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Ring Opening of Aziridines by Pendant Silanols Allows for Preparations of (±)-Clavaminol H, (±)-Des-Acetyl-Clavaminol H, (±)-Dihydrosphingosine, and (±)-*N*-Hexanoyldihydrosphingosine

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Abstract

We present a unique strategy for the synthesis of vicinal amino alcohols. Ring opening of aziridines with pendant silanols is compatible with a range of substrates. To engage productively in ring opening, the aziridine must be at least mildly activated, and a variety of such *N*-substituents are tolerated. The utility of this methodology is highlighted in facile preparations of the natural products (±)-Clavaminol H, (±)-dihydrosphingosine, and (±)-*N*-hexanoyldihydrosphingosine as well as a natural product analogue (±)-des-acetyl-Clavaminol H.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02496.
Experimental procedures, reasoning for structural assignments, NMR spectra, and crystallographic information. (PDF)

Accession Codes

CCDC 2177671–2177672 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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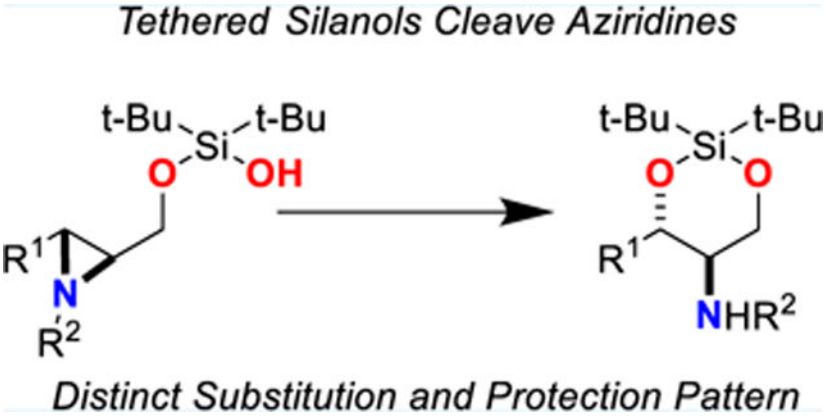
The authors declare no competing financial interest.



Amino alcohols are important constituents of biologically active molecules[1–3] and have inspired the invention of many elegant techniques for their construction (Scheme 1).[4,5,59] Pioneering efforts on syntheses of vicinal amino alcohols have focused on transition metal catalyzed processes to install both *N*- and *O*-moieties in a single transformation.[6–8] A complementary approach is the ring opening of epoxides with *N*-nucleophiles and of aziridines with *O*-nucleophiles.[9,10] This untethered approach[11–16] is convenient from the perspective of step counts, but challenges with regiocontrol often result in intractable product mixtures. Temporary tethering using Lewis acid templates affords excellent regiocontrol with epoxides,[17–22] but only one such report exists with aziridines.[23] Our laboratory has a programmatic focus on the development of the di-*tert*-butyl-silanol auxiliary into a uniquely reactive functional handle.[24–29] We envisioned a ring opening of aziridines by pendant di-*tert*-butyl silanol auxiliaries, which would afford protected amino alcohols in a single transformation. Here, we show our development of this reaction, and its application in the rapid assembly of select natural products and analogues.

Before we could begin work on our target reaction, we had to devise a way to access the starting materials (Scheme 2). There are many excellent protocols for the syntheses of aziridines.[30,31] Fortunately, many of these are compatible with the alkenyl silanol (Scheme 2A), and the majority of our substrates were prepared using the Sharpless,[32] Sudalai,[33] Che,[34,35] or Kürti reaction.[36] We have also found that the combination of $(t\text{-Bu})_2Si(OTf)_2$ (1.5 equiv) and 2,6-lutidine (3 equiv) allows for silanol attachment to aziridine alcohols (Scheme 2B).

Our work on the ring opening of epoxides with pendant silanols[25] informed our efforts with their aziridine relatives[37] (Scheme 3). Optimization experiments were performed using di-*tert*-butyl(2-((2S*,3S*)-3-ethyl-1-tosylaziridin-2-yl)ethoxy)-silanol, prepared in one step using a Sharpless aziridination of (*E*)-di-*tert*-butyl(hex-3-en-1-yloxy)silanol. Treating this aziridine silanol with 10 mol % of $Ph_3C^+BF_4^-$ and 1 equiv of $NaHCO_3$ afforded cyclized product in a 45% yield (Scheme 3, entry 1). Increasing the reaction time from 2 to 16 h did not lead to greater product formation (Scheme 3, entry 2), and decreasing the catalyst loading to 5 mol % was markedly deleterious (Scheme 3, entry 3). An increase in catalyst loading from 10 mol % to 20 mol % was not helpful (Scheme 3, entry 4). Switching to BINOL-phosphoric acid (loadings of 30 and 50 mol %) (Scheme 3, entries 5 and 6)

gave a modest boost to reaction performance. The best result came with using 1 equiv of BINOL-phosphoric acid in CH_2Cl_2 (Scheme 3, entry 7). Based on these studies, we chose two protocols [Protocol A: $Ph_3C^+BF_4^-$ (15 mol %)/$NaHCO_3$ (1 equiv)/CH_2Cl_2 and Protocol B: BINOL-Phosphoric acid/CH_2Cl_2] to test with a range of aziridine silanols.

We wished to establish the effect of various aziridine *N*-substituents on the performance of the cyclization reaction (Scheme 4). With N–H aziridine **1** (Scheme 4, entry 1), no reaction was observed, either with $Ph_3C^+BF_4^-$ or with BINOL-phosphoric acid. In contrast, with *N*-phthalimido aziridine **2**, cyclization afforded product in a 59% isolated yield (Scheme 4, entry 2). With more electron-withdrawing substituents, such as acetate (Scheme 4, entry 3) and tosylate (Scheme 4, entry 5) groups, cyclization markedly improved. Even appending naproxen, a remarkably bulky substituent, did not inhibit cyclization (Scheme 4, entry 4). Interestingly, even though benzyloxycarbonyl groups (Cbz) activate aziridines for ring opening (Scheme 4, entry 6), the yield of our cyclization dropped with *N*-Cbz aziridine **6**. The yield of product was excellent, however, with phosphoramidate **7**. Overall, a wide variety of *N*-substituents are tolerated by our cyclization protocol, but the aziridine must be at least somewhat activated to engage productively.

Many aziridine substrate classes were compatible with cyclization protocols A ($Ph_3C^+BF_4^-$/$NaHCO_3$) and B (BINOL-phosphoric acid), including *trans*-disubstituted aziridine silanols (Scheme 5, entries 1–5 and 8–9), *cis*disubstituted aziridine silanols (Scheme 5, entries 6 and 7), and trisubstituted aziridine silanols (Scheme 5, entries 10–12). Many functionalities were tolerated, including aryl halides (Scheme 5, entries 3 and 8), CF_3 groups (Scheme 5, entry 3), benzothiophene heterocycles (Scheme 5, entry 4), and alkyl ethers (Scheme 5, entry 11). Crystal structures of products **27** (Scheme 4) and **48** (Scheme 5) enabled us to confidently assign product identity and relative stereochemistry. In general, the best protocol for a substrate class was determined through empiric testing (as an example, see Scheme 5, entry 4). Thus, for substrates not shown here, we recommend unbiased evaluation of both protocols A and B.

Our success with the range of substrates shown in Schemes 4 and 5 prompted us to apply this reaction as a key step in the assembly of a variety of sphingosine-type natural products, a storied class whose members have demonstrated biological activity.[38,39] Commercially available (*E*)-dodec-2-en-1-ol was converted into silanol **51** using our laboratory's standard silylation protocol (Scheme 6A). A Kürti aziridination followed by acetylation gave cyclization precursor **53**. Cyclization with $Ph_3C^+BF_4^-$/$NaHCO_3$ formed **54** in a 75% yield. TBAF removal of the silyl group yielded (±)-Clavaminol H[40–44] which could be converted into (±)-des-acetyl-Clavaminol H[45–47] upon heating with 6 M aqueous HCl solution. A similar strategy was applied for the synthesis of (±)-*N*-hexanoyldihydrosphingosine[48] (Scheme 6B). (±)-*N*-Hexanoyldihydrosphingosine is commercially available, but to our knowledge, ours is the first synthesis of this target. Protecting **56** with CbzCl followed by our BINOL-phosphoric acid promoted cyclization furnished key intermediate **60**, which was then globally deprotected into (±)-Dihydrosphingosine (Scheme 6C).[49–58]

In summary, we present a unique strategy for the synthesis of vicinal amino alcohols. Ring opening of aziridines with pendant silanols is compatible with a variety of *N*-substituents

and alkyl chains. The utility of this methodology is demonstrated *via* facile preparations of (±)-Clavaminol H, (±)-Dihydrosphingosine, (±)-*N*-Hexanoyldihydrosphingosine, and (±)-des-acetyl-Clavaminol H. Given the ubiquity of the vicinal amino alcohol motif in targets of value, this technology is a welcome addition to the synthetic armory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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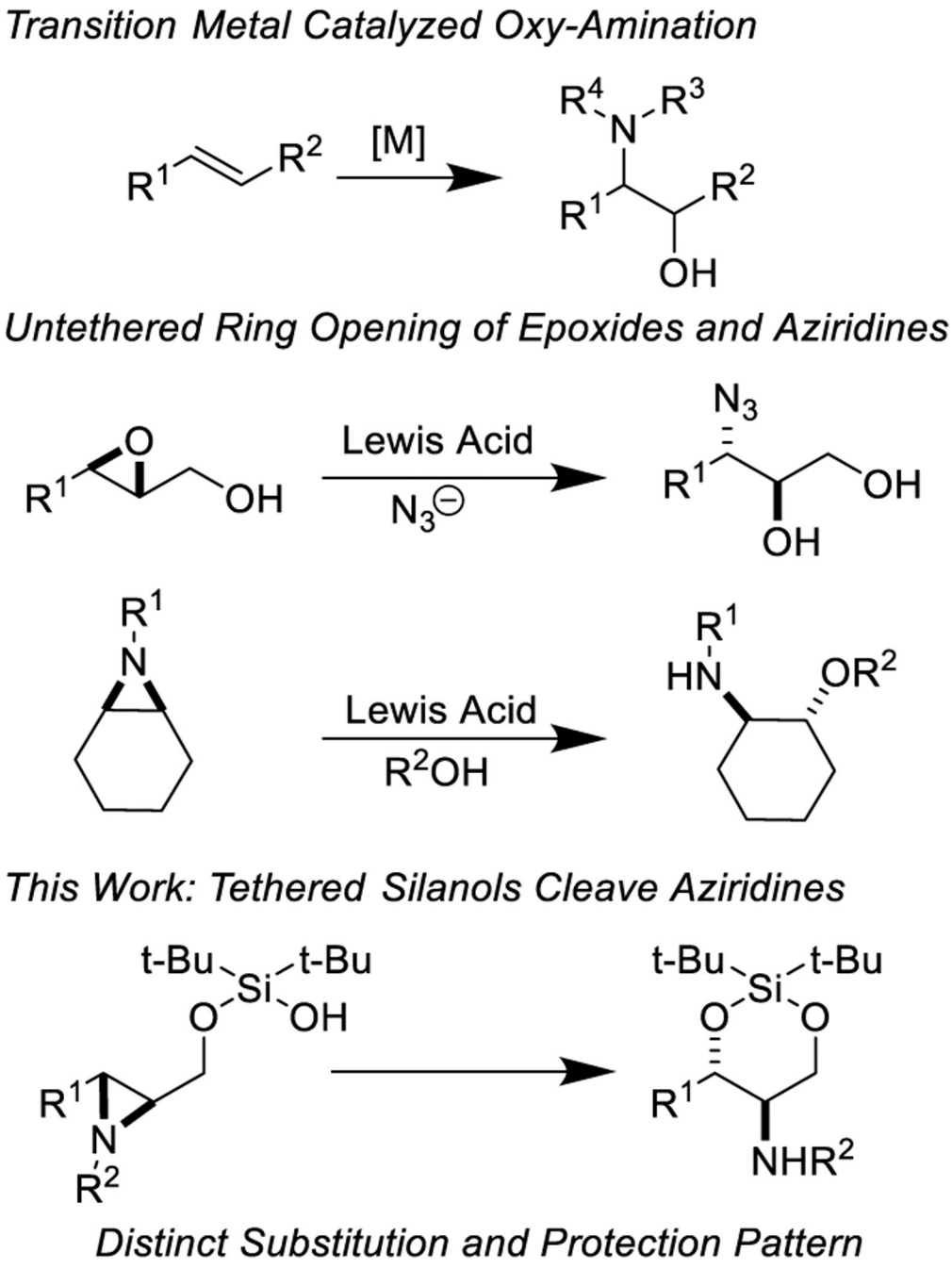
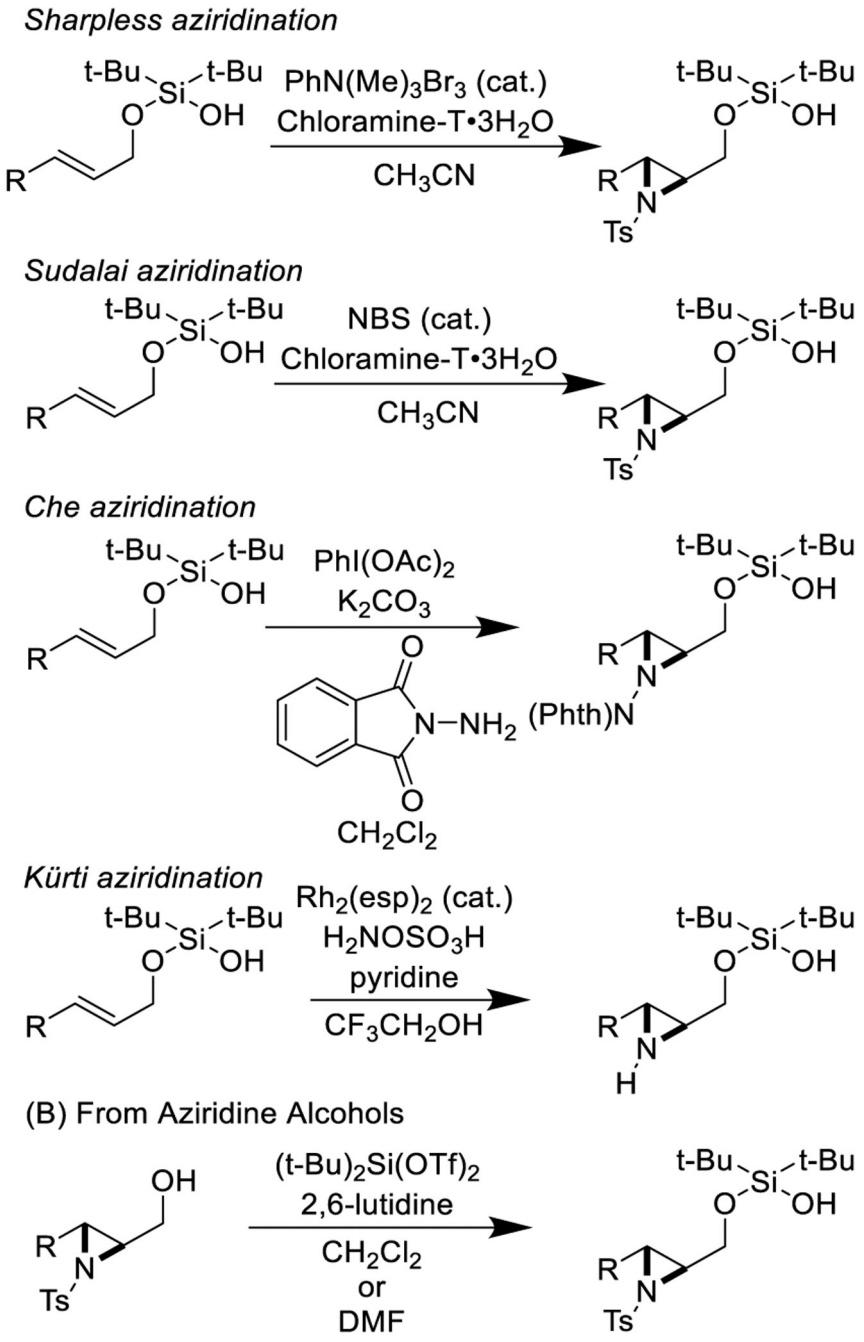


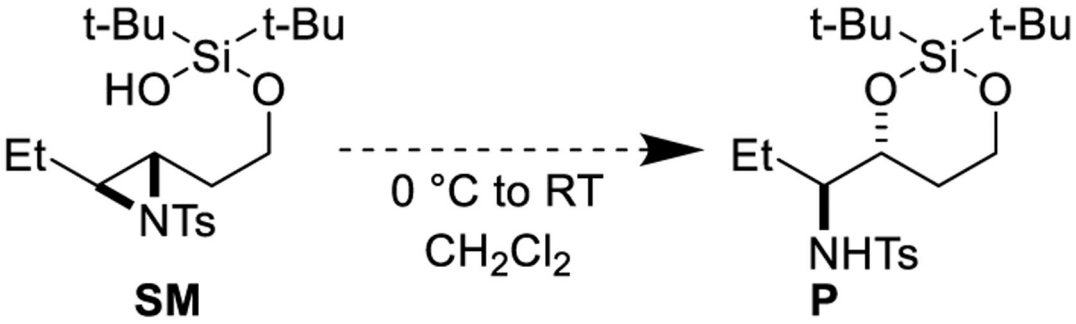
Scheme 1.

Approaches to Syntheses of *vic*-Amino Alcohols Juxtaposed with Our Work



Scheme 2.

Aziridine Silanols Can Be Prepared from (A) Alkenyl Silanols and (B) Aziridine Alcohols



SM **P**

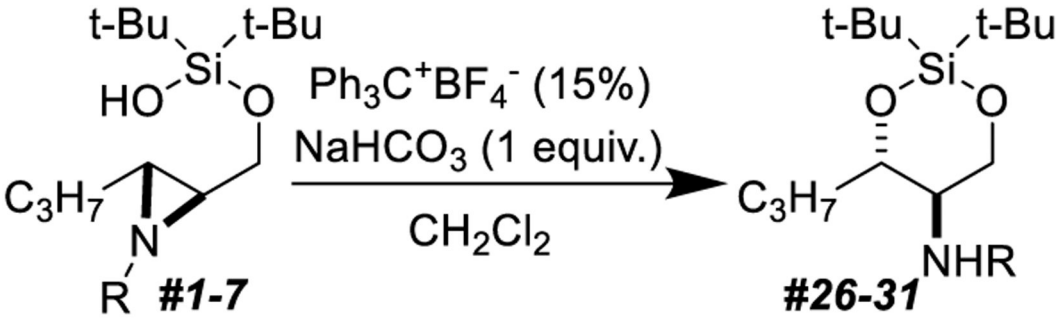
Entry	Conditions	Time	P[a]
1	$Ph_3C^+ BF_4^-$ (10%) $NaHCO_3$ (1 equiv.)	2 h	45%
2	$Ph_3C^+ BF_4^-$ (10%) $NaHCO_3$ (1 equiv.)	16 h	40%
3	$Ph_3C^+ BF_4^-$ (5%) $NaHCO_3$ (1 equiv.)	2 h	25%
4	$Ph_3C^+ BF_4^-$ (20%) $NaHCO_3$ (1 equiv.)	2 h	45%
5	BINOL-Phosphoric Acid (30%)[b]	16 h	50%
6	BINOL-Phosphoric Acid (50%)[b]	16 h	50%
7	BINOL-Phosphoric Acid (1 equiv.)[b]	16 h	60%

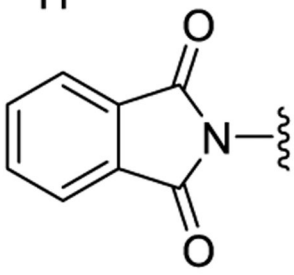
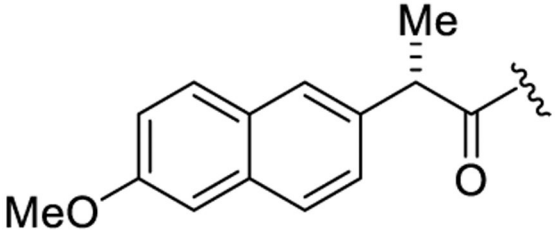
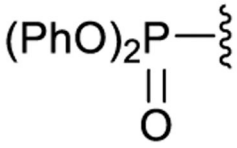
Scheme 3.

Reaction Optimization

[a]Yield estimated from ^{1}H NMR Integration with 4-nltrotoluene as an internal standard.

[b](*R*)-(−)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate, arbitrarily chosen.

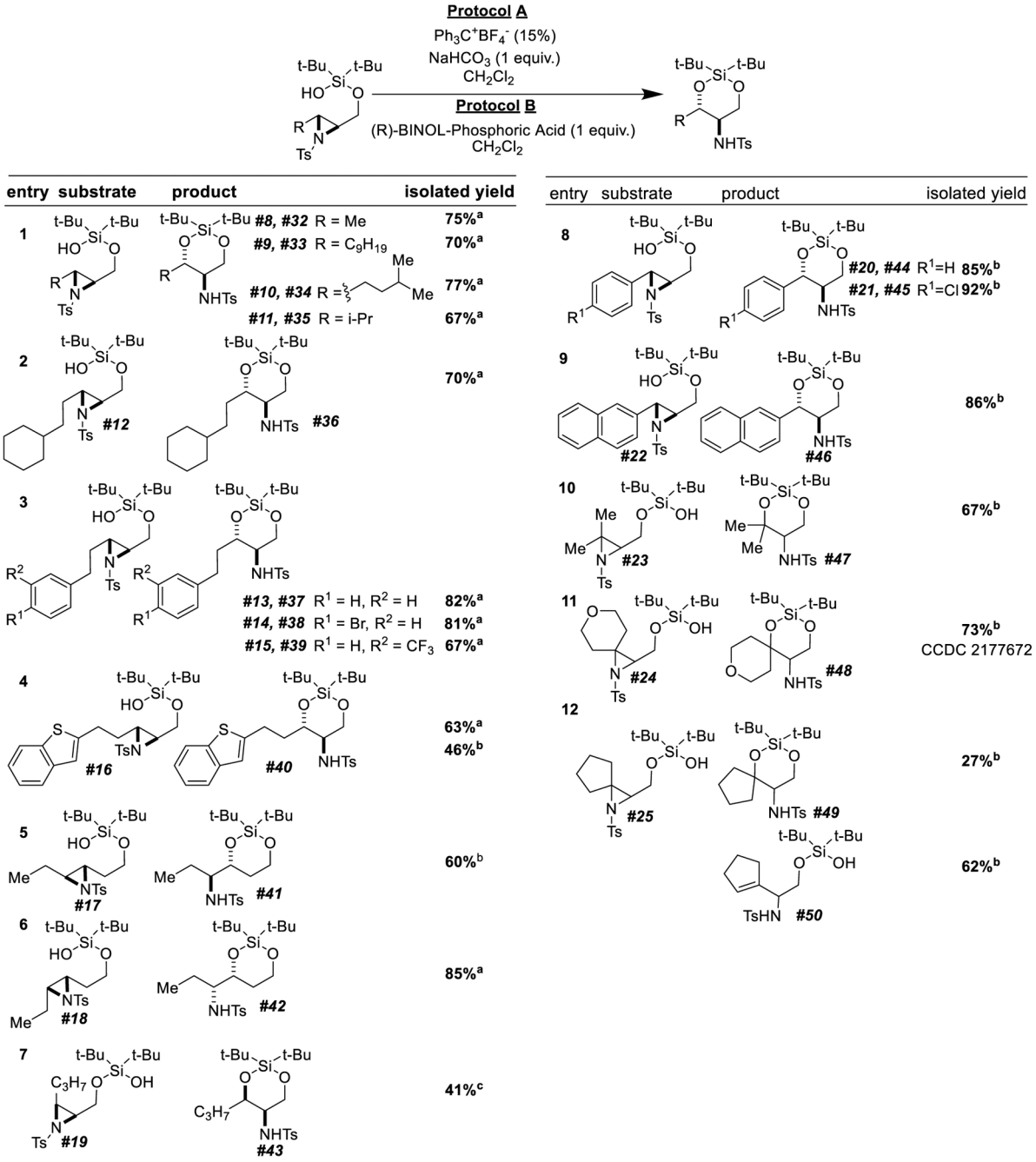


Entry	R		Isolated Yield
1	H	(#1)	No reaction[a]
2		(#2, #26)	59%
3	Ac[b]	(#3, #27)	80%[c]
4		(#4, #28)	69%
5	Ts[b]	(#5, #29)	83%
6	Cbz[b]	(#6, #30)	59%
7		(#7, #31)	80%

Scheme 4.

Effect of the Aziridine *N*-Substituent

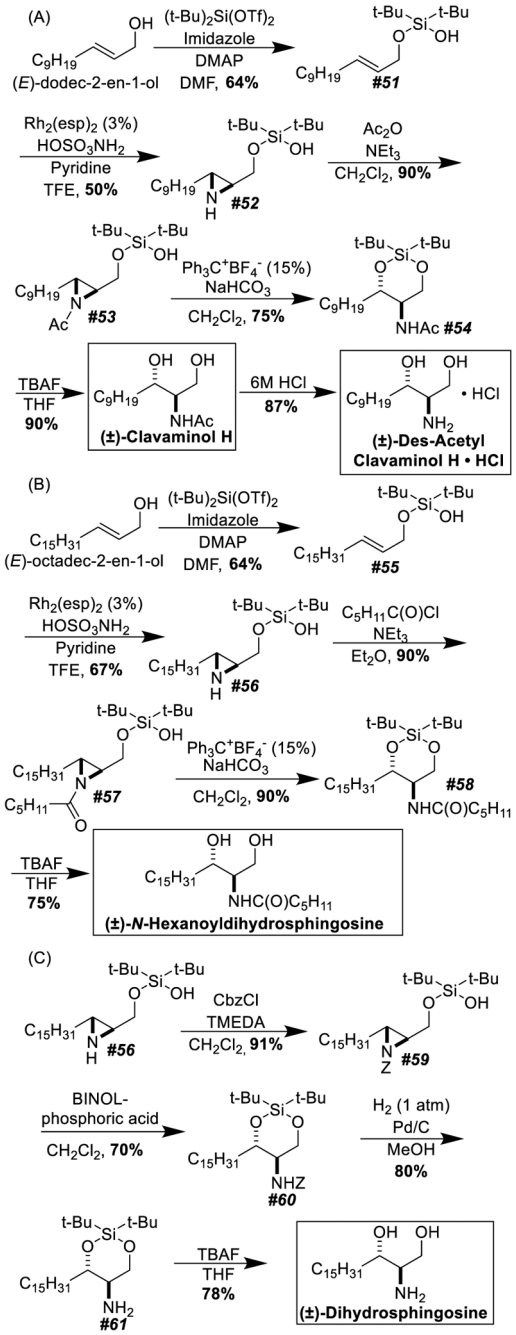
[a]Cyciization was also attempted with (*R*)-BINOL Phosphoric Acid, and starting material was recovered. [b]Ac = Acetyl; Ts = Tosyl; Cbz = benzyloxycarbonyl. [a]CCDC: 2177671.



Scheme 5.

Substrate Scope

[a]Protocol A. [b]Protocol B. [c]Protocol A but with 30 mol % $Ph_3C^+BF_4^-$ and reaction time of 12 h



Scheme 6.

Assembly of Some Natural Amino Alcohols