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The Tandem Cope-Type Hydroamination/[2,3]-Rearrangement Sequence: A Strategy to Favor the Formation of Intermolecular Hydroamination Products and Enable Difficult Cyclizations

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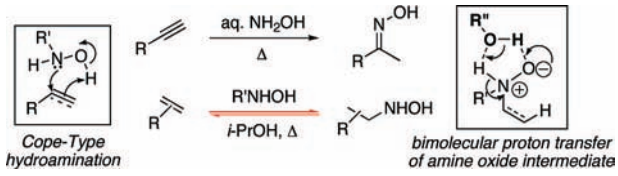
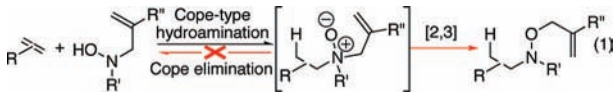
Given the prevalence and diversity of nitrogen-containing motifs in bioactive molecules, the development of efficient C−N bond-forming reactions is of paramount importance. The addition of a N−H bond across electron-rich, unsaturated C−C bonds stands out as one of the simplest and most desirable synthetic transformations for which no general solution currently exists. While significant progress has been achieved (primarily through transition metal catalysis),[1] issues such as limited reaction scope, functional group compatibility, and challenges linked to unfavorable thermodynamics for reactions of alkenes[2] continue to stimulate research directed at hydroamination reactivity. In recent efforts directed toward the development of metal-free alternatives, we reported that intermolecular reactions of hydroxylamine (aq. NH_2OH) and *N*-alkylhydroxylamines with alkenes and alkynes can be performed simply upon heating at 95−140 °C.[3] Under our conditions, alcoholic solvents mediate a facile bimolecular proton transfer of the *N*-oxide intermediate and *enable* the efficient formation of the alkene hydroamination products.

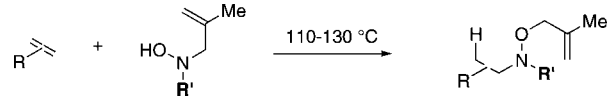


During these studies, modest yields were obtained for unstrained alkenes such as vinylarenes. Our observations are in line with Hartwig's recent report that intermolecular hydroaminations of vinylarenes are nearly thermoneutral.[2] Since substitution of both reagents can have a negative impact on $\Delta G^{\ddagger}$, and since the high temperatures required for unactivated alkenes to react disfavor the reaction entropically, the current synthetic reach of intermolecular hydroaminations is limited. To address this fundamental issue, we were drawn to tandem processes in which hydroamination is followed by a second irreversible reaction, thus providing access to more stable products for the hydroamination sequence. Herein, we report on a proof of concept, a tandem Cope-type hydroamination[4]/Meisenheimer rearrangement[5] sequence (eq 1) that allows intermolecular reactions of *N*,*N*-dialkylhydroxylamines to be more energetically favorable due to the formation of a neutral product, and illustrate the potential for related cyclizations in syntheses of coniine and norreticuline featuring difficult intramolecular hydroamination key steps.



Initial efforts were directed toward performing the intermolecular sequence with norbornene and *N*-allyl-*N*-methylhydroxylamine. While encouraging but variable conversions (∼20−70%) were obtained in various solvents at high concentrations (ca. 1 M) upon heating (1−3 days) at 110−130 °C, the use of forcing conditions led to multiple decomposition products. Careful isolation and analysis of some of these products revealed that an intermolecular hydroamination side reaction with the allyl side chain present in the reagent and product was occurring.[6] Fortunately, the use of the parent *N*-methallyl reagent suppressed most side reactions and allowed efficient reactivity with various alkenes, as shown below.

Table 1. Scope of the Intermolecular Hydroamination Sequence[a]



Entry	Alkene	R'C4H7NOH	Product	Yield[b]
1	**1a**	Me (**2a**)	**3a**	72%
2	**1a**	*n*-Pr (**2b**)	**3b**	48%
3[c]	**1a**	-$(CH_2)_3$OBn (**2c**)	**3c**	52%
4[c]	**1a**	Bn (**2d**)	**3d**	44%
5	**1a**	*i*-Pr (**2e**)	**3e**	21%
6	**X** = CH_2 (**4a**)	Me (**2a**)	**5a**	73%
7	**X** = O (**4b**)	Me (**2a**)	**5b**	81%
8	**X**=NBoc (**4c**)	Me (**2a**)	**5c**	86%
9	**6**	Me (**2a**)	**7**	65% (1:1)
10	**8**	Me (**2a**)	**9**	28%
11	**10**	Me (**2a**)	**11**	52%

[a] Conditions: Alkene (5−10 equiv) and R′(C_4H_7)NOH (1 equiv) in C_6H_6 (1.0 M), sealed tube, 110−130 °C (unless indicated otherwise). [b] Isolated yields. [c] In *n*-PrOH (1.0 M) with $NaBH_3CN$ (1 equiv) as additive.

Strained alkenes react efficiently upon heating at ca. 110 °C (entries 1 to 9). 4-Fluorostyrene and vinyltriphenylsilane also react under similar conditions, illustrating that the scope is not limited to strained alkenes (entries 10−11). This reaction sequence is also applicable for various *N*-alkyl-*N*-methallyl hydroxylamines, as shown in entries 1 to 5. Remarkably, primary hydroxylamines **2b** and **2c** only afford the rearranged products (entries 2−3), which

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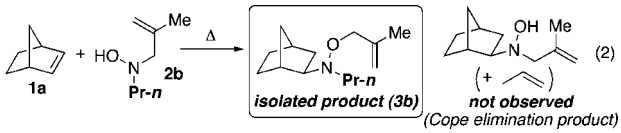
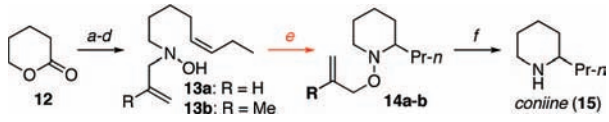
highlights that the Meisenheimer rearrangement is faster than a possible Cope elimination of the alkyl side chain (eq 2). This result is in contrast to the direct reaction of *n*-PrNHOH and norbornene, which does not lead to any hydroamination product under our previously reported reaction conditions,[3] likely due to the poor thermal stability associated with primary *N*-alkylhydroxylamines.[7]



The increased stability of such *N*-methallyl derivatives of primary hydroxylamines suggested that intramolecular variants of this tandem sequence could enable the synthesis of 2-alkylpiperidines. Such products are very difficult to form via hydroamination: examples of 6-membered ring formation are scarce, and most methodologies appear limited to terminal alkenes, suggesting that only 2-methylpiperidines can be accessed reliably with current methods.[8] These considerations, combined with the potential applicability of related hydroaminations in alkaloid synthesis (which requires the use of internal alkenes), led us to select coniine as the target for the study of intramolecular variants of this tandem sequence.[9]

The *N*-allyl and *N*-methallyl hydroamination substrates were readily prepared from δ-valerolactone (Scheme 1). After extensive optimization of the key hydroamination sequence, *N*-allyl derivative **13a** emerged as a slightly superior cyclization precursor for coniine, likely due to a more facile Meisenheimer rearrangement step (Scheme 1). With both substrates, the use of rigorously deoxygenated, dilute solutions (0.01 M) drastically minimized side reactions.[10] To put the 47% isolated yield (55% brsm) in context, all attempts to cyclize the simpler primary hydroxylamine precursor failed to provide more than 23% of the desired hydroamination product.[11]

Scheme 1. Synthesis of Coniine via a Tandem Intramolecular Hydroamination/Meisenheimer Rearrangement Sequence[a]

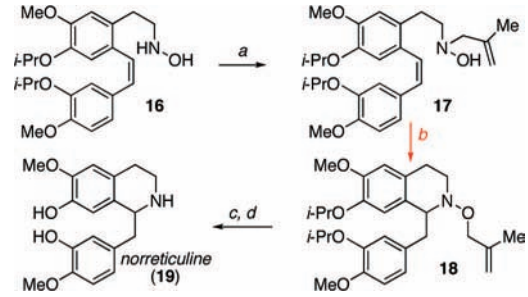


[a] Conditions: (a) DIBAL-H, PhMe, −60 °C; EtCH=PPh_3, THF, 0 °C to reflux (74%, *Z*/*E* = 7:1). (b) BocNHOBoc, DIAD, PPh_3, THF, 0 °C to rt (86%). (c) TFA, CH_2Cl_2 (91%). (d) **13a**: K_2CO_3, C_3H_5Br, THF (68%). **13b**: DBU, C_4H_7Cl, THF/DMF, reflux (37%). (e) C_6H_6 (0.01M), H_2O (10 equiv), sealed tube, 140 °C (**14a**: 47% + 15% **13a**; **14b**: 31%). (f) Zn/AcOH.

With optimized conditions developed in this unbiased system, we turned our attention to a related cyclization to access the alkaloid norreticuline (Scheme 2). Thus, cyclization precursors **16** and **17** were prepared from isovanillin and vanillin.[11] In this system, methallyl derivative **17** proved a superior cyclization precursor, affording the desired product **18** in 54% yield (32% of the trans isomer derived from **17**, likely formed via hydroamination/Cope elimination, was also isolated). Subsequent N−O bond cleavage was accomplished using standard conditions, and BCl_3-mediated cleavage of the *i*-Pr groups furnished norreticuline (**19**). Again, the use of simpler primary hydroxylamine precursor **16** failed to provide more than 27% of the desired hydroamination product.[11]

In summary, the tandem hydroamination/Meisenheimer rearrangement sequence was developed to address the issue of unfavorable reaction thermodynamics for intermolecular reactions of alkenes and to improve the scope of Cope-type hydroaminations.

Scheme 2. Synthesis of Norreticuline via a Tandem Intramolecular Hydroamination/Meisenheimer Rearrangement Sequence[a]



[a] Conditions: (a) DBU, C_4H_7Cl, THF/DMF, reflux (50%). (b) C_6H_6 (0.01M), H_2O (10 equiv), sealed tube, 120 °C (54% + 32% of *E*-**17**). (c) Zn, AcOH (78%). (d) BCl_3, CH_2Cl_2 (>99%).

This tandem sequence allows intermolecular reactions of *N*-alkyl-*N*-methallylhydroxylamines to be energetically more favorable and leads to increased efficiency in intramolecular systems as illustrated by syntheses of two alkaloids featuring difficult hydroamination key steps. Efforts directed at the development of other tandem sequences are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic characterization for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Such reactions are also referred to as "reverse Cope cyclizations" or reverse Cope eliminations in the literature. For an excellent review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

(5) See: Cope, A. C.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3423, and references cited therein.

(6) Oligomers formed from an "anti-Markovnikov" hydroamination pathway have been isolated. See Supporting Information.

(7) In contrast to *c*-$C_6H_{11}NHOH$,[3] which yields the HA product, gas evolution was observed with *n*-PrNHOH under identical reaction conditions.

(8) Reports of 6-membered piperidine ring formation via hydroamination onto an *internal* alkene are rare. For examples, see: (a) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (b) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938. (c) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

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(11) See Supporting Information for details.

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