Hydroamination

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Intermolecular Cope-Type Hydroamination of Alkenes and Alkynes**

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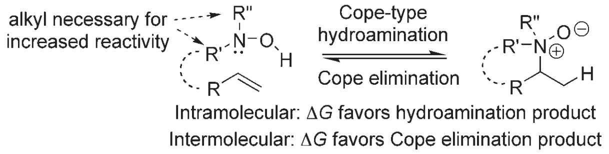
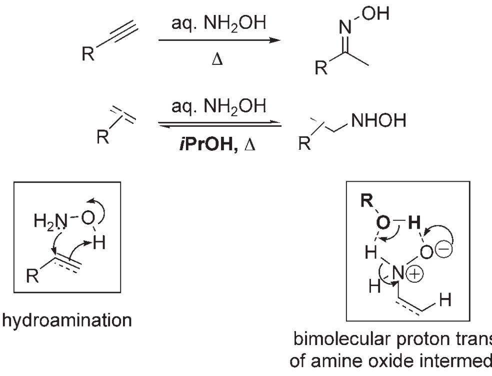
In memory of Nabi Magomedov

Nitrogen-containing functional groups are ubiquitous in natural products and pharmaceuticals. The hydroamination of unactivated alkenes and alkynes is an attractive approach for the synthesis of such molecules, but it is underdeveloped and remains challenging, especially for intermolecular reactions. Most recent progress has been accomplished using transition-metal catalysis,[1,2] or strong acids with less basic nitrogen nucleophiles,[3] but often procedures are limited to specific substrate classes and functional-group compatibility is either limited or yet undefined.[4] A conceptually different approach to the functionalization of alkenes and alkynes in intramolecular reactions is the Cope-type hydroamination (also referred to as reverse-Cope cyclization).[5,6] While this strategy has received some attention (particularly in the formation of five- and six-membered heterocycles), fundamental limitations have precluded its application in synthesis and in more challenging intermolecular reactions. Notably, the nitrogen atom is usually substituted to increase reactivity, but this severely limits the reaction scope, leading to the formation of amine oxides, which are less versatile synthetic intermediates and less stable products. Consequently, the intermolecular process is energetically unfavorable (Scheme 1).



Scheme 1. Impact of nitrogen substitution on Cope-type hydroamination reactivity.

To expand the use of this concerted hydroamination strategy, we sought a solution to this requirement for nitrogen substitution (R′, R″ = alkyl). Herein, we report that heating (unsubstituted) aqueous hydroxylamine with alkynes and alkenes affords the intermolecular hydroamination products under mild conditions and in the absence of a metal catalyst. We also present experimental and theoretical evidence which suggest that the reduced reactivity of less substituted hydroxylamines is associated with a difficult intramolecular proton-transfer step rather than a difficult hydroamination step (Scheme 2). Thus, the presence of alcohols or water in our reaction conditions is crucial to mediate a facile, bimolecular proton transfer of the amine oxide intermediate.



Scheme 2. For the intermolecular hydroamination the presence of alcohols or water is crucial to mediate a facile, bimolecular proton transfer of the amine oxide intermediate.

Under such conditions, this reaction is not limited to NH_2OH: hindered c-$C_6H_{11}NHOH$ can also be used for intermolecular hydroamination.

Reasoning that the side reactions described in the rare examples of intermolecular Cope-type hydroaminations could be due to hydroxylamine substitution,[7] we focused our initial studies on commercially available aqueous NH_2OH. In optimizing the reaction conditions, we found high concentration and solvent dependence. Under optimized conditions phenylacetylene underwent quantitative conversion upon heating with aqueous NH_2OH (2.5 equiv) at 113 °C overnight in concentrated solution in dioxane (1 M), leading to an 87 % yield of the Markovnikov product (M) along with 5 % yield of the anti-Markovnikov product (AM). The scope of alkyne substrates is shown in Table 1. Steric and electronic

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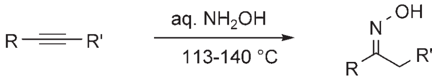
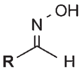
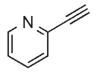
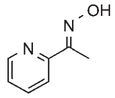
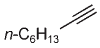
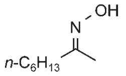
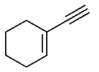
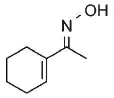
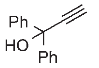
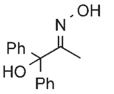
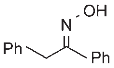
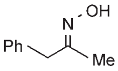
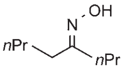
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Reaction of alkynes with aqueous NH$_2$OH.



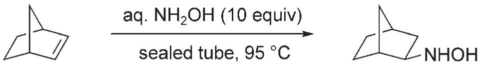
Entry	Substrate	Conditions[a]	Major product	Yield(s) [%][b]
1	R = Ph, R′ = H	A		87 (5)
2	R = 4-MeOC$_6$H$_4$, R′ = H	A		83 (3)
3	R = 4-FC$_6$H$_4$, R′ = H	A[c]		71 (8)
4	R = 2-MeC$_6$H$_4$, R′ = H	A		45 (11)
5	R = 3-MeC$_6$H$_4$, R′ = H	A		75 (2)
6	R = 4-MeC$_6$H$_4$, R′ = H	A		65 (3)
7		A[c]		73 (15)
8		B		62
		C		86 (2)
9		B		55 (1)
		C		72 (3)
10		C		63
11	R, R′ = Ph	B		71
12	R = Me, R′ = Ph	B		31 (3)
		C		53 (5)
13	R, R′ = *n*Pr	C		12

[a] Reaction conditions: A: alkyne (1 equiv), aq. NH$_2$OH (2.5 equiv), dioxane (1 M), sealed tube (behind a blast shield), 113 °C, 16–18 h; B: 140 °C, dioxane (2 M), 38–40 h; C: *i*PrOH (1 M), 140 °C (microwave), 5–10 h. [b] Yield of isolated products. Yield of regioisomer shown in parentheses. [c] 2 M in dioxane.

variations on the arene ring are well tolerated (Table 1, entries 1–7). Less reactive substrates, such as 1-octyne or disubstituted alkynes, require somewhat more forcing conditions, and the use of *i*PrOH as solvent is beneficial (Table 1, entries 8–13). In general, microwave irradiation of *i*PrOH solutions proved optimal, leading to higher yields in shorter reaction times (conditions C). In most cases, the unreacted starting material could be recovered, and the products were conveniently isolated by chromatography or recrystallization.

Initial reactions with alkenes were performed with norbornene, as strain could provide both higher reactivity and a favorable thermodynamic outcome[8] for the reaction (ΔG_r). Surprisingly, initial trials under the conditions initially used for alkynes showed almost no reaction. After considerable optimization, it was found that alcoholic solvents proved uniquely effective to obtain hydroamination products and minimize side reactions, which include oxidative hydroamination and 1,2-Meisenheimer rearrangement at higher temperatures. The importance of the solvent is illustrated in Table 2 (unoptimized conditions).

Table 2: Solvent effects in the hydroamination of norbornene.[a]

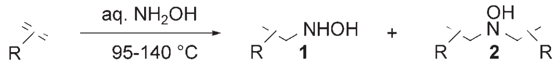


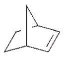
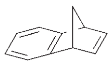
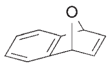
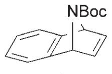
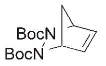
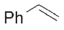
Entry	Solvent	Conversion [%][b]
1	C$_6$D$_6$	0
2	dioxane	3
3	CDCl$_3$	5
4	MeOH	26
5	EtOH	14
6	*i*PrOH	48
7	[D$_6$]DMSO	2
8	none	0[c]

[a] Reaction conditions: [alkene] = 1 M, aq. NH$_2$OH (10 equiv), 95 °C, 14 h. [b] Determined using styrene as an internal standard. [c] Biphasic mixture.

Subsequent reaction optimization focused on the encouraging lead obtained in *i*PrOH (Table 2, entry 6). Upon increasing reaction time and concentration, we observed quantitative conversion of norbornene (Table 3, entry 1). A preliminary survey of the reaction scope is presented in Table 3. A variety of strained alkenes showed excellent reactivity (Table 3, entries 1–5). Not surprisingly, mixtures of mono- and bis-hydroamination products formed under the reaction conditions (Table 3, entries 1–3). While the bis-hydroamination product **2** is typically favored in the presence of 2 equivalents of NH$_2$OH (conditions A), the mono-hydro-

Table 3: Reaction of aqueous NH$_2$OH with alkenes.[a]

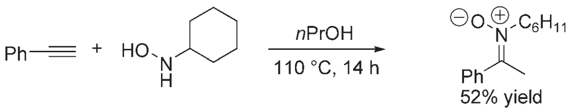


Entry	Substrate	Conditions	Yield **1**+**2** [%]	Ratio **1**/**2**
1		A	99	1:2.2
		B	65	7.1:1
2		A	98	1:1.5
		B	49	
3		A	95	1.9:1
4		A	48	only **1**
5		A	55	only **1**
6		C	39	1[b]:2.0

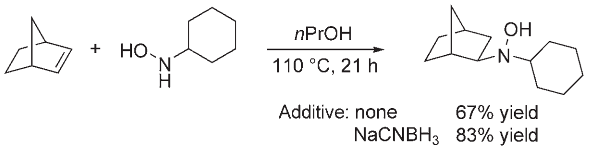
[a] Reaction conditions: A: alkene (1 equiv), aq. NH$_2$OH (2.5 equiv), *i*PrOH (1 M), sealed tube (behind a blast shield), 95 °C, 24–48 h; B: Similar to A but with 10 equiv NH$_2$OH; C: Similar to A but at 140 °C for 72 h; Boc = butyloxycarbonyl. [b] 12:1 mixture (M/AM).

amination product **1** is favored in the presence of excess NH_2OH (conditions B). In contrast, more hindered alkenes lead to selective formation of the primary hydroxylamine **1**. An encouraging result was obtained with styrene (Table 3, entry 6), showing this reactivity is not limited to strained alkenes. Hartwig et al. had reported that styrene hydroamination is essentially thermoneutral;[8] in line with this, reversibility experiments suggest this reaction with styrene has reached equilibrium.[9]

The results presented in Table 3 suggest that this intermolecular reaction is not limited to NH_2OH, as formation of bis-hydroamination products **2** must involve the reaction of mono-hydroamination product **1** and an additional molecule of alkene. Encouragingly, cyclohexylhydroxylamine also affords products of intermolecular hydroamination with both phenylacetylene [Eq. (1)] and norbornene [Eq. (2)].



(1)



(2)

DFT calculations were undertaken to compare the reactivity of alkenes and alkynes (Figure 1).[9,10] Activation free energies for hydroamination ($\Delta G^{\neq}_{HA}$) proceeding in a concerted fashion via a five-membered, planar transition state (TS) are similar for norbornene (32.0 kcal mol^{-1}) and phenylacetylene (M: 30.1 kcal mol^{-1}, AM: 33.2 kcal mol^{-1}). The amine oxide intermediate then undergoes proton transfer, generating the parent alkyl and alkenyl hydroxylamines, respectively. Two proton-transfer pathways are shown in Figure 1, and our calculations suggest a remarkably facile bimolecular proton transfer involving the amine oxide intermediate and a protic species such as H_2O and iPrOH.[9] Activation free energies for this proton transfer ($\Delta G^{\neq}_{BPT}$) for alkynes and alkenes are ca. 5 and 7 kcal mol^{-1}, respectively, in vacuum and ca. 8 and 10 kcal mol^{-1}, respectively, in methanol and are relatively independent of the nature of the proton shuttle (ROH). This pathway is favored over intramolecular proton transfer by ca. 15 kcal mol^{-1}. Overall, the thermodynamics of both reactions are favorable, with the formation of the norbornene adduct ($\Delta G_r = -7.0$ kcal mol^{-1}) significantly less favored than that of the phenylacetylene adduct, which is further stabilized upon formation of the oxime tautomer ($\Delta G_{r,M} = -33.4$ kcal mol^{-1}).[11]

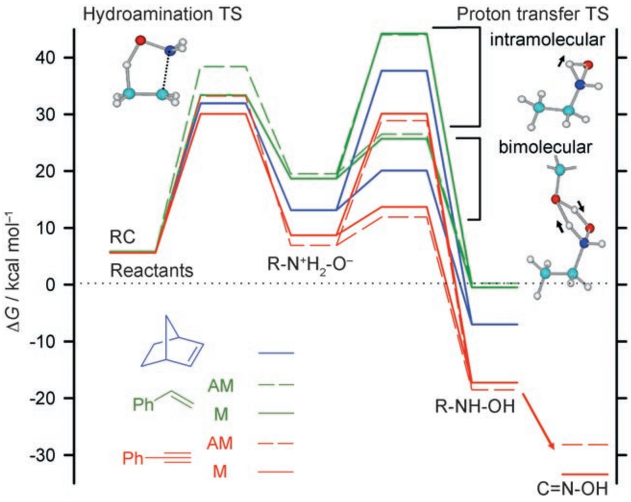


Figure 1. DFT calculations on NH_2OH-based hydroaminations highlighting the importance of the bimolecular proton transfer step.[13]

While the preceding discussion refers to DFT calculations in the gas phase, solvent effects on optimized structures are only minimal.[12] Therefore, the trends outlined in Figure 1 suggest that the proton-transfer step is of paramount importance for intermolecular reactions of alkenes. This picture is consistent with the beneficial effect of iPrOH in reactions of alkynes and the spectacular solvent effects shown in Table 2.

In summary, we have reported a unified, metal-free approach for the intermolecular hydroamination of alkynes and alkenes. We have shown that alkyl substitution of the hydroxylamine is not required to achieve high reactivity in Cope-type hydroaminations, as NH_2OH reacts efficiently; we have also highlighted the importance of the proton-transfer step on the reaction. These results suggest that the scope of Cope-type hydroaminations, notably intramolecular variants, can be significantly expanded. Extensions of this work are in progress and will be reported in due course.

Experimental Section

Experimental procedures, spectroscopic characterization of all new products, and computational details are provided in the Supporting Information.

CAUTION: Due to the high energy content of NH_2OH, appropriate care should be taken when conducting these experiments. The use of a blast shield is and should be a standard operating procedure. The hydroxylamine concentration should not be increased beyond 5–10 wt % (i.e. the typical reaction conditions). See the Supporting Information for a discussion.

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[9] See the Supporting Information for details.

[10] For calculations on the Cope elimination, see: a) I. Komaromi, J. M. J. Tronchet, *J. Phys. Chem. A* **1997**, *101*, 3554–3560; b) O. Acevedo, W. L. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 6141–6146.

[11] Other findings: 1) a similar energy profile for C_2H_4 and C_2H_2, 2) a nearly thermoneutral profile for the reaction of styrene ($\Delta G_r = -0.5$ kcal mol^{-1} for M; $\Delta G_r = 0.3$ kcal mol^{-1} for AM), 3) similar ΔG^{+}_{HA} values for the addition of MeNHOH (30.7 kcal mol^{-1}) and Me_2NOH (32.5 kcal mol^{-1}) to norbornene. Please see the Supporting Information for details.

[12] For example, ΔG_r for the reaction shown in Table 2 varies as follows: -7.0 kcal mol^{-1} (gas phase), -6.2 kcal mol^{-1} (C_6H_6), -5.2 kcal mol^{-1} ($CHCl_3$), -4.6 kcal mol^{-1} (DMSO) and -3.0 kcal mol^{-1} (MeOH).

[13] Free energies of reactants, intermediates, and products in the gas phase at 298 K and 1 atm, B3LYP/TZVP level of theory [RC: reactant complex ($\pi_{CC}\rightarrow$H-ONH$_2$)]. TS structures are shown for the reaction with C_2H_4.