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Hydrogen-Bond-Promoted Metal-Free Hydroamination of Alkynes

Janet Bahri[a]
Nour Tanbouza[b]
Thierry Ollevier[*b]
Marc Taillefer[*a]
Florian Monnier[*a,c]

[a] École Nationale Supérieure de Chimie de Montpellier, Institut Charles Gerhardt, CNRS UMR 5253, AM2N, 8 rue de l'école normale, 34296 Montpellier Cedex 05, France
marc.taillefer@enscm.fr
[b] Département de Chimie, 1045 avenue de la Médecine, Université Laval, Québec, QC, G1V 0A6, Canada
thierry.ollevier@chm.ulaval.ca
[c] IUF Institut Universitaire de France, 1 rue Descartes, 75231 Paris, France
florian.monnier@enscm.fr

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Abstract An original metal-free regio- and stereoselective intermolecular hydroamination of alkynes is described. Various (*E*)-enamines were obtained from arylacetylenes and aliphatic secondary amines in the presence of ethylene glycol as a solvent. The latter is assumed to play a major role in the mechanism through hydrogen bonding and proton exchange.

Key words hydroamination, alkynes, amines, metal-free, enamines, green chemistry

Developing and streamlining the construction of C–N bonds constitutes an important goal in organic synthesis. Nitrogen-containing molecules are often used as synthetic intermediates,[1] and they are present in a plethora of natural substances.[2] Among these, enamines are interesting building blocks because of their versatile reactivity toward alkylation, cycloaddition, and a range of related bond-forming reactions for heterocycle synthesis.[3] Hydroamination of alkynes is an atom-efficient process that affords enamines through Markovnikov or anti-Markovnikov direct addition of an amine onto an unsaturated C≡C bond.[4] This transformation is often catalyzed by systems involving lanthanides,[5] alkaline earth metals,[6] acids,[7] bases,[8] or transition metals.[4e,9] Catalytic systems based on Pd,[10] Rh,[11] and Au[12] have been successfully used, but they exhibit limitations that include the cost and toxicity of reagents, narrow reaction scope, and poor functional-group compatibility. Copper also shows an interesting catalytic activity for this transformation.[13,14] The ability of copper systems to catalyze the intramolecular hydroamination of alkynes has been known for decades[13] but there are few intermolecular examples of this reaction.[14] Recently, our group showed that this transformation can be catalyzed by CuCl to afford 1,4-disubstituted (1*E*,3*E*)-1,4-dienes regioselectively[15] and by CuCN to produce anti-Markovnikov (*E*)-enamines.[16] The use of hydroxylamines and hydrazines to perform metal-free hydroamination of alkynes has also been reported.[17,18] Inspired by these results, we investigated the possibility of conducting a catalyst-free hydroamination of alkynes to form enamines from arylacetylenes and secondary aliphatic amines. Here, we report the first example of a metal- and additive-free hydroamination of alkynes with secondary amines. This metal-free and atom-economic reaction uses the green solvent ethylene glycol (EG), which is presumed to be involved in driving the reaction forward. EG is recognized as green because it can be produced sustainably from biomass and is also a byproduct of the petrochemical industry.[19] Therefore, this is an appealing and original method for the stereoselective (only the (*E*)-enamine is obtained), efficient, and environmentally friendly synthesis of anti-Markovnikov enamines.

Our initial experiments were performed by using ethynylbenzene (**1a**) and dibutylamine (**2a**; 3 equiv) as model substrates in various solvents at 135 °C. No reactivity was detected in MeCN or THF, but traces of the anti-Markovnikov enamine **3a** were obtained in *N*-methylpyrrolidinone (NMP) (Table 1, entries 1–3). Slightly better yields were obtained by using hexan-1-ol as an alcoholic medium (entry 4). An encouraging yield of 50% of **3a**, albeit with incomplete conversion, was obtained by using EG as solvent (entry 5). Lower yields were obtained in diethylene glycol, triethylene glycol, or pinacol (entries 6–8). Therefore, we continued our studies by using ethylene glycol and raising the temperature from 135 °C to 150 °C. Doing so afforded an excellent 98% yield of the anti-Markovnikov enamine (*E*)-**3a** (entry 9). We found that when three equivalents of ethylene glycol were used in the reaction of ethynylbenzene (**1a**) with dibutylamine (**2a**) at 150 °C for eight hours, only a 76% yield of the corresponding enamine was ob-

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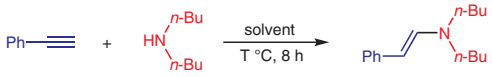
tained (entry 10). Decreasing the amount of the amine from three to two equivalents lowered the yield to 70% (entry 11), whereas the use of only one equivalent of the amine led to a 40% yield of **3a** (entry 12). Microwave irradiation did not reduce the reaction time for this transformation, as only 15% of the expected product was obtained after 15 minutes at 150 °C (entry 13). Other solvents were tried, but led to poor conversions (see the Supporting Information). Consequently, further screening was conducted with two equivalents of the amine in EG at 150 °C for eight hours.

Table 1 Hydroamination of Ethynylbenzene with Dibutylamine in Various Solvents[a,b]

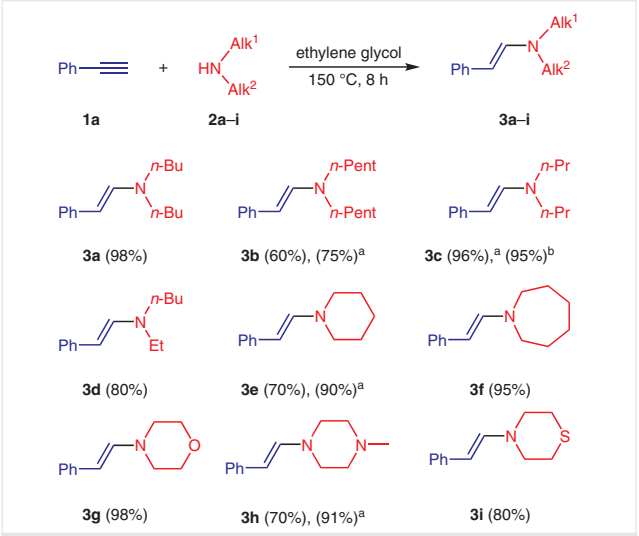


1a **2a** (*E*)-**3a**

Entry	Solvent	**2a** (equiv)	Temp (°C)	Yield (%)
1	MeCN	3	135	NR
2	THF	3	135	NR
3	NMP	3	135	9
4	hexan-1-ol	3	135	17
5	EG	3	135	50
6	diethylene glycol	3	135	34
7	triethylene glycol	3	135	28
8	pinacol	3	135	26
9	**EG**	**3**	**150**	**98**
10	EG[c]	3	150	76
11	EG	2	150	70
12	EG	1	150	40
13	EG	3	MW[d]	15

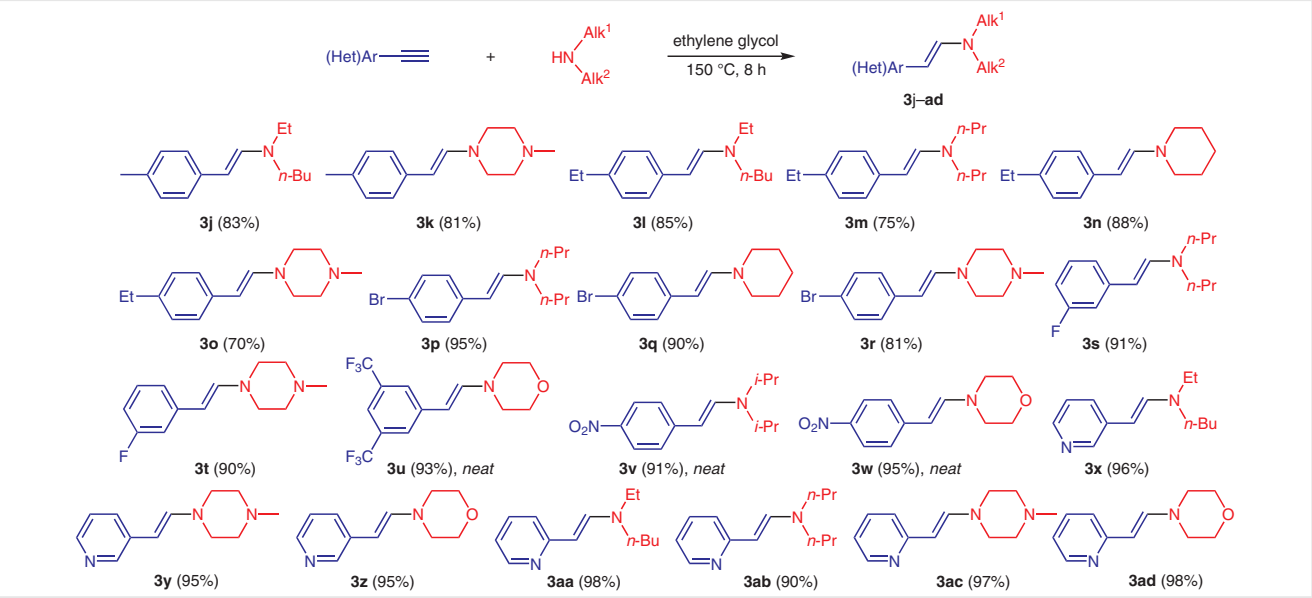
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), solvent (250 µL), 135 °C, 8 h, sealed vessel.
[b] NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.
[c] Reaction performed in the presence of three equivalents of ethylene glycol.
[d] Reaction performed under microwave irradiation at 150 °C and 200 °C for 15 min.

We then explored the substrate scope and functional-group tolerance of the reaction under the optimized conditions (Table 1, entry 9). Symmetrical and unsymmetrical secondary aliphatic amines, such as dipentylamine (**2b**), dipropylamine (**2c**), or butyl(ethyl)amine (**2d**), readily reacted with ethynylbenzene (**1a**) to give the anti-Markovnikov enamines **3b–d** in good to excellent isolated yields (60–96%) (Scheme 1). In the case of **3b**, the use of five equivalents of the corresponding amine improved the yield from 60 to 75%. The reaction of ethynylbenzene with amine **2c** proceeded on a gram scale with an unchanged yield. In the cases of cyclic secondary amines, those bearing different heteroatoms, such as azepane (**2f**), morpholine (**2g**), and thiomorpholine (**2i**) afforded the desired anti-Markovnikov compounds **3f**, **3g**, and **3i** in good to excellent isolated yields (80–98%). With piperidine (**2e**) or *N*-methylpiperazine (**2h**), a 70% yield of the corresponding anti-Markovnikov products **3e** and **3h** were obtained but when five equivalents of the amines were used, the yields increased to 90 and 91%, respectively. It should be noted that no reactivity was observed with aliphatic or internal alkynes, nor with primary or aromatic amines. The difference in the reactivity of the amines appears to correlate with their acidity/basicity and nucleophilicity; however, these differences cannot be rationalized at this stage.



Scheme 1 Hydroamination of phenylacetylene with various aliphatic secondary amines. *Reagents and conditions*: **1a** (0.5 mmol), amine (1.5 mmol), 150 °C, 8 h, ethylene glycol (250 µL). [a] General conditions, but with 2.5 mmol of amine.[b] Performed on a gram scale.

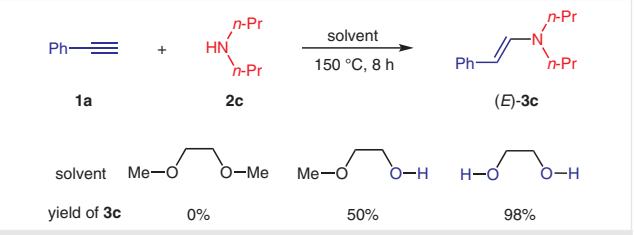
Next, we studied the influence of aromatic substituents on the terminal aromatic alkynes (Scheme 2). Reactions of derivatives of arylacetylenes bearing electron-donating groups such as methyl or ethyl in the *para*-position were tolerant toward both cyclic and acyclic secondary amines, the corresponding enamines **3j–o** being obtained in good yields (70–88%). Electron-withdrawing groups, such as halo substituents, in the *meta*- or *para*-positions showed better reactivity with various secondary cyclic or acyclic amines, and afforded the anti-Markovnikov (*E*)-enamines **3p–t** in excellent yields (81–98%). 1-Ethynyl-4-nitrobenzene and 1-ethynyl-3,5-bis(trifluoromethyl)benzene were also converted into the corresponding enamines **3u**, **3v**, and **3w** in excellent yields. We then proceeded to examine the reactions of heterocyclic acetylenes, and we found that 3-ethynylpyridine reacted with both cyclic and acyclic secondary amines to give the corresponding hydroamination products **3x–z** in excellent yields (95–96%). Products **3aa–ad** were obtained in yields ranging from 90 to 98% by the reaction of 2-ethynylpyridine with butyl(ethyl)amine, dipropylamine,



Scheme 2 Hydroamination-substituted (het)arylacetylenes with aliphatic secondary amines. *Reagents and conditions*: arylacetylene (0.5 mmol), amine (2.5 mmol), 150 °C, 8 h, ethylene glycol (250 μL).

N-methylpiperazine, and morpholine. This protocol exhibits excellent regio- and stereoselectivity, is experimentally simple to carry out, and does not require the presence of any catalyst or additive. At the end of the reaction, a simple extraction to remove the ethylene glycol suffices, while the excess amine was removed under vacuum to furnish the pure product.[20]

A radical mechanism was ruled out, as the addition of trapping agents such as galvinoxyl, TEMPO, or 2,6-di-*tert*-butylphenol did not inhibit the hydroamination reaction of ethynylbenzene (**1a**) with dipropylamine (**2c**); no products derived from a radical species were detected under these conditions. We then examined the possible involvement of hydrogen bonds between the amine and ethylene glycol as a driving force for this reaction by conducting the model reaction in 2-methoxyethanol and in 1,2-dimethoxyethane under the standard conditions (150 °C, 8 h; Scheme 3).[21] The provision of one hydrogen bond from 2-methoxyethanol halved the yield of the enamine (50%). When both hydrogen-bonding sites were eliminated by using 1,2-dimethoxyethane, the reaction did not proceed at all. Therefore, the presence of the two hydroxy groups of ethylene glycol appears to be crucial to approach a quantitative conversion (98%).

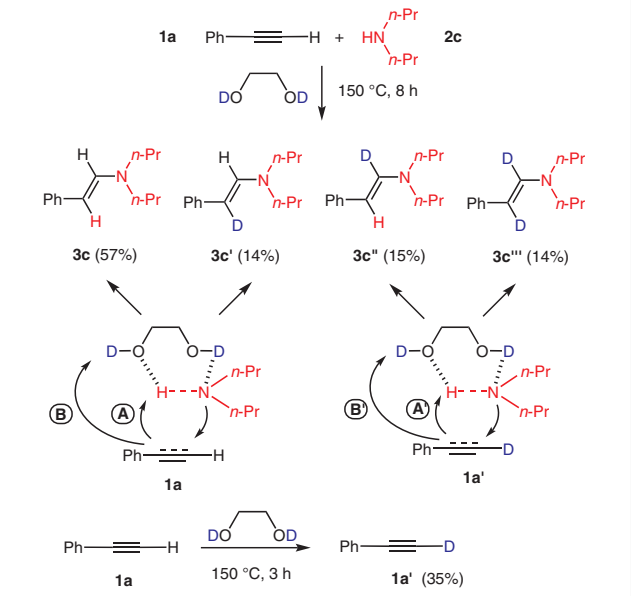


Scheme 3 Impact of the number of hydroxy groups of the solvent on the yield of enamine **3c**

The hydroamination of ethynylbenzene (**1a**) with dipropylamine (**2c**) was then carried out under standard conditions (150 °C, 8 h) in ethylene glycol-d_2 to test for scrambling (Scheme 4). This experiment led to the formation of a mixture of four compounds **3c**, **3c′**, **3c″**, and **3c‴** in a 57:14:15:14 ratio. The detection of **3c** as the major product might correspond to the addition of the nitrogen atom to the less-hindered carbon atom, followed by the reduction of the triple bonds by abstraction of hydrogen from the amine (Scheme 4, path A). The formation of **3c′**, albeit in a lower yield, might result from the abstraction of deuterium from ethylene glycol-d_2 (Scheme 4, path B). Products **3c″** and **3c‴** are formed by a similar type of mechanism (routes **A′** and **B′**, respectively) from the deuterated ethynylbenzene **1a′** formed in situ. We indeed observed in blank experiments performed under the standard conditions that a significant amount (35%) of **1a′** was formed as a result of exchange between the acetylenic proton of ethynylbenzene and ethylene glycol-d_2 is formed (Scheme 4).

A preliminary exchange between the deuterated ethylene glycol and the N–H proton of the dipropylamine might also explain the formation of **3c′** and **3c‴** from **1a** and **1a′**, respectively. These results support the conclusion that ethylene glycol facilitates proton transfer between the amine and alkyne reactants.

In summary, we have reported an unprecedented method for the regio- and stereoselective hydroamination of range of aromatic terminal acetylenes with aliphatic secondary amines under metal-free conditions.[22] The ethylene



Scheme 4 Control experiments involving deuterated species

glycol solvent appears to promote this reaction through a mechanism that might involve hydrogen bonding and proton exchange. Work is now in progress to extend the application of this protocol and to understand the mechanism of this system in more detail.

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Supporting Information

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References and Notes

(1) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773.
(2) (a) Glisan King, A.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105. (b) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *1*, 2862.
(3) (a) *Enamines: Synthesis Structure and Reactions, 2nd ed*; Cook, A. G., Ed.; Dekker: New York, **1988**. (b) Kuckländer, U. In *The Chemistry of Enamines, Part 1*; Rappoport, Z., Ed.; Wiley: Chichester, **1994**, 523. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
(4) For reviews on hydroamination, see: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Hartwig, J. F. *Pure Appl. Chem.* **2004**, *76*, 507. (d) Chemler, S. *Org. Biomol. Chem.* **2009**, *7*, 3009. (e) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596. (f) Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. *Catal. Sci. Technol.* **2015**, *5*, 2017. (g) Evano, G.; Gaumont, A.-C.; Alayrac, C.; Wrona, I. E.; Giguere, J. R.; Delacroix, O.; Bayle, A.; Jouvin, K.; Theunissen, C.; Gatignol, J.; Silvanus, A. C. *Tetrahedron* **2014**, *70*, 1529. (h) Schafer, L. L.; Yim, J. C. H.; Yonson, N. In *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A.; Bräse, S.; Oestreich, M., Ed.; Wiley-VCH: Weinheim, **2014**, Chap. 15, 1135.
(5) (a) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (b) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407. (c) Gils, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 3116. (d) Reznichenko, A. L.; Hultzsch, K. C. *Organometallics* **2013**, *32*, 1394.
(6) (a) Leitch, D. C.; Turner, C. S.; Shafer, L. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 6382. (b) Sarma, R.; Prajapati, D. *Chem. Commun.* **2011**, *47*, 9525. (c) Brinkmann, C.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 2193. (d) Liu, B.; Roisnel, T.; Carpentier, J. F.; Sarazin, Y. *Chem. Eur. J.* **2013**, *19*, 13445.
(7) (a) Moran, J.; Cebrowski, P. H.; Beauchemin, A. M. *J. Org. Chem.* **2008**, *73*, 1004. (b) Rizk, T.; Bilodeau, E. J. F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8325. (c) Ackermann, L.; Kozhushkov, S. I.; Yufit, D. S.; Marek, I. *Synlett* **2011**, 1515. (d) Fleisher, S.; Werkeister, S.; Zhou, S.; Junge, K.; Beller, M. *Chem. Eur. J.* **2012**, *18*, 9005. (e) Lin, J.-S.; Yu, P.; Huang, L.; Zhang, P.; Tan, B.; Liu, X.-Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7847.
(8) (a) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193. (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488. (c) Imahori, T.; Hori, C.; Kondo, Y. *Adv. Synth. Catal.* **2004**, *346*, 1090. (d) Alsabesh, P. G.; Lundgren, R. J.; Longobardi, L. E.; Stradiotto, M. *Chem. Commun.* **2011**, *47*, 6936. (e) Patel, M.; Saunthawal, R. K.; Verma, A. K. *Tetrahedron Lett.* **2014**, *55*, 1310. (f) Patel, M.; Saunthwal, R. K.; Verma, A. K. *Acc. Chem. Res.* **2017**, *50*, 240.
(9) (a) Doucet, H.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1997**, 807. (b) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246. (c) Kocięcka, P.; Czcluśniak, I.; Szymańska-Buzar, T. *Adv. Synth. Catal.* **2014**, *356*, 3319. (d) Slagbrand, T.; Vockov, A.; Trillo, P.; Tinnis, F.; Adolfsson, H. *ACS Catal.* **2017**, *7*, 1771.
(10) For Pd-catalyzed hydroamination, see: (a) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12670. (b) Salman, G. A.; Hussain, M.; Iaroshenko, V.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2011**, *353*, 331. (c) Bernhammer, J. C.; Chong, N. X.; Jothibasu, R.; Zhou, B.; Huynh, H. V. *Organometallics* **2014**, *33*, 3607. (d) Banerjee, D.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 1630; Corrigendum: *Angew. Chem. Int. Ed.* **2017**, *56*, 16436. (e) Lhristodoulou, M. S.; Giofrè, S.; Broggini, G.; Mazza, A.; Sala, R.; Beccalli, E. M. *Eur. J. Org. Chem.* **2018**, 6176. (f) Park, S.; Malcolmson, S. J. *ACS Catal.* **2018**, *8*, 8468.
(11) For Rh-catalyzed hydroamination, see: (a) Fukumoto, Y.; Asai, H.; Shimizu, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 13792. (b) Utsusomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608. (c) Shen, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 564. (d) Sakai, K.; Kochi, T.;

Kakiuchi, F. *Org. Lett.* **2011**, *13*, 3928. (e) Takano, S.; Kochi, T.; Kakiuchi, F. *Organometallics* **2016**, *35*, 4112. (f) Yang, X.-H.; Lu, A.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 14049. (g) Athira, C.; Changotra, A.; Sunoj, R. B. *J. Org. Chem.* **2018**, *83*, 2627. (h) Yang, S.; Li, Q.; Xu, C.; Xu, Q.; Shi, M. *Chem. Sci.* **2018**, *9*, 5074.

(12) For Au-catalyzed hydroamination, see: (a) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537. (b) Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 5224. (c) Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2009**, *131*, 8690. (d) Couce-Rios, A.; Kovács, G.; Ujaque, G.; Lledós, A. *ACS Catal.* **2015**, *5*, 815. (e) Timmerman, J. C.; Robertson, B. D.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 2251. (f) Wang, Y.; Ling, B.; Li, P.; Bi, S. *Organometallics* **2018**, *37*, 3035. (g) Liu, D.; Nie, Q.; Zhang, R.; Cai, M. *Adv. Synth. Catal.* **2018**, *360*, 3940. (h) Baron, M.; Battistel, E.; Tubaro, C.; Biffis, A.; Armelao, L.; Ramcan, M.; Graiff, C. *Organometallics* **2018**, *37*, 4213.

(13) (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 2163. (b) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. (c) Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1990**, *31*, 4887.

(14) (a) Zhou, L.; Bohle, D. S.; Jiang, H.-F.; Li, C.-J. *Synlett* **2009**, 937. (b) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423. (c) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38.

(15) Bahri, J.; Jamoussi, B.; Lee, A. V. D.; Taillefer, M.; Monnier, F. *Org. Lett.* **2015**, *17*, 1224.

(16) Bahri, J.; Blieck, R.; Jamoussi, B.; Taillefer, M.; Monnier, M. *Chem. Commun.* **2015**, *51*, 11210.

(17) Beauchemin's group has recently developed a series of Cope-type hydroaminations of alkenes and alkynes; see: (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410. (b) Cebrowski, P. H.; Roveda, J. G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492. (c) 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. (d) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895. (e) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J. G.; Beauchemin, A. M. *Chem. Commun.* **2011**, *47*, 562. (f) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874. (g) Zhao, S.-B.; Bilodeau, E.; Lemieux, V.; Beauchemin, A. M. *Org. Lett.* **2012**, *14*, 5082. (h) Beauchemin, A. M. *Org. Biomol. Chem.* **2013**, *11*, 7039.

(18) For a metal-free intermolecular hydroamidation of ynamides with *N*-sulfonamides, see: Peng, Z.; Zhang, Z.; Tu, Y.; Zeng, X.; Zhao, J. *Org. Lett.* **2018**, *20*, 5688.

(19) Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. *Chem. Rev.* **2018**, *118*, 747.

(20) It is also possible to recover the unused amine in a cold trap and then totally recycle it.

(21) Propargyl alcohol and oct-1-yne have also been tested; however, no product was obtained. This probably demonstrates that the solvent is the sole source of hydrogen bonding.

(22) **Hydroamination of Alkynes with Amines; General Procedure**
Under an atmosphere of argon, a screw-cap vial was charged with ethylene glycol (250 μL, 8.9 equiv) and the appropriate alkyne (0.5 mmol, 1 equiv) and amine (2.5 mmol) at r.t. The tube was sealed under a positive pressure of argon and the mixture was stirred and heated to 150 °C for 8 h. The mixture was cooled to r.t., diluted with EtOAc (5 mL), and washed with H_2O (3 × 2 mL) and brine (1 × 2 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure (rotary evaporator). Excess amine was then removed from the residue under high vacuum to give the desired enamine without any need for further purification. In the case of amines with high boiling points, such as dibutylamine or dipentylamine, the residues were dried by heating to 50 °C under high vacuum.
(*E*)-*N*,*N*-Dipentyl-2-phenylethylenamine (3b)
Solid; yield: 97 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.14 (m, 4 H), 6.95–6.92 (m, 1 H), 6.76 (d, *J* = 14 Hz, 1 H), 5.07 (d, *J* = 14 Hz, 1 H), 3.07 (t, *J* = 7.1 Hz, 4 H), 1.60–1.54 (m, 4 H), 1.39–1.33 (m, 4 H), 1.33–1.28 (m, 4 H), 0.92 (t, *J* = 7.2 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 138.5, 128.5, 123, 122.5, 96.3, 51.7, 29.2, 27.6, 22.5, 14.1. HRMS (ESI-TOF): *m/z* $[M + H]^+$ Calcd for $C_{18}H_{30}N$: 260.2300; found: 260.2301.