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COMMUNICATION

TMSOTf Mediated '5/6-*endo-dig*' Reductive Hydroamination for the Stereoselective Synthesis of Pyrrolidine and Piperidine derivatives

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TMSOTf mediated 5/6-*endo-dig* reductive hydroamination cascade on internal alkynylamines gave an expedient, stereoselective access to pyrrolidine and piperidine derivatives. We also demonstrate that protecting group on nitrogen has profound effect on the reactivity as well as diastereoselectivity of reductive hydroamination cascade.

The Pyrrolidine and piperidine structural motifs are present in many bioactive alkaloid natural products. Isosolenopsin (**1**) is a constituent of the venom of fire ant Solenopsis.[1a] It was found to be a blocker of the neuromuscular transmission and is also a potent selective inhibitor of the neuronal nitric oxide synthase.[1b-c] Coniine (**2**) is a volatile poisonous compound found in hemlock and other plants. It affects the motor nerves, causing paralysis and asphyxia (Fig. 1).[1d-e] McN-4612-Z (**3**) is a potential antidepressant agent.[1f] Cycloalkane-fused pyrrolidine derivatives such as rampiril (**4**) and trandolapril (**5**) are angiotensin-converting enzyme (ACE) inhibitors used for treating hypertension and congestive heart failure.[2]

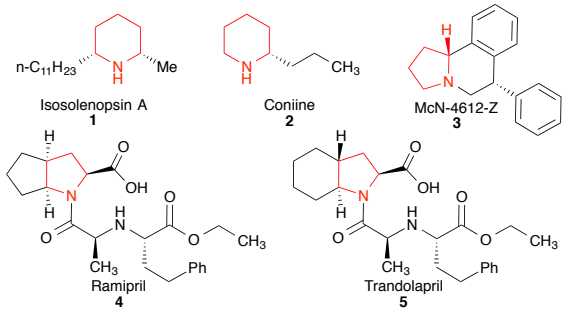
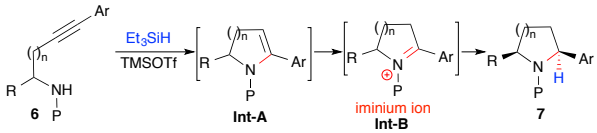


Figure 1. Natural products and bioactive molecules having pyrrolidines and piperidines core.

Recent years have seen emergence of transition metal catalyzed intramolecular hydroamination as a method of choice for the synthesis of *aza*-cycles.[3] Intramolecular hydroamination of *o*-alkynylanilines, which favoured due to formation of aromatic system (indole derivatives), has attracted more attention.[4] However, the corresponding hydroamination of alkynylamines is difficult and much less explored for the synthesis of dihydropyrrole and their derivatives. Complexes of transition metals such as gold, silver, platinum and palladium have been used to promote 5-*endo-dig* hydroamination of alkynylamines leading to dihydropyrroles.[5] Surprisingly, the *endo-dig* reductive hydroamination of alkynylamines leading to the synthesis of pyrrolidines and piperidines remains hitherto unknown.[3] In continuation of our interest on the synthesis of *oxa* and *aza*-cycles,[6] herein we disclose the first examples of transition metal free 5/6-*endo-dig* reductive hydroamination cascade mediated by TMSOTf for the stereoselective synthesis of pyrrolidines and piperidines. This general method is further used in the formal synthesis of biologically active compound McN-4612-Z.



Scheme 1: Envisioned 5/6-*endo-dig* reductive hydroamination for aza-cycle synthesis.

In a program directed at studying synthesis of various oxa- and aza-cycles using Lewis/Brønsted acid mediated alkyne functionalization, we envisioned that alkynylamines **6** in the presence of Lewis/Brønsted acid would form transiently more reactive cyclic enamine **Int-A** *via* *5/6-endo-dig* hydroalkoxylation. Enamine **Int-A** would subsequently generate iminium ion **Int-B** whose trapping with hydride would furnish aza-cyclic derivatives **7** (Scheme 1).

In order to test the proposed hypothesis, known alkynylamines **6a**,[7] derived from L-alanine, was subjected to treatment with $BF_3{\cdot}OEt_2$ (1 equiv) and Et_3SiH in CH_2Cl_2 as solvent. Gratifyingly, the reaction proceeded smoothly to give the desired pyrrolidine derivative **7a** in good yield as a single diastereomer (Table 1, entry 1). Various other Lewis as well as Brønsted acids were screened for optimizing the reaction. TfOH and TMSOTf were found to give the pyrrolidine derivative **7a** in comparable yield and diastereoselectivity (Table 1, entries 2-3). In order to make the process more economical, we tried to reduce the catalyst

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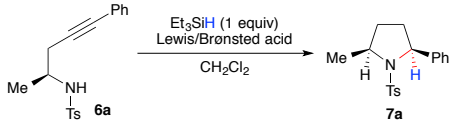
loading. Interestingly, 50 mol% of TfOH gave product **7a** in excellent yield, but further lowering catalyst loading to 10 mol%resulted in slight drop in efficiency (Table 1, entries 4-5).

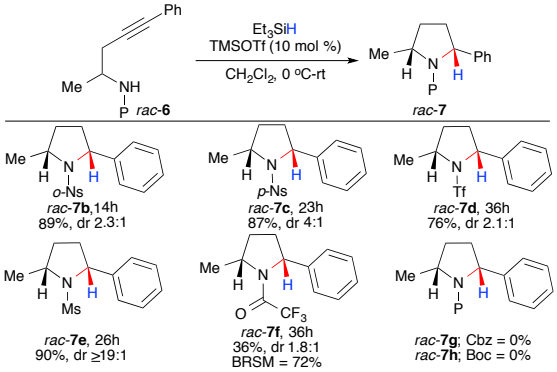
Table 1. Optimization of reductive hydroamination for the synthesis of pyrrolidine 7a.



entry	acid	equiv	temp (°C)	time (h)	yield (%)[a]	dr[b]
1	$BF_3{\cdot}OEt_2$	1	0-rt	11	70	≥19:1
2	TfOH	1	0-rt	10	70	≥19:1
3	TMSOTf	1	0-rt	8	74	≥19:1
4	TfOH	0.5	0-rt	23	80	≥19:1
5	TfOH	0.1	0-rt	24	61	≥19:1
6	TMSOTf	0.1	0-rt	24	83	≥19:1
7	Ag(OTf)	0.1	0-rt	48	84	≥19:1
8	$Cu(OTf)_2$	0.1	0-rt	48	-[c]	-
9	$FeCl_3$	0.1	0-rt	48	13	≥19:1
10	TMSOTf[d]	0.1	0-rt	48	-	-
11	TMSOTf[e]	0.1	0-rt	48	-[f]	-

[a]isolated yield. [b]measured on the crude reaction mixture by ^{1}H NMR. [c]starting material was recovered. [d]toluene was used as solvent. [e]CH_3CN was used as solvent. [f]corresponding hydrolyzed product 4-methyl-*N*-(5-oxo-5-phenylpentan-2-yl)benzenesulfonamide was obtained in 68% yield.

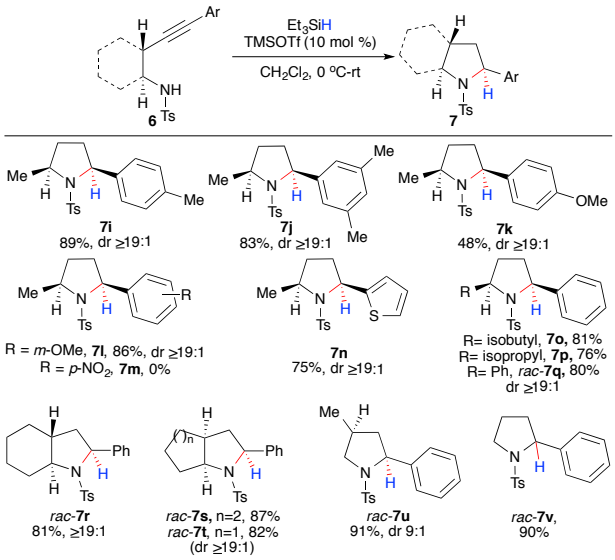
Using 10 mol% of TMSOTf or Ag(OTf) furnished the pyrrolidine **7a** in excellent yield with excellent diastereoselectivity, albeit latter required long reaction time (Table 1, entries 6-7). While $Cu(OTf)_2$ failed to furnish pyrrolidine **7a**, $FeCl_3$ reacted only sluggishly and most of the starting material was recovered back (Table 1, entries 8-9). Reaction didn't procced in toluene as solvent, whereas in acetonitrile, corresponding hydrolyzed product 4-methyl-*N*-(5-oxo-5-phenylpentan-2-yl)benzenesulfonamide was obtained (Table 1, entries 10-11). After all this screening, TMSOTf (0.1 equiv) and Et_3SiH (1 equiv) in CH_2Cl_2 at 0 °C to room temperature was identified as optimal condition to study the substrate scope. The stereochemistry of the major diastereomer was assigned as *cis* based on NOE experiments and was further confirmed by single crystal X-ray diffraction study.[8]



Scheme 2. Effect of nitrogen protecting group on the reductive hydroamination.

Next, different protective groups bearing alkynylamines were subjected to reductive amination under optimized conditions, to understand their effect on this cascade reaction. Alkynylamine bearing sulfonyl protecting groups such as *o*- and *p*-nosyl as well as triflate gave the corresponding pyrrolidine derivatives **7b-d** in good yield albeit with poor diastereoselectivity (Scheme 2). On the other hand, mesyl protected alkynylamine gave the pyrrolidine **7e** in good yield as a single diastereomer. Trifluroacetyl protected amine **6f** also provided the corresponding pyrrolidine derivative **7f**, albeit in lower yield. However, other protecting group such as Cbz and Boc failed to give corresponding pyrrolidine derivatives **7g-h** and only starting material was recovered back.

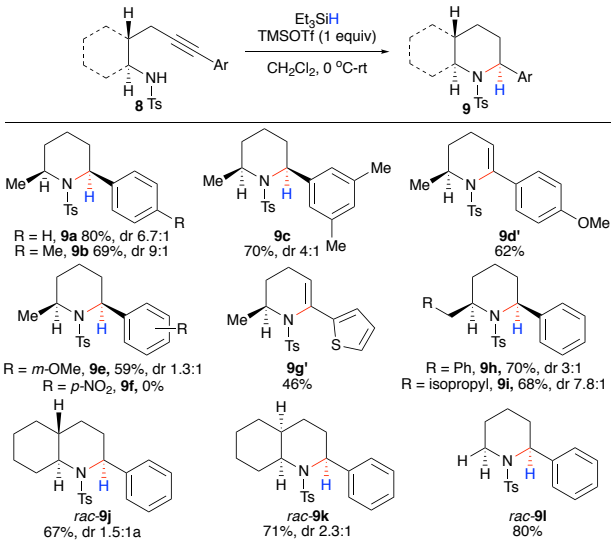
These results indicate that the reductive hydroamination is affected by nitrogen's nucleophilicity. Higher the ability of protecting group to coordinate with Lewis acid, lower is the nucleophilicity of nitrogen and slower is the rate of hydroamination step (amides and carbamate protection fared poorly). Similarly, Tf protection is more electron withdrawing compared to Ns, and was found to give sluggish reactions compared to latter, which in turn reacted slowly as against Ms and Ts protected derivatives.



Scheme 3. Reductive hydroamination for the stereoselective synthesis of pyrrolidines 7.

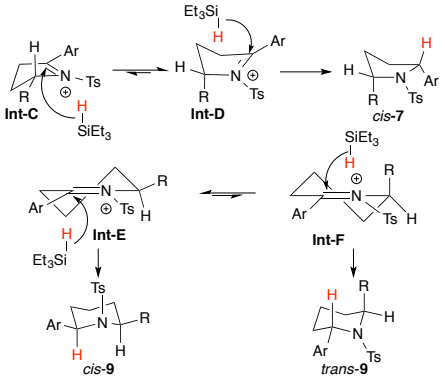
Further scope and limitation of the reductive hydroamination cascade for the synthesis of pyrrolidine derivatives was then investigated using optimized reaction conditions. Alkynylamines **6i-j** with electron releasing group on aryl ring gave corresponding pyrrolidine derivatives **7i-j** in good yield as a single diastereomer (Scheme 3). Alkynylamines **6k** bearing strong electron releasing OMe group in *para* position furnished desired pyrrolidine derivative **7k** in slightly lower yield, however, *meta*-OMe substitution gave good yield of the pyrrolidine **7l**. Alkynylamine **6m** with strongly electron withdrawing NO_2 substituent did not participated in the reductive hydroamination cascade. These observations are consistent with formation of enamine *via* a vinyl cation intermediate as the first step of cascade process. Heteroaryl

substituted pyrrolidine derivative **7n** was also obtained in good yield and excellent diastereoselectivity. Alkynylamines **6o-q** having isobutyl, isopropyl and phenyl substituent on carbon bearing amine group furnished corresponding pyrrolidine derivatives **7o-q** uneventfully. Both the *trans*- and *cis*-fused cyclohexyl pyrrolidine derivatives ***rac*-7r** (on 1.6 mmol scale) and ***rac*-7s** as well as *cis*-fused cyclopentyl pyrrolidine derivative ***rac*-7t** were obtained in good yield from corresponding alkynylamine ***rac*-6r-t**. These derivatives of cycloalkane-fused pyrrolidines ***rac*-7r-t** are found in the core structures of Ramipril and Trandolapril and could potentially serve as precursors for their synthesis.[9,5g] The 2,4-disubstitued pyrrolidine ***rac*-7u** was also obtained with good yield and diastereoselectivity. In all the cases the stereochemistry of the *cis*-diastereomer was confirmed by NOE studies. It was further confirmed by single crystal X-ray diffraction study on the pyrrolidine **7n**.[8]



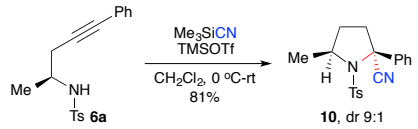
Scheme 4. Reductive hydroamination for the stereoselective synthesis of piperidines 9

To further expand the scope of the reductive hydroamination cascade, the strategy was applied to the synthesis of piperidine derivatives **9**. Thus, alkynylamine **8a** was subjected to optimized condition of pyrrolidine i.e. TMSOTf (0.1 equiv) and Et_3SiH (1 equiv) in CH_2Cl_2 at 0 °C, unfortunately only trace amount of conversion was observed. With further screening, it was found that when the reaction of alkynamine **8a** was carried out using TMSOTf (1 equiv) and Et_3SiH (2 equiv) in CH_2Cl_2 at 0 °C to room temperature, the piperidine derivative **9a** was obtained in good yield albeit with moderate diastereoselectivity. Alkynylamine **8b-c** with electron releasing group on aryl ring (Me) gave corresponding piperidine derivatives **9b-c** in good yield (Scheme 4). Alkynylamine **8d** bearing strong electron releasing OMe group on aryl ring gave hydrolyzed product instead of desired product, perhaps due to slow reduction of the enamine intermediate. However, intermediate cyclic enamine **9d'** could be isolate by stopping reaction early. Similarly, alkynylamine with heteroaryl ring **8g** also gave cyclic enamine **9g'** in 46 % yield instead of piperidine **9g**. Even in this case, alkynylamine **8f** with electron withdrawing NO_2 substituent on the aryl ring did not participate in reaction and starting material was recovered back completely. Furthermore, alkynylamine **8h-i** and ***rac*-8j-k** also lead to the requisite piperdine derivatives **9h-i** and ***rac*-9j-k** in good yield and poor to moderate diastereoselectivity. The stereochemistry of the major diastereomer was confirmed based on single crystal X-ray diffraction studies on the pyrrolidine **9a**, **9c**, **9d'**, **9h**.[8]



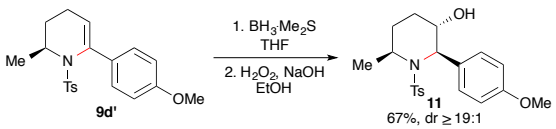
Scheme 5. Rationale for stereoselectivity.

The diastereoselectivity of reductive hydroamination cascade can be explain by model shown in Scheme 5. It is plausible that, because of the $A^{1,2}$ steric repulsion between the tosyl group and alkyl substituent at C5, **Int-C** is less stable than **Int-D**. Thus, 'inside attack' of hydride to the more stable iminium ion **Int-D** affords the pyrrolidine *cis*-**7** as the major product.[10] In the 6-membered cyclic iminium ion, half chair conformation **Int-E** having R in the *pseudo*equatorial position would be preferred over half chair conformation **Int-F**. Similar to oxonium ion trapping in six-membered rings, axial attack of the hydride to the iminium ion is preferred as it would generate more stable chair conformation (as against attack from equatorial side which generates twist boat conformation).[11] Thus, more stable iminium ion **Int-E** upon axial attack by hydride from triethylsilane gives the piperidine *cis*-**9** as the major product.



Scheme 6. Hydroamination-iminium ion trapping cascade for the synthesis of trisubstituted pyrrolidine 10.

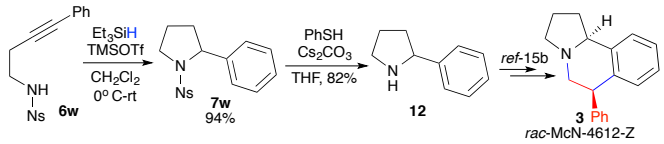
In continuation of this idea, we envisaged that the *in situ* generated iminium ion can be trapped by other nucleophiles. To test this hypothesis, alkynylamine **6a** was treated with TMSCN (2 equiv) and TMSOTf (1 equiv) in CH_2Cl_2. Gratifyingly, the trisubstituted pyrrolidine **10** was obtained in good yield and excellent diastereoselectivity (Scheme 6).



Scheme 7. Enantiospecific synthesis of 3-hydroxy piperidine 9d'.

Since the enamine **9d'** was readily available, we explored its functionalization to gain access to 3-hydroxy piperidine

derivative. Thus, piperidine **9d'** (*cf*. Scheme 4) was subjected to hydroboration using $BH_3{\cdot}SMe_2$ followed by oxidation to furnish the 3-hydroxy piperidine derivative **11** with excellent diastereoselectivity (Scheme 7). The stereochemistry of the 3-hydroxy piperidine **11** was confirmed by the single crystal X-ray diffraction studies.[11]



Scheme 8. Formal synthesis of McN-4612-Z.

Finally, this reductive hydroamination cascade was employed as a key step in the formal synthesis of McN-4612-Z **3**. Towards this end, alkynylamine **6w** (1 mmol) was subjected reductive amination cascade to furnish pyrrolidine **7w**. Deprotection of nosyl group using thiophenol led to the 2-phenylpyrrolidine **12** (Scheme 8). 2-Phenylpyrrolidine **12** was converted to McN-4612-Z **3** following the protocol developed by Hou and co-worker.[12] Thus, synthesis of 2-phenylpyrrolidine **13** constituted formal total synthesis of racemic McN-4612-Z ***rac*-3**.

In conclusion, we have developed transition metal free, Lewis acid mediated *5/6-endo-dig* reductive hydroamination cascade of alkynylamine for the stereoselective synthesis of pyrrolidine and piperidine derivatives. Protecting group on nitrogen alters it nucleophilicity, which in turn affects reactivity and diastereoselectivity of *5-endo-dig* reductive hydroamination cascade. The *in situ* generated iminium ion can also be trapped by another nucleophile to furnish trisubstituted pyrrolidine derivative. The developed method was applied in highly stereoselective synthesis of 3-hydroxy piperidine and in the forma total synthesis of biologically active compound McN-4612-Z.

Acknowledgment

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Conflicts of interest

"There are no conflicts to declare".

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8 CCDC 1907330-1907336 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.

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