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Hydroamination |*Hot Paper*|

Synthetic Efforts toward the *Lycopodium* Alkaloids Inspires a Hydrogen Iodide Mediated Method for the Hydroamination and Hydroetherification of Olefins

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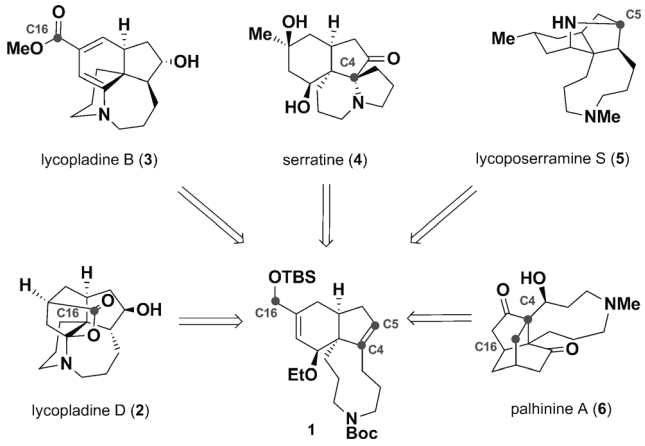
Abstract: Progress toward the total syntheses of a diverse set of fawcettimine-type *Lycopodium* alkaloids via a "Heathcock-type" 6–5–9 tricycle is disclosed. This route features an intermolecular Diels–Alder cycloaddition to rapidly furnish the 6–5-fused bicycle and a highly chemoselective directed hydrogenation to build the azonane fragment. While conducting these synthetic studies, trimethylsilyl iodide was found to effect a hydroamination reaction to furnish the tetracyclic core of serratine and related natural products. This observation has been expanded into a general method for the room temperature hydroamination of unactivated olefins with tosylamides utilizing catalytic "anhydrous" HI (generated in situ from trimethylsilyl iodide and water). The presence of the iodide anion is critical to the success of this Brønsted acid catalyzed protocol, possibly due to its function as a weakly coordinating anion. These conditions also effect the analogous hydroetherification reaction of alcohols with unactivated olefins.

Introduction

Natural products are selected as targets for synthesis for a variety of reasons. For example, many natural products display fascinating biological activity that can be more deeply investigated with ready access to the natural compound as well as unnatural derivatives. Structurally complex natural products offer opportunities to test and extend the scope of new methods and explore novel strategies for synthesis. Finally, the high density of functional groupings in natural products offer unique scenarios that often yield surprising transformations that may then be extended to other systems.

Our group has maintained an interest in the total synthesis of members of the *Lycopodium* alkaloid class of natural products over the last decade.[1] These alkaloids possess interesting biological activity as well as challenging structural complexity, which makes them attractive synthetic targets.[2] In our approach to a variety of architecturally unique fawcettimine-type *Lycopodium* alkaloids, we became drawn to a divergent strategy that would employ 6–5–9 "Heathcock-type" tricycle **1** (Scheme 1).[3] This synthetic plan has the potential to provide access to natural products including lycopladine D (**2**), lycopladine B (**3**), serratine (**4**), lycoposerramine S (**5**), and palhinine A (**6**).



Scheme 1. A divergent approach to a variety of *Lycopodium* alkaloids.

Strategies that employ a common intermediate related to **1** for the synthesis of *Lycopodium* alkaloids have been documented for almost 30 years.[2b] We were interested in extending this Heathcock-inspired strategy to the synthesis of a more diverse group of *Lycopodium* alkaloids in which additional carbon–carbon or carbon–heteroatom bonds exist. For example, lycopladine B (**3**) and lycopladine D (**2**) are further oxidized at C16. Serratine (**4**) and lycoposerramine S (**5**) both possess rare C–N bonds at C4 and C5, respectively. Finally, palhinine A (**6**) contains an additional C–C bond between C16 and C4 that results in a very congested 2.2.2 bicyclic core. We envisioned all of these natural products arising from the functionalization of a common, tricyclic intermediate (**1**). Tricycle **1** could be prepared from the elaboration of bicycle **7** (Scheme 2), which, in turn, could arise from diene **8** and dienophile **9** using a Diels–Alder reaction.

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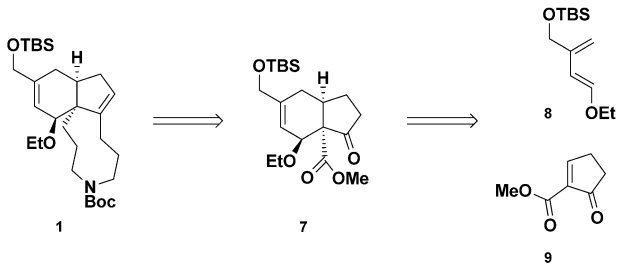


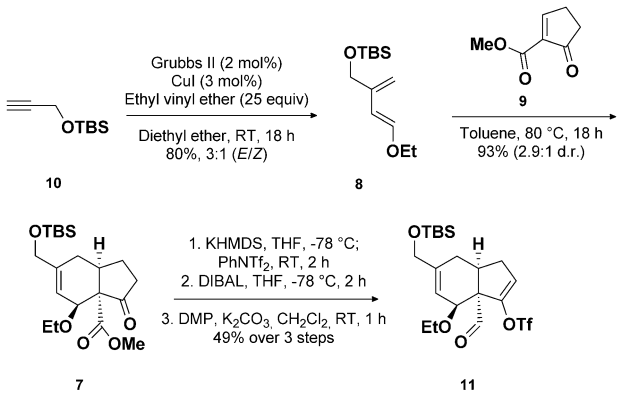
Scheme 2. Retrosynthesis of tricycle **1.**

In this paper, we describe the realization of this synthetic plan for the preparation of tricycle **1** and the advancement of this intermediate to the synthesis of the skeleton of serratine (**4**) using a late-stage transannular alkene hydroamination. This transformation has led to the development of more general alkene hydroamination and hydroalkoxylation protocols, the studies of which are also described.

Results and Discussion

Synthesis of "Heathcock-type" tricycle 1

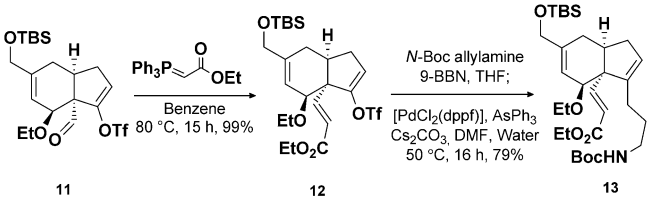
The synthesis of **1** commenced with the preparation of diene **8** and dienophile **9**. Given the established efficiency of an enyne metathesis approach for the synthesis of substituted dienes related to **8**,[4] we utilized this approach to rapidly synthesize large quantities of this requisite diene (Scheme 3). Ethyl



Scheme 3. Forward synthesis to aldehyde **11.**

vinyl ether was selected as the alkene partner in the enyne metathesis because of its low boiling point, which facilitates the removal of the excess olefin that is often required for good conversions. The enyne metathesis of ethyl vinyl ether and *tert*-butyldimethylsilyl (TBS)-protected propargyl alcohol (**10**) was most efficient under the conditions developed by the Lipshutz group (2 mol% Grubbs II, 3 mol% CuI),[5] which provided the desired diene (**8**) in 80% yield as a 3:1 mixture of *E*/*Z* isomers. Diene **8** was then used in a Diels–Alder reaction with readily available dienophile **9** to provide 6–5 bicycle **7** as a 2.9:1 mixture of diastereomers (major diastereomer illustrated; presumed to be *endo* relative to the ketone group). Bicyclic ketone **7** was converted to the corresponding vinyl triflate (not shown) using hard enolization conditions. The ester group was then reduced to the primary alcohol, which was oxidized with Dess–Martin periodinane to provide aldehyde **11** in 49% yield over three steps.

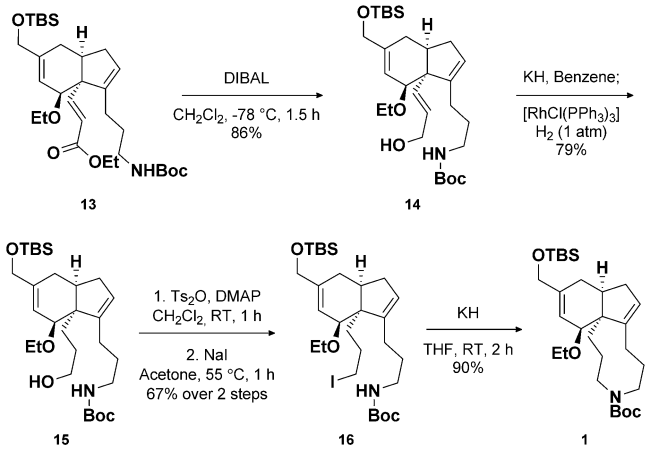
From aldehyde **11**, Wittig reaction gave enoate **12** (Scheme 4), which upon Suzuki cross-coupling with the borane



Scheme 4. Elaboration to amine **13.**

generated from *N*-Boc allylamine yielded *N*-Boc amine **13**. These cross-coupling conditions, based on precedent by Trost and Toste,[6] are uniquely effective for the Suzuki coupling of the sterically congested vinyl triflate. The introduction of the saturated three-carbon chain now installs all of the carbon atoms necessary for the targeted natural products. The synthesis of key intermediate **13** is achieved in 29% yield over seven steps from TBS-protected propargyl alcohol **10**.

Toward the synthesis of 6–5–9 tricycle **1**, ester **13** was reduced to provide allylic alcohol **14** (Scheme 5), which then



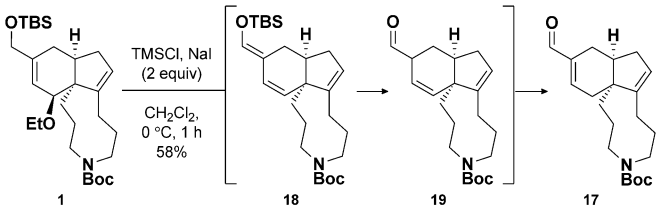
Scheme 5. Accessing 6–5–9 tricycle **1.**

served as a substrate in a directed hydrogenation with Wilkinson's catalyst to furnish **15**.[7] This hydrogenation was sensitive to both reaction time and the order of reagent addition, but typically proceeded in about 79% yield. Notably, it provided an avenue for chemo-differentiation of the three carbon–carbon double bonds in **14**. This is especially important because we were unable to effect a 1,4-reduction of enoate **13**. Activation of the primary alcohol (**15**) as the tosylate and dis-

placement with sodium iodide gave alkyl iodide **16** in 67% yield over the two steps. Alternatively, alcohol **15** could be converted to iodide **16** in one step using the Appel reaction, although this proceeded in lower yield as compared to the two-step procedure. Exposure of **16** to potassium hydride promoted the displacement of the iodide by the carbamate nitrogen to furnish the desired Heathcock-type 6–5–9 tricycle **1**.

Unexpected reactivity of tricycle 1

With tricycle **1** in hand, we began to investigate routes to diverge this versatile intermediate toward various fawcettimine-type *Lycopodium* alkaloids. Over the course of these studies, we observed the unexpected generation of enal **17** (Scheme 6)

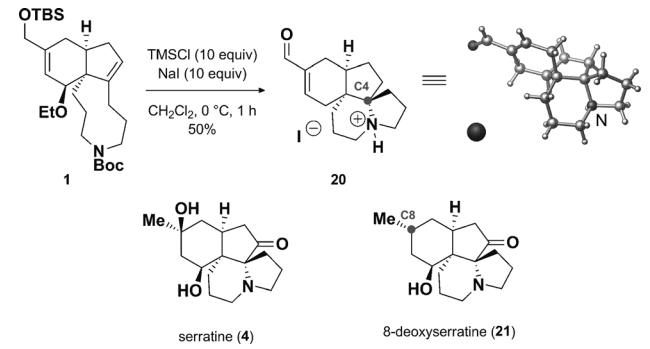


1 18 19 17

Scheme 6. Unexpected reactivity to furnish enal **17.**

when tricycle **1** was exposed to in situ generated trimethylsilyl iodide (TMSI). Enal **17** could potentially arise from trimethylsilyl or hydrogen iodide assisted loss of ethanol (to form **18**), followed by hydrolysis (to give **19**) and isomerization to the more thermodynamically favored enal (**17**).

To our delight, increasing the amount of TMSI from two to ten equivalents promoted the transformation of **1** to **20** (Scheme 7), which is the tetracyclic core of the natural prod-



1 20

Scheme 7. Unexpected reactivity to furnish tetracycle **20.**

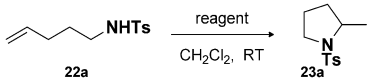
ucts serratine (**4**) and 8-deoxyserratine (**21**), in 50% yield. The structure of **20** was confirmed by X-ray crystallographic analysis of a single crystal.[8] In the remarkable conversion of **1** to **20**, not only was the bis allylic ether moiety on the six-membered ring converted to the enal motif (see Scheme 6), but also, the Boc-protecting group was cleaved and the resulting amine underwent transannular hydroamination with the carbon–carbon double bond in the five-membered ring to form a new C–N bond to the C4 position. Cleavage of Boc-protecting groups is known to be mediated by TMSI as well as strong acids,[9] so it is unsurprising that the secondary amine of **1** would be deprotected under these conditions. What was unanticipated is the efficient hydroamination under such mild conditions given the general difficulty of effecting these transformations. In our case, it is likely that the proximity of the secondary amine to the alkene group played a role in facilitating this reaction. Our hypothesis is that the azonane ring resides underneath the 6–5 bicycle in **1**, positioning the amine group very close to the carbon–carbon double bond.

Hydroamination studies

Even though the hydroamination of **1** to give **20** might be favored by virtue of proximity, it served as inspiration for further investigations into the scope and limitations for this type of hydroamination.[10] While acid-mediated hydration and hydroetherification of unactivated alkenes has been known for over a century,[11] the analogous acid-mediated reaction with nitrogen nucleophiles has been much more elusive. This is because hydroaminations are often thermoneutral or slightly exothermic and usually have associated negative reaction entropies.[12] Moreover, acid catalysis of hydroamination has the associated hurdle in that acidic conditions will protonate the amine, rendering it non-nucleophilic. It wasn't until 2002 that Hartwig et al. disclosed the first acid-catalyzed hydroamination of unactivated olefins in which they utilized triflic acid (TfOH) at elevated temperatures (100 °C) to effectively catalyze a C–N bond-forming process.[13] The nitrogen basicity problem was overcome in this case by employing tosylamides as nucleophiles. Tosylamides are basic enough to be protonated by triflic acid, yet the resulting tosylamidium ion is acidic enough to transfer its proton to the alkene group, thus allowing for productive C–N bond formation. A few other examples of acid-catalyzed hydroaminations have been reported since Hartwig's seminal report; however, most protocols require elevated temperatures to achieve good conversion.[14] We sought to build upon these previous studies and our observations (*en route* to syntheses of *Lycopodium* alkaloids) by exploring the role of TMSI in other hydroamination reactions.

We commenced our studies with alkenyl tosylamide **22a** (Table 1) as a test substrate. Using the same reagents (TMSCl/NaI) that had been employed in the conversion of **1** to **20**, al-

Table 1. Effect of various TMS-X species.



22a 23a

Entry	Reagent (equiv)	*t* [h]	Conversion [%]
1	TMSCl/NaI (2)	1	100
2	TMSCl (2)	20	0
3	TMSOTf (2)	2	47
4	TMSI (2)	1	100
5	TMSI (0.2)	4	97
6	TMSOTf (0.2)	4	21
7	TMSBr (0.2)	4	30
8	57% HI (2)	20	33

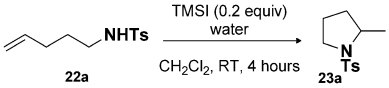
kenyl tosylamide **22a** was fully converted to afford pyrrolidine **23a** (entry 1, Table 1). In the absence of NaI (i.e., with TMSCl alone; entry 2), the starting material was recovered and none of the hydroamination product was observed. When a stronger silylating reagent (TMSOTf) was employed (entry 3), 47% conversion to the hydroamination product was achieved after 2 h at room temperature. We were pleased to find that using TMSI gave complete conversion to the hydroamination product after only 1 h (entry 4). Furthermore, a catalytic amount of TMSI (0.2 equiv) could be used, which led to 97% conversion of **22a** in 4 h (entry 5). In contrast, TMSOTf and TMSBr were sub-optimal when sub-stoichiometric amounts of these reagents were employed, leading only to 21% and 30% conversion, respectively, after 4 h (entries 6 and 7). Unfortunately, the hydroamination conditions using 20 mol% of TMSI were only specific for sulfonamides and not efficient for other amine substrates.

With the initially established conditions for the hydroamination of **22a** in hand, we next turned to investigating the mechanism of this transformation. The addition of base either shut down the reaction (0.2 equivalents triethylamine) or severely retarded the rate (15% conversion after 20 h with 0.2 equiv 2,6-di-*tert*-butylpyridine). This suggested that the generation of acid was vital to the success of this reaction. When HI (57% solution in water) was used instead of TMSI, the reaction proceeded at a sluggish rate, indicating that in situ generation of HI might not be the sole promoting factor (see Table 1, entry 8). From these observations, we hypothesized that a silylated amine intermediate could be responsible for the milder reaction temperatures enjoyed by the TMSI-promoted hydroamination relative to the triflic acid mediated conditions identified by Hartwig.[13] TMSI could silylate the tosylamide, thus generating an active ion pair that can participate in a facile protonation of the alkene group. However, we did not observe any silylated intermediates in the reaction mixture when the reaction was conducted in CD_2Cl_2 and monitored by ^1H NMR spectroscopy. We have also observed that for a mixture of *N*-methyl tosylamide and TMSI, the equilibrium lies towards the free tosylamide and TMSI as opposed to the silylated tosylamide.

Notably, the TMSI promoted conversion of **22a** to **23a** proceeded in a modest 76% conversion after 4 h when conducted on gram scale. This decreased reaction rate upon scale-up suggested that adventitious water could be playing an important role. To test this hypothesis, a series of experiments was carried out in which varying amounts of water were introduced. The results are summarized in Table 2 and show that the addition of 0.05 equivalents of water (entry 2) is optimal. It therefore seems unlikely that TMSI is the active catalyst in this reaction; rather, TMSI may serve as a precursor to generate HI and hexamethyldisiloxane (HMDSO) in the presence of trace water. We believe that larger quantities of water retard the reaction rate due to the Lewis basicity of the water oxygen atom (vide infra). Thus, TMSI in the presence of small amounts of water most likely serves as a source of 'anhydrous' HI.

All evidence up to this stage pointed toward a Brønsted acid catalyzed hydroamination, but we were intrigued by the fact that "anhydrous" HI could catalyze this reaction under milder conditions as compared to triflic acid. This difference is not explained by relative acid strength, since triflic acid ($pK_a = -12$) is more acidic as compared to HI ($pK_a = -10$). Moreover, both triflic acid and HI are strong enough to fully protonate the tosylamide (pK_a of an alkyl tosylamidium ca. -6).[15] This leveling effect should render both acid-catalyzed reactions identical in rate, since the active acid in both cases is the tosylamidium. However, this is not what was observed.

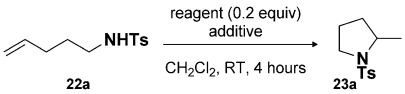
Table 2. Effect of added water on conversion.



Entry	Water [equiv]	Conversion [%]
1	0	76
2	0.05	96
3	0.10	88
4	0.25	89
5	0.50	78

To further elucidate the differences between the triflic acid and HI-mediated hydroaminations, we compared conversion at room temperature in the presence of various additives. As shown in Table 3, the conversion after 4 h was the same whether triflic acid or TMSOTf (in the presence of water; to generate TfOH in situ) was used (entries 1 and 2). Similar observations were made for the reaction conducted in the presence of triflic acid and HMDSO (0.05 equiv, entry 3). These comparisons indicate that HMDSO does not play a significant role in the hydroamination.[16]

Table 3. Additive effects.

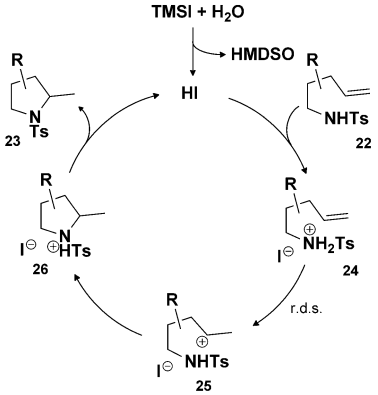


Entry	Reagent	Additive (equiv)	Conversion [%]
1	TfOH	–	20
2	TMSOTf[a]	–	21
3	TfOH	HMDSO (0.2)	19
4	TMSI[a]	–	97
5	TMSCl[a]	NaI (0.2)	94
6	TMSI[a]	NaOTf (0.2)	97
7	TMSOTf[a]	NaI (0.2)	76
8	TfOH	NaI (0.2)	83
9	TfOH	$NaBF_4$ (0.2)	22
10	TfOH	$NaBAr^F_4$ (0.2)	13

[a] Water (0.05 equiv) was also added to these reactions.

We next sought to ascertain the effect of the counter-anion on the rate of the hydroamination reaction. The importance of counter-anions is well documented in transition-metal-catalyzed hydroaminations, with less coordinating anions (e.g., OTf, OTs, and BAr_4) generally increasing the catalytic activity of the

metal.[17] However, the role of the counter-anion in Brønsted acid catalyzed hydroaminations is not as well studied.[18] To explore the role of the counter-anion for the HI-mediated hydroamination, we tested the effect of several salt additives (Table 3, entries 4–10). As noted previously, the use of in situ generated TMSI (from TMSCl/NaI) results in 94% conversion (entry 5). This conversion was retained when NaOTf was added to the standard conditions (entry 6). Interestingly, the addition of NaI to TMSOTf (entry 7) or to triflic acid (entry 8) increased the reaction conversion substantially to 76 and 83%, respectively, as compared to about 20% without added NaI (see entries 1 and 2). These results indicate that the iodide anion is essential to the success of the Brønsted acid catalyzed hydroamination at room temperature. Several other non-coordinating anions such as BF_4^- and $[B\{3,5\text{-}(CF_3)_2C_6H_3\}_4]$ ($BAr^F{}_4^-$; entries 9 and 10) were investigated with triflic acid; however, iodide was the only anion that substantially accelerated the reaction rate. The basis for this unique effect of iodide is still unclear, but we hypothesize that the iodide anion likely forms a loose ion pair with the tosylamidium (**24**, Scheme 8), which leads to an



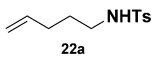
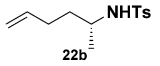
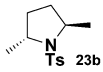
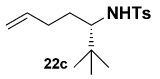
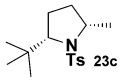
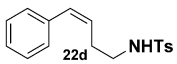
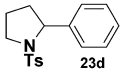
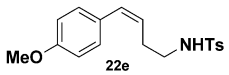
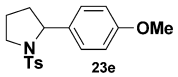
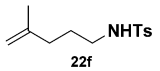
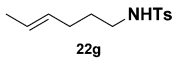
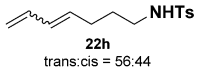
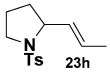
Scheme 8. Proposed catalytic cycle.

increase in the acidity of the tosylamidium relative to the tosylamidium triflate ion pair.[19] It is known that ion-pair acidities can differ substantially from standard ionic acidity.[20] This acidification would serve to accelerate intramolecular olefin protonation (**24** to **25**), which has been well established as the rate-determining step in Brønsted acid catalyzed hydroamination reactions.[13]

Scope of the HI-catalyzed hydroamination reaction

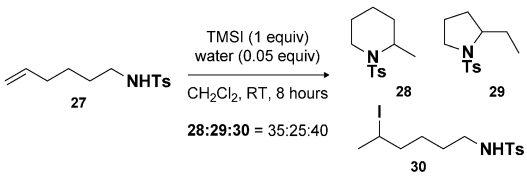
Following our optimization of reaction conditions for the HI-mediated tosylamide hydroamination of alkenes and investigation of the roles of each reagent and additive, we sought to examine the scope of the reaction (Table 4). We have found that primary and secondary alkyl tosylamides **22a–c** are efficient substrates. Styrenyl compounds **22d,e** also undergo facile hydroamination. Notably, this substrate list includes the *p*-anisole derivative **22e**, which is known to be sensitive to other, harsher, Brønsted acid mediated hydroamination conditions.[13] Various substitution patterns on the olefin component are also tolerated (**22f,g**). Diene **22h** also readily undergoes HI-catalyzed hydroamination to afford the corresponding allylic tosylamide (**23h**).

Table 4. Cyclizations of tosylamides with catalytic 'anhydrous' HI.

Reactant	Product	Yield[a] [%]
 22a	 23a	95
 22b	 23b	90 d.r.: 55:45
 22c	 23c	66 d.r.: 60:40
 22d	 23d	84[b]
 22e	 23e	87
 22f	 23f	78
 22g	 23g	47[b,c]
 22h trans:cis = 56:44	 23h	86 d.r.: 91:9

[a] Isolated yield. Reactions conducted using standard conditions: TMSI (0.2 equiv), water (0.05 equiv), CH_2Cl_2 (0.2 M), room temperature, 4 h. [b] 2×0.2 equiv TMSI used over a reaction time of 12 h. [c] Isolated an additional 14% unreacted starting material after 12 h.

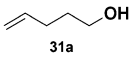
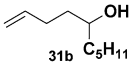
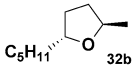
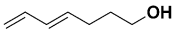
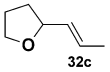
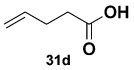
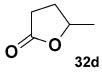
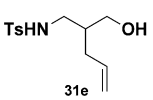
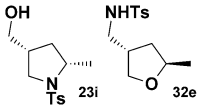
Although pyrolidine rings are easily accessible using this methodology, the corresponding piperidine rings are not as efficiently accessed. Thus, when hexenyl tosylamide **27** was subjected to the standard hydroamination conditions, a mixture of products was observed (**28**, **29**, **30**; Scheme 9). The analogous



Scheme 9. Reaction of hexenyl tosylamide.

cyclizations to form the five-membered rings are extremely fast, whereas cyclization to form the corresponding six-membered rings is somewhat slower. It would appear that the lower rate of hydroamination in these last cases permits undesired reaction pathways (e.g., hydride shifts or iodide addition) to compete with the desired cyclization pathway.[21]

Table 5. Cyclizations of oxygen nucleophiles

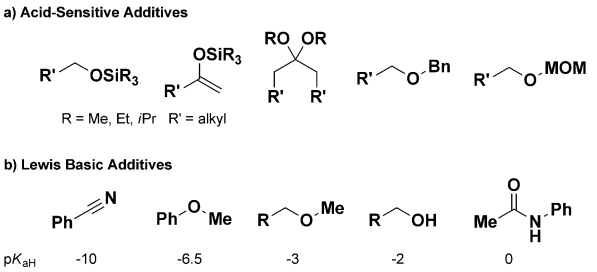
Reactant	Product(s)	Yield[a] [%]
 31a	 32a	84[b,c]
 31b	 32b	61 d.r.: 85:15
 31c	 32c	98[b] d.r.: 91:9
 31d	 32d	58[b,d]
 31e	 23i 32e	**23 i** = 31 d.r.: 75:25 **32 e** = 56 d.r.: 66:33

[a] Isolated yield. Reactions conducted using standard conditions: TMSI (0.2 equiv), water (0.05 equiv), CH_2Cl_2 (0.2 M), room temperature, 4 h. [b] NMR yield, CD_2Cl_2, mesitylene as internal standard. [c] Contained 13% unreacted starting material after 4 h. [d] Contained 30% unreacted starting material after 24 h, 2×0.2 equiv TMSI used.

Gratifyingly, the hydroamination methodology can be extended to the hydroetherification of alkenyl alcohols to provide a range of cyclic ethers (Table 5). Primary and secondary alcohols (**31 a–c**) readily undergo cyclization to the corresponding 2- and 2,5-functionalized tetrahydrofurans (**32 a–c**). Additionally, carboxylic acid **31 d** serves as a suitable oxygen nucleophile to provide lactone **32 d**, albeit at a lower reaction rate. In an effort to estimate the relative cyclization rates of alcohols and tosylamides, alkenyl hydroxyl tosylamide **31 e** was subjected to the standard set of cyclization conditions. The pyrrolidine product (**23 i**) was obtained in 31% yield and the tetrahydrofuran product (**32 e**) was obtained in 56% yield, indicating that hydroetherification occurs faster than the hydroamination of the tosylamide group.

Comparative robustness screen

Many of the previously reported Brønsted acid catalyzed hydroaminations require temperatures at or above 100 °C.[13] Since our newly developed conditions do not require elevated temperatures, we postulated that these conditions could provide better functional group tolerance, especially pertaining to acid-sensitive groups. To test this hypothesis, we compared our conditions to the standard triflic acid mediated hydroamination conditions (at 100 °C) in a "robustness screen" as recently popularized by Glorius and co-workers.[22] We began by testing a range of acid-sensitive additives including silyl ethers, silyl enol ethers, benzyl ethers, and acetals (Scheme 10 a). We found that our HI-mediated hydroamination conditions produced moderate product conversions and moderate additive recovery, though the additive recovery varied depending on the inherent stability of the additive.[23] In contrast, the triflic acid hydroamination conditions usually produced excellent



Scheme 10. Robustness screen additives.

product yields, but significantly lower recoveries of the robustness screen additives. The room temperature HI-mediated hydroamination conditions proved to be milder towards acid-sensitive functional groups; however, these functional groups also stalled the progress of the reaction. Thus, the functional group robustness screen demonstrates the complementary nature of HI and triflic acid in mediating the hydroamination reactions.

The inhibition of hydroamination by these additives is likely due to their mild Lewis basic character relative to the tosylamide. To test this hypothesis, we conducted another screen of additives, choosing additives that had conjugate acids with pK_a values ranging from −10 to 0 (Scheme 10 b). We found that indeed, additives with conjugate acids possessing a pK_a above −5 completely stopped the HI-mediated reaction, whereas less basic additives were tolerated without any drop in product yield.[23] Comparing these observations to the triflic acid mediated conditions at 100 °C, we found that more basic functional groups are tolerated under this latter set of conditions. Only additives possessing conjugate acids with pK_a above −1 completely inhibited the reaction. These conditions likely work in the presence of more basic additives due to the elevated temperature at which these reactions are run. Overall, while the HI-mediated reactions occur at a milder temperature, they do not necessarily result in improved reaction yields over the triflic acid mediated hydroamination reaction conditions. The HI-promoted conditions do, however, provide a complementary approach to hydroamination.

Conclusions

We have prepared and investigated the transformation of an advanced "Heathcock-type" 6–5–9 tricycle in our efforts to access a range of *Lycopodium* alkaloids. Using this versatile intermediate, we observed an unexpected HI-mediated transannular hydroamination reaction to provide the tetracyclic core of serratine and 8-deoxyserratine. The carbon skeleton of these natural products was obtained in 12 steps from *tert*-butyldimethylsilyl-protected propargyl alcohol. This fortuitously observed hydroamination reaction has led to further investigation of its limitations and scope. Through these studies, we have demonstrated the critical importance of the iodide anion in promoting this transformation. Due to the synthetic ease of generating "anhydrous" HI from TMSI as well as the effectiveness of this hydroamination method, we believe it will find

broad utility in the future development of acid-catalyzed carbon–heteroatom bond-forming reactions.

Experimental Section

Representative hydroamination procedure: Tosylamide **22a** (200 mg, 0.84 mmol) was dissolved in dry CH_2Cl_2 (3.8 mL). CH_2Cl_2 pre-saturated with water (0.38 mL wet CH_2Cl_2, 0.042 mmol water, 0.05 equiv water) was then added, followed by TMSI (24 μL, 0.17 mmol, 0.2 equiv). The reaction mixture was allowed to stir at room temperature. After 4 h, the mixture was quenched with saturated sodium bicarbonate (2 mL) and sodium sulfite (1 mL) and extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and purified by column chromatography (20% ethyl acetate in hexane) to yield pyrrolidine **23a** (189 mg, 95%).

Acknowledgements

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Keywords: Brønsted acid catalysis · hydroamination · *Lycopodium* alkaloids · total synthesis · trimethylsilyl iodide

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[16] Due to the difficult nature of dispensing exact amounts of pure, anhydrous HI, we were unable to conduct the analogous experiment with TMSI and HI. However, the introduction of exogenous hexamethyldisiloxane to the TMSI-promoted hydroamination did not lead to an appreciable increase the rate.

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[19] Alternatively, it is possible that small quantities of iodine are being generated and that iodination serves to acidify the tosylamidium species. However, addition of exogenous iodine to various reaction conditions failed to accelerate the reaction rate. Attempts to sequester any in situ formed iodine were met with inconclusive results as the basicity of the sequestering additives could often account for the variations in conversion.

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[23] See the Supporting Information for more details.

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FULL PAPER

Hydroamination

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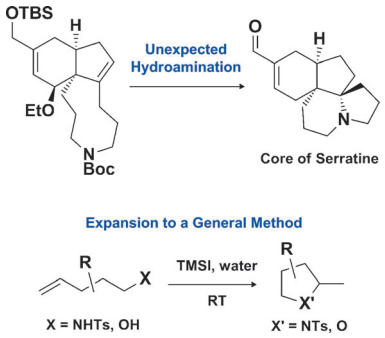
Synthetic Efforts toward the *Lycopodium* Alkaloids Inspires a Hydrogen Iodide Mediated Method for the Hydroamination and Hydroetherification of Olefins



Harnessing the unexpected: The expedient synthesis of a strategic synthetic intermediate en route to structurally diverse *Lycopodium* alkaloids has been accomplished. During these studies, in situ generated hydrogen iodide promoted an unanticipated hydroamination. This transformation has been thoroughly investigated and expanded into a general method for the hydrofunctionalization of unactivated olefins.