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Fun With Unusual Functional Groups: Sulfamates, Phosphoramidates, and Di-tert-butyl Silanols

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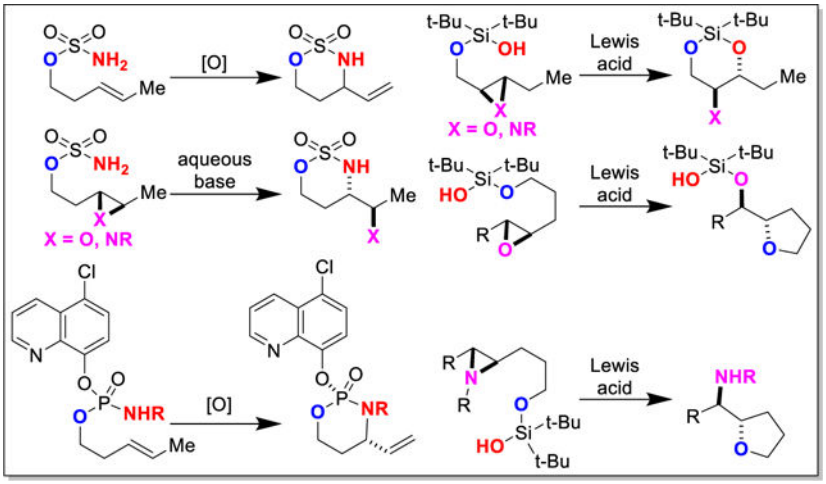
Abstract

Compared to ubiquitous functional groups such as alcohols, carboxylic acids, amines, and amides, which serve as central “actors” in most organic reactions, sulfamates, phosphoramidates, and di-*tert*-butyl silanols have historically been viewed as “extras”. Largely considered functional group curiosities rather than launch-points of vital reactivity, the chemistry of these moieties is under-developed. Our research program has uncovered new facets of reactivity of each of these functional groups, and we are optimistic that the chemistry of these fascinating molecules can be developed into truly general transformations, useful for chemists across multiple disciplines. In the ensuing sections, I will describe our efforts to develop new reactions with these “unusual” functional groups, namely sulfamates, phosphoramidates, and di-*tert*-butyl silanols.

Graphical Abstract



This is an account of our efforts to develop new reactions with “unusual” functional groups, namely sulfamates, phosphoramidates, and di-*tert*-butyl silanols.

Keywords

organic methodology; total synthesis; alkene functionalization; silanol; aza-Wacker

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1. Introduction

In this account, I reflect on my laboratory's research at the University of Kansas (KU) from 2019 to 2023. Early in my career, I conceptualized my program as the development of "tethered" alkene functionalization reactions. As the number and diversity of projects grew, I realized that this would not appropriately describe much of the chemistry we have explored. I believe that my program could better be described as an exploration of the reactivity of unusual functional groups. In the ensuing sections, I will describe our efforts to develop new reactions with these "unusual" functional groups, namely sulfamates, phosphoramidates, and di-*tert*-butyl silanols.

II. Sulfamate and Phosphoramidate Tethered *Aza*-Wacker Reactions

After I accepted a faculty position at the University of Kansas Department of Medicinal Chemistry, I realized that I had only a short time (3 years?) to build a fundable program of research. Many people had made it clear to me that a program has several related projects that are different enough to be independently published but that are linked by some common theme. I had several ideas for projects that I felt would be publishable if they worked as envisioned, but they were all discrete, without any common link. I would have to do better than that.

I knew of several successful research programs that were built on the development of new reactions and the application of those reactions to the syntheses of complex molecules. The key, of course, was finding such a broadly applicable reaction. Many new methods appear each day, but how many are applicable outside of the depicted substrate scope? Generality is a challenge that all organic chemists interested in methodology development face.

I had worked with sulfamates as a graduate student,[1] and it was clear from the literature that they were rarely used outside of C–H functionalization reactions, aziridinations, and cross-couplings.[2] Sulfamates are versatile because they can be activated by appending an electron-withdrawing group and then displaced in an S_N2 reaction, much like a tosylate or triflate.[3] After reading some excellent review articles on *aza*-Wacker chemistry written by the Stahl group,[4] I realized that sulfamates may serve as viable nucleophiles in intramolecular *aza*-Wacker reactions. The resulting oxathiazinanes could be activated and ring-opened to give a variety of allylic amine products. *Aza*-Wacker chemistry had been known for some time (since the 1970s[5]) but most reactions gave pyrrolidine or piperidine products. Variants utilizing detachable tethers were hardly known (<12 reports by my count![6]); such reactions are powerful because they remove the constraint of needing a pre-existing C–N bond to form a new one (Scheme 1). I knew that if such a reaction were possible, then my laboratory would be able to construct a program around it.

My first postdoctoral fellow Anand Shinde and I worked to develop such a reaction (Scheme 2). Within a few months, we were successful in optimizing a protocol for the first sulfamate-tethered *aza*-Wacker reaction, which involved heating an alkenyl sulfamate substrate with catalytic $Pd_2(dba)_3$ and stoichiometric $Cu(OAc)_2$ under 1 atm of O_2 in MeCN.[7] Our reaction was compatible with NH_2, *N*-alkyl, and *N*-aryl sulfamates. Furthermore,

we showed that *N*-aryl sulfamates were activated enough to undergo facile ring-opening reactions with phenoxides. Later, with Dr. Someshwar Nagamalla, we extended this protocol to include ring-openings with alkoxides and thiolates (Scheme 2).[8] Anand scaled our sulfamate-tethered reaction from 0.2 mmol to 10 mmol and showed that there was no loss of yield or selectivity.[9]

I wanted to test the limits of this transformation by using it as a key step in a total synthesis. I decided to focus on antibiotic targets, but I was having difficulty finding the right molecule. I wanted a 1,3-aminoalcohol antibiotic with a mechanism of action distinct from FDA-approved, clinically used compounds. I also didn't want a target that had been synthesized 20 times before; regardless of the molecule, it's hard to justify the 21st synthesis! Finally, my colleague at KU, Josephine Chandler, suggested bactobolin A, which had been the focus of her postdoctoral work.[10] Bactobolin A inhibits bacterial growth by binding to the L2 protein of the bacterial ribosomal 50S subunit, different from other ribosome-inhibiting antibiotics.[11] I was intrigued by its heteroatom-rich structure and its potent broad-spectrum antibiotic activity. Furthermore, at the time, it had only been the subject of one total synthesis, from the Weinreb group.[12] After we started working on the molecule, Švenda and co-workers published a second synthesis.[13] We have not yet finished a total synthesis of bactobolin A, but Someshwar has made much progress, including developing a very interesting homoallylic alcohol directed conjugate addition and demonstrating that our sulfamate-tethered *aza*-Wacker reaction is competent with densely functionalized intermediates (Scheme 3).[14]

Oxathiazinanes are protected 1,3-aminoalcohols, and I hypothesized that the sulfamate-tethered *aza*-Wacker reaction could serve as a key step in the preparation of a variety of nitrogen containing monosaccharides, which are abundant in aminoglycoside antibiotics. Dr. Debobrata Paul was successful in synthesizing a series of protected D-galactosamines using this strategy (Scheme 4).[15] He made the important discovery that using 4 Å molecular sieves and Fmoc-Gly-OH as a ligand greatly improves the efficiency of the *aza*-Wacker cyclization. While we don't fully understand the role of Fmoc-Gly-OH, in accord with the Yu laboratory's observations,[16] we believe that it helps promote the Pd(II)–Pd(0) catalytic cycle operative in *aza*-Wacker chemistry. Dr. Gour Mandal used these insights in his preparation of kasugamine, an *aza*-sugar common to the kasugamycin and minosaminomycin antibiotics (Scheme 5).[17]

Are there other versatile tethers that can be used in intramolecular *aza*-Wacker cyclization reactions? In 2020, my laboratory was shut down due to the emerging COVID-19 pandemic. During this time, one of Gilead's molecules remdesivir was receiving much attention as a potential treatment. I noticed that remdesivir was a phosphoramidate molecule, and I wondered if phosphoramidates could serve as competent nucleophiles in *aza*-Wacker cyclizations. Phosphoramidate tethers contain a stereocenter, and controlling the diastereoselectivity of the cyclization would be a major challenge (Scheme 6).

Anand and graduate student Annu Anna Thomas optimized the yield of the transformation within a few weeks, but, in all cases, mixtures of diastereomeric products were produced. These products were separable, but it was our goal to develop a highly diastereoselective

cyclization. A chiral auxiliary approach did not work; even phosphoramidate tethers bearing a chiral alcohol “arm” gave mixtures of diastereomeric heterocycles.

One day, Anand surprised me with a very nice and unexpected result. Phosphoramidate tethers containing a 5-chloro-8-hydroxyquinoline arm cyclized with >20:1 diastereoselectivity![18] We hypothesized that palladium chelation underlay this amazing stereocontrol. Indeed, a crystal structure of one of the products showed that the quinolinol auxiliary and the alkenyl arm were in a *syn* configuration, which is what one would expect if Pd had served as a bridge between these two moieties during the *aza*-Wacker cyclization (Scheme 6). We explored the capacity of related heterocycles to serve as chelating “arms”; for reasons unknown to us, 5-chloro-8-hydroxyquinoline was always superior.

Annu optimized protocols for the transformation of these cyclic phosphoramidates into 1,3-chloroamines and 1,3-aminoalcohols (Scheme 7).[19] Literature reports suggested that the phosphoramidate tether could be deprotected using lithium aluminum hydride; we found that these conditions were not general for a series of phosphoramidate heterocycles. Fortunately, heating these phosphoramidates with HCl/dioxane converted them into 1,3-chloroamine products; analogous treatment with aqueous HF gave 1,3-aminoalcohols. With the former reaction, there was an interesting diastereomeric preference; only the *syn* diastereomer reacted, presumably because of ground state destabilization. With the formation of 1,3-aminoalcohols, there was no such preference and both diastereomers reacted smoothly.

III. Intramolecular Ring-Opening Reactions of Epoxides and Aziridines by Pendant Sulfamates

We have begun exploring the use of sulfamates in contexts beyond *aza*-Wacker cyclizations. One of the first projects in this direction involved the ring-opening of epoxides by sulfamate tethers to give vicinal amino alcohols (Scheme 8).[20] In almost all cases examined, the ring-opening occurred with predictable regioselectivity and high diastereocontrol. Furthermore, the reaction conditions were very mild and generally involved stirring sulfamate epoxide with aqueous base at room temperature; for *N*-substituted sulfamates, mild elevation of temperature or extension of reaction time was required.

There was some serendipity to the discovery of these reaction conditions. I synthesized the test substrate for this reaction using an *m*CPBA epoxidation (the Prilezhaev reaction). To remove the *m*-chlorobenzoic acid byproduct, I dissolved the crude residue in Et_2O and washed with 1M aqueous NaOH solution. Subsequent ^1H NMR analysis of the organic layer showed complete conversion of starting material into a complex mixture of products. While disappointing at first, this was an important clue that the substrate was responsive to aqueous base. Subsequently, I found that using *1 equivalent* of aqueous 1M NaOH solution in Et_2O or 1 equivalent of $Bu_4NOH•30H_2O$ in a biphasic mixture of CF_3-toluene/H_2O was optimal.

Someshwar, Annu, and Dr. Appasaheb Nirpal used these reaction conditions to explore analogous ring-openings of aziridines (Scheme 9). These reactions provided a variety of vicinal diamine products.[21] I was particularly impressed by Someshwar’s conversion of these products into an array of interesting heterocycles.

IV. Reactions with Di-*tert*-butyl Silanol Tethers

The projects with di-*tert*-butyl silanol tethers started because I wanted an oxygen counterpart to the sulfamate auxiliary. I had read an excellent account from Overman describing his use of acetal tethers for olefin functionalization reactions.[22] Leighton had improved this reaction by demonstrating that aldehydes more readily available than anhydrous chloral were competent in this chemistry.[23] As a graduate student working in C–H functionalization chemistry, I was aware of work from the Gevorgyan group which made use of di-*tert*-butyl silanol auxiliaries to direct C–H hydroxylation and C– H alkenylation reactions.[24]

I hypothesized that di-*tert*-butylsilanol auxiliaries could be used for alkene functionalization reactions, analogous to the work of Overman and Leighton. Of course, we would have to find a way to synthesize allylic and homoallylic silanols. I worried about their stability, as I couldn't find examples of these types of compounds in the literature; Gevorgyan and co-workers had exclusively employed phenolic di-*tert*-butyl silanols in their research.

Anand devised the first method to access these compounds using imidazole, DMAP, and di-*tert*-butylsilyl ditriflate (Scheme 10) in DMF. Later, Debobrata showed that these compounds could also be synthesized using 2,6-lutidine and di-*tert*-butylsilyl ditriflate in CH_2Cl_2. There is always some luck in research, and we were lucky that these compounds were so readily synthesized *and* that they were stable to isolation and storage. Over the past few years, we have probably synthesized more than a 100 of these compounds for various applications.

I decided to try an intramolecular silanoxymercuration of alkenes using the di-t*ert*-butyl silanol mainly because Overman and Leighton had studied analogous mercuration reactions with their acetal tethers. Treatment of a simple allylic silanol with $Hg(OTf)_2$ gave a complex mixture of products which may be explained by the mechanism depicted in Scheme 11. I decided to focus on the first step of this reaction, but taming this cascade was much more difficult than I had initially expected. Eventually, my postdocs and I hypothesized that adventitious triflic acid was triggering the cascade; indeed, when I added 1 equivalent of $NaHCO_3$, the desired dioxasilinane product formed in excellent yield and was stable in the reaction milieu (Scheme 12). These conditions were general for a variety of allylic silanols, which Anand and I examined together.[25]

One morning, I added 1M aqueous HCl to the reaction mixture in an effort to remove Hg^{2+} salts during the workup. To my surprise, ^1H NMR analysis of the reaction mixture showed that the dioxasilinane had decomposed into a mixture of internal and terminal alkenes. Investigating this reaction further with postdoctoral fellow Dr. Ranjeet Dhokale showed that the distribution of alkenes was highly substrate dependent (Scheme 13). With acid sensitive substrates, demercuration could be achieved using $NaBH_4$ in DMF. Computational investigations by my friend from graduate school, Dr. Frederick J. Seidl, showed that the reaction was under thermodynamic control and that the di-*tert*-butyl silanol protecting group was essential for product selectivity. This sequence of mercuration-demercuration allows for a very interesting and counter-intuitive alkene transposition.[26]

Someshwar, Ranjeet, and I found that through careful control of the reaction conditions, products further down in the cascade could be synthesized in one-pot from the allylic silanol substrate (Scheme 14).[27] I have not seen an analogous transformation in the literature, and I am grateful to have stumbled onto this reactivity.

We hypothesized that electrophiles apart from Hg^{2+} could react with these alkenes. Ranjeet and I developed a silanoxy-iodination reaction, explored the scope, and studied applications of the products (Scheme 15).[28] Simply treating allylic silanols with several equivalents of I_2 and $NaHCO_3$ allowed for cyclization, but these conditions were too corrosive for an expanded substrate scope. We found that only 1 equivalent of I_2 was required when silver salts with a non-nucleophilic counteranion ($AgBF_4$ or AgOTf) were added. In all cases examined, only products from 6-*endo* attack on the transient iodonium intermediate formed. DME was the best solvent for the reaction; we (re)discovered by accident that I_2 causes a ring-opening polymerization of THF![29]

Dr. Harshit Joshi and I extended this work to silanoxyselenylation and hydroxyselenylation reactions (Scheme 16).[30] In both cases, *N*-(phenylseleno)phthalimide acted as the selenylating agent. Under acidic conditions, the products of silanoxyselenylation were exclusive. Unfortunately, these were unstable to chromatography on a variety of different media. Surprisingly, under basic conditions, this pathway was blocked and products of hydroxyselenylation were exclusive. These were perfectly stable for isolation and storage. In all cases, the regioselectivity and diastereoselectivity were excellent. What might account for high selectivity in the hydroxyselenylation reaction? We hypothesize that the di-*tert*-butylsilanol auxiliary plays a critical role in stabilization of the seleniranium intermediate.

The preceding projects have focused on the ring-opening of transient electrophiles (mercuronium, iodonium, and seleniranium ions) by pendant silanols. We have also explored the ring-opening of stable, strained electrophiles, namely epoxides and aziridines. This area became a focus because I was inspired by the Payne rearrangement, which is an epoxide transposition that occurs under basic conditions.[31] I wondered whether silanols could cleave epoxides in a similar manner as alcohols. Someshwar and I explored this reaction together (Scheme 17). The requisite epoxides could be synthesized by mCPBA epoxidation of the corresponding alkenyl silanol. One of the first test reactions with $Sc(OTf)_3$ gave measurable product, but there was a large amount of unproductive deprotection of the di-*tert*-butyl silyl group. Switching to the unusual Lewis acid Ph_3CBF_4 gave a much cleaner reaction. With certain substrates, switching from Lewis acids to Bronsted acids such as BINOL-phosphoric acid was necessary to prevent undue substrate decomposition. We were able to apply this reaction in a short synthesis of protected D-arabitol.[32]

Someshwar was interested in exploring ring-opening reactions with more remote epoxides. I predicted that if the ring-opening worked at all, we would form either 7 or 8-membered heterocycles. To our great surprise, a rearrangement reaction occurred instead (Scheme 18)! The proximal oxygen (rather than the distal one) attacked the epoxide, and then the silanol “jumped” to the resulting alkoxide. For the formation of tetrahydrofuran products, we termed this a [5,5]-rearrangement; for the formation of tetrahydropyran products, a [6,5]-rearrangement occurred. Harshit and Annu explored this reaction in more detail and

found that it was perfectly stereospecific in all cases. Di-substituted *trans*-epoxide silanols gave products with an *erythro* configuration; *cis*-disubstituted epoxide silanols gave products with a *threo* configuration. They used this reaction as a key step in a concise preparation of (±)-muricatacin (Scheme 19).[33]

Silanols can also be used to cleave aziridines with excellent regioselectivity and diastereoselectivity (Scheme 20). A variety of aziridine substrate classes engaged with our cyclization protocols, including *trans*-di-substituted aziridine silanols, *cis*-di-substituted aziridine silanols, and tri-substituted aziridine silanols. Someshwar and Debobrata used this methodology for the preparation of several sphingosine-type natural products, including (±)-clavaminol H, (±)-dihydrosphingosine, and (±)-*N*-hexanoyldihydrosphingosine.[34] As an example, our synthesis of dihydrosphingosine is shown in Scheme 20.

Appasaheb and I studied the ring-opening of aziridines more remote from the silanol with the hope that a [5,5]-rearrangement would take place. To our surprise, 1'-amino-tetrahydrofuran products did form, but there was no trace of the silanol (Scheme 21)! Since Si–N bonds are far more labile than Si–O ones, we hypothesize that the silanol was cleaved during reaction work-up. Furthermore, we found that the silanol was not required for product formation, and a variety of ethers engaged productively.[35]

Before Anand and Ranjeet left for new positions, they examined an intramolecular interception of palladium π-allyl species by di-*tert*-butylsilanols (Scheme 22).[36] Before joining my lab at KU, Anand was a postdoctoral fellow with Professor Barry Trost at Stanford. This project started out of a simple goal of combining an aspect of Trost chemistry with ours! Anand and Ranjeet found that allyl ethyl carbonates were the best precursors for the formation of palladium π-allyl intermediates and that $[(\text{Cinnamyl})\text{PdCl}]_2$/BINAP was superior to other Pd salt/ligand framework combinations. A very interesting result was that the reaction was perfectly stereospecific and proceeded *via* an *anti-syn* mechanism. This contrasts with reported analogous reactions of alcohols and phenols, known to proceed via an *anti-anti* mechanism.

Summary and Outlook

This short account describes my laboratory's exploration of the chemistry of unusual nucleophiles, namely sulfamates, silanols, and phosphoramidates. It is very gratifying to see how simple ideas evolved in many unexpected ways into an actual program of research. While I believed from the start that the *aza*-Wacker chemistry, if successful, would lead to multiple projects, I was less optimistic when I began exploring reactions of di-*tert*-butyl silanols. In fact, I wasn't even sure if the starting materials for these projects could be synthesized and whether they would be stable enough for any productive reactivity! I could never have predicted the diversity of reactions that are possible with them, including some beautiful rearrangement chemistry. I hope that what I have shown inspires others, especially students embarking on independent careers, to open myriad new research directions with each of these substrate types, beyond what I can imagine.

Acknowledgements

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Biography

Shyam Sathyamoorthi completed a B.S. degree in Cell and Molecular Biology with a minor in Chemistry at Tulane University, New Orleans, Louisiana, where he worked in the labs of Professor Ken Muneoka and Professor Robert A. Pascal, Jr. He then completed a PhD in chemistry at Stanford University under the guidance of Professor Richard N. Zare (2018) as well as a Doctor of Medicine degree at the Stanford University School of Medicine (2019). Since July 2019, he is an assistant professor in the Department of Medicinal Chemistry at the University of Kansas, Lawrence, KS, USA.

References

[1]. Sathyamoorthi S, Banerjee S, Du Bois J, Burns NZ and Zare RN, Chem. Sci 2018, 9, 100–104. [PubMed: 29629078]

[2] a). Roizen JL, Harvey ME and Du Bois J, Acc. Chem. Res 2012, 45, 911–922; [PubMed: 22546004] b) Alderson JM, Corbin JR and Schomaker JM, Acc. Chem. Res 2017, 50, 2147–2158; [PubMed: 28787131] c) Ide T, Feng K, Dixon CF, Teng D, Clark JR, Han W, Wendell CI, Koch V. and White MC, J. Am. Chem. Soc 2021, 143, 14969–14975;d) Kazerouni AM, McKoy QA and Blakey SB, Chem. Commun 2020, 56, 13287–13300;e) Macklin TK and Snieckus V, Org. Lett 2005, 7, 2519–2522. [PubMed: 15957880]

[3]. Espino CG, Wehn PM, Chow J. and Du Bois J, J. Am. Chem. Soc 2001, 123, 6935–6936.

[4]. a) Wang D, Weinstein AB, White PB and Stahl SS, Chem. Rev 2018, 118, 2636–2679; [PubMed: 28975795] b) Kotov V, Scarborough CC and Stahl SS, Inorg. Chem 2007, 46, 1910–1923. [PubMed: 17348722]

[5]. Hegedus LS, Allen GF, Bozell JJ and Waterman EL, J. Am. Chem. Soc 1978, 100, 5800–5807.

[6]. Thomas AA, Nagamalla S. and Sathyamoorthi S, Chem. Sci 2020, 11, 8073–8088. [PubMed: 34123081]

[7]. Shinde AH and Sathyamoorthi S, Org. Lett 2020, 22, 896–901. [PubMed: 31927967]

[8]. Shinde AH, Nagamalla S. and Sathyamoorthi S, Med. Chem. Res 2020, 29, 1223–1229. [PubMed: 37204993]

[9]. Shinde AH and Sathyamoorthi S, Org. Synth 2022, 99, 286–304.

[10]. Greenberg EP, Chandler JR and Seyedsayamdost MR, J. Nat. Prod 2020, 83, 738–743. [PubMed: 32105069]

[11] a). Chandler JR, Truong TT, Silva PM, Seyedsayamdost MR, Carr G, Radey M, Jacobs MA, Sims EH, Clardy J. and Greenberg EP, mBio 2012, 3, 10.1128/mbio.00499-12;b) Amunts A,

Fiedorczuk K, Truong TT, Chandler J, Greenberg EP and Ramakrishnan V, J. Mol. Biol 2015, 427, 753–755. [PubMed: 25562208]

[12]. Garigipati RS and Weinreb SM, J. Org. Chem 1988, 53, 4143–4145.

[13]. Vojáčková P, Michalska L, Nečas M, Shcherbakov D, Böttger EC, Šponer J, Šponer JE and Švenda J, J. Am. Chem. Soc 2020, 142, 7306–7311. [PubMed: 32285674]

[14]. a) Nagamalla S, Johnson DK and Sathyamoorthi S, Med. Chem. Res 2021, 30, 1348–1357; [PubMed: 37860778] b) Nagamalla S, Mague JT and Sathyamoorthi S, Tetrahedron 2022, 133112.

[15]. Paul D, Mague JT and Sathyamoorthi S, J. Org. Chem 2023, 88, 1445–1456. [PubMed: 36649480]

[16]. Shao Q, Wu K, Zhuang Z, Qian S. and Yu J-Q, Acc. Chem. Res 2020, 53, 833–851. [PubMed: 32227915]

[17]. Mandal GH and Sathyamoorthi S, J. Org. Chem 2023, DOI: 10.1021/acs.joc.3c02292.

[18]. Shinde AH, Thomas AA, Mague JT and Sathyamoorthi S, J. Org. Chem 2021, 86, 14732–14758.

[19]. Thomas AA, Seidl FJ, Mague JT and Sathyamoorthi S, Tetrahedron 2023, 137, 133390.

[20]. Nagamalla S, Mague JT and Sathyamoorthi S, Org. Lett 2023, 25, 982–986. [PubMed: 36744823]

[21]. Nagamalla S, Thomas AA, Nirpal AK, Mague JT and Sathyamoorthi S, J. Org. Chem 2023, 88, 15989–16006.

[22]. Overman LE and Campbell CB, J. Org. Chem 1974, 39, 1474–1481.

[23]. Sarraf ST and Leighton JL, Org. Lett 2000, 2, 403–405. [PubMed: 10814334]

[24]. a) Wang Y. and Gevorgyan V, Angew. Chem. Int. Ed 2015, 54, 2255–2259;b) Huang C, Chattopadhyay B. and Gevorgyan V, J. Am. Chem. Soc 2011, 133, 12406–12409.

[25]. Shinde AH and Sathyamoorthi S, Org. Lett 2020, 22, 8665–8669. [PubMed: 33095992]

[26]. Dhokale RA, Seidl FJ and Sathyamoorthi S, Molecules 2021, 26, 3829. [PubMed: 34201779]

[27]. Nagamalla S, Dhokale RA, Seidl FJ, Mague JT and Sathyamoorthi S, Org. Chem. Front 2021, 8, 5361–5368. [PubMed: 34868598]

[28]. Dhokale RA, Seidl FJ, Shinde AH, Mague JT and Sathyamoorthi S, J. Org. Chem 2021, 86, 9233–9243. [PubMed: 34128664]

[29]. Cataldo F, Eur. Polym. J 1996, 32, 1297–1302.

[30]. Joshi H. and Sathyamoorthi S, J. Org. Chem 2022, 87, 5017–5028. [PubMed: 35294203]

[31]. Hanson Epoxide Migration RM (Payne Rearrangement) and Related Reactions, in Organic Reactions pp. 1–156 (2004).

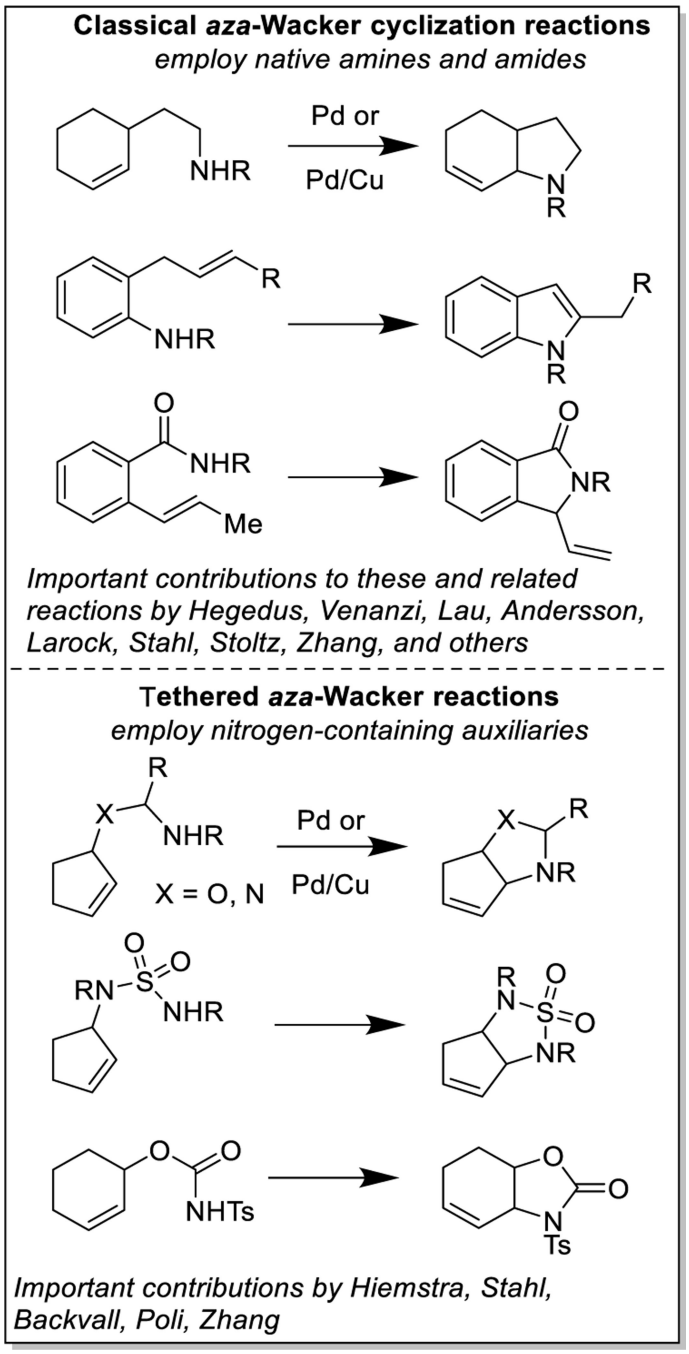
[32]. Nagamalla S, Mague JT and Sathyamoorthi S, Org. Lett 2022, 24, 939–943. [PubMed: 35041437]

[33]. Joshi H, Thomas AA, Mague JT and Sathyamoorthi S, Org. Chem. Front 2023, 10, 2556–2562. [PubMed: 38037597]

[34]. Nagamalla S, Paul D, Mague JT and Sathyamoorthi S, Org. Lett 2022, 24, 6202–6207. [PubMed: 35951966]

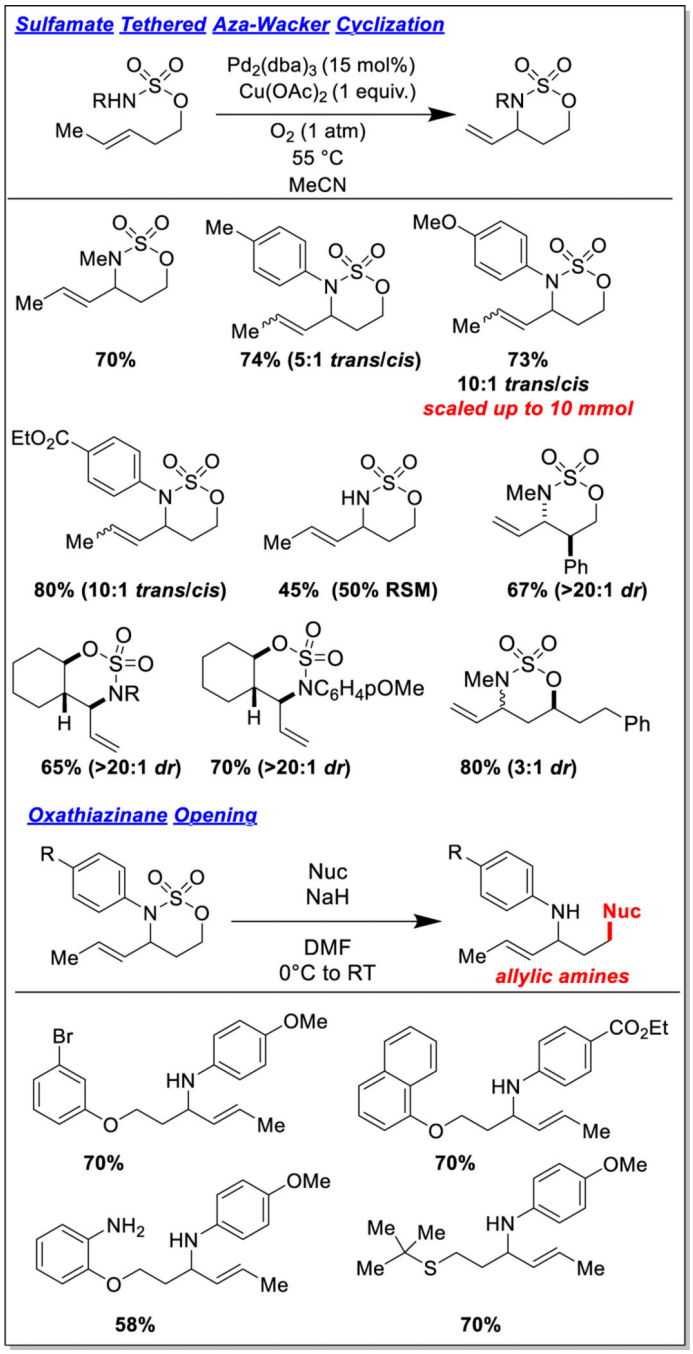
[35]. Nirpal AK, Nagamalla S, Mague JT and Sathyamoorthi S, J. Org. Chem 2023, 88, 9136–9156. [PubMed: 37253098]

[36]. Shinde AH, Dhokale RA, Mague JT and Sathyamoorthi S, J. Org. Chem 2022, 87, 11237–11252.



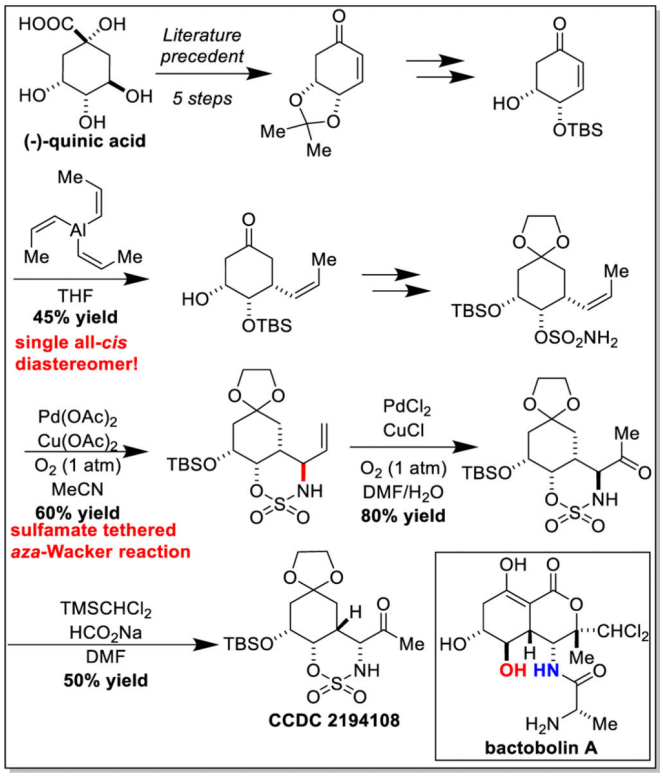
Scheme 1.

Classical and tethered *aza*-Wacker cyclization reactions at the time of our laboratory's entry into the field.

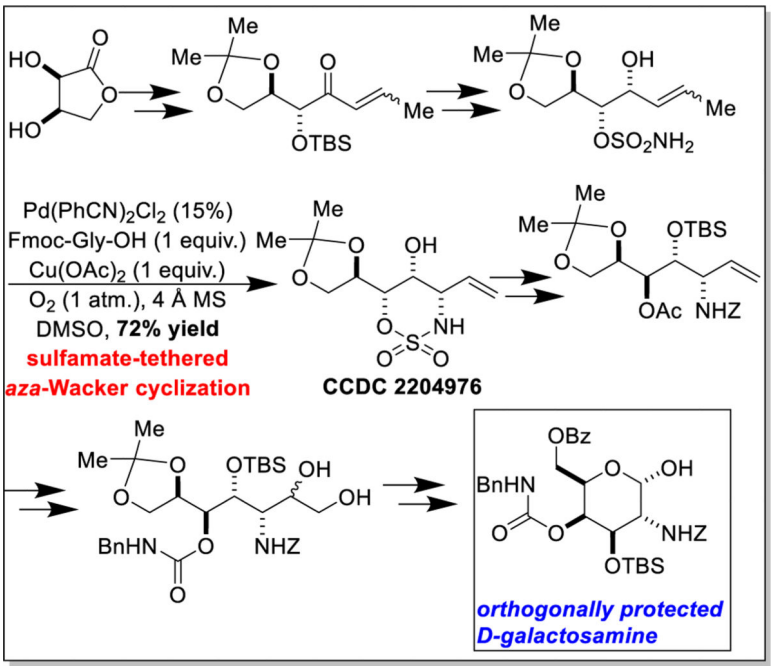


Scheme 2.

Sulfamate-tethered aza-Wacker cyclization reactions give alkenyl oxathiazinane products, which are allylic amine surrogates.

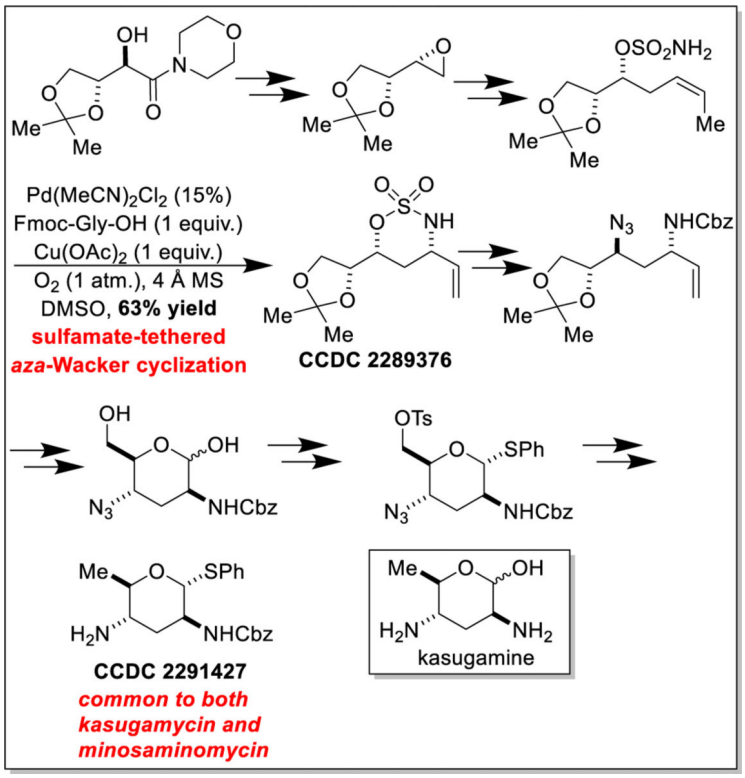


Scheme 3.
Our progress towards bactobolin A.



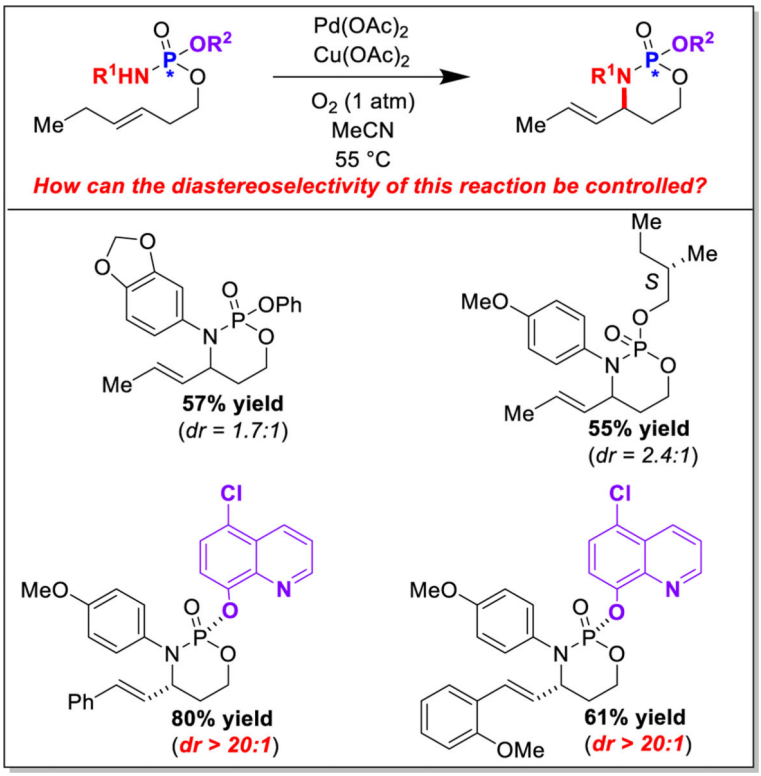
Scheme 4.

Application of our sulfamate-tethered *aza*-Wacker cyclization to the preparation of orthogonally protected D-galactosamines.



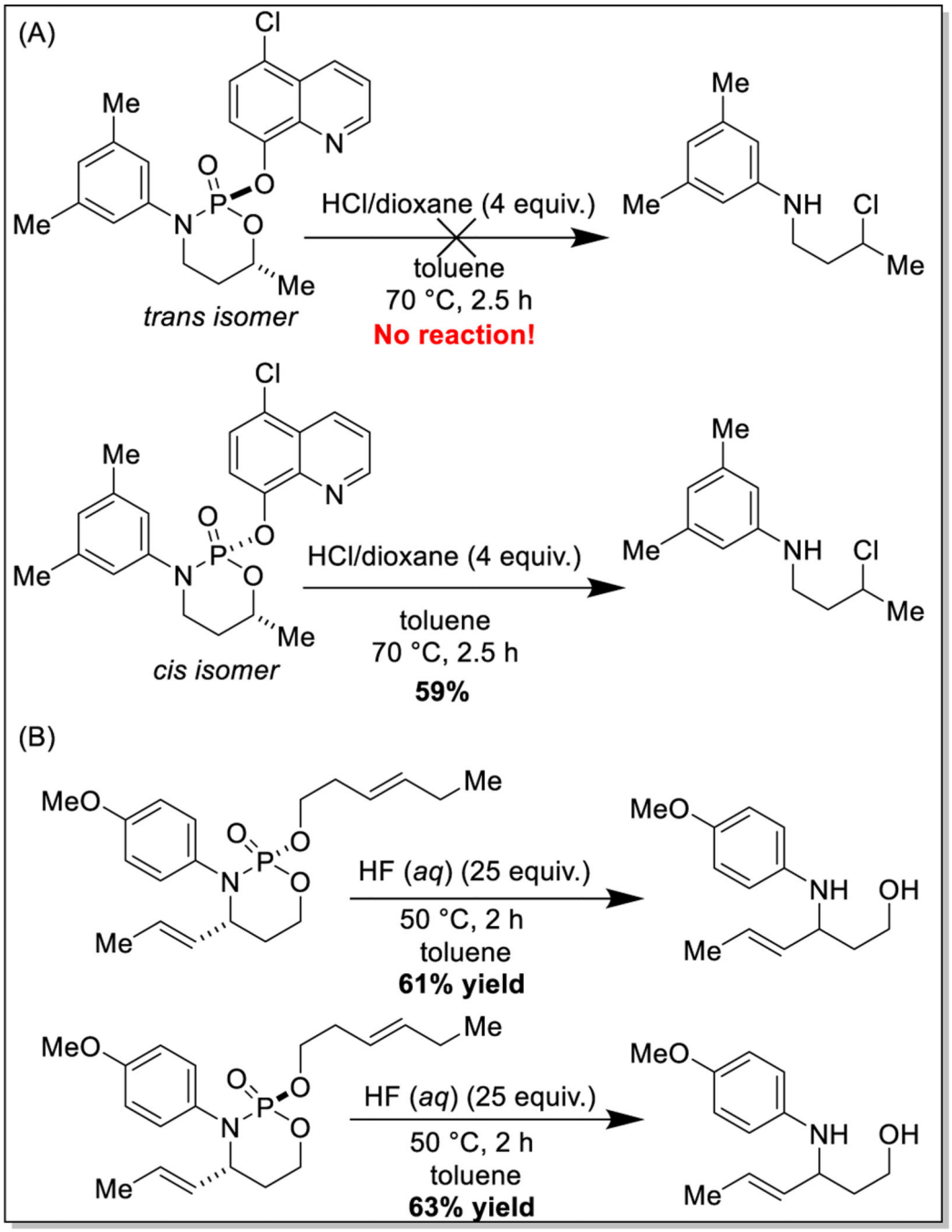
Scheme 5.

Application of our sulfamate-tethered *aza*-Wacker cyclization to the preparation of a kasugamine synthon.



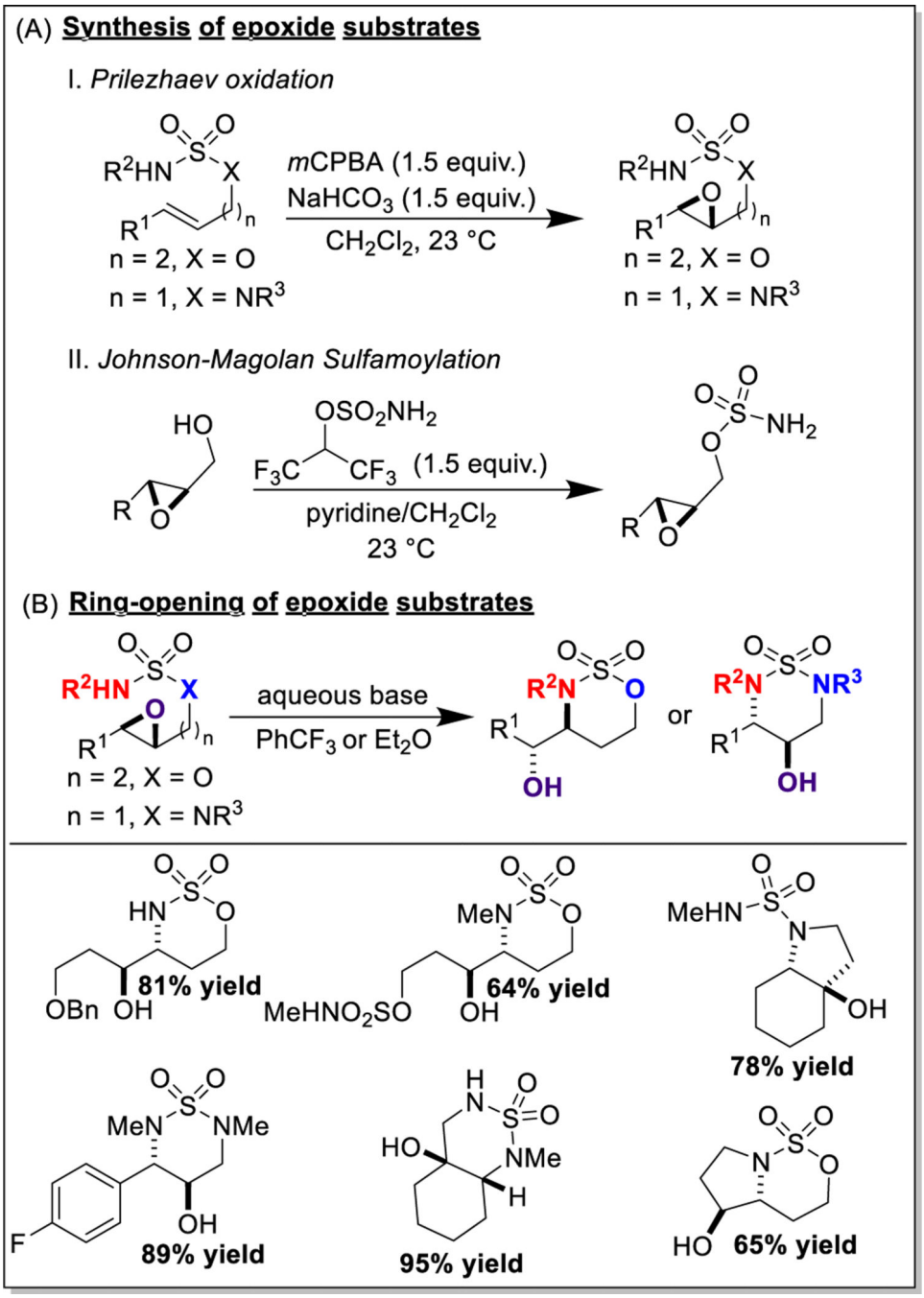
Scheme 6.

An unusual 5-chloro-8-hydroxyquinoline arm allows for complete diastereocontrol in our phosphoramidate tethered *aza*-Wacker cyclization.



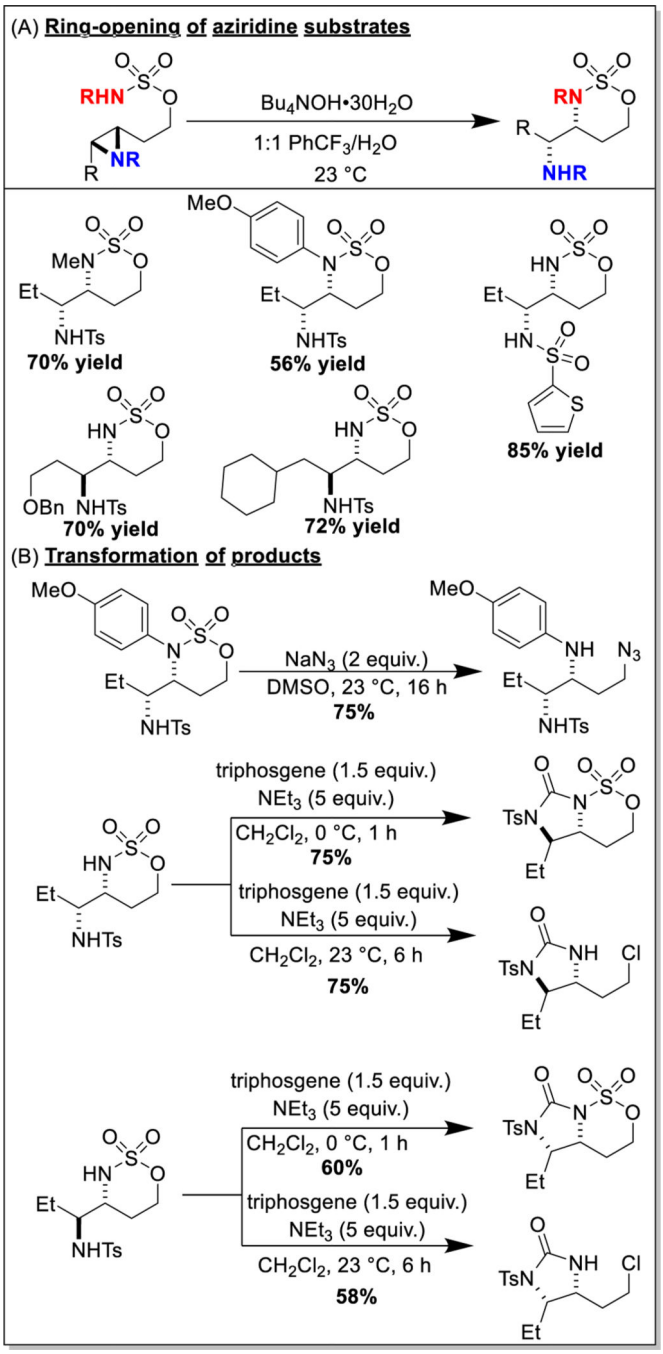
Scheme 7.

Conversion of cyclic phosphoramidates into (A) 1,3-chloroamines and (B) 1,3-aminoalcohols.



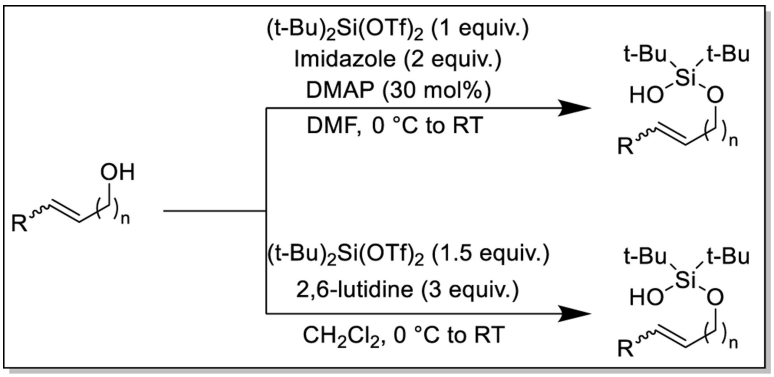
Scheme 8.

(A) Synthesis and (B) ring-opening of sulfamate epoxide substrates.

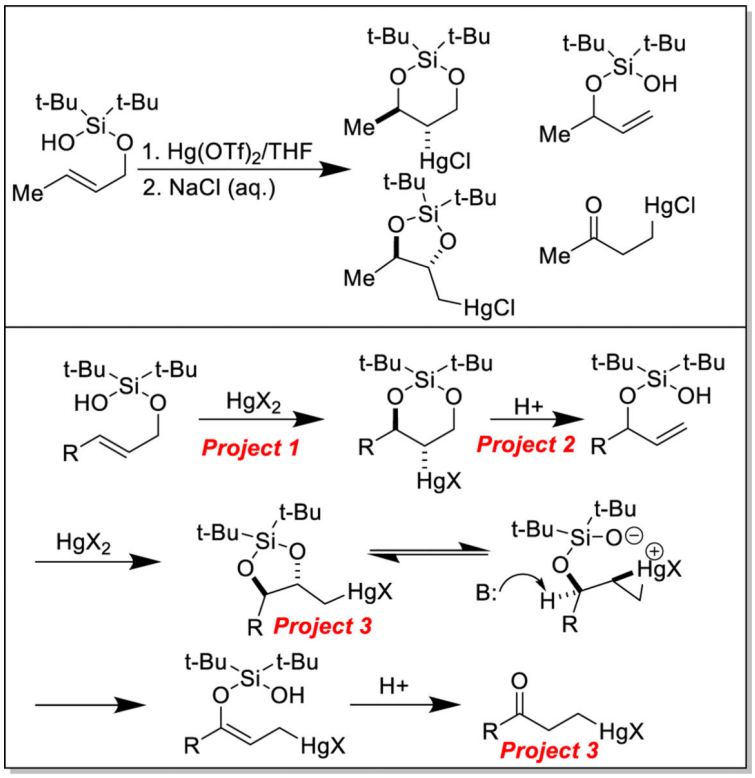


Scheme 9.

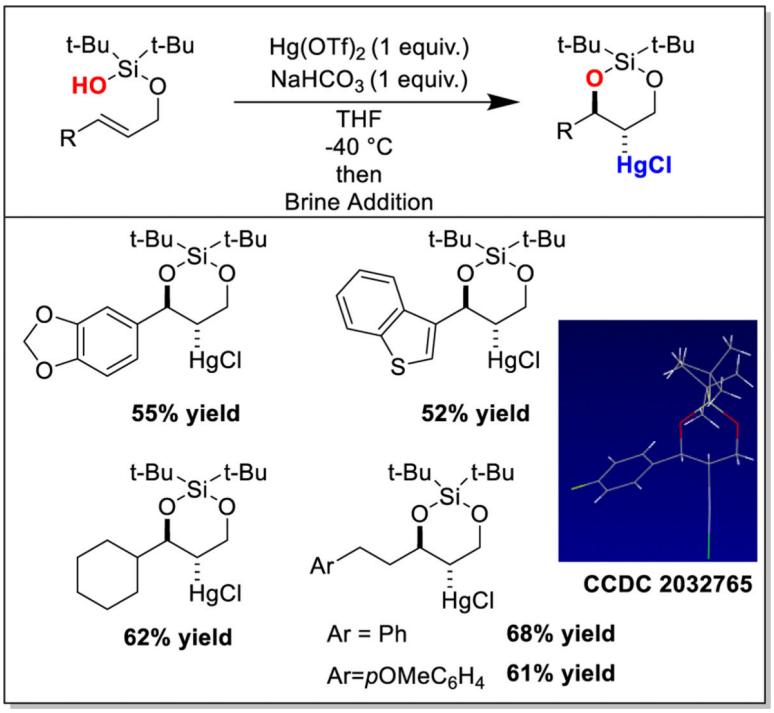
(A) Ring-opening of aziridines by pendant sulfamates. (B) Functionalization reactions of the products.



Scheme 10.
Synthesis of alkenyl silanols.

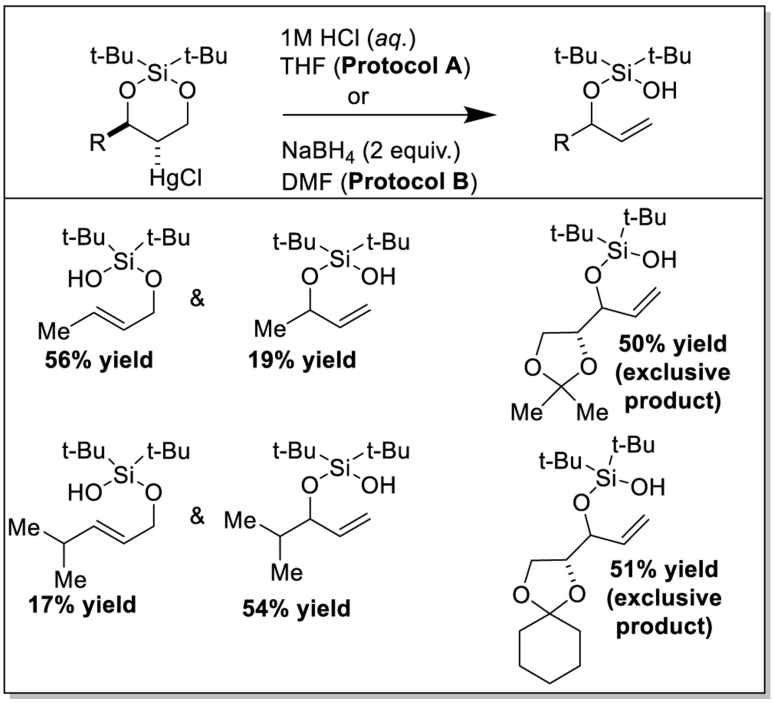


Scheme 11.
A remarkable cascade, likely triggered by adventitious TfOH.

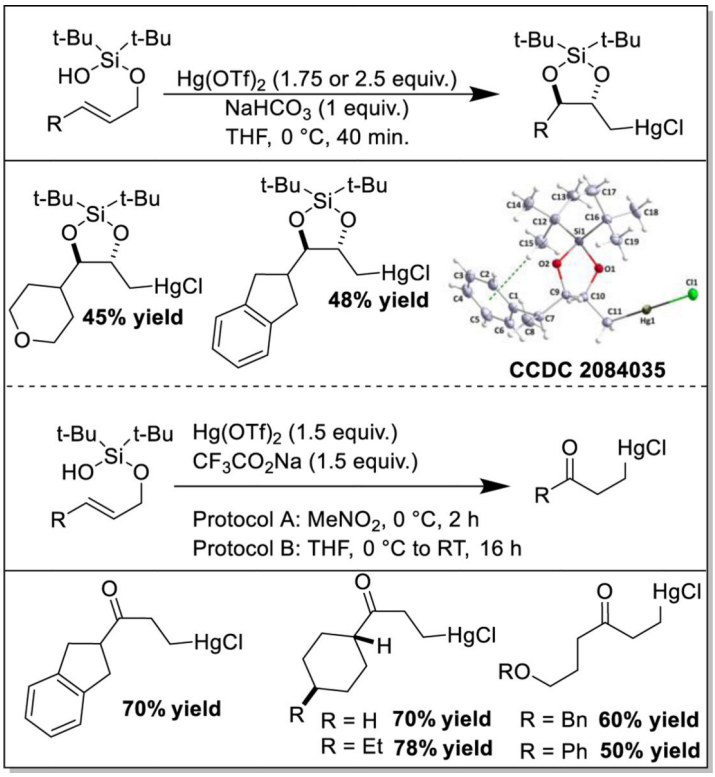


Scheme 12.

1 equivalent of $NaHCO_3$ stabilizes the dioxasilinane product.

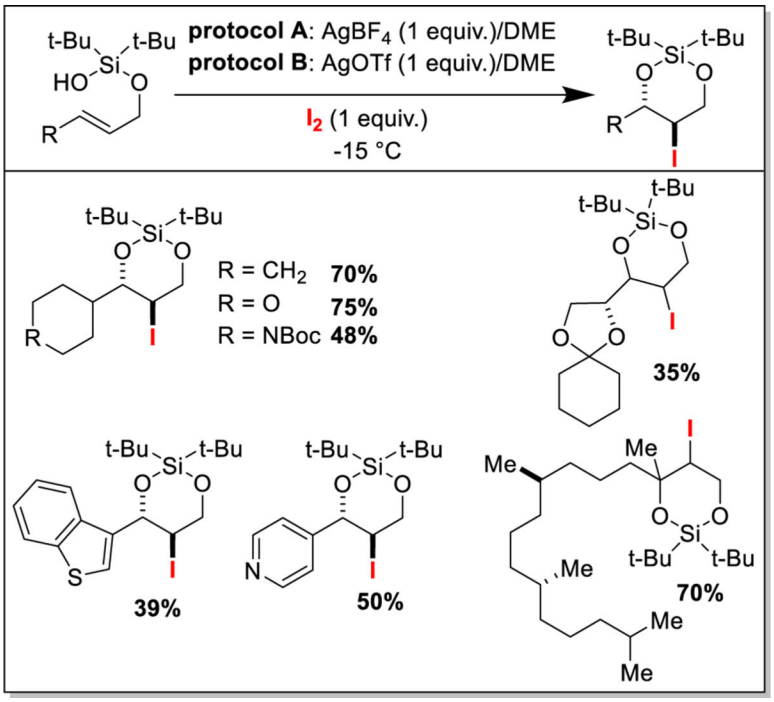


Scheme 13.
Formal rearrangement of allylic silanols.

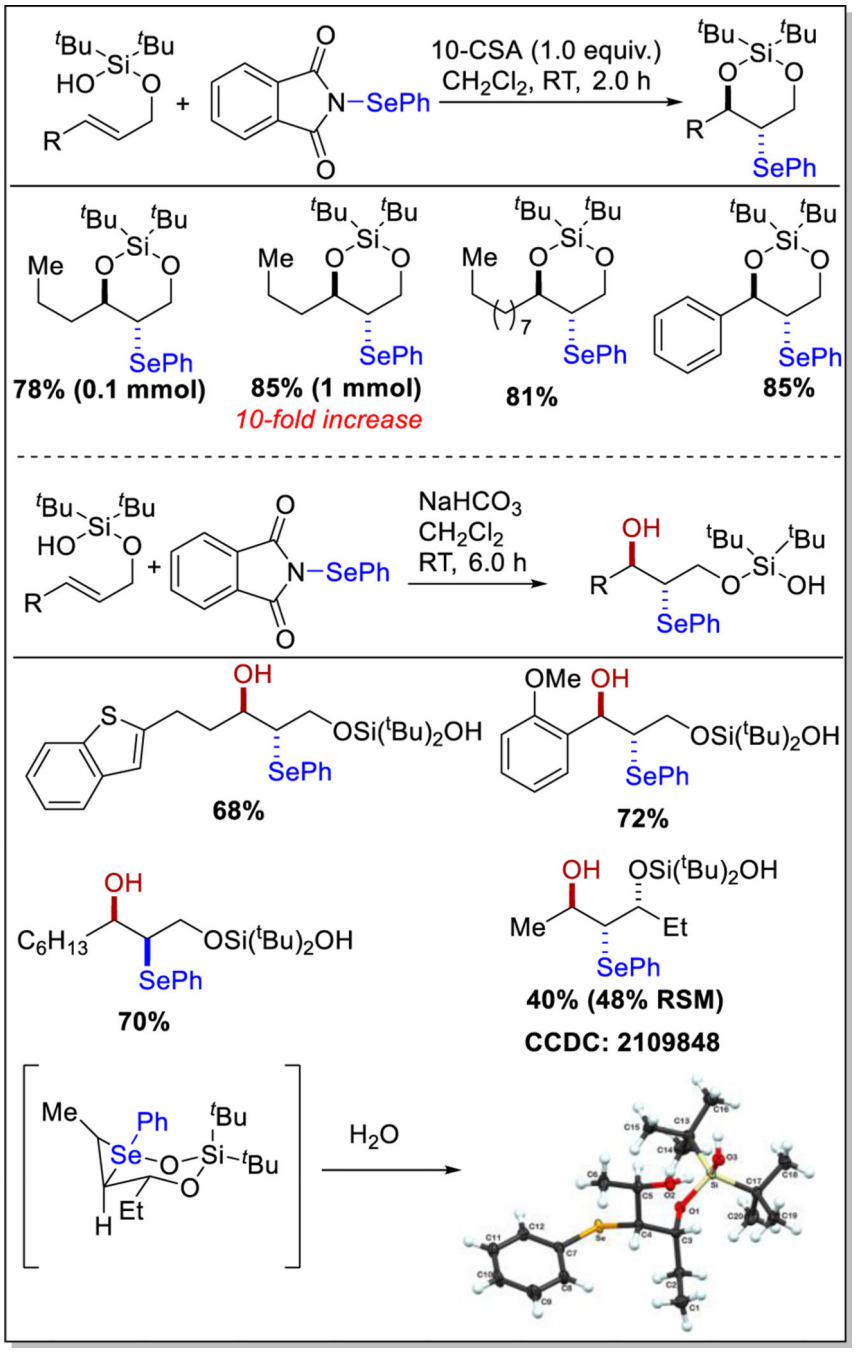


Scheme 14.

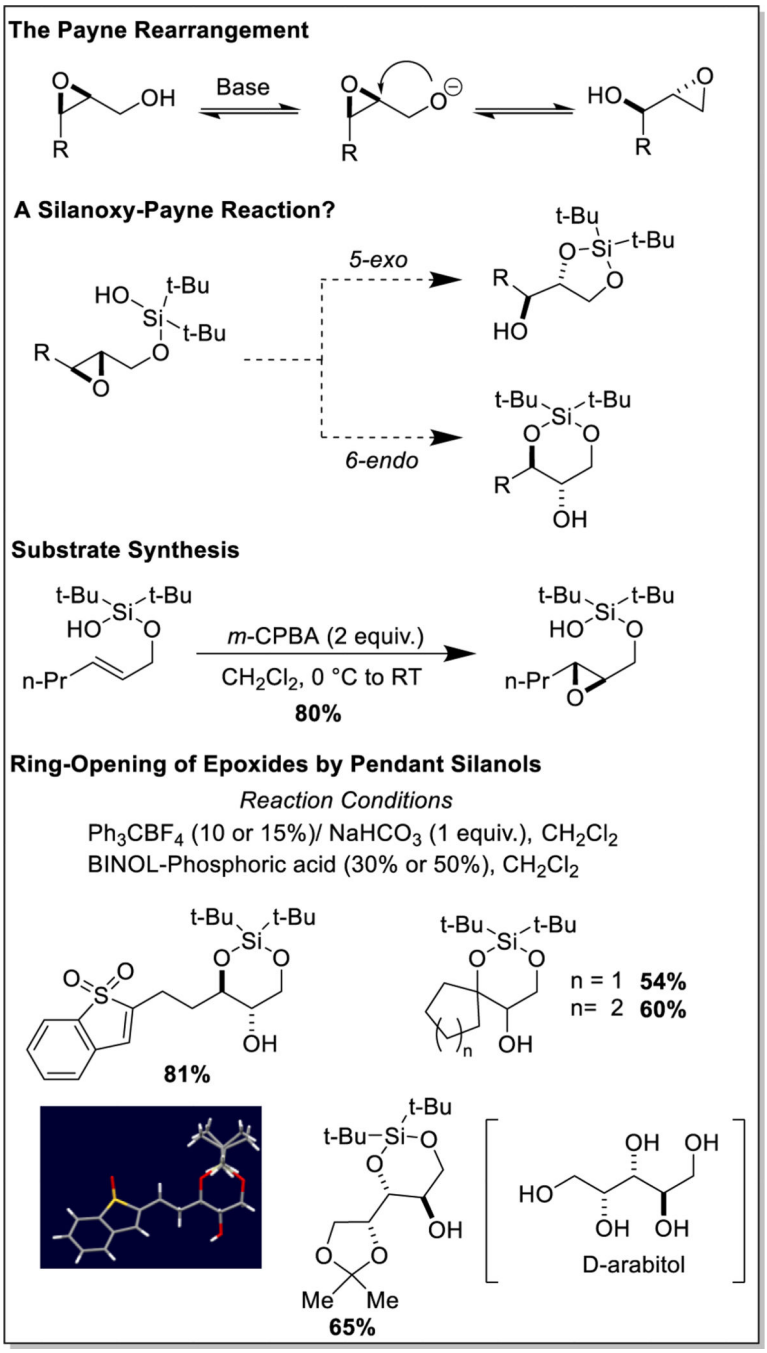
Dioxasilolanes and organomercury ketones from allylic silanols.



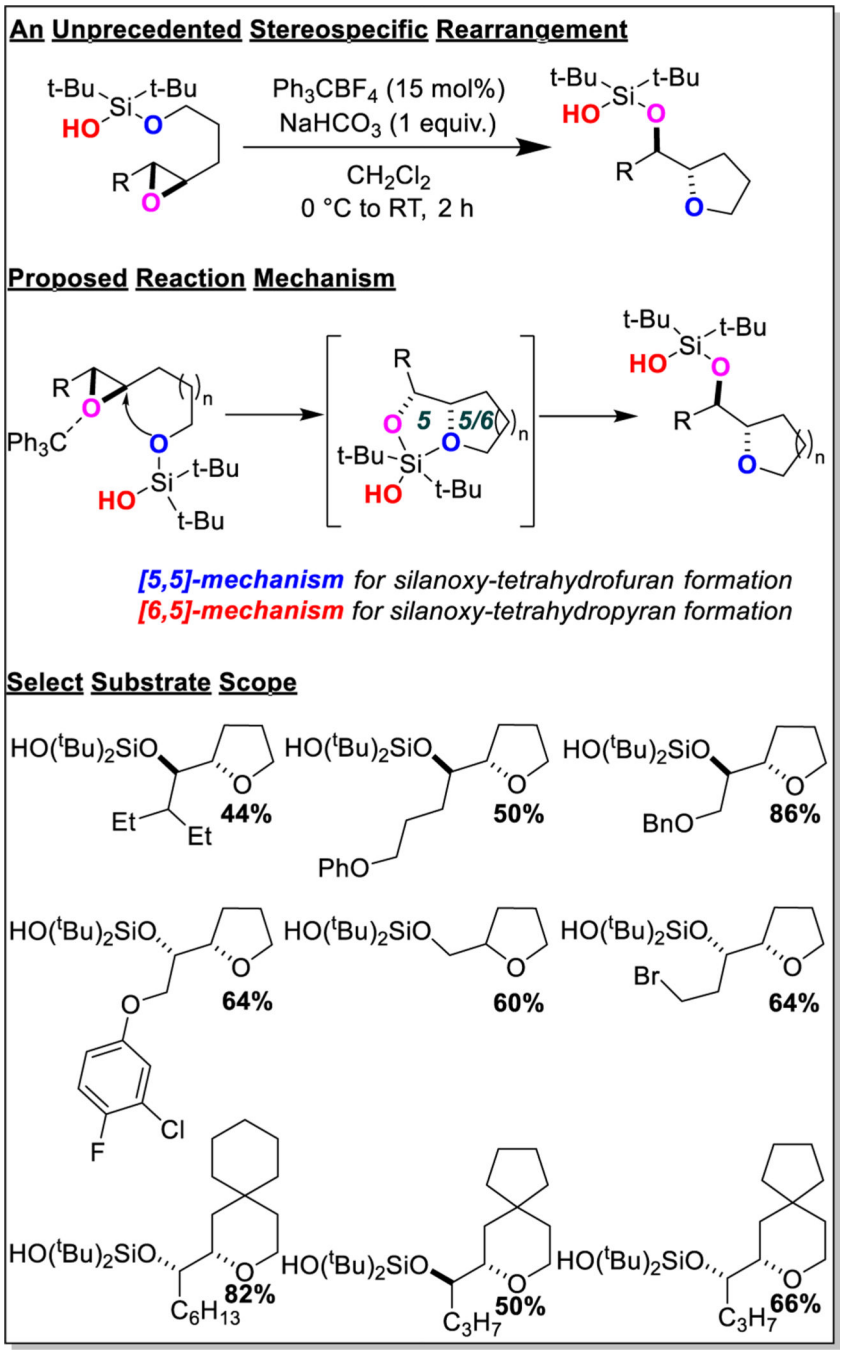
Scheme 15.
A tethered silanoxy-iodination reaction.



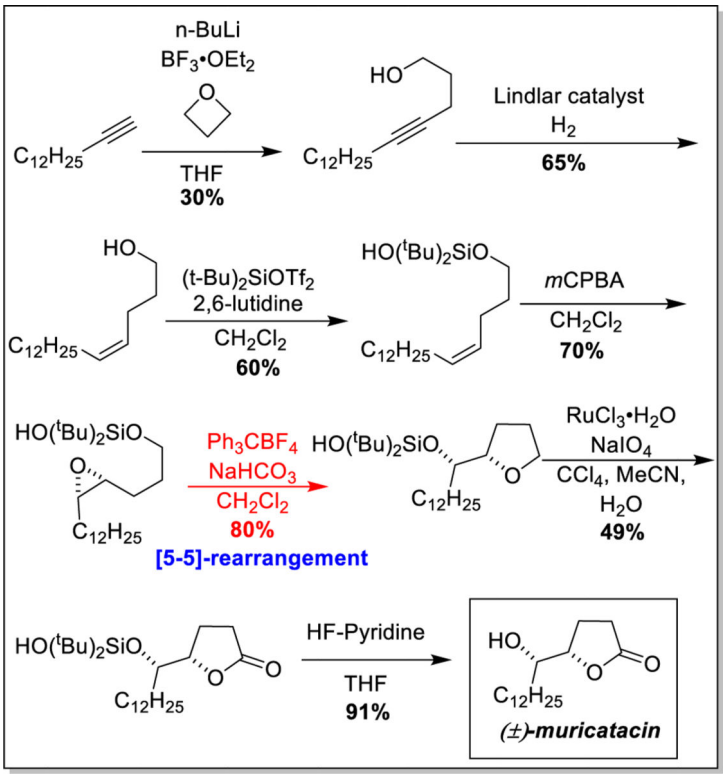
Scheme 16.
Silanoxyselenylation and hydroxyselenylation reactions.



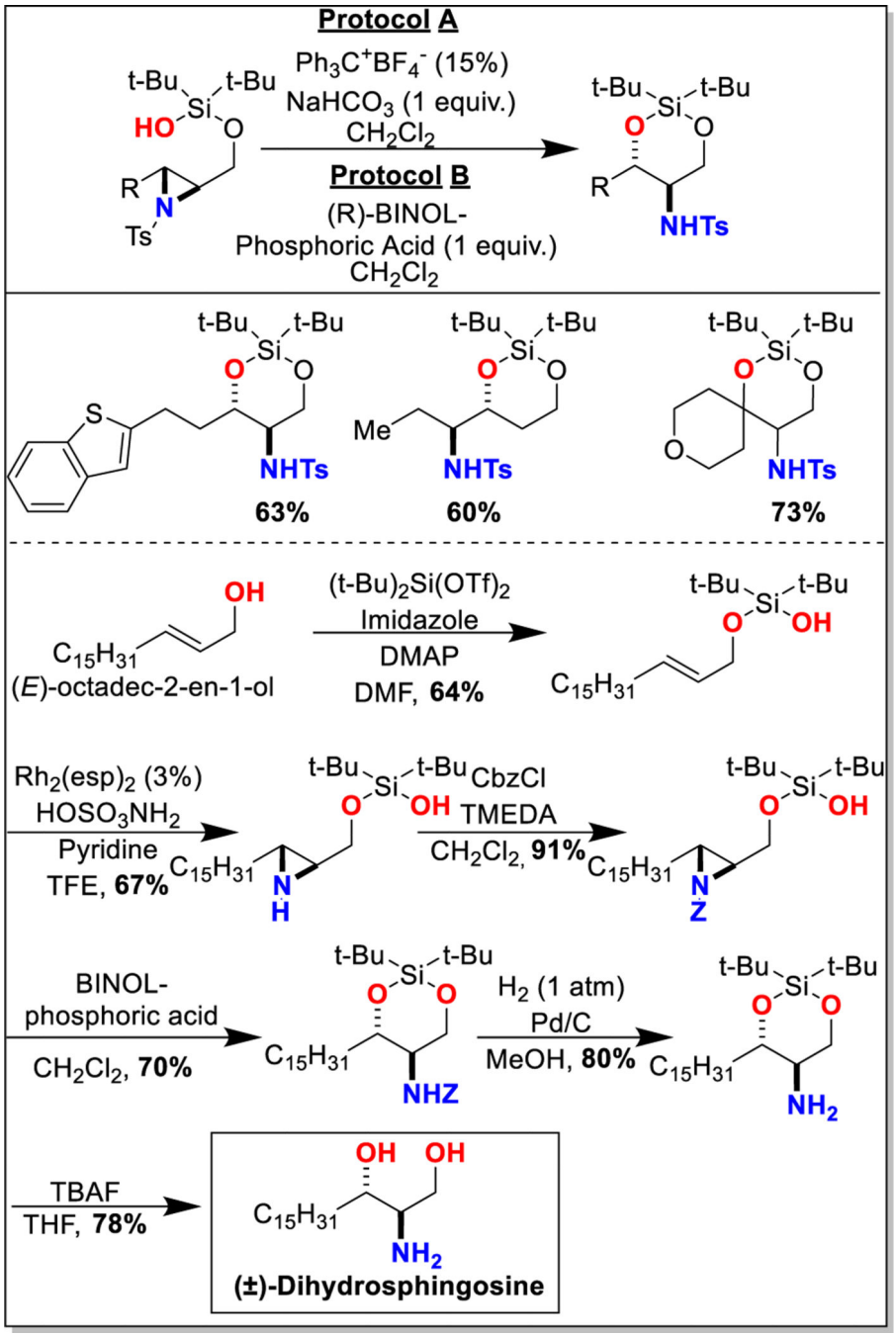
Scheme 17.
Cleavage of epoxides with silanol tethers.



Scheme 18.
"Dancing" silanols.

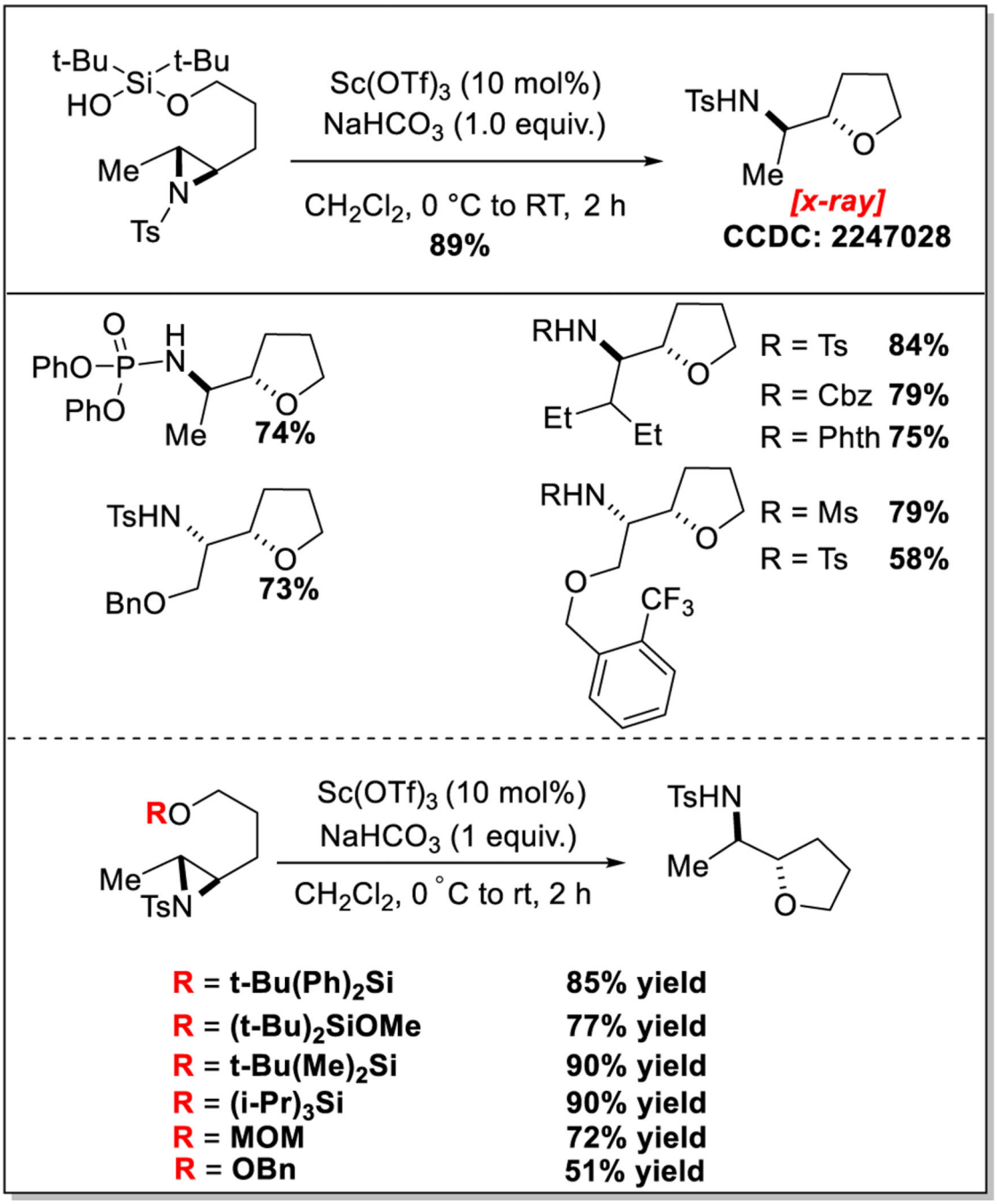


Scheme 19.
A short preparation of muricatacin.

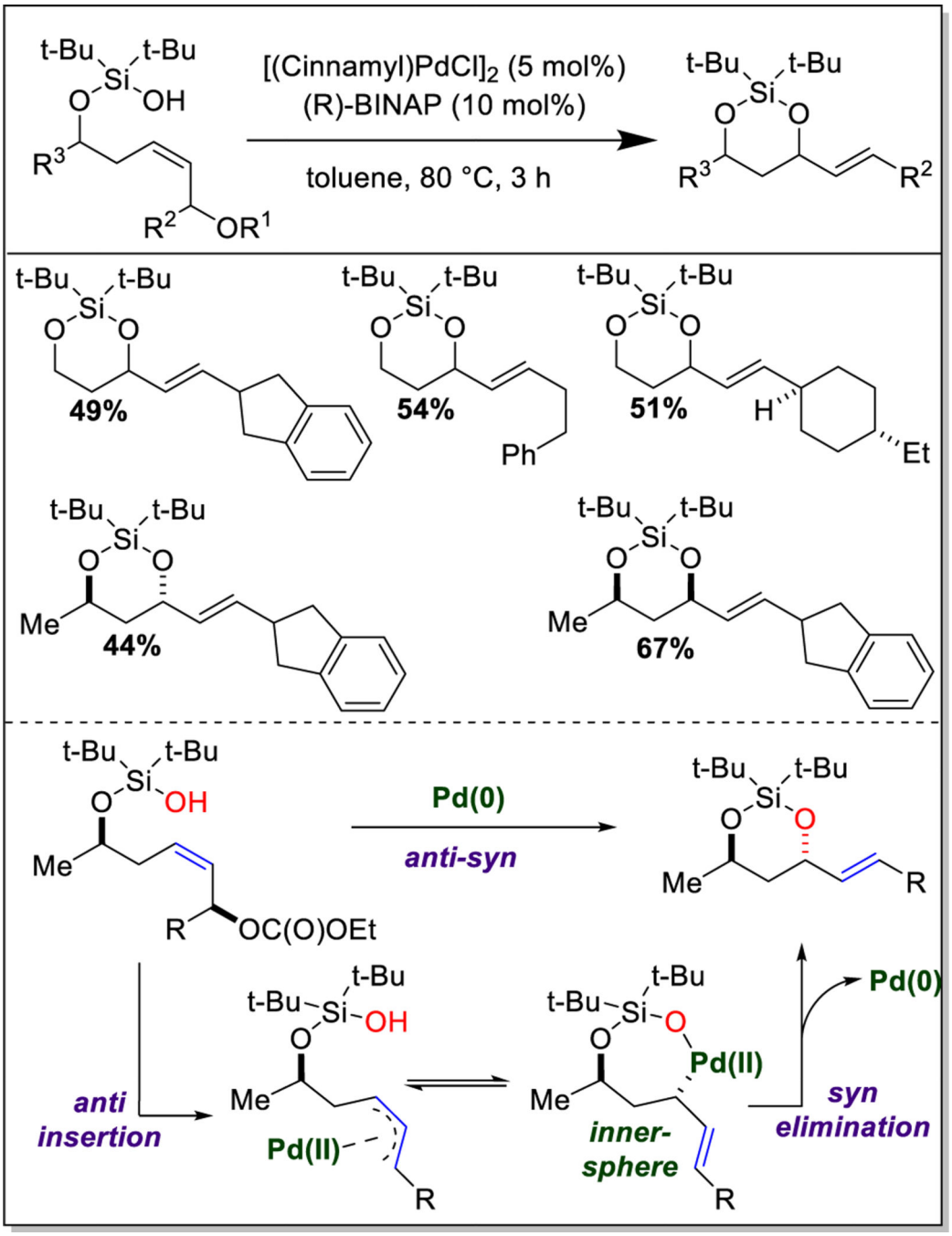


Scheme 20.

Ring opening of aziridines by pendant silanols allows for the preparation of sphingosine-type natural products.



Scheme 21.
Stereospecific preparation of 1’-amino-tetrahydrofurans.



Scheme 22.
Interception of palladium pi-allyl species by pendant silanols.