 100 ºC until TLC indicated total conversion of starting materials. The reaction mixture was concentrated *in vacuo*, and the residue purified by flash column chromatography (silica, 10% ethyl acetate in hexanes) to afford a white solid (246 mg, 57% yield).

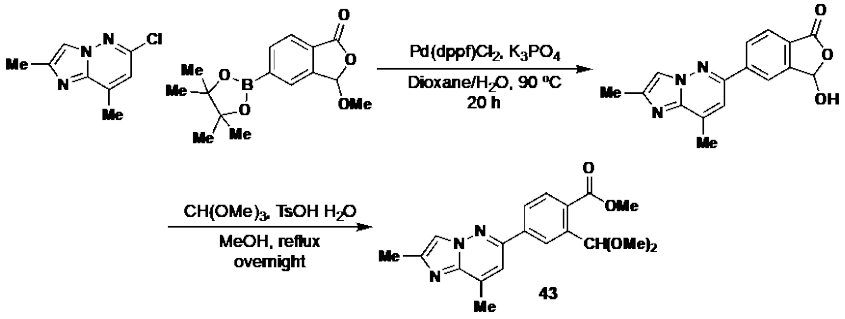
Physical state: white solid. $\mathbf{R_f}$ = 0.5 (25% ethyl acetate in hexane, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.85 (d, *J* = 7.8 Hz, 1H), 6.29 (s, 1H), 3.61 (s, 3H), 1.35 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.77, 143.91, 137.11, 129.70, 129.44, 124.58, 103.52, 84.69, 83.61, 56.93, 25.02, 24.96.

HRMS: Calculated for $C_{15}H_{20}BO_5^+$: 291.1398 [M+H$^+$]; found: 291.1389.

Methyl 2-(dimethoxymethyl)-4-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)benzoate (43)



To a 25 mL round bottom flask equipped with a magnetic stir bar under argon was added 6-chloro-2,8-dimethylimidazo[1,2-*b*]pyridazine (200 mg, 1.10 mmol, 1 eq), dioxane (8 mL) and water (1.6 mL). 3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isobenzofuran-1(3*H*)-one (479 mg, 1.65 mmol, 1.5 eq) was added, followed by potassium phosphate tribasic (704 mg, 3.32 mmol, 3 eq). The reaction mixture was degassed with argon for 10 minutes, followed by addition of $Pd(dppf)Cl_2$ (81.0 mg, 0.111 mmol, 10 mol%). The reaction mixture was back-flushed with argon and stirred overnight at 90 ºC until TLC indicated total conversion of starting materials. The reaction mixture was passed through celite, washed with methanol and concentrated *in vacuo.* To the residue, methanol (10 mL) was added, followed by trimethyl orthoformate (1.16 g, 1.21 mL, 11.0 mmol, 10 eq) and *p*-toluenesulfonic acid monohydrate (1.05 g, 5.50 mmol, 5 eq) and stirred under reflux overnight. The reaction mixture was poured into a separatory funnel, 10% NaOH (50 mL) was added and extracted with ethyl acetate (30 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 80% ethyl acetate in hexanes) to afford a white solid (243 mg, 62% yield over two steps).

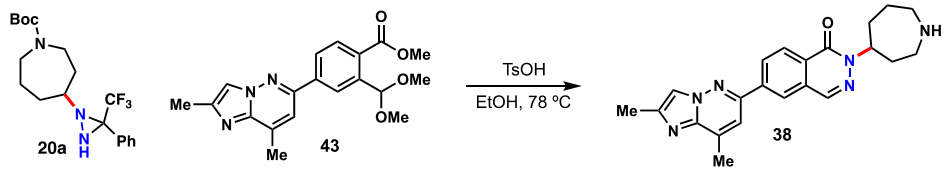
Physical state: white solid. $\mathbf{R_f}$ = 0.4 (ethyl acetate, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.0 Hz, 1H), 8.00 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 0.9 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 6.15 (s, 1H), 3.95 (s, 3H), 3.43 (s, 6H), 2.72 (d, *J* = 1.1 Hz, 3H), 2.54 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.78, 149.86, 143.53, 139.64, 139.21, 138.99, 135.96, 130.77, 130.65, 126.64, 125.49, 115.03, 114.70, 100.62, 54.22, 52.40, 16.89, 14.85.

HRMS: Calculated for $C_{19}H_{22}N_3O_4^+$: 356.1605 [M+H$^+$]; found: 356.1607.

2-(azepan-4-yl)-6-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)phthalazin-1(2*H*)-one (38)



To a 10 mL round bottom flask equipped with a magnetic stir bar under argon was added *tert*-butyl 4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)azepane-1-carboxylate (86.0 mg, 0.223 mmol, 1 eq) and ethanol (3 mL). Methyl 2-(dimethoxymethyl)-4-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)benzoate (87.2 mg, 0.245 mmol, 1.1 eq) and *p*-toluenesulfonic acid monohydrate (255 mg, 1.32 mmol, 6 eq) were added and the reaction mixture stirred at 78 ºC for 24 h, until LC-MS indicated the disappearance of starting materials. The reaction mixture was poured into separatory funnel, 10% NaOH (50 mL) was added, extracted with ethyl acetate (30 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash

column chromatography (basic alumina, 5% MeOH in DCM to 10% MeOH in DCM) to afford **38** as a pale yellow solid (55.8 mg, 64% yield).

The ^{1}H NMR spectrum matched with previously reported ^{1}H NMR.[50]

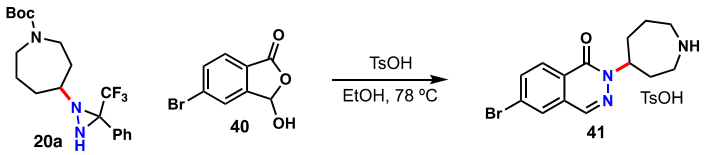
Physical state: pale yellow solid. $\mathbf{R_f}$ = 0.4 (20% MeOH in DCM, vis. UV).

^{1}H NMR (500 MHz, DMSO) δ 8.53 (s, 2H), 8.46 – 8.27 (m, 2H), 8.06 (s, 1H), 7.72 (s, 1H), 5.32 – 4.97 (m, 1H), 2.90 (dt, *J* = 10.7, 5.7 Hz, 2H), 2.86 – 2.66 (m, 2H), 2.60 (s, 3H), 2.40 (s, 3H), 2.14 – 1.90 (m, 3H), 1.91 – 1.71 (m, 2H), 1.60 (dt, *J* = 10.4, 5.4 Hz, 1H).

^{13}C NMR (126 MHz, DMSO) δ 157.17, 148.45, 143.39, 139.64, 138.49, 137.75, 136.06, 129.52, 129.33, 127.29, 126.79, 124.76, 114.64, 114.59, 56.44, 48.74, 45.31, 36.03, 32.53, 27.51, 16.28, 14.62.

HRMS: Calculated for $C_{22}H_{25}N_6O^+$: 389.2084 [M+H$^+$]; found: 389.2090.

2-(azepan-4-yl)-6-bromophthalazin-1(2*H*)-one 4-methylbenzenesulfonate (41)



To a 5 mL round bottom flask equipped with a magnetic stir bar was added *tert*-butyl 4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl)azepane-1-carboxylate (34.0 mg, 0.088 mmol, 1 eq) and ethanol (0.75 mL). 5-Bromo-3-hydroxyisobenzofuran-1(3*H*)-one (22.2 mg, 0.097 mmol, 1.1 eq) and *p*-toluenesulfonic acid monohydrate (33.6 mg, 0.176 mmol, 2 eq) were added and the reaction mixture stirred at 78 ºC for 24 h, until LC-MS indicated the disappearance of starting materials. Around half of the ethanol was concentrated *in vacuo* and the mixture kept at -20 ºC overnight. The solid that formed was collected by filtration and dried *in vacuo*, affording **41** (38.7 mg, 89% yield) as a white solid.

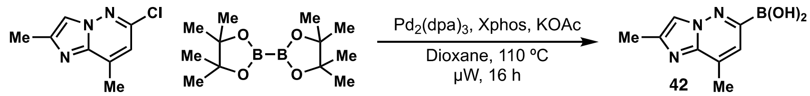
Physical state: white solid.

^{1}H NMR (500 MHz, DMSO) δ 8.58 (s, 2H), 8.46 (s, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.03 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.16 – 7.04 (m, 2H), 5.19 (tt, *J* = 9.6, 5.0 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.29 – 3.18 (m, 2H), 3.14 (s, 1H), 2.28 (s, 3H), 2.27 – 2.19 (m, 1H), 2.17 – 2.08 (m, 1H), 2.08 – 1.93 (m, 3H), 1.92 – 1.76 (m, 1H).

^{13}C NMR (126 MHz, DMSO) δ 157.69, 146.28, 138.02, 137.44, 135.50, 130.94, 129.66, 128.90, 128.51, 127.77, 126.35, 125.97, 55.43, 46.20, 42.33, 31.82, 30.09, 21.72, 21.25.

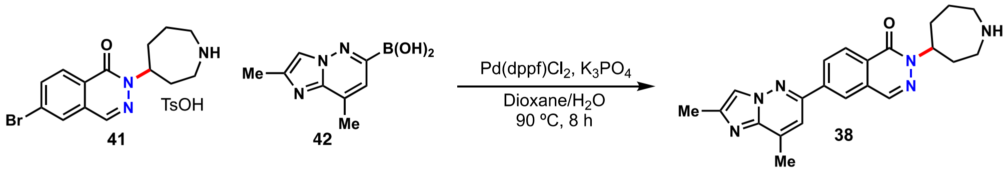
HRMS: Calculated for $C_{14}H_{17}BrN_3O^+$: 322.0550 [M+H$^+$]; found: 322.0557.

(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)boronic acid (42)



To a septum capped microwave reaction vial equipped with a magnetic stir bar under argon was added 6-chloro-2,8-dimethylimidazo[1,2-*b*]pyridazine (80.0 mg, 0.440 mmol, 1 eq), bis(pinacolato)diboron (168 mg, 0.661 mmol, 1.5 eq), dioxane (3 mL), potassium acetate (130 mg, 1.32 mmol, 3 eq) and Xphos (68.2 mg, 0.143 mmol, 0.3 eq) sequentially. The mixture was degassed with argon for 10 minutes, then $Pd_2(dpa)_3$ (68.4 mg, 0.065 mmol, 0.15 eq) was added, the reaction vial filled with argon, and stirred in a microwave reactor for 16 h at 110 ºC. The reaction vial cooled to room temperature, passed through celite, washed with ethyl acetate and concentrated *in vacuo*. The residue was used directly without further purification.

2-(azepan-4-yl)-6-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)phthalazin-1(2*H*)-one (38)



To a 25 mL round bottom flask equipped with a magnetic stir bar under argon was added 2-(azepan-4-yl)-6-bromophthalazin-1(2*H*)-one 4-methylbenzenesulfonate (**38**) (18.6 mg, 0.038 mmol, 1 eq), dioxane (1 mL) and water (0.2 mL). (2,8-Dimethylimidazo[1,2-*b*]pyridazin-6-yl)boronic acid (10.7 mg, 0.056 mmol, 1.5 eq) was added, followed by potassium phosphate tribasic (32.3 mg, 0.152 mmol, 4 eq). The reaction mixture was degassed with argon for 10 minutes, followed by addition of $Pd(dppf)Cl_2$ (2.8 mg, 0.004 mmol, 10 mol%). The reaction

mixture was back-flushed with argon and stirred for 8 h at 90 ºC, until TLC indicated total conversion of starting materials. The reaction mixture was poured into a separatory funnel, 10% NaOH (10 mL) was added. The mixture was extracted with ethyl acetate (10 mL x 3), washed with brine (20 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (basic alumina, 5% MeOH in DCM to 10% MeOH in DCM) to afford the product (11.3 mg, 77% yield) as a pale yellow solid.

Physical state: pale yellow solid. $\mathbf{R_f}$ = 0.4 (20% MeOH in DCM, vis. UV).

Characterization data matched with **38**.

Synthesis of ^{15}N Diazirine:

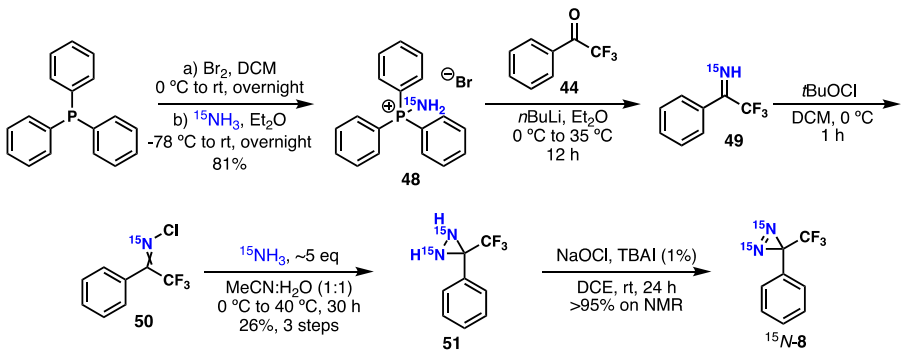
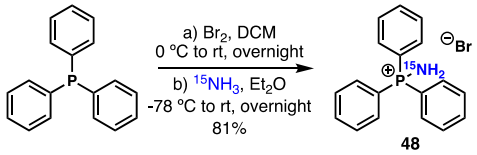


Figure S9: Synthetic route towards ^{15}N Diazirine (^{15}N-**8**).

(Amino-^{15}N)triphenylphosphonium bromide (48)



To a flame-dried 50 mL sealed tube fitted with a rubber stopper was added triphenylphosphine (2.00 g, 7.62 mmol, 1 eq) and anhydrous dichloromethane (10 mL). The tube was back-flushed with argon, cooled to 0 ºC, and bromine (1.24 g, 0.40 mL, 7.77 mmol, 1.02 eq) was added via syringe with stirring. The formation of a precipitate was observed during the addition. The mixture was warmed to room temperature after addition and stirred overnight.

Dichloromethane was removed under vacuum. Anhydrous ether (15 mL) was added via syringe and the reaction mixture was sonicated until it became a suspension. The mixture was cooled to -78 ºC and ^{15}N-ammonia (~1 g) was bubbled into the mixture with a long needle placed at the bottom of the sealed tube (no stirring) (Figure **S13**). After bubbling, the tube was sealed with a cap (wrapped with parafilm and further taped on the outside) and stirred at room temperature overnight.

(Note: the volume of ammonia gas was estimated with an oil bubbler, which was calibrated with unlabeled ammonia with a similar tank. By bubbling the unlabeled ammonia gas through the bubbler and counting the bubbles per minute (adjusted to be 1 bubble per second); the rate was kept constant for an hour and the tank was weighed before and after to estimate consumption. This

experiment was repeated several times to establish precision and used to adjust the rate when bubbling the labeled ammonia in order to control the volume of gas in the system with a timer.)

Figure S10: Bubbling $^{15}NH_3$ gas into the PPh_3Br_2 suspension with oil bubbler as a flowmeter.

(Note: color change from orange to white observed after reaction completion.)

The reaction mixture was cooled to -78 ºC, opened, and warmed up to room temperature slowly. Ether was then removed under vacuum and chloroform (10 mL) added. The resulting mixture was stirred for an hour, filtered, and the cake washed with chloroform (5 mL). To the filtrate, ether (100 ml) was added with stirring and the formed solid was collected with vacuum filtration, washed with ether (10 mL), affording **48** (2.29 g, 81% yield) as a white solid.

Physical state: White solid. **Melting point:** 241.2 ºC – 241.6 ºC.

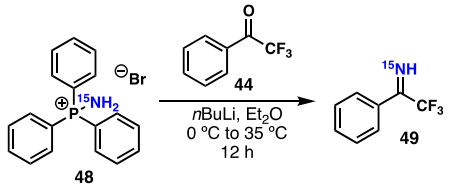
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.95 – 7.78 (m, 6H), 7.68 (dddd, *J* = 8.8, 7.1, 2.9, 1.3 Hz, 3H), 7.61 – 7.52 (m, 6H), 6.87 (d, *J* = 3.5 Hz, 1H), 6.73 (d, *J* = 3.5 Hz, 1H).

^{13}C NMR: (151 MHz, $CDCl_3$) δ 134.40 (d, *J* = 2.7 Hz), 133.52 (d, *J* = 11.4 Hz), 129.66 (d, *J* = 13.6 Hz), 123.54 (d, *J* = 104.1 Hz).

^{31}P NMR: (243 MHz, $CDCl_3$) δ 36.00.

HRMS: Calculated for $C_{18}H_{17}{}^{15}NP^+$ 279.1063; found 279.1070.

2,2,2-trifluoro-1-phenylethan-1-imine-^{15}N

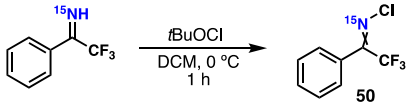


To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar under argon was added **48** (2.23 g, 6.21 mmol, 1.1 eq) and anhydrous ether (15 mL). Freshly titrated *n*BuLi (1.7 M, 3.8 mL, 6.49 mmol, 1.15 eq) was added at 0 ºC dropwise. An orange color developed after addition. The reaction mixture was stirred at room temperature for 15 min, followed by addition of 2,2,2-trifluoro-1-phenylethan-1-one (983 mg, 5.64 mmol, 1 eq) in one portion and stirred at 35 ºC overnight. Ether was removed under vacuum with a needle and the residue fitted with a micro

distillation system and distilled with an oil pump. The colorless oil was collected and quickly sealed under an argon atmosphere and used without further purification.

(Note: the product is not very stable to air; slow decomposition is observed when exposed; storage in sealed vial is recommended)

_N_-chloro-2,2,2-trifluoro-1-phenylethan-1-imine-^{15}N (50)



To a 50 mL flame-dried flask equipped with magnetic stir bar under argon was added imine from last step (983 mg, theoretical yield from last step) and dichloromethane (10 mL) and the flask back-flushed with argon. To the resulting mixture, freshly prepared *t*BuOCl (674 mg, 703 μL, 6.21 mmol, 1.1 eq) in dichloromethane (10 mL) was added dropwise at 0 ºC and the reaction mixture stirred at 0 ºC for 1 h, until crude ^{19}F NMR indicated total conversion of the starting material. The reaction mixture was concentrated *in vacuo* and passed through a short column (silica gel, 3% ethyl acetate in hexanes) yielding **50** (1.20 g, crude weight, the compound is volatile and unstable), which was used directly in the next step without further purification.

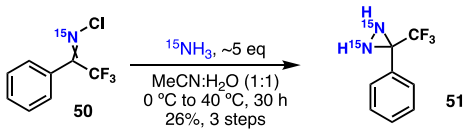
Physical state: colorless oil. $\mathbf{R_f}$ = 0.6 (10% ethyl acetate in hexanes, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$, crude) δ 7.70 – 7.52 (m, 3H), 7.53 – 7.37 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$, crude) δ 131.36, 128.89, 128.64, 127.29.

^{19}F NMR: (471 MHz, $CDCl_3$, crude) δ -63.55 (d, J = 3.5 Hz), -68.01 (d, J = 5.2 Hz).

3-phenyl-3-(trifluoromethyl)diaziridine-1,2-$^{15}N_2$ (51)



To a 10 mL flame-dried sealed tube equipped with a stir bar and rubber stopper was added **51** (1.20 g, crude), acetonitrile (1 mL) and water (1 mL). ^{15}N-ammonia gas (~0.5 g) was bubbled into the reaction mixture via a long needle at 0 ºC. The tube was then quickly sealed and stirred at 40 ºC for 30 h.

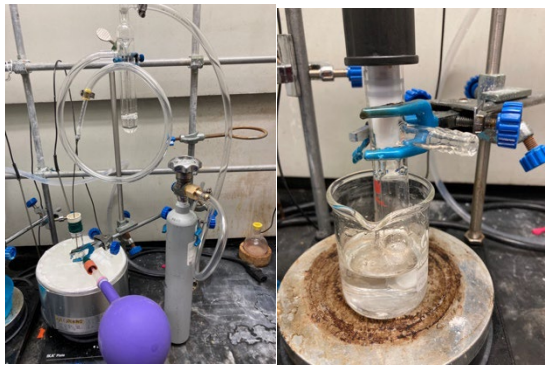


Figure S11: Synthesis of Diaziridine **51**. **Left:** Bubbling $^{15}NH_3$ gas into a solution of **50** in ether with an oil bubbler as a flowmeter; **Right:** The lid was fully sealed after required amount of $^{15}NH_3$ was bubbled into solution and heated with an oil bath.

The reaction mixture was poured into water (10 mL) and extracted with ether (15 mL x 3), washed with brine, dried over *anhydrous* Na_2SO_4, and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica gel, 3 –10 % ethyl acetate in hexanes) yielding **51** (252 mg, 26% yield over 3 steps).

Physical state: white solid. $\mathbf{R_f}$ = 0.2 (10% ethyl acetate in hexanes, UV).

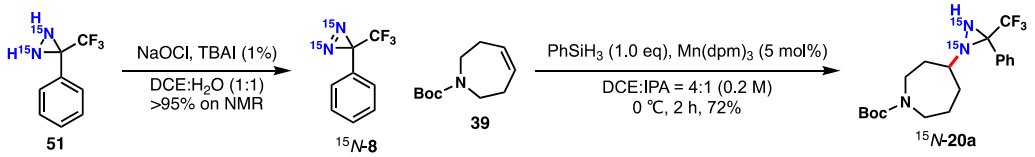
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 2.0 Hz, 2H), 7.52 – 7.40 (m, 3H), 3.01 – 2.67 (m, 1H), 2.41 – 2.13 (m, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 131.74, 131.71, 130.17, 128.77, 128.14, 123.54 (d, *J* = 272.9 Hz), 58.04 (d, *J* = 35.9 Hz).

^{19}F NMR: (471 MHz, $CDCl_3$) δ -75.58.

HRMS: Calculated for $C_8H_7F_3{}^{15}N_2$, 191.0580 [M+H$^+$]; found 191.0591.

***tert*-butyl (4*S*)-4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl-1,2-$^{15}N_2$)azepane-1-carboxylate (^{15}N-20a)**



To a septum capped vial equipped with a magnetic stir bar was added 3-phenyl-3-(trifluoromethyl)diaziridine-1,2-$^{15}N_2$ (**51**) (30.0 mg, 0.157 mmol, 1.6 eq) and dichloroethane (0.5 mL). Tetrabutylammonium iodide (0.4 mg, 1 mol%) was added, followed by bleach (200 µL) at 0 ºC. The reaction mixture was stirred at room temperature overnight. On the second day, another portion of bleach (100 µL) was added, and the reaction mixture stirred for another 12 h at room temperature, until ^{19}F NMR indicated total conversion of starting materials. The organic layer was washed with water (100 µL), then *sat.* Na_2SO_3 (100 µL) and brine (100 µL), and dried over a short pipette of *anhyd.* Na_2SO_4 into a flame-dried reaction vial. To the septum capped vial containing the reaction mixture above was added freshly dried isopropyl alcohol (100 µL), *tert*-butyl-2,3,6,7-tetrahydro-1*H*-azepine-1-carboxylate (**39**) (19.7 mg, 0.100 mmol, 1 eq), and $Mn(dpm)_3$ (3.0 mg, 5 mol%). The vial was back-flushed with argon, cooled to 0 ºC and $PhSiH_3$ (12.3 µL, 1 eq) was added with syringe and stirred at that temperature for 2 h. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, 10% ethyl acetate in hexanes) to afford product ^{15}N-**20a** (28.0 mg, 72% yield) as a pale-yellow oil.

Physical state: pale yellow foam. $\mathbf{R_f}$ = 0.3 (10% ethyl acetate in hexanes, vis. iodine).

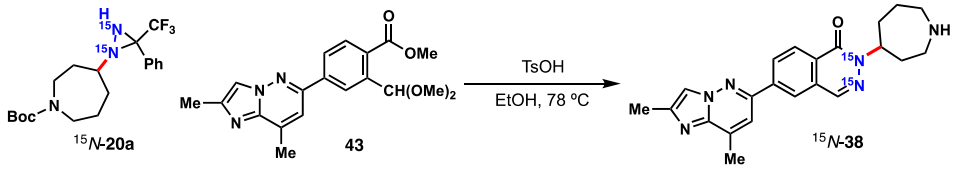
^{1}H NMR (500 MHz, $CDCl_3$, mixture of isomers) δ 7.76 – 7.57 (m, 2H), 7.53 – 7.30 (m, 3H), 3.58 – 2.87 (m, 5H), 2.02 – 1.48 (m, 6H, merged with water peak), 1.42 – 1.31 (m, 9H), 1.08 – 0.92 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of isomers) δ 155.40, 155.31, 155.26, 130.27, 130.25, 130.08, 128.52, 128.50, 128.47, 128.15, 128.12, 128.08, 123.78 (d, J = 274.3 Hz), 79.29, 79.22, 79.20, 79.17, 64.00 (d, J = 36.3 Hz), 61.15, 61.08, 61.05, 60.90, 60.68, 46.95, 46.69, 46.38, 45.82, 44.30, 44.29, 43.69, 43.67, 43.18, 43.16, 42.62, 34.36, 34.33, 33.99, 32.65, 32.62, 32.51, 31.94, 31.90, 31.85, 31.80, 30.71, 30.34, 30.30, 29.85, 28.59, 28.55, 28.49, 25.09, 25.06, 24.87, 24.28, 24.26, 23.87, 23.85.

^{19}F NMR (471 MHz, $CDCl_3$, mixture of isomers) δ -74.04, -74.09, -74.18, -74.19.

HRMS: Calculated for $C_{19}H_{27}F_3N^{15}N_2O_2^+$ 388.1991. [M+H$^+$]; found 388.1994.

2-(azepan-4-yl)-6-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)phthalazin-1(2*H*)-one-$^{15}N_2$ (^{15}N-38)



To a septum capped vial equipped with a magnetic stir bar was added *tert*-butyl 4-(3-phenyl-3-(trifluoromethyl)diaziridin-1-yl-1,2-$^{15}N_2$)azepane-1-carboxylate (**33**) (28.0 mg, 0.072 mmol, 1 eq) and ethanol (1 mL). Methyl 2-(dimethoxymethyl)-4-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)benzoate (**21**) (30.9 mg, 0.087 mmol, 1.2 eq) and *p*-toluenesulfonic acid monohydrate (82.2 mg, 0.432 mmol, 6 eq) were added and the reaction mixture stirred at 78 ºC for 24 h, until LC-

MS indicated the disappearance of starting materials. The reaction mixture was poured into a separatory funnel, 10% NaOH (20 mL) was added and the micture extracted with ethyl acetate (30 mL x 3), washed with brine (50 mL), dried over *anhyd.* Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (basic alumina, 5% MeOH in DCM to 10% MeOH in DCM) to afford product ^{15}N-**38** as a pale yellow solid (23.1 mg, 75% yield).

Physical state: pale yellow solid. $\mathbf{R_f}$ = 0.4 (20% MeOH in DCM, vis. UV).

^{1}H NMR (500 MHz, DMSO) δ 8.66 – 8.52 (m, 2H), 8.48 (dd, *J* = 8.5, 1.9 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H), 7.78 (s, 1H), 5.19 (dq, *J* = 9.9, 5.5 Hz, 1H), 3.08 – 2.71 (m, 4H), 2.63 (s, 3H), 2.42 (s, 3H), 2.12 – 1.95 (m, 3H), 1.91 – 1.80 (m, 2H), 1.67 (tq, *J* = 10.4, 2.9 Hz, 1H).

^{13}C NMR (126 MHz, DMSO) δ 157.28, 148.57, 143.45, 139.79, 138.55, 137.87, 136.16, 129.69, 129.42, 128.31, 127.37, 126.89, 124.92, 114.70, 56.20, 48.07, 44.56, 34.71, 32.33, 31.30, 16.31, 14.64.

HRMS: Calculated for $C_{22}H_{25}N_4{}^{15}N_2O^+$: 391.2025 [M+H$^+$]; found: 391.2015.

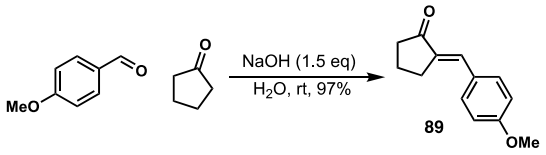
APPENDIX B: SUPPLEMENTARY INFORMATION FOR CHAPTER TWO

General Experimental:

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Anhydrous methylene chloride (DCM) and ether (Et_2O) were obtained by passing the previously degassed solvent through an activated alumina column (PPT Glass Contour Solvent Purification System) unless otherwise stated. Tetrahydrofuran (THF) was dried over a sodium/benzophenone system and stored over 4 Å MS under argon. Methanol (MeOH) and Ethanol (EtOH) were purchased as highest quality and used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by Liquid Chromatography Mass spectrometry (LC/MS) or Thin Layer Chromatography (TLC) carried out on 250 μm SiliCycle SiliaPlates (TLC Glass-Backed TLC Extra Hard Layer, 60 Å), using visualizing agents such as shortwave UV light, iodine, $KMnO_4$, CAM, PMA, ninhydrin or *p*-anisaldehyde with heat as the developing agent. Flash column chromatography was performed with a Biotage Isolera One (ZIP or SNAP Ultra cartridges) or with traditional glass flash columns using SiliCycle SiliaFlash® P60 (particle size 40 - 63 μm). NMR spectra were recorded on a Bruker Ascend^{TM} 500 MHz instrument and were calibrated using residual undeuterated solvent as an internal reference (Chloroform-*d*: 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; DMSO-*d6*: 2.50 ppm ^{1}H NMR, 39.5 ppm ^{13}C NMR). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd

= doublet of doublet, tt = triplet of triplet, ddt = doublet of doublet of triplet, m = multiplet. High resolution mass spectra (HRMS) were recorded on an Agilent 6230 LC–MS TOF mass spectrometer.

2-(4-methoxybenzylidene)cyclopentan-1-one



Followed by reported protocol.[103] To a 1000 mL round-bottom flask equipped with magnetic stir bar and addition funnel, *p*-methoxybenzaldehyde (7.8 g, 57.3 mmol, 1 eq) and cyclopentone (11.5 g, 137.5 mmol, 2.4 eq) was added. The resulting mixture stirred vigorously and sodium hydroxide (40 g) in water (360 mL) was added slowly with an addition funnel. After addition, the mixture stirred vigorously overnight, then the precipitate collected by filtration, washed with water (100 mL x 5), dried over vacuum overnight, gave **89** as a yellow solid (11.2 g, 97%).

The ^{1}H NMR spectrum matched with previously reported spectra.[103]

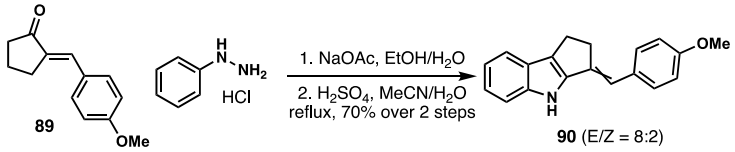
Physical state: Yellow solid. $\mathbf{R_f}$ = 0.5 (25 % EA in hexanes, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.42 (m, 2H), 7.34 (t, *J* = 2.7 Hz, 1H), 6.97 – 6.81 (m, 2H), 3.82 (s, 3H), 2.93 (td, *J* = 7.3, 2.7 Hz, 2H), 2.37 (t, *J* = 7.9 Hz, 2H), 2.01 (p, *J* = 7.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.17, 160.61, 133.77, 132.37, 132.25, 128.31, 114.30, 55.42, 37.81, 29.34, 20.21.

HRMS: Calculated for $C_{18}H_{27}O_3^+$ 203.1067 [M+H$^+$]; found 203.1069.

3-(4-methoxybenzylidene)-1,2,3,4-tetrahydrocyclopenta[*b*]indole



To a 1000 mL round-bottom flask equipped with magnetic stir bar, **89** (11.7 g, 57.8 mmol) and phenylhydrazine hydrochloride (9.2 g, 63.6 mmol, 1.1 eq) was added, followed by addition of ethanol (300 mL) and water (300 mL). Resulting mixture stirred for 10 min, then sodium acetate (10.4 g, 126.8 mmol, 2.2 eq) was added in one portion. A condenser was attached, and the mixture was refluxed for 16 h, until disappearance of starting materials. The mixture cooled to room temperature and solid collected by filtration, washed with 1:1 mixture of ethanol and water (100 mL) and pure ethanol (20 mL), dried over vacuum for 1 h, gave hydrazone as a yellowed solid (15.0 g, 51.3 mmol), which was used without purification.

(Note: hydrazone from this step is unstable on benchtop, keep it for too long on vacuum or on benchtop will observe a color change from yellow to red and results in decrease of yield in next step.)

To a 500 mL round-bottom flask equipped with magnetic stir bar, hydrazone from last step was added, followed by addition of acetonitrile (200 mL) and water (20 mL), the mixture cooled to 0 ºC, and sulfuric acid (2.83 mL, 52.8 mmol, 1.03 eq of hydrazone) added dropwisely at that temperature. After addition, a condenser attached, argon replaced and stirred for 1 h at 80 ºC. Then the hot mixture poured into 300 g of ice and 10 g of sodium bicarbonate mixture, stirred for 30 min, and solid collected by filtration. Crude product purified by column chromatography on silica gel (hexane : dichloromethane = 2:1), gave **90** as an off-white solid (11.1 g, 70%).

(Note: **90** is very sensitive to acid, the amount of sulfuric acid and reaction time will seriously affect the final yield. Column chromatography needs to be fast, stay too long on silica will decrease the yield.)

Physical state: Off-white solid. $\mathbf{R_f}$ = 0.7 (25 % EA in hexanes, vis. UV).

E-isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.53 – 7.47 (m, 1H), 7.43 – 7.35 (m, 2H), 7.33 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.23 – 7.05 (m, 3H), 6.95 – 6.87 (m, 2H), 6.42 (t, *J* = 2.4 Hz, 1H), 3.84 (d, *J* = 2.0 Hz, 3H), 3.41 (dt, *J* = 7.8, 2.6 Hz, 2H), 3.09 – 3.00 (m, 2H).

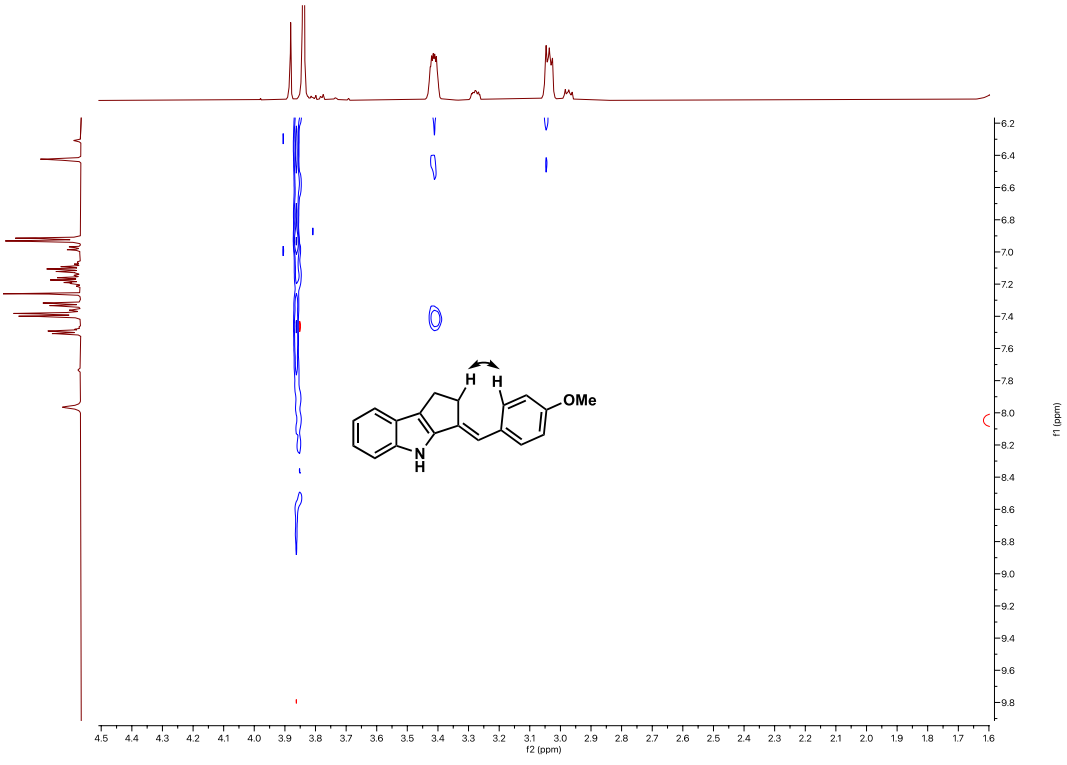
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.84, 144.94, 141.84, 133.64, 131.13, 129.10, 126.43, 124.99, 122.52, 120.01, 119.25, 115.30, 114.03, 111.62, 55.34, 35.06, 23.79.

Z-isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.35 (m, 13H), 7.23 – 7.06 (m, 15H), 7.00 – 6.96 (m, 2H), 6.31 (d, *J* = 2.1 Hz, 1H), 3.88 (d, *J* = 1.6 Hz, 3H), 3.28 (ddd, *J* = 7.8, 3.4, 2.1 Hz, 2H), 3.01 – 2.93 (m, 2H).

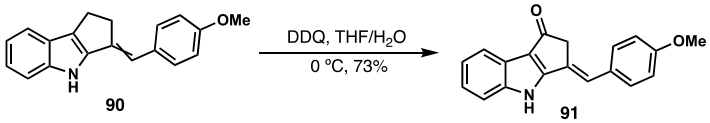
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.40, 141.48, 140.89, 134.73, 131.63, 130.10, 128.75, 124.14, 122.90, 119.86, 119.33, 115.69, 114.25, 113.36, 55.39, 36.85, 22.75.

HRMS: Calculated for $C_{19}H_{18}NO^+$ 276.1383 [M+H$^+$]; found 276.1391.

The E/Z isomer on NMR was differentiate by NOSEY experiment



(*E*)-3-(4-methoxybenzylidene)-3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one



To a 500 mL round-bottom flask equipped with magnetic stir bar, **90** (4.07 g, 14.9 mmol) was added, followed by addition of tetrahydrofuran (200 mL) and water (10 mL). The resulting mixture was cooled with an ice bath, before 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (7.41 g, 32.6 mmol, 2.2 eq) was added portionwisely. Mixture stirred at 0 ºC for 1 h, until TLC indicated disappearance of starting materials. Solvent removed *in vacuo*, and to the residue chloroform (100 mL) and saturated sodium bicarbonate solution (100 mL) was added, the suspension stirred for 1 h. Solid collected by filtration, washed with deionized water until water became colorless, dried on vacuum, gave **91** as off-white solid (3.14 g, 73%).

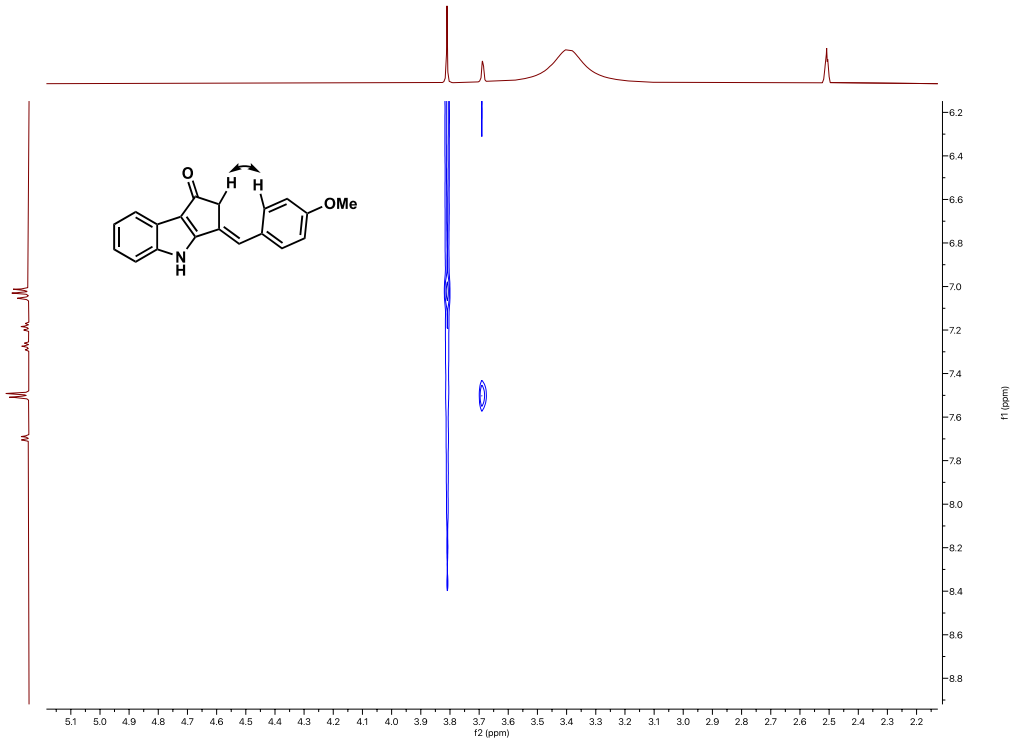
Physical state: Off white solid. $\mathbf{R_f}$ **=** 0.7 (66 % EA in hexanes, vis. UV).

^{1}H NMR (500 MHz, DMSO) δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.59 – 7.41 (m, 3H), 7.26 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.23 – 7.12 (m, 1H), 7.11 – 6.91 (m, 3H), 3.80 (s, 3H), 3.68 (d, *J* = 1.8 Hz, 2H).

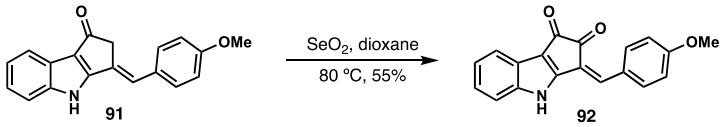
^{13}C NMR (126 MHz, DMSO) δ 191.30, 163.60, 159.52, 144.07, 130.99, 129.22, 124.55, 124.46, 122.87, 122.24, 121.73, 120.51, 120.37, 114.93, 113.47, 55.71, 45.91.

HRMS: Calculated for $C_{19}H_{16}NO_2^+$ 290.1176 [$M+H^+$]; found 290.1169.

Conformation was determined by NOSEY experiment



(*Z*)-3-(4-methoxybenzylidene)-3,4-dihydrocyclopenta[*b*]indole-1,2-dione



To a 25 mL round-bottom flask equipped with magnetic stir bar, **91** (330 mg, 1.14 mmol) was added, followed by addition of dioxane (5 mL) and selenium dioxide (250 mg, 2.25 mmol, 2 eq). The reaction mixture stirred for 3h at 80 ºC, until TLC indicated the disappearance of starting materials. Reaction mixture dried on silica gel and residue purified by column chromatography (dichloromethane : methanol = 99:1), gave **92** as a black solid (163 mg, 55%).

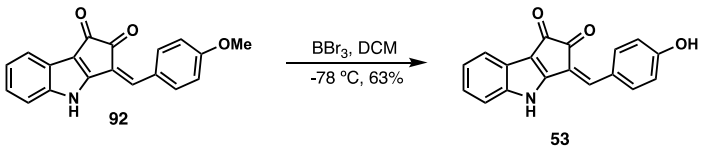
Physical state: Black solid. $\mathbf{R_f}$ = 0.4 (50 % EA in hexanes, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.07 (dq, *J* = 7.8, 1.0 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.50 (s, 1H), 7.45 – 7.40 (m, 2H), 7.37 (ddd, *J* = 8.2, 5.0, 3.4 Hz, 1H), 7.13 – 7.06 (m, 2H), 3.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.94, 177.80, 161.59, 158.65, 139.22, 130.20, 128.85, 127.43, 125.19, 124.74, 122.84, 121.75, 121.61, 115.43, 112.52, 55.75.

HRMS: Calculated for $C_{19}H_{14}NO_3^+$ 304.0968 [$M+H^+$]; found 304.0975.

Nostodione A



To a 5 mL round-bottom flask equipped with magnetic stir bar, was added **92** (50.0 mg, 0.165 mmol) in dichloromethane (5 mL), and cooled to -78 ºC. Argon replaced and boron tribromide (78.1 μL, 0.825 mmol, 5 eq) was added slowly as a solution in dichloromethane (2.5 mL). After addition, the mixture was stirred overnight at room temperature. The mixture poured into 50 mL of water and extracted with ethyl acetate (25 mL x 3); organic phase washed with sat. sodium bicarbonate, then brine, dried over anhydrous sodium sulfate, and solvent removed *in vacuo*.

Residue purified by column chromatography (silica gel, 50% ethyl acetate in hexane), gave nostodione A as an orange solid (30.2 mg, 63%).

Physical state: Orange solid. $\mathbf{R_f}$ = 0.4 (ethyl acetate/hexane/methanol=2:1:0.5, vis. UV).

Z-isomer: **^{1}H NMR** (600 MHz, Acetone) δ 11.33 (s, 1H), 9.13 (s, 1H), 7.94 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.64 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.07 – 6.99 (m, 2H).

E-isomer: **^{1}H NMR** (600 MHz, Acetone) δ 11.88 (s, 1H), 9.19 (s, 1H), 8.26 – 8.11 (m, 2H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 3.0 Hz, 1H), 7.35 – 7.33 (m, 1H), 7.30 – 7.27 (m, 1H), 6.97 (dd, *J* = 8.7, 1.9 Hz, 2H).

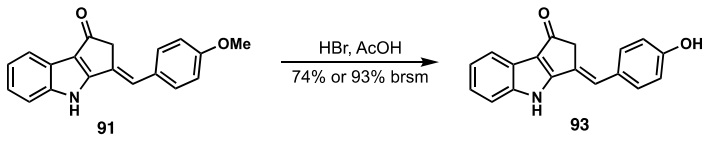
HRMS: Calculated for $C_{18}H_{12}NO_3^+$ 290.0812 [$M+H^+$]; found 290.0816.

Comparison of ^{1}H NMR signal between synthetic and natural nostodione A.

Major isomer	
Synthetic	Natural[68]
11.33 (s, 1H)	-
9.13 (s, 1H)	-
7.94 (dt, *J* = 7.7, 1.0 Hz, 1H)	7.92 (d, *J* = 7.5 Hz, 1H)
7.78 – 7.71 (m, 2H)	7.76 (d, *J* = 8.6 Hz, 2H)

7.64 (dt, *J* = 8.3, 0.9 Hz, 1H)	7.62 (d, *J* = 8.3 Hz, 1H)
7.43 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H)	7.40 (dd, *J* = 8.0, 8.3 Hz, 1H)
7.40 – 7.34 (m, 2H)	7.37 (s, 1H)
	7.33 (dd, *J* = 7.5, 8.0 Hz, 1H)
7.07 – 6.99 (m, 2H)	7.00 (d, *J* = 8.6 Hz, 2H)
Minor isomer	
Synthetic	Natural
11.88 (s, 1H)	-
9.19 (s, 1H)	-
8.26 – 8.11 (m, 2H)	8.17 (d, *J* = 8.7 Hz, 2H)
7.86 (d, *J* = 7.5 Hz, 1H)	7.85 (d, *J* = 7.5 Hz, 1H)
7.60 (d, *J* = 8.1 Hz, 1H)	7.58 (d, *J* = 8.3 Hz, 1H)
7.39 (d, *J* = 3.0 Hz, 1H)	7.40 (dd, *J* = 8.0, 8.3 Hz, 1H)
7.35 – 7.33 (m, 1H)	7.33 (dd, *J* = 7.5, 8.0 Hz, 1H)
7.30 – 7.27 (m, 1H)	7.26 (s, 1H)
6.97 (dd, *J* = 8.7, 1.9 Hz, 2H)	6.95 (d, *J* = 8.7 Hz, 2H)

(*E*)-3-(4-hydroxybenzylidene)-3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one



To a 5 mL sealed tube equipped with magnetic stir bar, was added **91** (100 mg, 0.346 mmol), hydrobromic acid (1 mL), and acetic acid (200 μL). The tube was sealed and stirred at 120 ºC for 12 h. Reaction mixture poured into 50 mL of water and extracted with ethyl acetate (50 mL x 3), organic phase washed with brine, dried over anhydrous sodium sulfate. Solvent removed *in vacuo*, gave mixture of **93** and **91** as a brown solid (88.8 mg, with 80% of **85** based on NMR, 74%). **93** can be purified by column chromatography (silica gel, 50%-70% acetone in hexane).

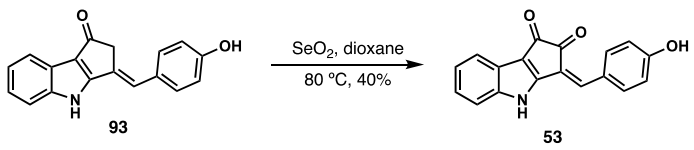
Physical state: Brown solid. $\mathbf{R_f}$ **=** 0.6 (ethyl acetate/hexane/methanol=2:1:0.5, vis. UV).

^{1}H NMR (500 MHz, DMSO) δ 12.36 (s, 1H), 9.85 (s, 0H), 7.71 – 7.67 (m, 1H), 7.51 – 7.47 (m, 1H), 7.44 – 7.38 (m, 1H), 7.28 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.20 (td, *J* = 7.5, 1.0 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 3.67 (d, *J* = 1.8 Hz, 1H).

^{13}C NMR (126 MHz, DMSO) δ 191.57, 163.26, 158.10, 143.28, 131.22, 127.56, 124.68, 123.70, 122.92, 122.45, 121.54, 120.52, 120.20, 116.37, 113.15, 45.90.

HRMS: Calculated for $C_{18}H_{14}NO_2^+$ 276.1019 [M+H$^+$]; found 276.1011.

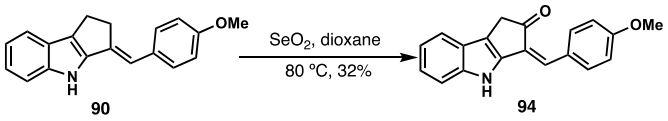
Nostodione A



To a 5 mL reaction vial equipped with a magnetic stir-bar and rubber-lined cap under argon atmosphere was added **93** (11.2 mg, 0.040 mmol), dioxane (700 μL), and selenium dioxide (50.9 mg, 0.459 mmol, 11.5 eq). The mixture was stirred at 80 ºC for 12 h, dried on silica gel and purified by column chromatography (silica gel, 50% ethyl acetate in hexane), gave nostodione A as an orange solid (4.6 mg, 40%).

^{1}H NMR agreed with nostodione A from another route.

3-(4-methoxybenzylidene)-3,4-dihydrocyclopenta[*b*]indol-2(1*H*)-one



To a 100 mL round-bottom flask equipped with magnetic stir bar, was added **90** (1.08 g, 3.92 mmol), selenium dioxide (500 mg, 4.51 mmol, 1.1 eq), and dioxane (50 mL). The mixture was heated at 80 ºC overnight until TLC indicated disappearance of starting materials, then the reaction mixture dried on silica gel, and purified by column chromatography (silica gel, 20% ethyl acetate in hexane), gave **94** as an orange solid (360 mg, 32%).

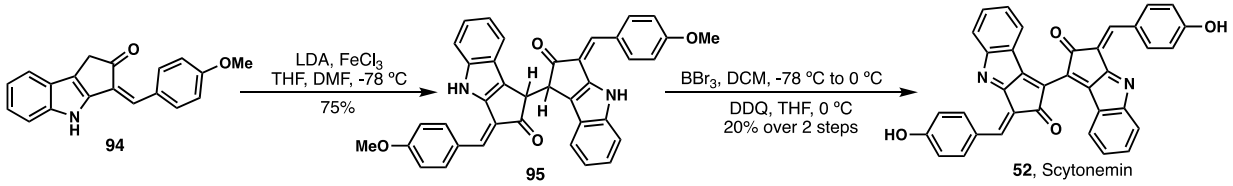
Physical state: Orange solid. $\mathbf{R_f}$ = 0.4 (25% ethyl acetate in hexane, vis. UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.66 – 7.57 (m, 2H), 7.55 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.35 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.25 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 5H), 7.19 – 7.13 (m, 2H), 7.09 – 7.00 (m, 2H), 3.91 (s, 3H), 3.56 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.62, 160.35, 140.20, 138.87, 129.61, 128.78, 127.86, 124.37, 124.31, 124.28, 120.96, 120.36, 119.83, 114.81, 111.86, 55.50, 36.52.

HRMS: Calculated for $C_{19}H_{16}NO_2^+$ 290.1176 [M+H$^+$]; found 290.1181.

Scytonemin



Followed Mårtensson's protocol.[72] To a 100 mL flame dried round-bottom flask equipped with magnetic stir bar, was added diisopropamine (88.4 μL, 2 eq) and tetrahydrofuran (8 mL). Argon was replaced and the mixture cooled to 0 ºC. To the mixture, *n*-BuLi (653 μL, 1.06M, 2.2 eq) was added slowly with a syringe, and the mixture stirred at 0 ºC for 30 min, then cooled to -78 ºC. To the mixture, **94** (91.2 mg, 0.314 mmol) was added as a solution in tetrahydrofuran (6.5 mL) and stirred at that temperature for 10 minutes. Then iron(III) chloride was added as a solution in dimethyl formaldehyde (3.45 mL, 0.2 M, 2.2 eq). The mixture was stirred at room temperature for another 24 h, before quenched with 3 M hydrochloride (50 mL). After stirred for 30 min, the mixture was extracted with ethyl acetate (20 mL x 3), then organic phase washed with 10% lithium chloride (50 mL) and brine, dried over anhydrous sodium sulfate and solvent removed in vacuo,

purified by column chromatography (silica gel, 40% ethyl acetate in hexane) gave **95** as orange solid (68.1 mg, 75%). The product was used without further purification.

To a 10 mL flame dried round-bottom flask equipped with magnetic stir bar, was added **95** (23.0 mg, 0.040mmol) and dichloromethane (2 mL). The mixture cooled to -78 ºC and boron tribromide (15.3 μL, 0.160 mmol, 4 eq) was added through a syringe, then the resulting mixture warmed to 0 ºC and stirred for 30 h at that temperature. The resulting mixture quenched with water (10 mL) and extracted with ethyl acetate (25 mL x 3). Organic phase washed with brine, dried over anhydrous sodium sulfate, gave brown solid.

The brown solid from last step was dissolved in 4 mL of tetrahydrofuran, followed by addition of DDQ (50 mg), and the mixture stirred overnight until TLC indicates disappearance of starting materials. The mixture dried on silica gel and purified by column chromatography (1-2% methanol in dichloromethane), gave scytonemin as an orange solid (4.4 mg, 20 % from **95**).

Physical state: Orange solid. $\mathbf{R_f}$ = 0.4 (10% methanol in dichloromethane, vis. UV).

^{1}H NMR (500 MHz, Pyridine-D_5) δ 8.96 (d, *J* = 8.3 Hz, 4H), 7.97 (s, 2H), 7.85 (d, *J* = 7.4 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 4H), 7.24 (d, *J* = 8.6 Hz, 2H).

HRMS: Calculated for $C_{36}H_{21}N_2O_4^+$ 545.1496 [M+H$^+$]; found 545.1501.

Comparison of ^{1}H NMR signal between synthetic and natural scytonemin

Synthetic	Natural[66]
7.73 (d, *J* = 7.7 Hz, 2H)	7.76 (d, *J* = 7.7 Hz)
7.46 (t, *J* = 7.6 Hz, 2H)	7.49 (ddd, *J* = 7.7, 7.6, 1.1 Hz)
7.24 (d, *J* = 8.6 Hz, 2H)	7.22 (dd, *J* = 7.6, 7.2 Hz)
7.85 (d, *J* = 7.4 Hz, 2H)	7.89 (d, *J* = 7.2 Hz)
7.97 (s, 2H)	8.00 (s)
8.96 (d, *J* = 8.3 Hz, 4H)	9.00 (d, *J* = 8.7 Hz)
7.31 (d, *J* = 8.3 Hz, 4H)	7.34 (d, *J* = 8.7 Hz)