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Intermolecular Cope-Type Hydroamination of Alkenes and Alkynes using Hydroxylamines

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Abstract: The development of the Cope-type hydroamination as a method for the metal- and acid-free intermolecular hydroamination of hydroxylamines with alkenes and alkynes is described. Aqueous hydroxylamine reacts efficiently with alkynes in a Markovnikov fashion to give oximes and with strained alkenes to give *N*-alkylhydroxylamines, while unstrained alkenes are more challenging. *N*-Alkylhydroxylamines also display similar reactivity with strained alkenes and give modest to good yields with vinylarenes. Electron-rich vinylarenes lead to branched products while electron-deficient vinylarenes give linear products. A beneficial additive effect is observed with sodium cyanoborohydride, the extent of which is dependent on the structure of the hydroxylamine. The reaction conditions are found to be compatible with common protecting groups, free OH and NH bonds, as well as bromoarenes. Both experimental and theoretical results suggest the proton transfer step of the *N*-oxide intermediate is of vital importance in the intermolecular reactions of alkenes. Details are disclosed concerning optimization, reaction scope, limitations, and theoretical analysis by DFT, which includes a detailed molecular orbital description for the concerted hydroamination process and an exhaustive set of calculated potential energy surfaces for the reactions of various alkenes, alkynes, and hydroxylamines.

1. Introduction

Given the ubiquitous nature of nitrogen-containing molecules and the ready availability of inexpensive olefins, it is not surprising that the hydroamination of alkenes and alkynes has become the subject of intense research. Although in recent years the hydroamination of alkynes has been achieved with fairly general scope via several different catalytic approaches,[1,2] a correspondingly general intermolecular reactivity of alkenes has been much more elusive.[3]

Intermolecular acid-catalyzed additions of arylamines to alkenes were first reported by Hickinbottom in 1932, requiring high temperatures (250−300 °C) and giving very low yields.[4] Other strong Brønsted acids have since been found to catalyze the transformation, though the required harsh conditions inherently preclude broad functional group tolerance and require electronically deactivated amines (e.g., nitriles,[5] anilines,[6] azoles,[7] hydrazines,[8] sulfonamides,[9] and amides[9c]) whose decreased basicity allows for alkene protonation. Strong base catalysis is also possible but does not allow for any functional groups more acidic than an amine and requires electronically biased alkenes.[10] As a result of these limitations, significant

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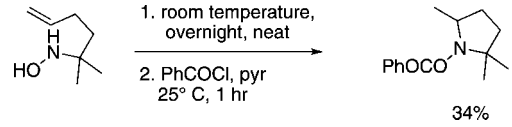
(3) For general reviews on alkene hydroamination, see refs 2a and 2j. Even in intramolecular cases, reactivity is only general for 5-membered cyclizations, and is diminished by alkene substitution. For selected recent examples of intramolecular catalytic hydroamination of alkenes, see: (a) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570. (b) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2008**, 2741. (c) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Chem. Commun.* **2008**, 1422. (d) Zhang, W.; Werness, J. B.; Tang, W. *Org. Lett.* **2008**, *10*, 2023. (e) Bauer, E. B.; Andavan, G. T. S.; Hollis, T. K.; Rubio, R. J.; Cho, J.; Kuchenbeiser, G. R.; Helgert, T. R.; Letko, C. S.; Tham, F. S. *Org. Lett.* **2008**, *10*, 1175. (f) Dochnahl, M.; Löhnwitz, K.; Pissarek, J.-W.; Roesky, P. W.; Blechert, S. *Dalton Trans.* **2008**, 2844. (g) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (h) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (i) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (j) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354.

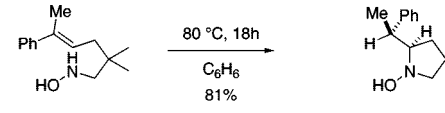
effort has been invested into the development of organometallic hydroamination catalysts. Lanthanide and early metal-based catalysts have been successful particularly in intramolecular cases, but suffer from high sensitivity to air or moisture, as well as low functional group compatibility.[11] Recently, superb work featuring the use of late transition metals has in some cases exhibited higher tolerance of polar functional groups,[12] and highlighted the thermodynamic limitations of intermolecular hydroaminations.[13] Alternatively, methods based on electrophilic nitrogen sources[14] or free radicals[15] offer complementary reactivity. Asymmetric approaches stemming from several of these activation modes have been developed, but intermolecular examples are rare.[3i,j,16] Despite this encouraging progress, hydroamination of alkenes stands out as one of the simplest and most desirable synthetic transformations for which no general solution exists and remains a largely unused tool in the synthesis of complex organic molecules.[17]

A conceptually different approach to hydroamination presents itself in the form of the microscopic reverse of the Cope elimination. The reverse Cope cyclization was first reported by House and co-workers in 1976 to form pyrrolidines from alkenylhydroxylamines simply upon standing at room temperature via a proposed free radical mechanism (eq 1). [18]

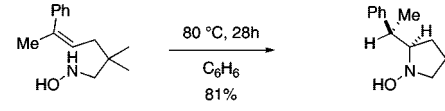


(1)

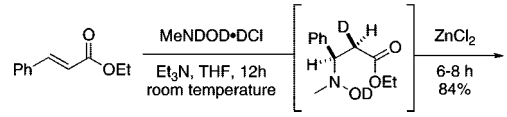
Seminal studies by Ciganek revealed the scope and limitations of this hydroamination reaction, however several observations, as well as those of Black and Doyle, seemed to be more consistent with a concerted mechanism.[19] Finally in 1994, Oppolzer and co-workers provided compelling stereochemical evidence for such a mechanism, which proceeds through a suprafacial five-membered transition state (eqs 1 and 3).[20] These reports revived interest in this reactivity and subsequent contributions from Holmes, Knight, Jäger and others expanded the scope to include alkynes,[21] investigated its use in saturated heterocycle synthesis[22] and introduced creative ways to access the cyclization precursors from nitrones.[23]



(2)



(3)



(4)

In stark contrast, although Niu and Zhao reported that *N*-methylhydroxylamine undergoes a stereospecific 1,4-addition to α,β-unsaturated esters via a concerted mechanism (eq 4), synthetically useful intermolecular variants that do not involve a biased electrophilic olefin have yet to appear in the literature.[24] A report by Laughlin in 1973 hinted that intermolecular Cope-type hydroamination might have occurred, although the reaction pathway was obscured by subsequent complex side reactions (Scheme 1).[25] The formation of amines may be rationalized by an intermolecular Cope-type hydroamination reaction to give

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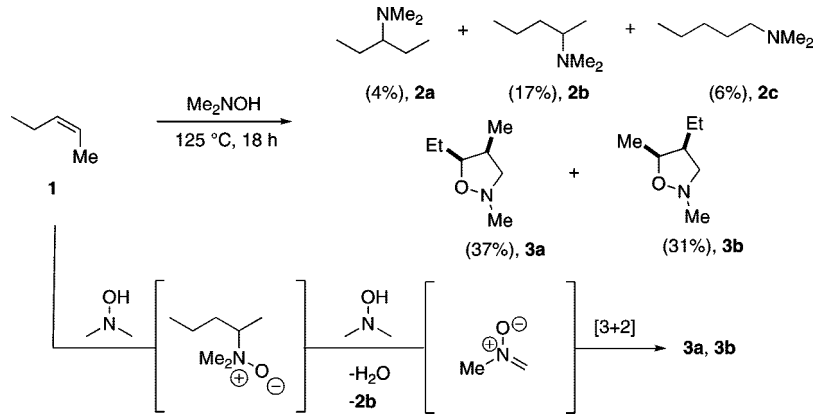
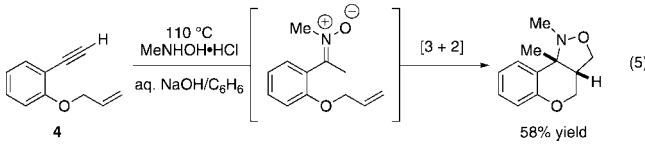
Scheme 1. Laughlin's Report of Amination Reactivity between Alkenes and *N,N*-Dimethylhydroxylamine



regioisomeric amine *N*-oxides, followed by reduction with another molecule of *N*,*N*-dimethylhydroxylamine to give a nitrone and amines **2a**−**c**. The resulting nitrone could then undergo subsequent [3 + 2] cycloaddition reactions to give the observed isoxazolidines **3a** and **3b**.

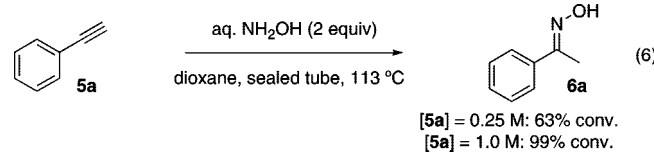
Padwa and Wong reported three examples in which an aryl acetylene (e.g., **4**) reacts with an *N*-alkylhydroxylamine to form a nitrone intermediate which is then efficiently trapped by a [3 + 2] cycloaddition (eq 2).[26] However, the reaction could not be extended to simpler substrates lacking a pendant dipolarophile such as phenyl acetylene, for example.



In light of the excellent progress in intramolecular systems over the past three decades,[27] we set out to develop efficient intermolecular Cope-type hydroaminations where the reactivity of the products is controlled. Indeed, we recently reported the successful addition of aqueous hydroxylamine and *N*-cyclohexylhydroxylamine to both alkynes and strained alkenes.[28] Herein, we provide a full account of our work, including reaction optimization, improved conditions, functional group compatibility studies and expanded scope with respect to both the hydroxylamine and unsaturated reaction partners. In addition, experimental and theoretical (DFT) insights into the reaction mechanism are described.

2. Results and Discussion

2.1. Intermolecular Cope-Type Hydroamination of Alkynes with Aqueous Hydroxylamine. In an attempt to avoid the side products associated with oxidation of *N*,*N*-dialkylhydroxylamines observed by Laughlin, we began our investigation with the reaction of phenylacetylene with hydroxylamine itself, as a cheap commercially available 50 wt% aqueous solution. We reasoned that the weaker π bond of an alkyne, combined with the stability of the oxime products would allow for the greatest chance of achieving the desired reactivity. Gratifyingly, encouraging conversions to acetophenone oxime were observed upon heating phenylacetylene and hydroxylamine in a sealed tube in a variety of organic solvents (dioxane, *i*-PrOH, DMSO, etc.). Further optimization using dioxane as solvent revealed that the reaction is most efficient at higher concentrations (eq 1), giving near quantitative conversion to the desired oxime (see Table A of Supporting Information for more details).



The scope of alkyne substrates is shown in Table 1. In general, terminal aryl alkynes react well under these reaction conditions, with both steric and electronic variations on the arene ring being well tolerated (entries 1−7). Enynes and alkylacetylenes are also reactive, requiring higher temperatures to achieve good yields (entries 8−10). Notably, the reaction is compatible with alkynes bearing a basic pyridine group, free hydroxyl groups,[29] and common protecting groups (entries 7, 11−15, 17−19). However, a tetrahydropyran-protected substrate led to

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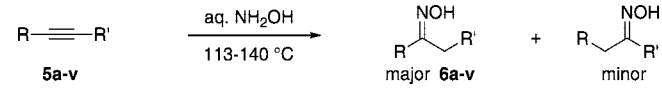
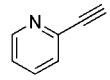
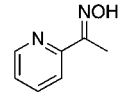
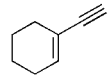
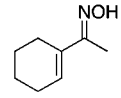
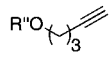
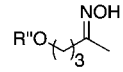
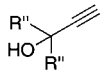
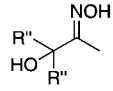
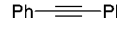
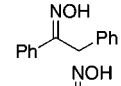
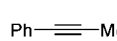
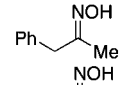
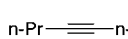
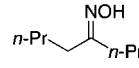
Table 1. Reaction of Alkynes with Aqueous NH_2OH



entry	substrate	conditions[a]	major product		yield(%)[b]
1	R= Ph, R' = H	A		**6a**	87(5)
		B			90(8)
2	R= 4-OMeC$_6$H$_4$, R' = H	A		**6b**	83(3)
3	R= 4-FC$_6$H$_4$, R' = H	A[c]		**6c**	71(8)
4	R= 2-MeC$_6$H$_4$, R' = H	A		**6d**	45(11)
5	R= 3-MeC$_6$H$_4$, R' = H	A		**6e**	75(2)
6	R= 4-MeC$_6$H$_4$, R' = H	A		**6f**	65(3)
7		A[c]		**6g**	73(15)
8		C		**6h**	55(1)
		D			72(3)
9	R= *n*-C$_6$H$_{13}$, R' = H	C		**6i**	62
		D			86(2)
10	R= *c*-C$_6$H$_{11}$, R' = H	D		**6j**	72
11	 R"= H	D		**6k**	91
12	R"= TBS	D		**6l**	86
13	R"= Bn	D		**6m**	98
14	R"= Piv	D		**6n**	90
15	R"= PMB	D		**6o**	98
16	R"= THP	D		**6p**	0[d]
17	 R"= H	E		**6q**	89(<1)
18	R"= Me	D		**6r**	75(<1)
19	R"= Ph	D		**6s**	63(1)
20		C		**6t**	71
21		C		**6u**	31(3)
		D			53(5)
22		C		**6v**	7
		D			12

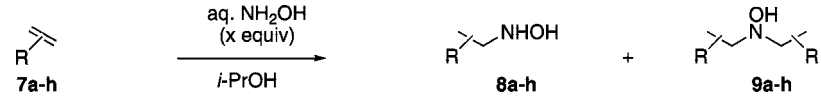
[a] Reaction conditions: A: alkyne (1 equiv), aq. NH_2OH (2.5 equiv), dioxane (1 M), sealed tube (behind a blast shield), 113 °C, 16−18 h; B: reflux condenser, 1-butanol (1 M), 16 h; C: 140 °C, dioxane (2 M), 38−40 h; D: *i*-PrOH (1 M), 140 °C (microwave), 5−10 h; E: 110 °C, *i*-PrOH (2 M), 70 h, sealed tube. [b] Yield of isolated products. Yield of minor regioisomer shown in parentheses. [c] 2 M in dioxane. [d] Led to isolation of unprotected oxime in 65% yield.

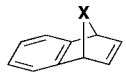
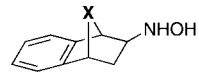
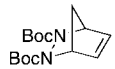
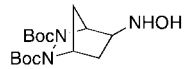
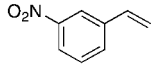
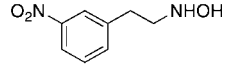
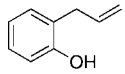
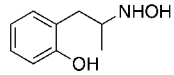
the isolation of the deprotected product in 65% yield (entry 16). In general, heating to 140 °C in *i*-PrOH under microwave irradiation was found to give improved yields for less reactive terminal (entries 8−19) and internal alkynes (entries 20−22). In most cases, the unreacted starting material could be recovered and the products were conveniently isolated by chromatography or recrystallization. The transformation has been carried out easily on scales of over 4 g, and can also be performed without the use of a sealed tube under typical reflux conditions by employing a higher boiling solvent such as 1-butanol (entry 1, condition B).

All control experiments performed appear consistent with a Cope-type hydroamination pathway. For example, to address the possibility of hydration of the alkyne to the ketone and subsequent oxime formation as a mechanistic pathway, phenylacetylene, 1-octyne and 1,1-diphenylpropargyl alcohol were heated to 140 °C in aqueous *i*-PrOH under microwave irradiation and no ketone products were detected in all cases.[2b,30] Control

(24) (a) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456. See also: (b) Moglioni, A. G.; Muray, E.; Castillo, J. A.; Álvarez-Larena, Á.; Moltrasio, G. Y.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2002**, *67*, 2402.
(25) Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.
(26) Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125.
(27) For an excellent review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.
(28) (a) Beauchemin, A.; Moran, J.; Lebrun, M.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410. For analogous reactivity of hydrazines, see: (b) Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492–493.
(29) For applications of α-hydroxy oximes as ligands in ferromagnetically coupled complexes see: (a) Pathmalingam, T.; Gorelsky, S. I.; Burchell, T. J.; Bédard, A.-C.; Beauchemin, A. M.; Clérac, R.; Murugesu, M. *Chem. Commun.* **2008**, 2782.
(30) For selected reviews on the hydration of alkynes, see: (a) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121. (b) Oestrich, M. In *Science of Synthesis*, Vol. 25; Brüchner, R., Ed.; Thieme: Stuttgart, 2006; p 199. (c) Figadière, B.; Franck, X. In *Science of Synthesis*, Vol. 26; Cossy, J., Ed.; Thieme: Stuttgart, 2004; p 401. (d) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

Table 2. Reaction of Aqueous NH_2OH with Alkenes[a]

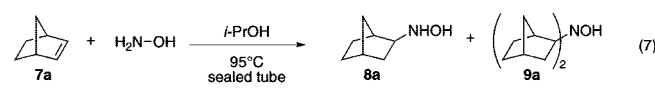


entry	alkene		monoaddition product		x	T (°C)	yield **8**+**9** (%)	ratio (**8**:**9**)
1		**7a**		**8a**	2	95	99	1:2.2
2					10	95	65	7.1:1
								
3	**X** = CH_2 (**7b**)		**8b**		2	95	98	1:1.5
4	**7b**		**8b**		10	95	49	14:1
5	**X** = O (**7c**)		**8c**		2	95	95	1.9:1
6	**X** = NBoc (**7d**)		**8d**		2	95	48	> 20:1
7		**7e**		**8e**	2	95	55	> 20:1
8		**7f**		**8f**	2	140	39	2.2:1[b]
9		**7g**		**8g**	2	95	30	> 20:1
10		**7h**		**8h**	2	115	13	> 20:1

[a] Conditions: alkene (1 equiv), aq. NH_2OH (x equiv, 5 M in *i*-PrOH), sealed tube (+ blast shield), 24−48 h. [b] 12:1 mixture of regioisomers (branched:linear).

experiments involving heating phenylacetylene in the presence of either NH_2OMe or Me_2NOH (in *i*-PrOH) showed little or no reactivity (see Supporting Information).

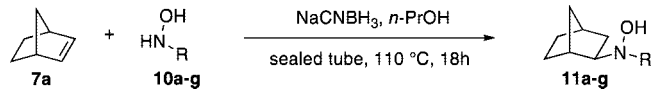
2.2. Intermolecular Cope-Type Hydroamination of Alkenes with Aqueous Hydroxylamine. Stimulated by the success with alkynes, investigations were initiated toward the intermolecular Cope-type hydroamination of alkenes. Success in this venture would allow for the rapid synthesis of *N*-alkyl- and *N*,*N*-dialkylhydroxylamines, which can be easily reduced to the parent amines, but also have applications as monoamine oxidase inhibitors,[31] lipid antioxidants,[32] and as photographic developers.[33] Initial reactions were performed with norbornene, whose strain energy renders it significantly more reactive and provides a thermodynamic driving force, although it was not known if the produced *N*-alkylhydroxylamines would survive the reaction conditions.[34,35] After extensive experimentation, the reaction was found to be very sensitive to solvent and concentration effects. Surprisingly, initial trials in dioxane under the conditions used for aromatic alkynes showed almost no reaction. Starting materials were consumed when DMSO-d_6 was employed as solvent, but despite considerable effort, a complex reaction mixture containing little desired product was produced. For alkenes, unlike alkynes, alcoholic solvents proved uniquely effective to obtain hydroamination products and minimize side reactions (Table B of the Supporting Information). *i*-PrOH was found to be the most effective alcohol for this reaction, most likely due to its ability to solubilize both aqueous hydroxylamine and norbornene. Compounds **8a** and **9a** were formed in 53% combined conversion (**8a**:**9a** = 9.6:1) simply upon heating to 95 °C in *i*-PrOH for 14 h. As the reaction appeared to be very sensitive to changes in the water to *i*-PrOH ratio, both concentration and equivalents of aqueous hydroxylamine had to be studied independently in order to maximize conversion. At the optimum concentration (5.0 M in *i*-PrOH), selectivity for either the mono- or bis-hydroamination product can be achieved by varying the equivalents of NH_2OH. A 10-fold excess of hydroxylamine gave monohydroamination product **8a** with good selectivity, while a 2-fold excess resulted in a slight preference for bishydroamination product **9a** in 99% combined yield (eq 2).

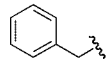
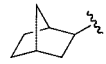


A variety of strained alkenes displayed excellent reactivity under these optimized reaction conditions (Table 2). Predictably, mixtures of mono- and bis-hydroamination products were observed. While the bis-hydroamination product **9** is typically favored in the presence of 2 equivalents of NH_2OH (entries 1 and 3), the monohydroamination product **8** is favored in the

(31) Benington, F.; Morin, R. D.; Clark, L. C., Jr. *J. Med. Chem.* **1965**, *8*, 100.
(32) Van Der Veen, J.; Weil, J. T.; Kennedy, T. E.; Olscott, H. S. *Lipids* **1970**, *5*, 509.
(33) Green, M.; Adnan, S. A.; Ulrich, H. Aminoalkyl hydroxylamines as photographic developers. U.S. Patent 3,287,125, November 22, 1966.
(34) For selected examples of norbornene in catalytic hydroamination reactions, see: refs 6a,9b,12b,15b,c. See also: (a) Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561. (b) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640. (c) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, *6*, 2515. (d) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519. (e) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857.
(35) For an example of an alternate route to *exo*-norbornylamines, see: Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedron Lett.* **2005**, *46*, 7831.

Table 3. Reaction of *N*-Alkylhydroxylamines with Norbornene[a]

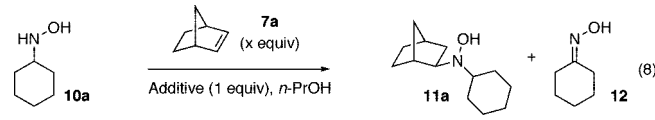


entry	R	product	conversion (%)[b]	yield (%)[c]
1		**11a**	91 (67[d])	83
2		**11b**	98	90
3		**11c**	99 (18[d])	73
4		**11d**	75 (8[d])	63[e]
5		**11e**	86	78
6		**11f**	72	68
7		**11g**	23	7

[a] Conditions: alkene (2 equiv), hydroxylamine (1 equiv), additive: $NaCNBH_3$ (1 equiv), *n*-PrOH (0.6 M), sealed tube, 110 °C, 18 h. [b] Conversion determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard. [c] Isolated yield after column chromatography. [d] No $NaCNBH_3$. [e] dr = 1:1.

presence of excess NH_2OH (entries 2 and 4). More hindered strained alkenes also led to selective formation of the mono-hydroamination product **8** (entries 6−7). Given their lack of strain release energy and a report by Hartwig that hydroamination of vinylarenes are approximately thermoneutral,[13] such substrates were expected to be more challenging. Gratifyingly, simply heating styrene and other vinylarenes under similar conditions gave hydroamination products (entries 8−9). Even the unconjugated 2-allylphenol was found to be reactive, albeit in very low yield (entry 10). Both the regioselectivity and preference for forming either the mono- or bis-hydroamination product were found to be substrate specific, as was the yield. Nonetheless, these results offered promise that greater alkene generality was possible.

2.3. Cope-Type Hydroamination of Alkenes with *N*-Alkylhydroxylamines. Besides greatly expanding the synthetic scope of the reaction, the use of *N*-alkylhydroxylamines as starting materials also promises to simplify its outcome by eliminating the possibility of bis-hydroamination. However, initial attempts to effect the addition of *N*-cyclohexylhydroxylamine to norbornene using our previously developed conditions did not prove fruitful as the major product was found to be the oxidation byproduct cyclohexanone oxime **12**. *N*-Alkylhydroxylamines are known to undergo such oxidation chemistry simply upon dissolution in degassed polar solvents.[36] Investigation of other alcohols revealed *n*-PrOH as a superior solvent, and the screening of a large number of additives revealed that sodium cyanoborohydride partially inhibited this oxidative pathway (Table C of Supporting Information). Increasing the temperature to 110 °C and employing a 2-fold excess of alkene allowed for a more efficient reaction even without additive. Finally, combining these improved conditions with the beneficial effects of $NaCNBH_3$ led to a 91% conversion (83% isolated yield) with no observable oxime byproduct (eq 3). Expectedly, control experiments confirmed that the sodium cyanoborohydride was not simply reducing the oxime back to the hydroxylamine under the reaction conditions, as acid is typically required to activate the oxime for such a transformation.[37] The additive instead appears to inhibit the decomposition of both the hydroxylamine starting materials and the products at the required reaction temperatures.[38]



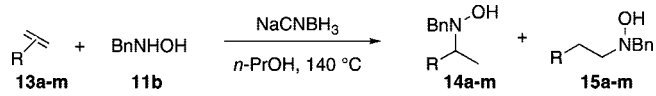
1 equiv. **7a**, no additive, 95 °C : 30% **11a** + 31% **12**
2 equiv. **7a**, no additive, 110 °C : 67% **11a** + 16% **12**
2 equiv. **7a**, $NaCNBH_3$, 110 °C : 91% **11a** + <1% **12**

With new conditions compatible with *N*-alkylhydroxylamines in hand, we investigated the scope of the reaction with respect to the alkyl substituent on the hydroxylamine. A variety of *N*-alkylhydroxylamines successfully perform Cope-type hydroamination in good yields when heated to 110 °C with norbornene in the presence of sodium cyanoborohydride in *n*-PrOH (Table 3). Products possessing accessible β-hydrogens did not appear to undergo degradation via Cope elimination (entries 1 and 3−4). Unfortunately, *sec*-butylhydroxylamine did not provide any diastereoselectivity in our hands (entry 4). Hydroxylamines possessing bulky alkyl substituents such as neopentyl and norbornyl groups performed well under these conditions (entries 5−6). *N*-Phenylhydroxylamine underwent

(36) (a) Horiyama, S.; Suwa, K.; Yamaki, M.; Kataoka, H.; Katagi, T.; Takayama, M.; Takeuchi, T. *Chem. Pharm. Bull.* **2002**, *50*, 996. (b) Beckett, A. H.; Rashid Purkaystha, A.; Morgan, P. H. *J. Pharm. Pharmacol.* **1977**, *29*, 15. (c) Lindeke, B.; Anderson, E. *Acta Pharm. Sueu.* **1975**, *12*, 183. (d) Posner, T. *Ann. Chim.* **1912**, *389*, 1. (e) Fischer, E.; Scheibler, H.; Groh, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2020. (f) Posner, T. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2316.

(37) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

Table 4. Reaction of *N*-Benzylhydroxylamine with Vinylarenes and Triphenylvinylsilane[a]



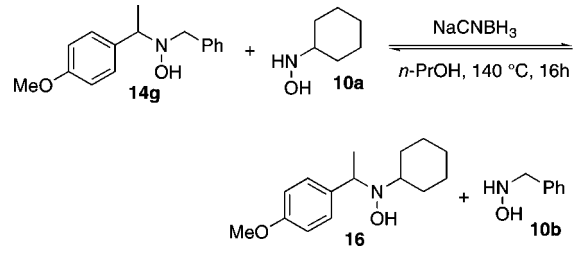
entry	reactant	major product		ratio (**14**:**15**)	yield (%)[b]
1	R = H		**14a**	>20:1	58
2	R = 4-F		**14b**	4.6:1	49
3	R = 4-Ph		**14c**	2.1:1	49
4	R = 3-Me		**14d**	>20:1	54
5	R = 4-Me		**14e**	>20:1	51
6	R = 2,4-Me		**14f**	>20:1	33
7	R = 4-OMe		**14g**	>20:1	49
8	R = 4-NH_2		**14h**	>20:1	36
9	R = perfluoro		**15i**	<1:20	66
10	R = CF_3		**15j**	1:2.7	59
11	R = 2-Br		**15k**	1:1.1	79
12			**14l**	>20:1	36
13	Ph_3Si		**15m**	<1:20	71

[a] Conditions: alkene (2 equiv), *N*-alkylhydroxylamine (1 equiv), *n*-PrOH (0.6 M), sealed tube, 140 °C, 14−18 h. [b] Isolated yield after column chromatography.

hydroamination albeit in low conversions, despite its propensity to oxidize[39] and its predicted nucleophilic deactivation due to the adjacent phenyl ring (entry 7).[40] The extent of the beneficial effect of sodium cyanoborohydride varies drastically with the alkyl substitution of the hydroxylamine. For example, the conversion drops from 91 to 67% if sodium cyanoborohydride is not employed with *N*-cyclohexylhydroxylamine (entry 1), but drops from 99 to 18% if it is not present when *N*-isopropylhydroxylamine undergoes addition (entry 3).

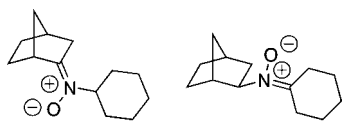
Reinvestigation of alkene scope with *N*-alkylhydroxylamines revealed more efficient reactivity with vinylarenes than was previously observed with aqueous hydroxylamine. A variety of vinylarenes reacted with *N*-benzylhydroxylamine in modest to good yields, consistent with precedent that hydroamination with such alkenes displays near thermoneutral reaction thermodynamics (Table 4).[13] In most cases, the mass balance was unreacted starting material and the products could be conveniently isolated by column chromatography. Steric variations near the alkene are well tolerated (entries 6−11), while electronic variations on the arene ring give slightly better yields while influencing regioselectivity. The more electron poor arenes favored the anti-Markovnikov (**15**) products, offering a simple route to bioactive phenethylamines.[41] Styrene itself and other relatively less electron poor arenes favored the formation of the Markovnikov (**14**) adducts. The complementary nature of this procedure versus metal-catalyzed methodologies is perhaps best illustrated by the successful reaction of alkenes possessing an aniline (entry 8) or aryl bromide moiety (entry 11). Triphenylvinylsilane was also reactive under these conditions, giving exclusively **15m** in 71% yield.

Crossover experiments were designed to test the assertion that the addition to vinylarenes is indeed under thermodynamic control. Hydroamination product **14g** was heated to 140 °C in a sealed tube in the presence of one equivalent of *N*-cyclohexylhydroxylamine (**10a**) and $NaCNBH_3$. After 16 h, 37% of crossover product **16** was detected in the unpurified reaction mixture by ^{1}H NMR spectroscopy (eq 2).[42,43] To ensure a direct comparison, hydroxylamine **16** was synthesized independently using 4-methoxystyrene and *N*-cyclohexylhydroxylamine (**10a**) under the conditions described in Table 4.[42]



(9)

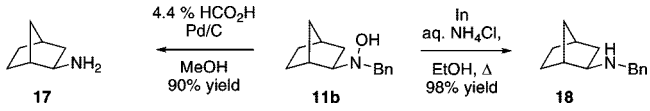
(38) *N*-Cyclohexyl-*N*-hydroxy-*exo*-bicyclo[2.2.1]heptan-2-amine (**11a,** 0.10 g, 0.48 mmol) in *n*-propanol (0.8 mL) was stirred in a sealed tube under an argon atmosphere while heating to 140 °C in an oil bath for 21 hrs. The tube was cooled to ambient temperature, concentrated under reduced pressure and taken up in $CDCl_3$. TLC analysis (5% MeOH/CH_2Cl_2) and ^{1}H NMR spectra of this solution showed significant decomposition to compounds believed to be nitrones **11ai** and **11aii** (isolated as an inseparable mixture by column chromatography; 5% MeOH/CH_2Cl_2). The same experiment, but with the addition of sodium cyanoborohydride (0.030 g, 0.48 mmol), resulted in nearly quantitative recovery of starting materials. Only traces of the ^{1}H NMR resonances thought to correspond to nitrones **11ai** and **11aii** could be observed under these conditions.



11ai **11aii**

(39) Becker, A. R.; Sternson, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2003.

Scheme 2. Access to Reduced Derivatives of *N*-Norbornyl-*N*-benzylhydroxylamine (**11b**)

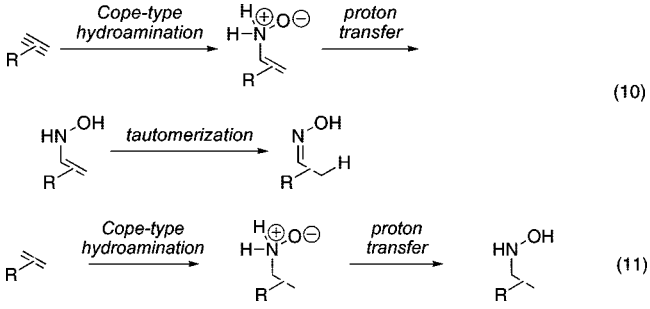


It should be noted that *N*-benzylhydroxylamine might be viewed as either an ammonia or a benzylamine equivalent in the context of the Cope-type hydroamination, as products can be selectively and efficiently deprotected to give either the *N*-alkylamine[44] or the *N*-alkyl-*N*-benzylamine[45] in one step (Scheme 2).[46]

3. DFT Calculations and Discussion

Density functional theory (DFT) calculations were performed to obtain insight on various aspects of this intermolecular reactivity of alkenes and alkynes. Related calculations on the Cope elimination have been reported by Komaromi and Tronchet,[47] and Acevedo and Jorgensen,[48] but these only provide information regarding the microscopic reverse of the intermolecular hydroamination reactivity *of alkenes* reported herein (i.e., the Cope elimination). Thus, DFT calculations were performed in parallel to the experiments detailed previously and were primarily directed at: (1) mapping the potential energy surface (PES) of the reactions of alkenes and alkynes, including activation energies and the evaluation of the thermodynamic driving force for the reactions (ΔG_r), as a specific issue is the near-thermoneutral nature of some reactions of alkenes; (2) study the nature of the hydroamination and proton transfer transition state structures; (3) determination of the impact of alkene and nitrogen substitution on the reaction rate and product distribution, which includes the issue of Markovnikov vs anti-Markovnikov selectivity with specific substrates.

3.1. Mapping the Potential Energy Surface of the Reactions. Initial calculations were directed at determining the thermodynamic profiles for the reactions of alkenes and alkynes with NH_2OH (monohydroamination). The relative energies of reactants, intermediates and products, as well as the energies of the transition states (TSs) for both the hydroamination and proton transfer steps (see eqs 10 and 11) were thus first calculated in the gas phase at the B3LYP/TZVP level of theory (298 K and 1 atm). The potential energy surfaces for reactions of alkynes (acetylene, C_2H_2, and phenylacetylene, C_8H_6) and alkenes (ethylene, C_2H_4, and norbornene, C_7H_{10}) are shown in Figures 1 and 2, respectively, and calculated free energies are included in Table 5.



These results reveal both similarities and differences between the reactivity of alkynes and alkenes. For example, the similar activation energies calculated for the Cope-type hydroamination transition states (see Section 3.2) of alkynes and alkenes ($\Delta G^{\ddagger}_{HA}$,

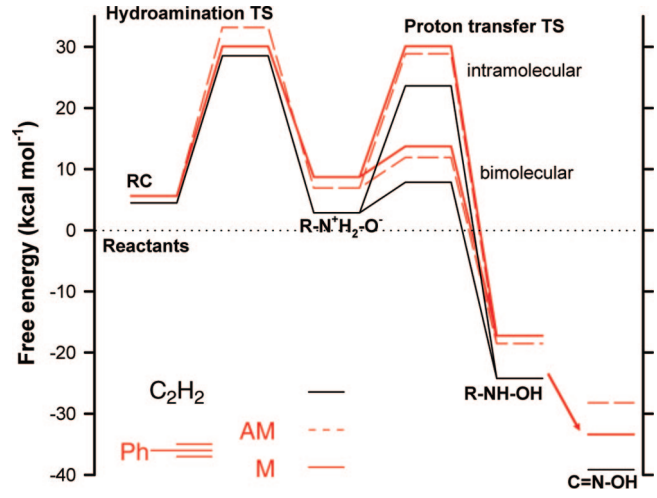


Figure 1. Free energies of reaction species and transition states for hydroamination of acetylene, C_2H_2 (black lines) and phenylacetylene, C_8H_6 (red lines) at the B3LYP/TZVP level of theory.

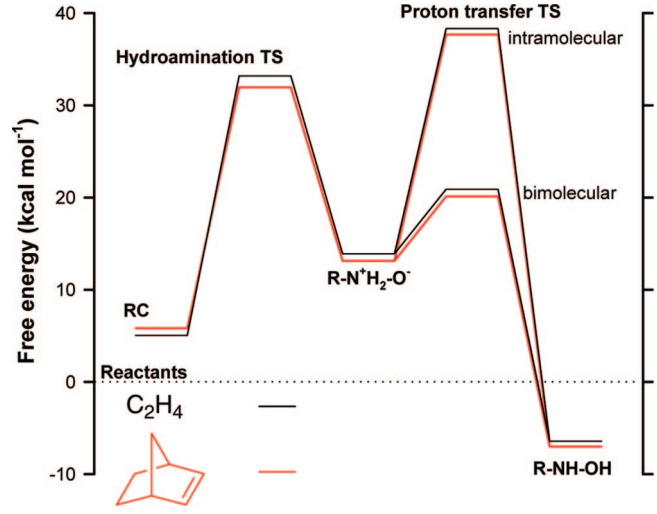


Figure 2. Free energies of reaction species and transition states for hydroamination of ethylene, C_2H_4 (black lines) and norbornene, C_7H_{10} (red lines) at the B3LYP/TZVP level of theory.

30.1 vs 32.0 kcal/mol for $PhCCH_{(M)}$ and C_7H_{10}, respectively) correlate well with the ability of these substrates to undergo hydroamination at similar temperatures (ca. 100 °C). However, the calculated energies of: i) the *N*-oxide intermediates; ii) the TSs of the proton transfer step; and iii) reaction products are very different for the reactions of alkynes and alkenes. These differences likely result from the weaker π bond of alkynes relative to alkenes (ca. 15 kcal/mol difference), which translates into increased stability of alkenyl *N*-oxide intermediates relative to the alkyl *N*-oxide intermediates (ΔG_{NO}, 2.9 vs 13.9 kcal/mol for the C_2H_2 and C_2H_4 adducts, respectively; 8.7, 13.1 and 18.7 kcal/mol for the $PhCCH_{(M)}$, C_7H_{10} and $PhCHCH_2$ adducts, respectively). The relative stability of these *N*-oxide intermediates is important as it determines the likelihood of the reverse reaction (the Cope elimination) relative to the subsequent proton transfer step, which leads to the hydroamination products. *This is important since in the absence of a proton shuttle (vide infra), the activation energy required to access the TS of the intramolecular proton transfer step ($\Delta G^{\ddagger}_{PT}$) is high and kinetically relevant (see section 3.3).* While for alkynes the energy barrier for the proton transfer is close in magnitude to the barrier for

Table 5. Free Energies (kcal/mol) of the Reaction Species for Hydroamination Reactions (NH_2OH) with Alkenes and Alkynes (Evaluated at 298 K and 1 atm)[a]

	alkenes			alkynes		
Species	CH_2CH_2	$PhCHCH_{2\ AM}$	$PhCHCH_{2\ M}$	HCCH	$PhCCH_{AM}$	$PhCCH_M$
RC[b]	5.1	5.9	5.9	4.5	5.6	5.6
Hydroamination TS	33.2	38.4	33.4	28.5	33.2	30.1
$R\text{-}NH_2^+O^-$	13.9	19.5	18.7	2.9	6.9	8.7
Intramolecular H^+ transfer TS	38.3	44.0	44.2	23.6	28.9	30.1
bimolecular H^+ transfer TS[c]	20.9	26.5[d]	25.7[d]	7.9	11.9[d]	13.7[d]
R-NHOH	−6.4	0.3	−0.5	−24.2	−18.5	−17.2
C═N−OH				−39.2	−28.2	−33.4

[a] Energies are relative to the free reactants. [b] Reactants complex. [c] Transition state for proton transfer between $R\text{-}NH_2^+O^-$ and *i*-PrOH. [d] Energy of the transition state was evaluated using the calculated activation free energy for the proton transfer for the $C_2H_5{-}NH_2O\cdots$*i*-PrOH complex (to form $C_2H_5{-}NHOH\cdots$*i*-PrOH) for alkenes and the $C_2H_3{-}NH_2O\cdots$*i*-PrOH complex (to form $C_2H_3{-}NHOH\cdots$*i*-PrOH) for alkynes (7.0 and 5.0 kcal/mol in vacuum, respectively and 9.7 and 7.5 kcal/mol in methanol). See ref 49.

the hydroamination step ($\Delta G^{\ddagger}_{HA} = 28.5$ vs $\Delta G^{\ddagger}_{PT} = 23.6$ kcal/mol for C_2H_2, and $\Delta G^{\ddagger}_{HA} = 30.1$ vs $\Delta G^{\ddagger}_{PT} = 30.1$ kcal/mol for $PhCCH_{(M)}$), the *intramolecular* proton transfer step is rate limiting for reactions of alkenes ($\Delta G^{\ddagger}_{HA} = 33.2$ vs $\Delta G^{\ddagger}_{PT} = 38.3$ kcal/mol for C_2H_4, and $\Delta G^{\ddagger}_{HA} = 32.0$ vs $\Delta G^{\ddagger}_{PT} = 37.7$ kcal/mol for C_7H_{10}). These results are consistent with the observed reactivity difference in aprotic solvents: while the hydroamination of phenylacetylene can be performed in various solvents (eq 1 and Table A, Supporting Information), the hydroamination of norbornene could not be performed satisfyingly in aprotic solvents (eq 2 and Table B, Supporting Information).[50] Fortunately, alcoholic solvents appeared uniquely effective to enable Cope-type hydroamination of alkenes (vide infra), and also provided improved reactivity with challenging alkyne substrates (see Table 1, entries 8−22). Finally, the thermodynamic driving force (ΔG_r) for the reactions of alkynes and alkenes are also markedly different. For alkynes, the formation of the hydroamination products is very favorable due to the relative weakness of the alkyne π bond and due to the ability of the resulting *N*-hydroxyenamine intermediates to form more stable oxime products. For example, formation of the *N*-hydroxyenamines is favorable for both C_2H_2 (−24.2 kcal/mol) and $PhCCH_{(M)}$ (−17.2 kcal/mol) and the formation of the related oximes is more favorable ($\Delta G_r = -39.2$ and −33.4 kcal/mol, respectively). In contrast, the formation of the *alkene* hydroamination products is very dependent on the nature of the alkene. For example, formation of the products is moderately favored for C_2H_4 ($\Delta G_r = -6.6$ kcal/mol) and C_7H_{10} ($\Delta G_r = -7.0$ kcal/mol). However, both substrates are biased: ethylene is less stable than most alkenes since it is unsubstituted and the reaction of norbornene benefits from partial release of strain energy. For the more stable vinylarenes, our calculations suggest that the reaction is thermoneutral ($\Delta G_r = -0.5$ and 0.3 kcal/mol, respectively, for the Markovnikov and anti-Markovnikov styrene adducts), in agreement with the moderate yields reported in Table 4. Furthermore, these results are in agreement with Hartwig's observation that the reaction of vinylarenes and anilines is thermoneutral.[13]

3.2. Nature of the Cope-Type Hydroamination TS. Pioneering work by Ciganek[19b,c] and Oppolzer[20a] on intramolecular Cope-type hydroaminations provides strong evidence for a concerted process, rather than the radical-based mechanism postulated by House in 1976.[18] Notably, the cyclizations presented in eqs 1 and 3 highlight that at 80 °C alkene stereochemical information is transferred to the products. Based on this experimental evidence, it appears very likely the intermolecular reactions documented herein, which are performed at 90−140 °C, are also concerted. Seeking to obtain more information about the nature of the Cope-type hydroamination, transition state structures were determined for the hydroamination of several alkenes and alkynes (Figures 3 and 4). In all cases the 5-membered, coplanar transition states involve a concerted hydroamination process. For the hydroamination of norbornene (C_7H_{10}, Figure 3), the high *exo* selectivity observed experimentally (Tables 24) was also found to be consistent with the calculated activation energies for the hydroamination step (39.1 vs 32.0 kcal/mol for endo and exo additions, respectively.

To analyze how the electronic structure of alkenes and alkynes influence hydroamination, an activation-strain analysis was performed (eq 12). The energetic cost (distortion energy, E_{dist}) associated with distortion of NH_2OH and alkenes/alkynes (CC) from ground state to TS geometries, as well as the energetic

(40) The difficult product isolation in this case was likely due to the propensity of *N*-phenyl, *N*-alkylhydroxylamines to form stable nitroxyl radicals.
(41) Parker, E. M.; Cubeddon, L. X. *J. Pharmacol. Exper. Ther.* **1988**, *245*, 199.
(42) See Supporting Information for details.
(43) For reversibility experiments using a *N*,*N*-dialkylhydroxylamine and NH_2OH, see Supporting Information of ref 28a.
(44) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442.
(45) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.
(46) For other representative methods for the reduction of *N*,*N*-disubstituted hydroxylamines, see: (a) Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973. (b) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 6469. (c) Murahashi, S.-I.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645. (d) Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett.* **1985**, *26*, 4633. (e) Kodera, Y.; Watanabe, S.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2542. (f) Merino, P.; Anoro, S.; Franco, S.; Gascon, J. M.; Martin, V.; Merchan, F. L.; Revuelta, J.; Tejero, T.; Tunon, V. *Synth. Commun.* **2000**, *30*, 2989. (g) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159.
(47) Komaromi, I.; Tronchet, J. M. J. *J. Phys. Chem. A* **1997**, *101*, 3554–3560.
(48) Acevedo, O.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2006**, *128*, 6141–6146.
(49) These activation energies show little variability to the nature of the proton shuttle. For example, the activation free energy for the proton transfer for the $C_2H_5\text{-}NH_2O\cdots HOH$ and $C_2H_3\text{-}NH_2O\cdots HOH$ complexes in vacuum are 7.3 and 5.3 kcal/mol, respectively. The energies of the other hydroamination reaction species (minima and TSs) were also evaluated in the presence of H-bound *i*-PrOH. However, this produced only a minor energy change for the hydroamination reaction steps in Figure 1 (except in the proton transfer step).
(50) For example, only low conversions were observed in dioxane and DMSO-d_6 at 95 °C and attempts at higher temperatures were not successful due to side reactions.

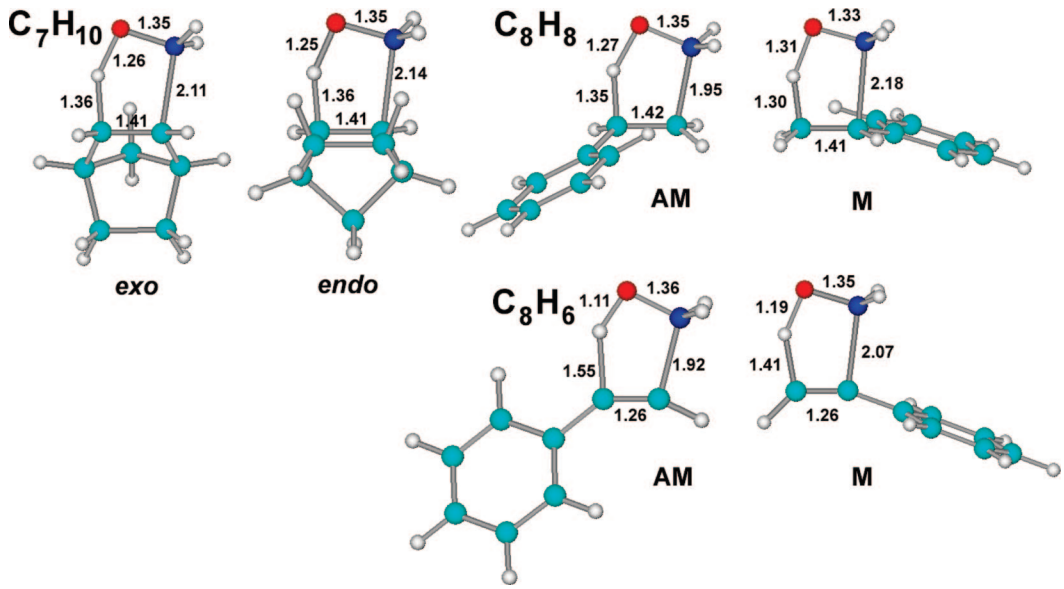


Figure 3. Transition state structures for hydroamination of alkenes and alkynes at the B3LYP/TZVP level of theory; M = Markovnikov product, AM = anti-Markovnikov product. The internuclear distances (Å) are shown only for relevant chemical bonds.

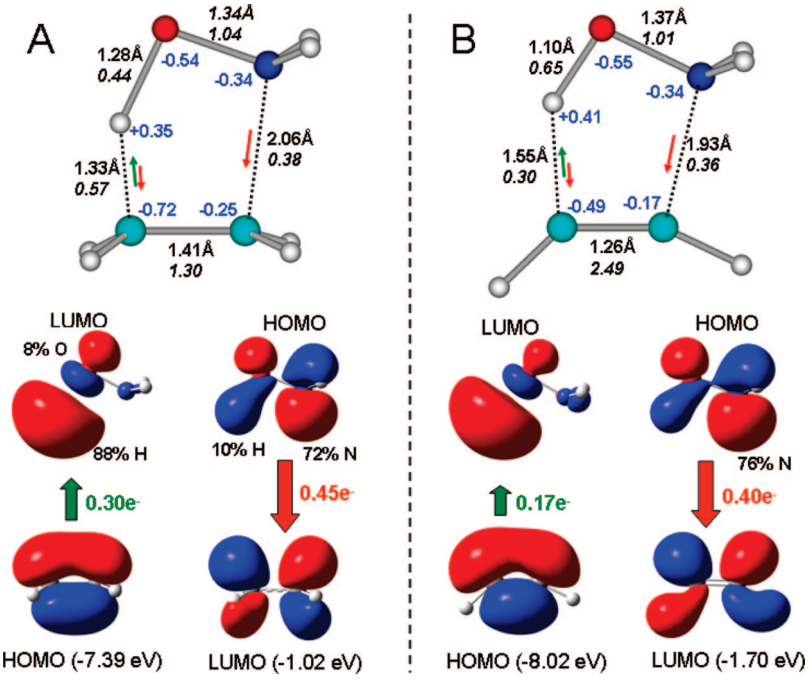


Figure 4. (Top) The transition states for hydroamination of C_2H_4 (left) and C_2H_2 (right) showing the internuclear distances and bond orders (italics) and NPA charges (blue). (Bottom) Two most important donor−acceptor interactions that contribute to bond formation between NH_2OH and C_2H_4 (left) and C_2H_2 (right).

gain arising from bringing the fragments together to form the TS (electronic interaction energy, E_{int}) were determined (Table 6):

$$\Delta E^{\ddagger} = E_{dist}(CC) + E_{dist}(NH_2OH) + E_{int} \qquad (12)$$

The E_{int} reflects the strength of electronic interactions between alkenes/alkynes and NH_2OH in the transition state structure. In order to identify the most important donor−acceptor interactions that contribute toward E_{int}, the fragment orbital (FO) analysis has been performed and the charge transfer between alkenes/alkynes and NH_2OH was evaluated from the charge in fragment orbital populations (Table 6). In all cases except reactions with phenylacetylene and styrene, the bond formation between alkenes/alkynes and NH_2OH involves only two donor−acceptor FO interactions: $HOMO_{NH2OH} \rightarrow LUMO_{CC}$ and $HOMO_{CC} \rightarrow LUMO_{NH2OH}$ (Figure 4). The reactions of phenylacetylene and styrene with NH_2OH involves other occupied and unoccupied FOs of alkenes/alkynes, due to conjugation of the π and π^* orbitals of the double and triple C−C bonds with the π and π^* orbitals of the phenyl ring. The charge transfer Q from NH_2OH to alkenes/alkynes via the $HOMO_{NH2OH} \rightarrow LUMO_{CC}$ interaction is somewhat greater for alkenes (0.43−0.50 e^-) than for alkynes (0.38−0.43 e^-, Table 6).

Due to the higher energies of the HOMOs of alkenes relative to alkynes, the charge transfer from alkenes/alkynes to NH_2OH via the $HOMO_{CC}-LUMO_{NH2OH}$ interaction is greater for alkene

Table 6. Electronic Energies (kcal/mol), Charge Decomposition Analysis, and Mayer Bond Orders for C−H and C−N Bonds Being Formed in Hydroamination Transition States

		$\Delta E^{\ddagger}$	$E_{dist}(CC)$	$E_{dist}(NH_2OH)$	E_{int}	$Q_{CC\rightarrow HA}$	$Q_{HA\rightarrow CC}$	B_{C-H}	B_{N-C}
				Alkynes					
C_2H_2		18.7	21.5	12.7	−15.5	0.17	0.40	0.30	0.36
CH_3CCH	AM	23.6	21.3	18.7	−16.3	0.20	0.39	0.34	0.33
	M	20.7	21.7	18.6	−19.7	0.21	0.38	0.32	0.31
CF_3CCH	AM	12.5	18.8	5.3	−11.7	0.11	0.37	0.17	0.32
	M	12.7	21.8	8.7	−17.7	0.14	0.43	0.19	0.34
PhCCH	AM	22.1	22.4	13.6	−13.9	0.16	0.38	0.30	0.36
	M	20.1	18.7	23.8	−22.4	0.23	0.38	0.35	0.26
Alkenes									
CH_2CH_2		22.6	13.5	36.3	−27.2	0.30	0.45	0.57	0.38
CH_3CHCH_2	AM	26.9	14.8	39.4	−27.3	0.30	0.45	0.61	0.37
	M	23.1	14.8	36.7	−28.4	0.30	0.43	0.55	0.36
CF_3CHCH_2	AM	19.3	18.5	24.8	−24.0	0.24	0.50	0.50	0.46
	M	22.5	15.5	36.7	−29.7	0.28	0.49	0.55	0.37
$PhCHCH_2$	AM	26.4	15.9	34.6	−24.0	0.28	0.44	0.63	0.42
	M	21.8	12.7	40.9	−31.7	0.30	0.45	0.53	0.36

hydroamination TSs (0.24−0.30 e$^-$) than for alkyne hydroamination TSs (0.11−0.23 e$^-$). Since the LUMO of the NH_2OH fragment is the antibonding O−H orbital, σ^*_{OH}, the charge transfer from alkenes/alkynes to NH_2OH determines how concerted the process of the C−H bond formation and the O−H bond cleavage is. For hydroamination of alkenes, strong charge transfer from the HOMO (π) of alkenes to the σ^*_{O-H} orbital of NH_2OH ensures that the cleavage of the O−H bond and the formation of the C−H bond are synchronous and the E_{int} values are sufficiently negative to compensate for the cost of the O−H bond elongation ($E_{dist}(NH_2OH)$). For hydroamination of alkynes, charge transfer from the HOMO (π) of alkynes to σ^*_{O-H} is not strong enough to produce a symmetric TS structure and the E_{int} values are less negative than those for the corresponding alkenes.

3.3. Importance of the Proton Transfer Step: the Beneficial Effects of Protic Solvents. The formation of the Cope-type hydroamination products must involve proton transfer from the *N*-oxide to the hydroxylamine products, and the experimental results highlight that this step is kinetically relevant. The calculated transition state energies of the intramolecular proton transfer process are high, due to its three-membered nature (Figure 5, **A**). In accord with the experimental data, the lowest energy transition state (Figure 5, **B**) was found for a bimolecular proton transfer step involving the amine oxide intermediate and a protic species such as *i*-PrOH and H_2O. Activation free energies for this proton transfer ($\Delta G^{\ddagger}_{BPT} - \Delta G_{NO}$) for alkynes ($C_2H_2$) and alkenes ($C_2H_4$) are ca. 5 and 7 kcal/mol, respectively, in the gas phase and ca. 8 and 10 kcal/mol, respectively, in methanol and are relatively independent of the nature of the proton shuttle (ROH). This pathway involving a bimolecular proton transfer is favored over an intramolecular alternative by ca. 15 kcal/mol. Alternatively, an *N*-oxide dimer such as **C** (Figure 5) would collapse to the reaction products.[51] However, the formation of such a dimer is kinetically unlikely and does not account for the beneficial solvent effect observed with alcohols (conditions D, Table 2). Optimized transitions state structures are shown in Figure 6.

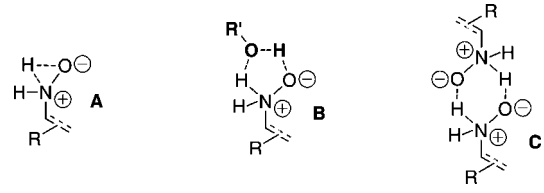


Figure 5. *N*-Oxide proton transfer pathways investigated computationally.

Alcoholic solvents are likely also beneficial through increased stabilization of the *N*-oxide intermediate in polar solvents. To evaluate the effect of various solvents on the potential energy surface of the reaction, DFT calculations were performed for the hydroamination of C_7H_{10} in C_6H_6, $CHCl_3$, DMSO and MeOH (Table 7). Two important trends are observed: (A) The *N*-oxide intermediate is best stabilized in polar solvents due to its polar nature (Table 7), for example the calculated free energies for the C_7H_{10}-derived *N*-oxide intermediate is 13.1 kcal/mol in the gas phase and 8.3 kcal/mol in methanol (for C_2H_4: 13.9 and 4.9 kcal/mol in gas phase and methanol, respectively). Ciganek has also observed experimentally the increased stabilization of *N*-oxides in polar ($CHCl_3$) and protic (MeOH) solvents.[19b,c] (B) Polar solvents also appear to reduce the calculated thermodynamic driving force (ΔG_r). For the reactions for C_7H_{10} and NH_2OH, ΔG_r is −7.0 and −3.1 kcal/mol in the

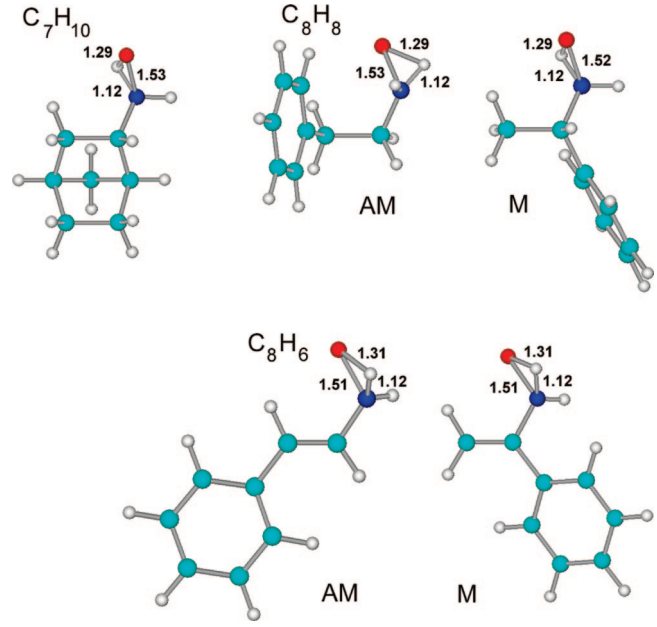


Figure 6. Transition state structures for intramolecular and bimolecular proton transfer in the hydroamination reactions of ethylene and acetylene at the B3LYP/TZVP level of theory. The internuclear distances (Å) are shown only for relevant chemical bonds. The TS structures for bimolecular proton transfer are shown for reactions R-$NH_2^+O^-$ with *i*-PrOH.

Table 7. Gas-Phase Dipole Moments (Debye) and Free Energies (kcal/mol) of the Reaction Species for Hydroamination Reactions (NH_2OH) with C_7H_{10} in C_6H_6, $CHCl_3$, DMSO, and MeOH (Evaluated at 298 K)[a]

		ΔG_{298K} (kcal/mol) in				
species	*D* (Debye)	vacuum	C_6H_6	$CHCl_3$	DMSO	MeOH
Reactant Complex	0.84	5.8	8.0	8.6	9.4	11.0
Hydroamination TS	3.03	32.0	31.9	32.4	32.4	34.3
R-$NH_2^+O^-$	5.44	13.1	11.0	10.5	9.2	8.3
Intramolecular H^+ transfer TS	4.02	38.3	37.4	38.0	37.8	38.8
bimolecular H^+ transfer TS	–	–	–	–	–	18.1
R-NHOH	0.88	−7.0	−6.1	−5.1	−4.6	−3.1

[a] Energies are relative to the free reactants in solvent.

Table 8. Nitrogen Substitution: Free Energies (kcal/mol) of the Reactions and Activation Free Energies for Hydroamination Reactions of Various Hydroxylamines with C_7H_{10} and C_8H_6 in the Gas Phase (Evaluated at 298 K and 1 atm)[a]

alkene/alkyne	hydroxylamine	regioselectivity	$\Delta G^{\ddagger}_{HA}$ kcal/mol	ΔG_r kcal/mol
C_7H_{10}	NH_2OH	–	32.0	−7.0
C_7H_{10}	NH(Me)OH	–	30.7	−3.7
C_7H_{10}	$N(Me)_2OH$	–	32.5	+14.9
PhCCH	NH_2OH	AM	33.2	−28.2
		M	30.1	−33.4
PhCCH	NH(Me)OH	AM	32.1	−18.3
		M	29.7	−14.8
PhCCH	$N(Me)_2OH$	AM	31.3	+5.4
		M	30.3	+12.0

[a] Energies are relative to the free reactants.

gas phase and in MeOH, respectively, due to increased stabilization of NH_2OH relative to the hydroamination product in polar solvents.

3.4. Reactions under Kinetic Vs Thermodynamic Control. The calculations and experimental results presented above suggest that the product distribution observed with alkynes and norbornene is consistent with kinetic control as the reactions are thermodynamically favorable. For terminal alkynes, the observed product distribution favors nitrogen incorporation on the internal carbon and for methylphenylacetylene, substitution occurs on the carbon atom proximal to the methyl group (Table 1). Typically, C−N bond formation will occur on the carbon atom that is best able to stabilize a developing positive charge in the alkyne hydroamination TS. Overall, the calculated differences in activation energies leading to both hydroamination regioisomers are in good agreement with the observed Markovnikov selectivity (vide infra). In contrast, product distribution with alkenes (except norbornene) appears consistent with thermodynamic control.[13] The observed preference for the Markovnikov or anti-Markovnikov adducts and yields (33−79%) vary significantly depending on the substitution present on the vinyl arene (Table 4). The experimental observation of reversibility with stryrene (eq 2) and DFT calculations showing the near thermoneutral nature of the reaction (i.e., similar stabilities of the styrene HA regioisomers) are consistent with this variability.

3.5. Impact of Substitution. The impact of nitrogen and alkene or alkyne substitution in *intramolecular* Cope-type hydroaminations has been delineated experimentally and discussed in a recent review by Cooper and Knight.[27] In general, π bond substitution translates into a more difficult hydroamination step, with substitution at the distal position of the unsaturation having a significant impact on rates of cyclization (up to ∼25 times slower). In contrast, nitrogen substitution is found to be beneficial in intramolecular systems: *N*-methyl-*N*-alkenylhydroxylamine substrates cyclize significantly faster than the parent (N−H) *N*-alkenylhydroxylamines. The latter trend is in contrast with our experimental results presented in Tables 2 and 3, as hydroaminations with NH_2OH and *N*-alkylhydroxylamines proceed under similar reaction conditions. Therefore, a comprehensive set of calculations was performed to provide insight into the substitution effects with respect to both reacting partners.

Several trends emerge from the data presented in Tables 8 and 9. First, the activation energy for the hydroamination step does not vary significantly with increased substitution on the hydroxylamine used (NH_2OH vs MeNHOH vs Me_2NOH). This theoretical data also suggests that the increased reactivity of *N*-methyl-*N*-alkenylhydroxylamine with respect to the parent (N−H) *N*-alkenylhydroxylamines substrates in intramolecular systems cannot be attributed to a more facile Cope-type cyclization step. *A possible rationale for this trend could be, in analogy to the findings documented herein, that the proton transfer step from the N-oxide intermediate to the hydroxylamine product is kinetically relevant for Cope-type cyclizations of (N−H) N-alkenylhydroxylamines, and that such cyclizations would also benefit from the presence of a proton shuttle.*

DFT studies on π bond substitution (Table 9) correlate well with the experimental data with respect to the reaction temperatures required with the various substrates presented in Tables

Table 9. Free Energies (kcal/mol) of the Reaction Species for Hydroamination Reactions (NH_2OH) with CH_3- and CF_3-Substituted Ethylene and Acetylenes (Evaluated at 298 K and 1 atm)[a]

	alkenes				alkynes			
	CH_3CHCH_2		CF_3CHCH_2		CH_3CCH		CF_3CCH	
species	AM	M	AM	M	AM	M	AM	M
RC[b]	5.3	5.3	6.5	6.5	5.7	5.7	7.7	7.7
Hydroamination TS	38.3[c]	34.5[c]	31.2	33.1	34.4[d]	31.2[d]	24.9	25.0
R-$NH_2^+O^-$	18.9	15.8	15.3	17.8	8.1	6.9	0.7	2.1
Intramolecular H^+ transfer TS	43.2	40.8	40.5	42.1	29.5	28.5	20.4	23.2
R-NHOH	−1.6	−3.9	−4.8	−3.7	−16.9	−19.0	−30.2	−25.1
C=N−OH	–	–	–	–	−29.7	−35.0	−41.3	−39.8

[a] Energies are relative to the free reactants. [b] Reactants complex. [c] 38.2 kcal/mol for the hydroamination of *cis*-CH_3−CH=CH−CH_3. [d] 35.5 kcal/mol for the hydroamination of CH_3−CC−CH_3.

1, 2, and 4, and with the trends documented for intramolecular Cope-type hydroaminations.[27] Importantly and likely due to the increased stability inherently linked to π bond substitution, activation free energies for the hydroamination step increase with π bond substitution. Increased stability of the alkene or alkyne starting material thus translates into reduced relative stability of the *N*-oxide intermediates and hydroamination products. Conversely, electron-withdrawing substituents reduce the activation energy required for anti-Markovnikov Cope-type hydroaminations of alkenes and alkynes, in accord with a more important $HOMO_{NH2OH} \rightarrow LUMO_{CC}$ interaction. Finally, for intermolecular reactions of alkenes, substitution can have a direct impact on reaction efficiency since for styrene the reaction is nearly thermoneutral.[13] Therefore, *at 298 K*, hydroaminations of ethylene, strained and terminal alkenes are slightly more favorable (thermodynamically) than reactions of vinylarenes. Disubstituted alkenes are also predicted to be more challenging substrates, both kinetically and thermodynamically. Due to the negative entropy of intermolecular reactions, the position of the equilibrium depends on the reaction temperature and the formation of hydroamination products is obviously more favorable at lower temperatures. The data regarding the thermodynamic driving force of the reactions (ΔG_r) should be used from this perspective, keeping in mind that more challenging hydroamination substrates often require higher reaction temperatures, which translate into less favorable reaction thermodynamics.

4. Conclusion

In summary, an intermolecular Cope-type hydroamination has been developed for unsaturated substrates including terminal and internal alkynes, strained alkenes and terminal vinylarenes. The use of alcoholic solvents is beneficial for reactions of alkynes and is generally necessary for reactions of alkenes to proceed: it is proposed that the solvent participates in a facile *bimolecular* proton transfer of the *N*-oxide intermediate, thus facilitating product formation. In addition, a beneficial additive effect observed with sodium cyanoborohydride has allowed for the extension of this reactivity from aqueous hydroxylamine to *N*-alkylhydroxylamines. All reactions can be carried out in concentrated alcoholic solvents, do not require rigorous exclusion of water and are easily scalable. The practicality and functional group tolerance (toward common protecting groups, free OH and NH bonds, aryl bromides, etc.) of this procedure highlight its complimentary role among existing intermolecular hydroamination methods. DFT calculations were also performed to provide insight into this reactivity, including information on the potential energy surface of the reactions and on the nature of the hydroamination and proton transfer transition states. A detailed molecular orbital description for the concerted hydroamination transition states is provided, and highlights the high electronic tunability of this process with respect to the alkene, alkyne and hydroxylamine reaction partners. Extensions and applications of this reactivity, including intramolecular variants, are underway and will be reported in due course.

5. Experimental Section

CAUTION: Hydroxylamine Free Base (HAFB) − 50 wt % Aqueous Solution. Hydroxylamine free base does not cause any problems if handled with care. For example, it is currently produced by BASF (>7000 ton/year) and used for a variety of industrial applications. However, HAFB can decompose spontaneously with the liberation of large volumes of gas if not handled properly. Violent decomposition of hydroxylamine can be caused by metal (especially iron) and metal ion impurities, oxidizing and reducing agents, bases, high temperatures above 75 °C, or high concentrations of hydroxylamine, for example due to evaporation. The use of more dilute solutions is inherently safer.[52] *Therefore, under standard reaction conditions, the hydroxylamine (HAFB) content of the solution being heated is in the 5−10 wt % range.* Hydroxylamine concentration should not be increased. The use of a blast shield to perform the experiments in sealed tubes or in flask equipped with a reflux condensor should be a standard operating procedure. Alternatively, commercially available microwave synthesizers are designed for safe operation at elevated temperatures and pressure, and were used regularly for reactions with aqueous NH_2OH. During the course of our studies (>500 experiments using NH_2OH, using the experimental setups described above), we have performed reactions up to a 5-g scale and have observed only minimal gas evolution (ie. a bit of pressure was released upon opening the sealed tubes to air, at room temperature, at the end of the reaction). No incidents occurred.

Computational Details. Density functional theory (DFT) calculations have been performed using the *Gaussian 03* program.[53] Optimized molecular geometries were calculated using the B3LYP[54] exchange-correlation functional.

The triple-ζ TZVP[55] basis set and tight SCF convergence criteria were used for calculations. Wave function stability calculations were performed to confirm that the calculated wave functions corresponded to the ground state. Harmonic frequency calculations were performed to ensure that the stationary points were true energy minima or transition states (TSs) and to calculate vibrational zero point energy and thermal corrections. The unscaled frequencies were used for calculating Gibbs free energies of the species (at 298 K and 1 atm). Intrinsic reaction coordinate (IRC)[56] calculations were used to confirm the reaction pathways through the transition states (TSs) for all reactions.

The calculation of solvation energies of the species in solvents (benzene, $CHCl_3$, DMSO, and methanol) were performed by using the polarizable continuum model (PCM) with the united atom topological (UAHF) atomic radii. Solvation energies were then used to evaluate the free energies of species in solvents.

Orbital compositions were calculated using Mulliken population analysis (MPA)[57] using the *AOMix* program.[58] The analysis of the orbital compositions of the hydroamination transition states in terms of molecular orbitals of the fragment molecules was performed using the *AOMix-CDA* program.[59,60] Mayer bond orders[61] were calculated using the *AOMix-L* program.[60] Atomic charges were evaluated by using the natural population analysis (NPA).[62]

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(51) Due to the remarkable efficiency of the bimolecular proton transfer pathway **B** (Figure 5), investigations into alternative bimolecular pathways were not pursued using DFT calculations. Experimentally, various attempts using either mildly basic (Et_3N) or acidic (AcOH) additives did not result in significant rate accelerations.

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Supporting Information Available: Typical experimental procedures, experimental details, optimization tables, characterization for all new compounds and complete ref 53. This material is available free of charge via the Internet at http://pubs.acs.org.

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