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Hydrogen Bonding Directed Intermolecular Cope-Type Hydroamination of Alkenes

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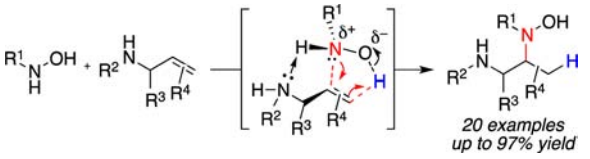
ABSTRACT



Intermolecular hydroamination of unactivated alkenes represents a significant synthetic challenge. An efficient Cope-type hydroamination is achieved under mild conditions for reactions of *N*-alkylhydroxylamines with allylic amines, using hydrogen bonding to achieve increased reactivity and high regioselectivity. This approach provides a number of highly functionalized vicinal diamine motifs as Markovnikov addition products.

Amine derivatives pervade fine chemicals, pharmaceuticals, and natural products.[1] Millions of tons of amine products are used annually worldwide. Consequently there is much interest in the conversion of simple precursors into nitrogen-containing molecules. Hydroamination is a highly atom-economical transformation that can provide access to various amines by directly adding a N−H bond to an unsaturated C−C bond.[2,3] However achieving intermolecular alkene hydroamination remains very challenging.[2,4] Besides suffering from a high activation energy due to electrostatic repulsion between the π-electrons and the lone pair of the nitrogen atom, the process is also typically only slightly exothermic or even thermoneutral.[5] The efficiency of intermolecular alkene hydroaminations, which display a negative reaction entropy, can thus be negatively impacted if the reaction is performed at high temperatures or if more stable alkenes (e.g., polysubstituted or conjugated) are used.

Catalysis based on Brønsted/Lewis acids, strong bases, and transition metals (e.g., actinides, lanthanides, early and late transition metals) has been exploited to enable hydroamination reactions.[2−4] Approaches based on electrophilic nitrogen sources[6] and radical routes[7] have also been developed as useful alternatives. Strategically, the catalysis of hydroamination reactions usually involves activation of either the alkene π-bond or the amine nucleophile. While significant progress has been achieved,[2,3] issues such as limited reaction scope, functional group

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compatibility, and in particular challenges linked to unfavorable thermodynamics continue to stimulate efforts toward the hydroamination of unactivated alkenes.[4]

The Cope-type hydroamination reactivity of hydroxylamines and hydrazines constitutes a conceptually different yet efficient thermal alternative that operates under metal-free conditions.[8] Intramolecular Cope-type hydroaminations are mild and synthetically versatile and proceed through a concerted five-membered transition state.[9] In contrast, intermolecular variants are limited and typically require the use of biased substrates at high temperatures (e.g., norbornene: 110 °C; vinylarenes: 140 °C).[10] To address this limitation, we have been exploring pre-association-based strategies (i.e., catalysis via temporary intramolecularity[11]) to achieve increased reactivity. Recently, we reported that aldehydes catalyze the addition of *N*-alkylhydroxylamines to allylic amines (Scheme 1).[12] In this system, efficient catalysis occurs by *inducing temporary intramolecularity* via *in situ* formation of a *mixed* aminal intermediate. A highly stereoselective variant of this reaction is also possible using chiral aldehydes. The current limitations associated with this reactivity (high catalyst loadings and applicability limited to terminal allylic amines) and the importance of the vicinal diamine motif[13] led us to explore other approaches.[14] Herein we report a complementary mode of activation and show that hydrogen bonding allows for mild *directed* intermolecular hydroaminations and enables the synthesis of complex diamine motifs from allylic amines (Scheme 1).

In our previous studies on tethered hydroaminations,[12] we observed that a slow background reaction is present for some allylic amines and hydroxylamines. We thus embarked on improving this reactivity, which appeared to be promoted by hydrogen bonding.[15] Selected results of reaction optimization efforts are shown in Table 1.

Scheme 1. Approaches to Directed Hydroaminations

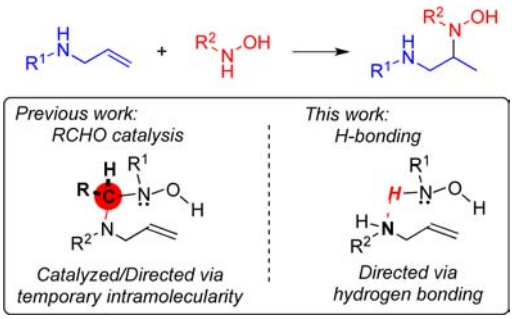
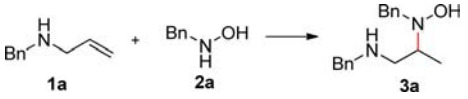


Table 1. Optimization of Reaction of **1a** with **2a**[a]



entry	solvent	temp	time (h)	NMR yield (%)[b]
1	neat	rt	24 (170)	2 (24)
2	neat	70 °C	17	96
3	neat	80 °C	6	99
4	C_6H_6	80 °C	6	41
5	EtOAc	80 °C	6	42
6	DMF	80 °C	6	72
7	EtOH	80 °C	6	94
8	*i*-PrOH	80 °C	6	93
9	*t*-BuOH	80 °C	6	98
10	CF_3CH_2OH	80 °C	6	11
11	$(CF_3)_2CHOH$	80 °C	6	trace
12	Et_3N	80 °C	6	79

[a] Conditions: **1a** (2 equiv), **2a** (1 equiv), neat or 1.0 M in solution, rt or heated in a sealed tube. [b] NMR yield using 1,4-dimethoxybenzene as an internal standard.

Previously we noticed that *N*-allylbenzylamine (**1a**) slowly reacts with *N*-benzylhydroxylamine (**2a**) at room temperature yielding ~2% of **3a** within 24 h or ~24% after a week (Table 1, entry 1).[15] Fortunately, temperature exhibited a pronounced effect on the reaction (Table 1): **2a** underwent an essentially quantitative reaction with **1a** when heated at 80 °C under neat conditions. Similar reactivity was also observed in various aprotic and protic solvents, with more polar solvents generally giving better yields (entries 4–9). However the use of protic solvent with increased acidity leads to poor reactivity (entries 10–11). Despite its basicity, Et_3N was compatible with the reactivity (entry 12). The relative loading between **1a** and **2a** also considerably affected the reaction. To probe the effect, reactions varying the relative loading of **1a** to **2a** were performed (neat, 80 °C, 2 h). ^{1}H NMR analyses revealed

(8) For an excellent review on the Cope-type hydroamination, see: (a) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243. Such reactions are also often called reverse Cope eliminations or reverse Cope cyclizations in the literature. For early examples, see: (b) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (c) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863. (d) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.

(9) (a) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. (b) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139. (c) Ciganek, E.; Read, J. M., Jr. *J. Org. Chem.* **1995**, *60*, 5795.

(10) (a) Beauchemin, A.; Moran, J.; Lebrun, M.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893. (c) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895. (d) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, *47*, 562.

(11) For an excellent recent review on temporary intramolecularity in catalysis, see: Tan, K. L. *ACS Catal.* **2011**, *1*, 877.

(12) (a) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100. (b) Guimond, N.; MacDonald, M. C.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**10.1021/ja303320x.

(13) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

(14) For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(15) See supporting information of reference 12a. In comparison 1-decene failed to react with **2a** even after prolonged heating (> 24 h) at 100 °C. These observations provided initial support for a possible hydrogen-bonding promoted pathway. For intermolecular Cope-type hydroamination reactivity of unactivated alkenes, see: Laughlin, R. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

that the conversion of hydroxylamine **2a** increased rapidly with increased loadings of allylic amine **1a**, as indicated by the plot in Figure 1. In contrast, the conversion of **1a** responded negatively to increased loadings of **2a**.[16,17]

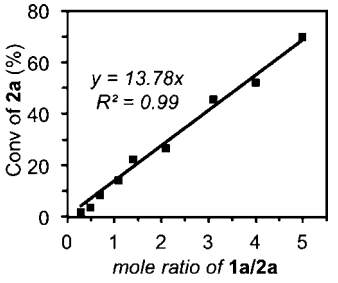


Figure 1. Conversion of hydroxylamine **2a** on varying the relative loading of allylic amine **1a** (neat, 80 °C, 2 h).

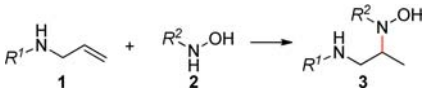
Under the optimized conditions shown in Table 2, a variety of hydroxylamine and allylamine derivatives efficiently underwent this transformation. Excellent yields were typically obtained with substrates bearing primary alkyl groups. Amides and various functional groups (MeO, F, CF_3, NO_2) were well-tolerated, even if electron-withdrawing ones generally slowed down the reaction (e.g., entries 5 and 10). However extension of this method to substrates bearing bulky substituents seemed more challenging (e.g., entries 7 and 15). Allylamine itself also showed reduced reactivity in comparison with its *N*-alkyl derivatives (entries 1−4 vs 8). In general, the use of different solvents failed to improve the most challenging reactions (e.g., *t*-BuOH, entry 6).

Given that aldehyde-catalyzed intermolecular Cope-type hydroaminations were limited to unsubstituted allylic amines,[12] we explored the scope of this hydrogen bonding reactivity to access more complex vicinal diamine motifs. Several disubstituted derivatives were examined (Table 3). Substrates with distal alkene substituents worked well but more slowly, and surprisingly the *cis*- and *trans*-isomers displayed no reactivity difference (entries 1−2). The hydroamination of *N*-benzylcinnamylamine was much slower; however increasing the temperature to 100 °C reduced the reaction time and led to an efficient hydroamination process (entries 3 vs 4). The more sterically congested isobutenylamine derivative reacted slowly to afford a modest yield of product **3q** (entry 5). Nevertheless, these conditions lead to an unprecedented substrate scope for

(16) See Supporting Information for details.

(17) This likely reflects competitive formation of different H-bonding species. A possible explanation is that hydroxylamine **2a** prefers to dimerize (or aggregate) via intermolecular hydrogen bonding. A high loading of allylic amine **1a** could shift the equilibrium towards the mixed H-bonding pair, and subsequently lead to the desired product.

Table 2. Scope of H-Bonding Directed Hydroamination[a]



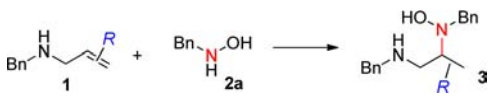
entry	product (**3**)	time (h)	yield (%)[b]
1	*X* = H (**3a**)	6	94
2	*X* = F (**3b**)	9	92
3	*X* = NO_2 (**3c**)	17	95
4	**3d**	6	92
5	**3e**	40 96	81[c] 80[d]
6	**3f**	72	25 (trace[e])
7		72	0
8	**3g**	17	56
9	*R* = Bn, *X* = OMe (**3h**)	6	90
10	*R* = Bn, *X* = CF_3 (**3i**)	17	82
11	*R* = Me, *X* = OMe (**3j**)	6	92
12	*R* = Me, *X* = CF_3 (**3j**)	17	89
13	**3l**	40	89
14	**3m**	12	97
15	**3n**	72	31 (66[f])

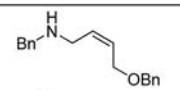
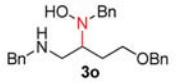
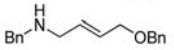
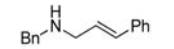
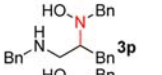
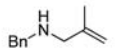
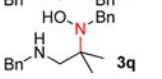
[a] Reaction conditions: **1** (2.0 equiv), **2** (1.0 equiv), neat, 80 °C. [b] Yield of isolated products. [c] NMR yield. [d] To simplify purification, only 1.0 equiv of 2-(allylamino)-*N*,*N*-diethylacetamide was used. [e] *t*-BuOH as the solvent (1 M). [f] With 5.0 equiv of **1a**.

the intermolecular hydroamination reactivity. It is also worth noting that the diamine products are stable toward Cope elimination: **3q** remained intact even after prolonged heating at 80 °C (72 h, in C_6D_6). Given the thermoneutral nature of intermolecular alkene hydroaminations (*vide supra*),[5] stabilization of the products via hydrogen bonding could also be critical to the outcome shown in Table 3.

We then turned our attention to allylamines substituted at the allylic position. Unexpectedly, excellent diastereocontrol was observed in the hydroamination of benzyl *sec*-butenylamine. A single diastereomer (**3r**) was obtained in 57% isolated yield (eq 1), and its structure was confirmed by X-ray diffraction analysis.[16] This stereochemical outcome is consistent with a H-bonding directed reaction with the favored Cope hydroamination transition state being

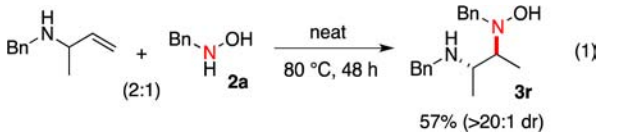
Table 3. Scope of H-Bonding Directed Hydroamination[a]



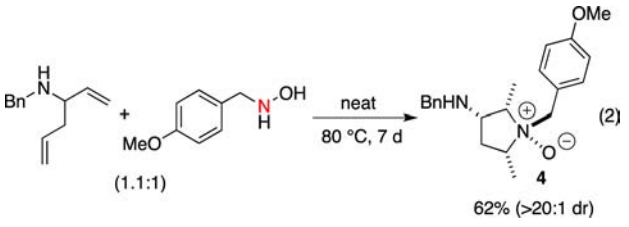
entry	allylic amine	product	time (h)	yield (%)[b]
1		 **3o**	48	74 (79)
2			48	77 (80)
3		 **3p**	96	(41)
4			17	78[c]
5		 **3q**	48	37 (42)

[a] Conditions: allylic amine (2.0 equiv), hydroxylamine (1.0 equiv), neat, 80 °C. [b] Yield of isolated products; NMR yields in parentheses. [c] Reaction was carried out at 100 °C.

positioned *trans* to the methyl group to minimize non-bonding interactions.



We also speculated that more complex substrates might be subject to a cascade hydroamination sequence.[18] To test this hypothesis, *N*-benzyl hexa-1,5-dien-3-amine was synthesized.[16] A hydroamination cascade indeed took place with this substrate, directly providing the pyrrolidine *N*-oxide **4** in ~60% yield, again as a single diastereomer (eq 2). Detailed NMR analysis including NOE studies supports a structure with all-*cis* substituents on the pyrrolidine ring.[16] This stereochemical outcome is expected, building on the diastereoselectivity observed in the formation of **3r**, as well as on the propensity of Cope-type cyclizations to be stereospecific.[19]



To gain further support for a hydrogen bonding directed hydroamination and additional insight on the impact of N-substitution, the relative reactivity between **1a** and several benzylic allylamines (*p*-OMe, *p*-F, and *p*-NO_2) was assessed by performing competition reactions with hydroxylamine **2a**.[16,20] Fitting the obtained data to a Hammett plot afforded a linear progression with a negative ρ of -0.33 (R^2 ~0.96).[16] When the *para*-methoxybenzyl or 3-phenylpropyl hydroxylamine derivatives competed with the parent hydroxylamine **2a** to react with **1a,** relative rates of 1.14 and 1.42 were obtained, respectively.[16] These experiments suggest a transition state with the buildup of positive charges at both N-atoms. These data and the reactivity trends shown in Table 2 support the proposed transition state model illustrated in Figure 2. The exclusive formation of vicinal diamines **3** thus likely originates from the synergy between the H-bonding effect and the propensity of Cope-type hydroaminations to favor Markovnikov addition products.[8,10]

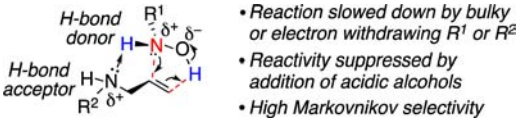


Figure 2. Proposed transition state model for the H-bonding directed Cope-type hydroamination.

In conclusion, a hydrogen bonding promoted Cope-type hydroamination process was developed, which allows the conversion of allylic amines into functionalized vicinal diamine motifs. Further studies building on preassociation to enable difficult intermolecular hydroaminations are underway and will be reported in due course.

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Supporting Information Available. Complete experimental procedures, characterization data, X-ray crystall structure of **3r** and NMR spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

(18) For pioneering work in intramolecular systems (bicyclizations), see: (a) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 4391. (b) Jiang, T.; Livinghouse, T. *Org. Lett.* **2010**, *12*, 4271. (c) Jiang, T.; Livinghouse, T.; Lovick, H. M. *Chem. Commun.* **2011**, *47*, 12861.

(19) (a) See references in ref 9. (b) Hanrahan, J. R.; Knight, D. W. *Chem. Commun.* **1998**, 2231.

(20) Competition reactions were performed to minimize potential differences in solvation behaviors.

The authors declare no competing financial interest.