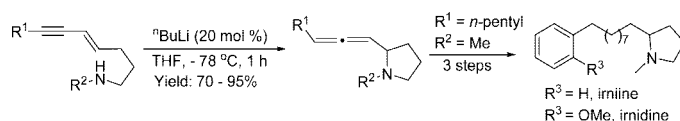


Base-Catalyzed Intramolecular
Hydroamination of Conjugated EnynesWen Zhang,[†] Jenny B. Werness,[‡] and Weiping Tang^{*,†}*The School of Pharmacy and Department of Chemistry, University of Wisconsin,
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Received February 19, 2008

ABSTRACT



A de novo intramolecular hydroamination of conjugated enynes was developed using commercially available *n*-BuLi as a precatalyst. This hydroamination reaction successfully afforded allenyl-substituted pyrrolidines with up to 95% yield. One of the resulting allenyl pyrrolidines was converted to the natural products iriniine and iridine in three steps.

New methods for producing nitrogen heterocycles in a catalytic manner are of fundamental importance in organic chemistry and pharmaceutical sciences. Intramolecular hydroamination of alkenes¹ would be, in terms of an optimum material balance, a superior atom-economical process.² Impressive progress has been made recently for transition metal catalyzed intramolecular additions of amides and sulfonamides to alkenes, allenes, and dienes.³ The addition of unprotected amines to alkenes, arguably the most important donors and acceptors,⁴ has been studied in very limited systems. The intramolecular addition of unprotected amines to monosubstituted alkenes has been tested in a number of catalytic systems based on rare earth metals,⁵ titanium and

zirconium,^{6,7} zinc,⁸ alkali metals,^{9,10} and late transition metals.¹¹ A few catalysts were developed for the intramolecular addition of unprotected amines to 1,1-disubstituted alkenes^{12,13} and 1,2-disubstituted alkenes.¹⁴ To extend the scope of olefin substrates for the preparation of nitrogen

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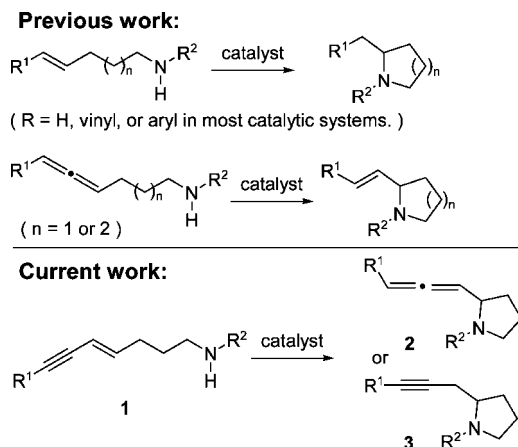
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heterocycles bearing key substituents present in naturally occurring compounds, conjugated amino dienes,^{15,16} vinyl arenes,^{7,9,17} and highly reactive aminoallenes¹⁸ have been used to prepare substituted nitrogen heterocycles via intramolecular hydroamination.

Despite impressive progress on the hydroamination of carbon–carbon multiple bonds, the intramolecular hydroamination of conjugated enynes has never been explored (Scheme 1).¹⁹ An interesting question arises because two

Scheme 1. Intramolecular Hydroamination of Alkenes



potential hydroamination products can be formed—allenyl amine **2** and homopropargyl amine **3** as shown in Scheme

1. Herein, we report the first intramolecular hydroamination of conjugated enyne **1**, which selectively affords allenyl amine **2**.

Alkali metals have been used to catalyze the addition of amines to monosubstituted alkenes,^{9,10} 1,1-disubstituted alkenes,¹² 1,3-butadienes,^{16,20} and conjugated vinyl arenes^{9,21} including electron-rich vinylarenes²² via deprotonation of the amine followed by addition to the double bonds.²³ In an effort to develop a catalyst that is cost-effective and readily accessible, we decided to explore the potential of alkali metals for the intramolecular hydroamination of conjugated enynes.

When we first treated aminoenyne **1a**²⁴ with 120 mol % of *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ in THF, compound **1a** was completely cycloisomerized to allenyl pyrrolidine **2a** with a 1.8:1 diastereomeric ratio after 1 h. We then reduced the amount of *n*-BuLi to 20 mol % and increased the concentration of the aminoenyne to 0.4 M in THF. A 100% conversion was achieved at $-78\text{ }^{\circ}\text{C}$ with a 1.6:1 diastereomeric ratio after 1 h. No homopropargyl amine **3** was observed under these conditions.

We then investigated the scope of the hydroamination of conjugated aminoenynes using 20 mol % of *n*-BuLi as a precatalyst (Table 1). Amino enynes with different substituents on the amino group all worked well under optimal conditions with no significant changes of the yields and diastereomeric ratios. Surprisingly, increasing the steric bulk of the alkyne improved the diastereomeric ratio from 2:1 to 5:1 (Table 1, entries 3 and 7). It is worth mentioning that amines with a removable benzyl group worked well (Table 1, entries 6 and 8). A phenyl substituted enyne also provided a high yield of the hydroamination product (Table 1, entry 9). Substituted pyrrolidine **2j** was obtained as a mixture of two diastereomers, which yielded only the *cis*-1,2-disubstituted pyrrolidine upon hydrogenation (Table 1, entry 10). Efforts toward the formation of six-membered-ring heterocycles via hydroamination of enynes were not successful (Table 1, entry 11).

The proposed mechanism for the base catalyzed hydroamination of XXenynes is shown in Scheme 2.²³ The

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(24) The aminoenynes can be prepared in two to four steps from commercially available materials. See the Supporting Information for details.

Table 1. Hydroamination of Conjugated Enynes^a

entry	enyn	product	yield (%)	dr ^b
1			93	1.6:1
2			79	2.1:1
3			83	2.0:1
4			95	1.8:1
5			80	1.8:1
6			70	2.1:1
7			73	5.0:1
8			72	1.7:1
9			78	1.0:1
10			88	1.3:1
11		complex mixture		

^a All reactions were performed at -78°C with *n*-BuLi (20 mol %) in THF (0.4 M). ^b Ratios were determined using NMR in CD_3COCD_3 .

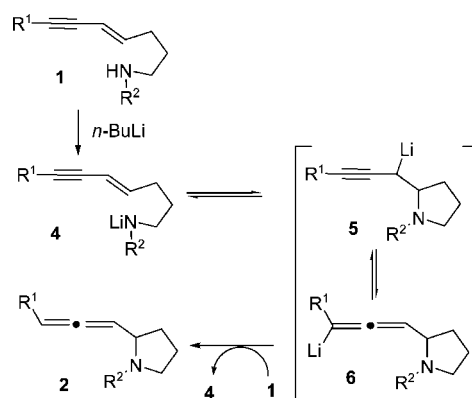
amine N–H was first deprotonated by *n*-BuLi to form lithium amide **4** which presumably served as the catalytic species. A 5-*exo-trig* cyclization could generate propargyllithium **5** and/or allenyllithium **6**,²⁵ which could then be protonated by amino enyne **1** to give allenylamine **2** and catalyst **4**.

Substituted pyrrolidines exist in numerous natural products and pharmaceutical agents and display a broad spectrum of biological activities.²⁶ For example, irniine **12** (Scheme 3) was isolated from the tubers of *Arisarum vulgare*, a toxic amceae responsible for human and animal poisonings in Morocco.²⁷ Irniine²⁸ displayed significant antibacterial and

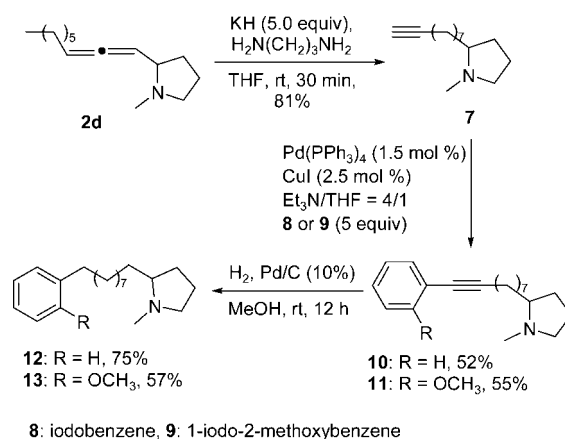
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Scheme 2. A Proposed Mechanism

antimycotic activity²⁹ and a strong binding affinity for DNA.³⁰ From the same natural source, derivatives of irniine such as irmidine **13** have also been isolated.³¹ We envisioned

Scheme 3. Short Syntheses of Irniine and Irmidine

that an alkyne-zipper reaction³² could convert the allene functional group next to the pyrrolidine ring in **2a–f** to a terminal alkyne, which can then be further transformed to a desired functionality. Indeed, treatment of hydroamination product **2d** with excess potassium hydride in a solution of 1,3-diaminopropane completely isomerized allene **2d** to terminal alkyne **7**. Sonogashira cross-coupling reactions³³ between alkyne **7** and iodobenzene **8** or 1-iodo-2-methoxybenzene **9** provided penultimate intermediates **10** and **11**. Palladium catalyzed hydrogenation of alkyne **10** and **11** then cleanly afforded natural products irniine **12** and its congener irmidine **13**.

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In summary, we report the first intramolecular hydroamination of conjugated enynes. The reaction was catalyzed by lithium amide to yield allenylpyrrolidines in up to 95% yield. A stereogenic center and an axial chiral allene were generated in this cycloisomerization reaction, and a diastereomeric ratio of up to 5:1 was achieved. The resulting allene could be further functionalized³⁴ as demonstrated in the divergent synthesis of the natural products iriniine and irnidine. The sequential enyne-hydroamination followed by alkyne-zipper reaction should be applicable to the synthesis of other pyrrolidines with remote functional groups, such as the family of broussonetine iminosugars.²⁶ The low cost of

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commercially available *n*-BuLi precatalyst and the mild conditions make this hydroamination feasible for industrial production of substituted pyrrolidines. The current results also encourage further development of a catalytic, diastereo-, and enantioselective hydroamination method for conjugated enynes.

Acknowledgment. We thank Professor Richard Hsung (UW—Madison) for helpful discussions, the University of Wisconsin Graduate School and the School of Pharmacy for generous startup funding, and the School of Pharmacy Analytical Instrument Center (AIC) for mass spectrometry services and NMR support.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL800334M