Angewandte Highlights

Hydroamination

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Copper-Catalyzed Regio- and Enantioselective Hydroamination of Alkenes with Hydroxylamines

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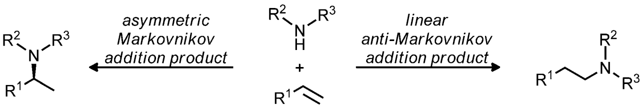
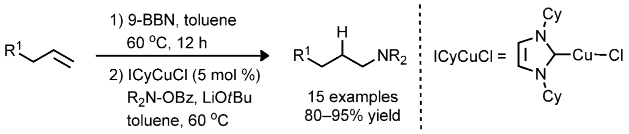
amines · asymmetric · copper · hydroamination · umpolung

The development of new methods for the asymmetric synthesis of amines from readily available monomer feedstocks is an important research area that has profound implications for expedited drug discovery and the production of pharmaceuticals.[1] In this context, the catalytic hydroamination of alkenes with amines is a powerful transformation that holds promise to rapidly deliver value-added chiral amines from simple and accessible starting materials.

Despite the significant advancements of transition-metal-catalyzed hydroaminations,[2] there still exist several limitations that have precluded the more general application of this reaction. In particular, the ability to establish both regio- and enantioselective control for intermolecular additions of amines to alkenes with unactivated substrates remains a considerable challenge (Scheme 1). For hydroamination reactions that are regioselective for the Markovnikov branched-amine products, there exists the opportunity to develop powerful asymmetric amine syntheses. However, the reported examples of enantioselective additions have either been limited to the use of aryl amines with simple styrenes or strained alkenes as reaction partners, or have achieved only a moderate degree of enantioselection.[3] In addition, the identification of general conditions for the synthesis of linear alkyl amines by the anti-Markovnikov addition of amines to unactivated alkenes has also been limited to a few reported examples.[4] Recently, significant progress has been made towards addressing these limitations through the investigation of an alternative umpolung approach to the hydroamination of alkenes using a Cu-catalyzed electrophilic amination with easily accessible O-benzoyl hydroxylamines.[5]



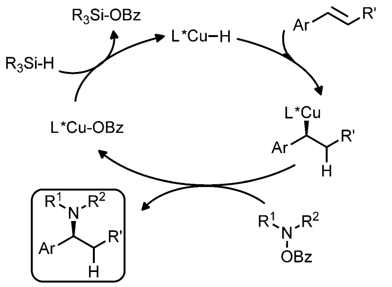
Scheme 1. General examples of challenging regio- and enantioselective hydroamination reactions.



Scheme 2. One-pot alkene hydroboration/Cu-catalyzed electrophilic amination sequence for linear amine synthesis. 9-BBN = 9-borabicyclo-[3.3.1]nonane, Bz = benzoyl.

Lalic and co-workers reported an elegant two-step, one-pot procedure for the synthesis of linear tertiary amines, which proceeds through the formal anti-Markovnikov hydroamination of terminal alkenes (Scheme 2).[6] Although this reaction does not represent a true catalytic alkene hydroamination, but rather a stepwise stoichiometric hydroboration/copper-catalyzed electrophilic amination sequence, this report documents the concept of using alternative reversed polarity sources of amines to install new C(sp^3)–N bonds using widely available alkene feedstocks.

Recently, the groups of Miura[7] and Buchwald[8] have independently reported mild, Cu-catalyzed conditions for the highly enantioselective synthesis of branched tertiary amines. Using a mechanistically distinct electrophilic alkene amination approach, in the presence of a suitable hydride source, these methods have provided access to a breadth of highly substituted chiral alkyl amines (Scheme 3). In contrast, previous metal-mediated hydroamination strategies for accessing similar products have relied heavily on nucleophilic addition or oxidative addition/alkene insertion/reductive elimination mechanisms.[2]



Scheme 3. Proposed catalytic cycle for the Cu-catalyzed hydroamination of alkenes with substituted O-benzoyl hydroxylamines (L* = chiral phosphine ligand).

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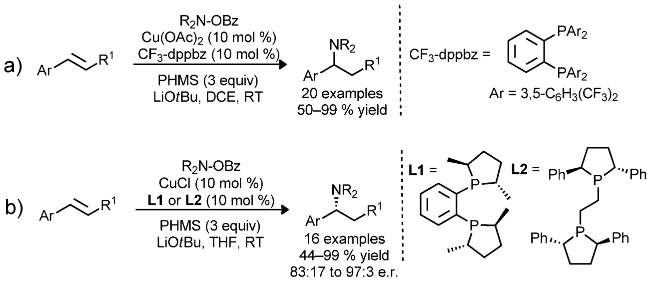
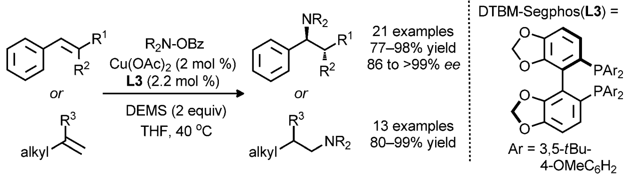
Building on their previous work concerning the Cu-catalyzed aminoboration of vinylarenes,[9] Hirano, Miura, and co-workers have recently described a Cu-catalyzed method for the enantioselective hydroamination of substituted styrenes with exclusive Markovnikov regioselectivity.[7] Following optimization studies, a catalytic mixture of Cu(OAc)$_2$/CF$_3$-dppbz (10 mol %), in the presence of LiO*t*Bu and polymethylhydrosiloxane (PMHS) as the hydride source, were identified as optimal for the regioselective hydroamination of styrene with *O*-benzoyl-*N*,*N*-diethylhydroxylamine as the electrophilic amine source. These conditions were shown to be effective for the hydroamination of a variety of α- and α,β-substituted styrenes with a range of *N*,*N*-dialkyl hydroxylamines to generate the racemic branched amines in good to excellent yields (Scheme 4a). Moving beyond these initial conditions, an enantioselective version of this reaction was realized using a combination of CuCl (10 mol %) with either (*S*,*S*)-Me-DuPhos (**L1**) or (*R*,*R*)-Ph-BPE (**L2**) ligands, which provided chiral amine products with enantiomeric ratios ranging from 83:17 to 97:3 (Scheme 4b). Despite showing good scope in substituted styrenes and hydroxylamines, the extension of this work to include substrates featuring *cis* olefins or simple aliphatic alkenes was not possible using the described conditions.



Scheme 4. Cu-catalyzed Markovnikov (asymmetric) hydroamination of styrenes with *O*-benzoyl hydroxylamines. DCE = 1,2-dichloroethane.

Independent of the work described by Miura and Hirano, Buchwald and co-workers have documented similar Cu-catalyzed conditions for both the asymmetric synthesis of branched amines and the anti-Markovnikov hydroamination of terminal aliphatic alkenes (Scheme 5).[8] After screening several conditions, the use of a Cu(OAc)$_2$ and (*R*)-DTBM-Segphos (2 mol % Cu; Cu/L = 1:1.1), with diethoxymethylsilane (DEMS) serving as a suitable hydride source, were identified as optimized conditions for the mild asymmetric hydroamination of styrene with *O*-benzoyl *N*,*N*-dibenzyl hydroxylamine. Importantly, this system is differentiated from the previously described example by its ability to accommodate substrates featuring *cis*-β-substituted alkenes, such as indene, 1,2-dihydronaphthalene, and α,β,β-trisubstituted styrenes, with high levels of enantiomeric excess. In addition to these advantages, the same conditions were also shown to be effective for the hydroamination of terminal aliphatic alkenes to generate linear tertiary amines, resulting from regioselective anti-Markovnikov addition, in high yields. This divergence in regioselectivity has been attributed to the lack of an electronic advantage for Cu to form a 2° alkyl bond, as was the case for the Markovnikov hydroamination of styrenes, over a less sterically encumbered terminal Cu-intermediate.



Scheme 5. Enantio- and regioselective Cu-catalyzed hydroamination of styrenes and terminal olefins with *O*-benzoyl hydroxylamines.

In conclusion, through the use of an innovative electrophilic amination strategy, the methods described in this highlight have demonstrated significant advancements to the field of alkene hydroamination. In particular, the development of mild, Cu-catalyzed procedures for the highly enantioselective synthesis of branched tertiary amines from readily available substrate feedstocks has been established. In addition, the anti-Markovnikov hydroamination of terminal aliphatic amines has been described using similar Cu-based methods. Despite this progress, important challenges still remain for the identification of conditions that achieve the asymmetric synthesis of branched amines from unactivated internal and terminal alkenes and alkylamines.[10] Future efforts to address these and other remaining challenges in the field of hydroamination with an electrophilic amination approach will render such reactions well-suited for application in drug discovery and development.

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[1] a) *Chiral Amine Synthesis* (Ed: T. C. Nugent), Wiley-VCH, Weinheim, **2010**; b) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600; c) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713.

[2] For reviews, see: a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675; b) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2006**, *106*, 3795; c) K. D. Hesp, M. Stradiotto, *ChemCatChem* **2010**, *2*, 1192; d) J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Sausalito, CA, **2010**, p. 700; e) J. Hannedouche, E. Schulz, *Chem. Eur. J.* **2013**, *19*, 4972; f) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368.

[3] For lead references on asymmetric intermolecular hydroaminations, see: a) S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2012**, *14*, 780; b) C. S. Sevov, J. Zhou, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 11960; c) J. R. Zhou, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 1345; d) K. L. Butler, M. Tragni, R. A. Widenhoefer, *Angew. Chem.* **2012**, *124*, 5265; *Angew. Chem. Int. Ed.* **2012**, *51*, 5175.

[4] For lead references on anti-Markovnikov hydroaminations, see: a) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller, O. R. Thiel, *Chem. Eur. J.* **1999**, *5*, 1306; b) M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J.*

Am. Chem. Soc. **2003**, *125*, 5608; c) M. Utsunomiya, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 2702; d) C. Brinkmann, A. G. M. Barrett, M. S. Hill, P. A. Procopiou, *J. Am. Chem. Soc.* **2012**, *134*, 2193.

[5] For reviews and lead references on the preparation and use of electrophilic nitrogen sources in synthesis, see: a) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680; b) E. Erdik, M. Ay, *Chem. Rev.* **1989**, *89*, 1947; c) T. J. Barker, E. R. Jarvo, *Synthesis* **2011**, 3958; d) G. Lalic, R. P. Rucker, *Synlett* **2013**, 269.

[6] R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *J. Am. Chem. Soc.* **2012**, *134*, 6571.

[7] Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2013**, *125*, 11030; *Angew. Chem. Int. Ed.* **2013**, *52*, 10830.

[8] S. Zhu, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 15746.

[9] N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2013**, *135*, 4934.

[10] For seminal reports on the asymmetric synthesis of branched amines by hydroamination of terminal alkyl olefins, see: a) Z. B. Zhang, S. D. Lee, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 5372; b) A. L. Reznichenko, H. N. Nguyen, K. A. Hultzsch, *Angew. Chem.* **2010**, *122*, 9168; *Angew. Chem. Int. Ed.* **2010**, *49*, 8984.