A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: CuH-Catalyzed Asymmetric Hydroamidation of Vinylarenes

Authors: Yujing Zhou, Oliver D Engl, Jeffrey S Bandar, Emma D Chant, and Stephen L. Buchwald

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201802797
Angew. Chem. 10.1002/ange.201802797

Link to VoR: http://dx.doi.org/10.1002/anie.201802797
http://dx.doi.org/10.1002/ange.201802797

WILEY-VCH

10.1002/anie.201802797

WILEY-VCH

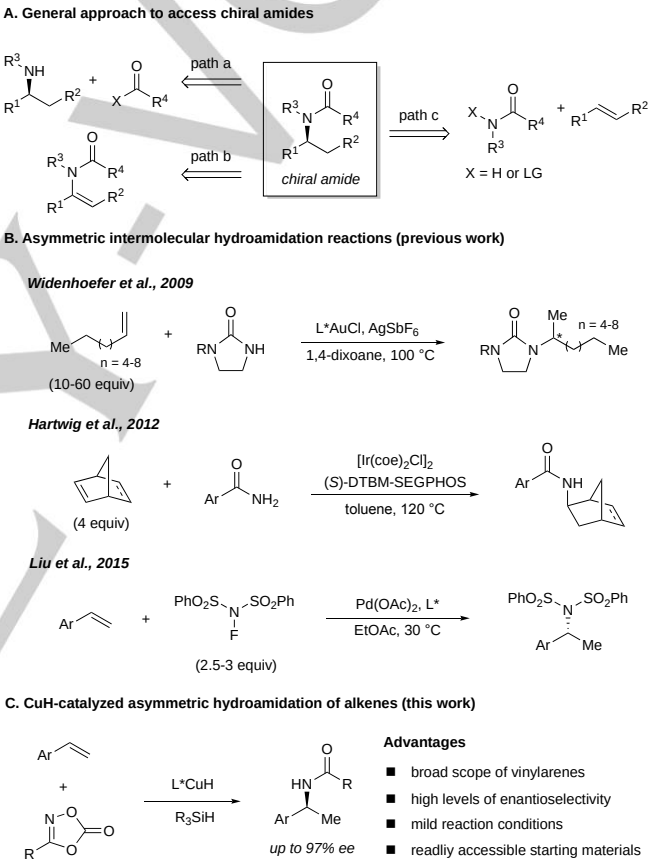
CuH-Catalyzed Asymmetric Hydroamidation of Vinylarenes

Yujing Zhou†, Oliver D. Engl†, Jeffrey S. Bandar, Emma D. Chant, and Stephen L. Buchwald*[a]

Abstract: A CuH-catalyzed enantioselective hydroamidation reaction of vinylarenes has been developed using readily accessible 1,4,2-dioxazol-5-ones as electrophilic amidating reagents. This method provides a straightforward and efficient approach to synthesize chiral amides in good yields with high levels of enantiopurity under mild conditions. Moreover, this transformation tolerates substrates bearing a broad range of functional groups.

The enantioselective synthesis of chiral amides with a stereogenic center adjacent to the nitrogen atom is of great importance due to the presence of this substructure in many natural products and biologically active molecules.[1] Commonly used synthetic strategies involves the coupling of an activated carboxylic acid with an enantioenriched amine[2] (Scheme 1A, path a), as well as the asymmetric hydrogenation of enamides (Scheme 1A, path b).[3] An attractive alternative is the asymmetric hydroamidation of olefins, in which an olefin is formally inserted into an amide N-H bond (Scheme 1A, path c). This transformation allows direct access to complex amides from simple achiral precursors, and is typically catalyzed by Brønsted acids or transition metals.[4] However, few enantioselective intermolecular variants have been reported (Scheme 1B).[5] In one example, an asymmetric coupling of cyclic urea derivatives with unactivated terminal olefins using a chiral gold complex was developed by Widenhoefer.[5a] Later, Hartwig disclosed an Ir-catalyzed hydroamidation of aliphatic alkenes, and enantioselective examples were shown when norbornene or norbornadiene was used as the olefin.[5b] In 2015, Liu reported that styrene derivatives react with *N*-fluorobenzenesulfonimide in the presence of palladium acetate and a pyridine-oxazoline type ligand to afford chiral sulfonamides.[5c] Despite the progress in this field, existing methods often require the use of high reaction temperatures, activated substrates, or large excesses of the alkene. In order to expand the synthetic utility of this transformation, highly enantioselective and general olefin hydroamidation reactions that proceed under mild conditions are highly desirable.

Recently, the CuH-catalyzed asymmetric hydroamination of olefins has been developed as a general and efficient method to access chiral amines with high regio- and enantioselectivity.[6,7] The key step in these protocols involves the catalytic generation of enantioenriched alkylcopper nucleophiles via the addition of a L*CuH species across an alkene. This species can be then intercepted by an electrophilic amination reagent to produce optically active amine products. We envisioned that the hydrocupration-electrophilic trapping sequence described above could also be exploited to synthesize amides. Herein we describe the realization of this strategy using readily accessible 1,4,2-dioxazol-5-ones[8] as the electrophilic amidating reagents. This operationally simple procedure allows for direct access to chiral amides from vinylarenes in good yields and high levels of enantioselectivity under mild conditions (Scheme 1C).



Scheme 1. A) General approaches to enantioenriched amides, B) Previous and C) Current work on asymmetric hydroamidation of alkenes.

Initially, we evaluated the effectiveness of *N*-benzoyloxy benzamide (**E1**) as an electrophile under typical CuH-catalyzed hydroamination conditions (Table 1, entry 1).[7] Only a trace amount of the desired product was detected by GC-MS analysis. Instead, decomposition of the electrophile was primarily observed. Changing the leaving group on the electrophile from benzoate (**E1**) to pivalate (**E2**) did not circumvent the undesired decomposition process (Table 1, entry 2). We also evaluated several electrophilic amidating reagents originally employed in C-H amidation reactions by Chang.[8] Among these, 3-phenyl-1,4,2-dioxazol-5-one (**2a**) demonstrated increased stability in the presence of L*CuH species and provided a moderate yield of desired hydroamidation product **3a** with good enantioselectivity (40% yield, 88% ee, Table 1, entry 4). The choice of Ph-BPE as the supporting ligand[9] and diphenylsilane as the hydride source was based on an examination of common chiral phosphine

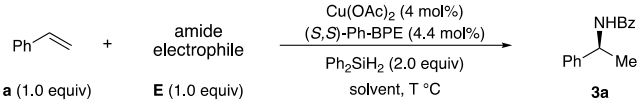
[a] Y. Zhou[†], Dr. O. D. Engl[†], Dr. J. S. Bandar, E. D. Chant, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: sbuchwal@mit.edu
[†] These authors contributed equally.

Supporting information for this article is given via a link at the end of the document.

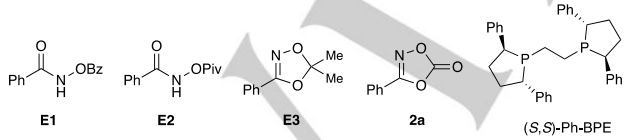
10.1002/anie.201802797

ligands and hydrosilane reagents. At higher temperature, the decomposition of the electrophile is more rapid, resulting in lower yield of the desired product (Table 1, entry 5). Therefore, the reaction was conducted at 4 °C, which significantly increased the yield (Table 1, entry 6). Further optimization of the reaction conditions revealed that the employment of 1,4-dioxane as solvent led to the improvement of enantioselectivity (Table 1, entries 8-10). Since a lower reaction temperature had been observed to be beneficial for the reaction yield, mixtures of THF and 1,4-dioxane were tested in order to allow the reaction to be performed at 4 °C without freezing the solvent.[10] A 4:1 ratio of 1,4-dioxane: THF provided the best results, affording the amide product in 75% isolated yield and 94% ee (Table 1, entry 11). It is notable from a practical perspective that only one equivalent of the electrophile was needed to achieve high yields.

Table 1. Optimization of hydroamidation reaction conditions.[a]



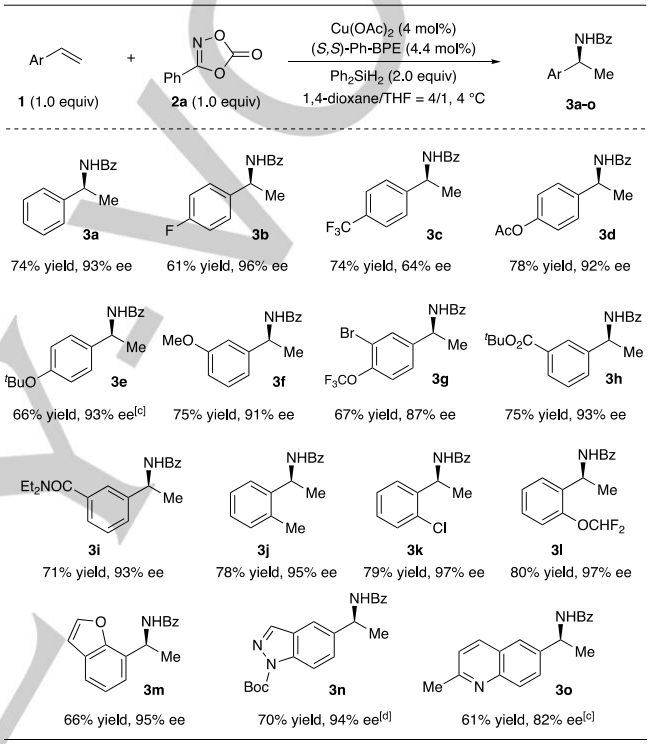
Entry	E	Temp., °C	Solvent	Yield **3a**, %[b]	ee, %
1	**E1**	rt	THF	trace	ND
2	**E2**	rt	THF	trace	ND
3	**E3**	rt	THF	0	ND
4	**2a**	rt	THF	40	88
5	**2a**	45	THF	23	88
6	**2a**	4	THF	85	87
7	**2a**	–15	THF	51	84
8	**2a**	4	MTBE	15	86
9	**2a**	4	toluene	10	93
10	**2a**	rt	1,4-dioxane	57	96
11	**2a**	4	1,4-dioxane /THF (4/1)	80 (75)[c]	94
12	**2a**	4	1,4-dioxane /THF (3/2)	77	93
13	**2a**	4	1,4-dioxane /THF (1/1)	60	92



[a] Conditions: 0.25 mmol styrene (1.0 equiv), 3-phenyl-1,4,2-dioxazol-5-one (1.0 equiv), copper(II) acetate (4 mol%), (*S*,*S*)-Ph-BPE (4.4 mol%), diphenylsilane (2.0 equiv), in solvent (0.50 mL), see the Supporting Information for further details. **E** = amide electrophile. [b] Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield in parenthesis.

Having identified the optimal reaction conditions, the reactivity of a range of vinylarenes was next investigated (Table 2). Both electron-rich and electron-deficient styrenes reacted smoothly with **2a** to form **3a-o** in good yields (61–80%) and enantioselectivity (64–97% ee), although a slightly higher catalyst loading was required for the electron-rich derivatives to achieve high conversion (**3e**).[11] Functional groups, including esters (**3d**, **3h**), amides (**3i**), and aryl halides (**3g**, **3k**), remained intact under the reaction conditions. Moreover, styrenes bearing *ortho* substituents (**3j**, **3k**, **3l**) were all efficiently converted to the desired amide products in good yields and with high levels of enantiopurity. Vinylarenes that contain heterocycles such as a benzofuran (**3m**), an *N*-Boc protected indazole (**3n**), and a quinoline (**3o**), were also accommodated. However, β-substituted styrenes, which are less reactive towards hydrocupration, failed to engage in this hydroamidation reaction.[12]

Table 2. Vinylarene scope of the hydroamidation reaction.[a,b]



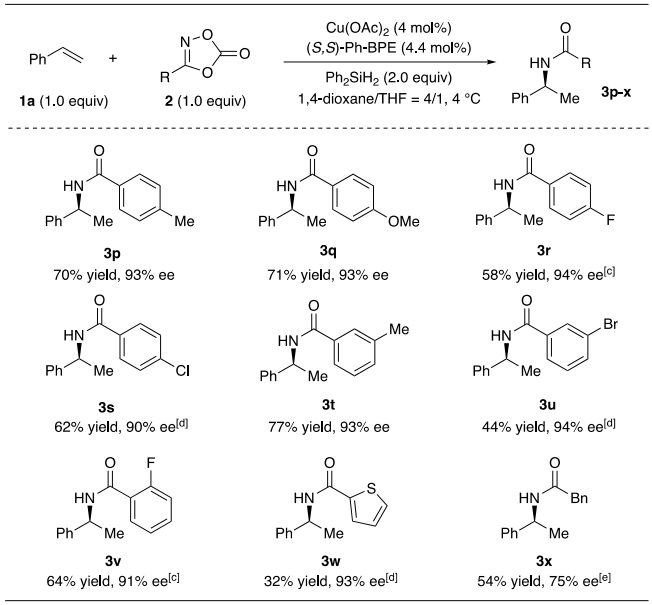
[a] Conditions: 0.50 mmol alkene (1.0 equiv), **2a** (1.0 equiv), copper(II) acetate (4 mol%), (*S*,*S*)-Ph-BPE (4.4 mol%), Ph_2SiH_2 (2.0 equiv) in 1,4-dioxane/THF (4/1, 0.5 M), see the Supporting Information for details. [b] Average isolated yield from two experiments. [c] 4 mol% + 2 mol% catalyst was used. [d] 4 mol% + 4 mol% catalyst was used.

A range of aromatic amide electrophiles was examined in this reaction using styrene as the alkene component (Table 3). Regardless of the substitution pattern on the benzene ring of the electrophile, the corresponding amide products **3p**-**3v** were obtained in moderate to good yields (44–77%) and with excellent enantioselectivity (90–94% ee). Based on experimental observations, we conclude that the electron-deficient electrophiles are more prone to decompose than their electron-rich counterparts. We hypothesized that an unidentified species is slowly generated and attenuates the reactivity of the CuH catalyst, resulting in poor conversion of starting materials.[13] In order to solve this problem, a second batch of L*CuH solution was added to improve the conversion for these substrates, thereby enabling the formation of the corresponding amides in synthetically useful yields. We found that a heterocyclic electrophile was also effective in this transformation (**3w**). In contrast, an electrophile bearing an alkyl 3-substituent (**2j**, R = Bn) provides the corresponding amide **3x** in poor yield due to the rapid nonproductive consumption of **2j**. However, when **2j** was slowly added over 2 h to the reaction mixture, the amide

10.1002/anie.201802797

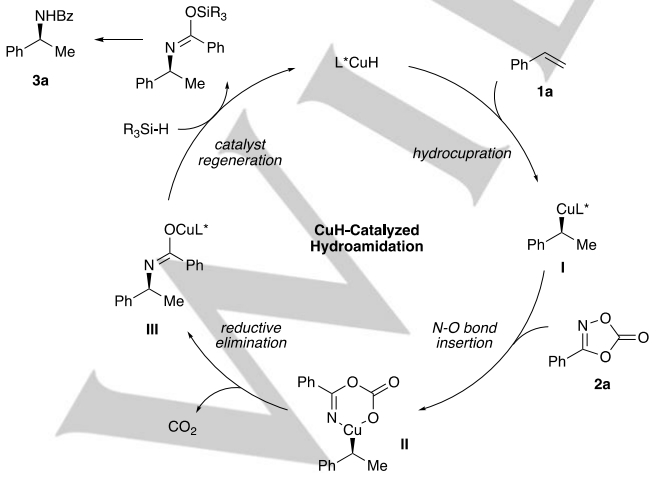
product was obtained in moderate yield (54%) and with useful enantioselectivity (75% ee).

Table 3. Electrophile scope of the hydroamidation reaction.[a,b]



[a] Conditions: 0.50 mmol **1a** (1.0 equiv), 1,4,2-dioxazol-5-ones (1.0 equiv), copper(II) acetate (4.0 mol%), (*S,S*)-Ph-BPE (4.4 mol%), Ph_2SiH_2 (2.0 equiv) in 1,4-dioxane/THF (4/1, 0.5 M), see the Supporting Information for details. [b] Average isolated yield from two experiments. [c] 4 mol% + 2 mol% catalyst was used. [d] 4 mol% + 4 mol% catalyst was used. [e] Slow addition of the amide electrophile solution was required; see the Supporting Information for details.

Based on previously reported CuH-catalyzed hydrofunctionalization reactions,[14] a mechanism was postulated for this transformation, which is shown in Scheme 2. Initially, the styrene undergoes stereoselective migratory insertion into a Ph-BPE-ligated copper hydride, which produces chiral benzylcopper intermediate **I**. This intermediate participates in oxidative insertion into the N-O bond in electrophile **2a**, followed by the extrusion of CO_2 and reductive elimination to form species **III**.[15] Subsequent metathesis with a hydrosilane regenerates the L*CuH catalyst, as well as releasing the desired amidation product.



Scheme 2. Proposed mechanism of CuH-catalzyed hydroamidation reaction.

In conclusion, a highly enantioselective hydroamidation reaction of vinylarenes is reported using 1,4,2-dioxazol-5-ones as electrophilic amidating reagents. Since these reagents can be readily prepared from the corresponding carboxylic acids[8a, 8b], this protocol provides a straightforward and efficient method to access chiral amides from readily accessible achiral coupling partners. Products with diverse substitution patterns and various functional groups were afforded in good yields and high levels of enantiopurity. Efforts towards developing hydroamidation protocols with broader alkene scope are ongoing.

Acknowledgements

Research reported in this publication was supported by the National Institutes of Health (GM58160, GM122483). We also thank the NIH for a supplemental grant for the purchase of supercritical fluid chromatography (SFC) equipment (GM058160-17S1) and for a postdoctoral fellowship for J. S. B. (GM112197). Dr. O. D. Engl thanks the Swiss National Science Foundation (SNSF) for a postdoctoral fellowship (P2EZP2_175140). We acknowledge Richard Liu, Dr. Andy Thomas, and Dr. Christine Nguyen for advice on the preparation of this manuscript.

Keywords: amides • alkenes • copper • enantioselectivity • amidation

[1] For selected examples, see: a) V. S. Ananthanarayanan, S. Tetreault, A. Saint-Jean, *J. Med. Chem.* **1993**, *36*, 1324; b) A. A. Patchett, *J. Med. Chem.* **1993**, *36*, 2051; c) R. Naito, Y. Yonetoku, Y. Okamoto, A. Toyoshima, K. Ikeda, M. Takeuchi, *J. Med. Chem.* **2005**, *48*, 6597; d) S. K. Branch, I. Agranat, *J. Med. Chem.* **2014**, *57*, 8729; e) S. Mikami, S. Sasaki, Y. Asano, O. Ujikawa, S. Fukumoto, K. Nakashima, H. Oki, N. Kamiguchi, H. Imada, H. Iwashita, T. Taniguchi, *J. Med. Chem.* **2017**, *60*, 7658.

[2] For reviews on chiral amine synthesis, see: a) *Chiral Amine Synthesis* (Ed.: T. C. Nugent), Wiley, Weinheim, **2010**; b) *Stereoselective Formation of Amines, Vol. 343 of Topics in Current Chemistry* (Eds.: W. Li, X. Zhang), Springer, Berlin, **2014**.

[3] For a recent review on the asymmetric hydrogenation of enamides, see: J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* **2012**, *41*, 4126.

[4] For selected reviews on alkene hydroamination and hydroamidation, see: a) L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 2596; b) E. Bernoud, C. Lepori, M. Mellah, E. Schulz, J. Hannedouche, *Catal. Sci. Technol.* **2015**, *5*, 2017; c) J. Hannedouche, E. Schulz, *Chem. Eur. J.* **2013**, *19*, 4972; d) J. S. Yadav, A. Antony, T. S. Rao, B. V. S. Reddy, *J. Organomet. Chem.* **2011**, *696*, 16; e) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795; f) K. C. Hultzsch, *Adv. Synth. Catal.* **2005**, *347*, 367.

[5] For examples of enantioselective intermolecular hydroamidation reactions of olefins, see: a) Z. Zhang, S. D. Lee, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 5372; b) C. S. Sevov, J. Zhou, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 11960; c) F. Yu, P. Chen, G. Liu, *Org. Chem. Front*. **2015**, *2*, 819.

[6] For reviews on the CuH-catalyzed hydroamination reactions, see: a) M. T. Pirnot, Y.-M. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 48; b) A. J. Jordan, G. Lalic, J. P. Sadighi, *Chem. Rev.* **2016**, *116*, 8318.

[7] For selected examples of CuH-catalyzed asymmetric hydroamination reactions, see: a) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2013**, *52*, 10830; b) S. Zhu, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 15746; c) D. Niu, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 9716; d) Y. Yang, S.-L. Shi, D. Niu, P. Liu, S. L. Buchwald, *Science* **2015**, *349*, 62; e) H. Wang, J. C. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **2017**, *139*, 8428. Also see reference 6a and references therein.

10.1002/anie.201802797

[8] a) Y. Park, K. T. Park, J. G, Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4534; b) Y. Park, S. Jee, J. G, Kim, S. Chang, *Org. Process Res. Dev.* **2015**, *19*, 1024; c) J. Park, S. Chang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14103; d) H. Wang, G. Tang, X. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 13049; e) V. Bizet, L. Buglioni, C. Bolm, *Angew. Chem. Int. Ed.* **2014**, *53*, 5639.

[9] For applications of BPE ligands, see: a) M. J. Burk, *Acc. Chem. Res.* **2000**, *33*, 363; b) I. C. Lennon, C. J. Pilkington, *Synthesis* **2003**, *11*, 1639.

[10] The melting point of 1,4-dioxane is 12 °C.

[11] The hydrocupration step is slower for the electron-rich alkenes compared to the electron-deficient ones. Thus, the decomposition of the amide electrophiles, as well as the deactivation of the catalyst, was more pronounced in the cases of electron-rich substrates.

[12] Other substrates, including terminal alkyl-substituted and 1,1-disubstituted olefins, did not afford the desired hydroamidation products in this protocol. We believe that sluggish hydrocupration of these substrates under the current conditions accounts for the failure of these transformations.

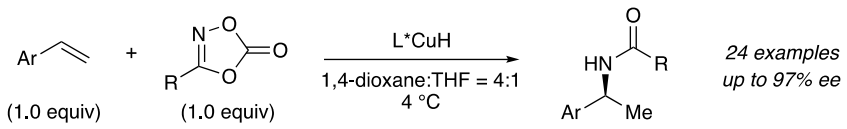
[13] Both starting materials, as well as diphenylsilane, remained in the reaction mixture after 24 h. Prolonged reaction time did not lead to further increase in conversion.

[14] a) J. S. Bandar, M. T. Pirnot, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 14812; b) S. Tobisch, *Chem. Eur. J.* **2016**, *22*, 8290; c) Y. Xi, J. F. Hartwig, *J. Am. Chem. Soc.* **2017**, *139*, 12758; d) J. Lee, S. Radomkit, S. Torker, J. del Pozo, A. H. Hoveyda, *Nat. Chem.* **2018**, *10*, 99.

[15] At this point, we are not able to determine the precise position of the decarboxylation step in the mechanism. Although significant bubbling is observed during the MeOH workup, this can be ascribed to either the generation of H_2 from R_3Si-H species or the release of CO_2 from some compounds, or both.

10.1002/anie.201802797

COMMUNICATION



24 examples
up to 97% ee

*Yujing Zhou, Oliver D. Engl, Jeffrey S. Bandar, Emma D. Chant, Stephen L. Buchwald**

Page No. – Page No.

CuH-Catalyzed Asymmetric Hydroamidation of Vinylarenes