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ARTICLE

Copper-Catalyzed Enantioselective Carbonylation Toward α-Chiral Secondary Amides

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Secondary amides are omnipresent structural motifs in peptides, natural products, pharmaceuticals, and agrochemicals. The copper-catalyzed enantioselective hydroaminocarbonylation of alkenes described in this study provides a direct and practical approach for the construction of α-chiral secondary amides. Electrophilic amine transfer reagent possesses a 4-(dimethylamino)benzoate group was the key to the success. This method also features broad functional group tolerance and proceeds under very mild conditions, affording a set of α-chiral secondary amides in high yields (up to 96% yield) with unprecedented levels of enantioselectivity (up to >99 ee). α,β-Unsaturated secondary amides can also be produced though the method by using alkynes as substrate.

Introduction

Transition-metal-catalyzed hydrocarbonylations are one of the most fundamental and ideal reactions for the synthesis of numerous value-added carbonyl containing compounds from readily available alkenes.[1] Within this class of reactions, hydroaminocarbonylation, also called hydroamidation, represents a straightforward route for the conversion of alkenes into amides.[2] The original catalytic systems for hydroaminocarbonylations based on cobalt,[3] nickel,[4] iron,[5] and ruthenium complexes[6] are required severe conditions such as high temperatures and high pressures and often accompanied by aminoformylation side reactions, thus leading to poor chemoselectivity and limited substrate scope. palladium-catalyzed hydroaminocarbonylation reactions have been extensively developed over the past decades. Recently, ligand-controlled regiodivergent palladium-catalyzed hydroaminocarbonylations to access either linear or branched amides under relatively mild conditions, which involved palladium-hydride species, have been independently developed by the groups of Beller,[7] Cole-Hamilton,[8] Liu,[9] Huang,[10] and Alper[11] (Figure 1a).[12] Despite these advances, asymmetric Pd-catalyzed hydroaminocarbonylations of alkenes with control of the regio- and enantioselectivity are still less explored, and the substrate scope of amines is limited to arylamines. The only elegant work was reported from the Guan group, they presented a novel asymmetric Markovnikov hydroaminocarbonylation of alkenes with anilines enabled by Pd-monodentate phosphoramidite catalysis.[13]

In general, the use of monodentate ligands favors Markovnikov selectivity in palladium-catalyzed hydroaminocarbonylations for the formation of branched amides.[7c,9,10b,11,14] However, the challenge of monodentate ligand-assisted Pd-catalyzed enantioselective carbonylations is the critical competitive coordination between CO and chiral ligand-palladium species, resulting in no "chelate effect", especially under high temperatures and pressures.[15] To conquer this issue, an alternative way is to change palladium into a metal with slightly weaker coordination ability to carbon monoxide and copper might be a choice. Recent developments in copper hydride chemistry enabled a new approach to the hydroamination of alkenes based on the hydrocupration of the alkene and subsequent amination of the reactive alkyl copper intermediate with electrophilic amine reagents.[16] We proposed to carry out the hydrocupration of alkenes with amine electrophiles under CO atmosphere to achieve a selective hydroaminocarbonylation reaction. Indeed, we do realize this Cu-catalyzed hydroaminocarbonylation reaction to prepare branched tertiary amides (Figure 1b).[17] Nevertheless, this approach to hydroaminocarbonylation has been limited to the synthesis of tertiary amides with hydroxyamines (R^2NOBz, R = alkyl) as the dialkylamine transfer reagents.

Secondary amides (-NH-CO-), including chiral secondary amides, are omnipresent structural motifs in peptides, natural products, pharmaceuticals, and agrochemicals (Figure 1c).[18] It is therefore highly desired to develop an efficient and practical methodology that can achieve secondary amides with high regio- and enantioselectivity by using cheap catalysts under mild conditions. Herein we report the development of a copper-catalyzed hydroaminocarbonylation process to directly synthesize α-chiral secondary amides from alkenes and modified amine transfer reagents; The method can also be extended to the synthesis of α,β-unsaturated secondary amides by using alkynes as the substrate (Figure 1d).

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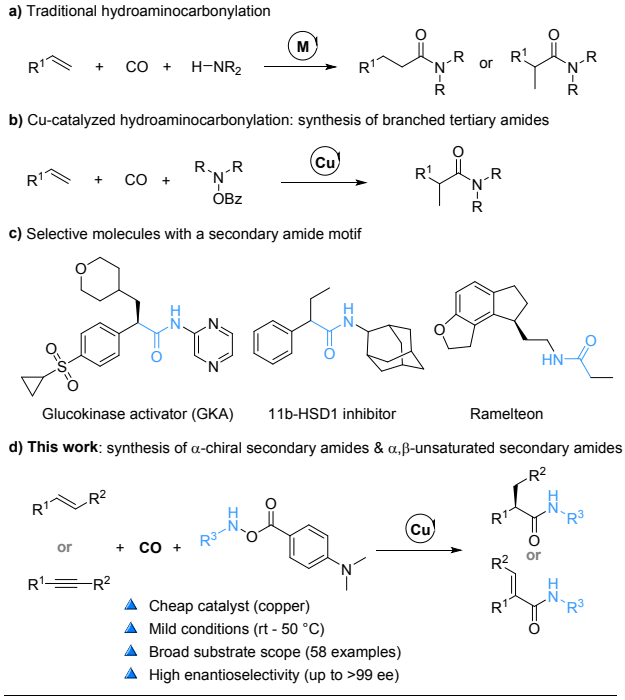
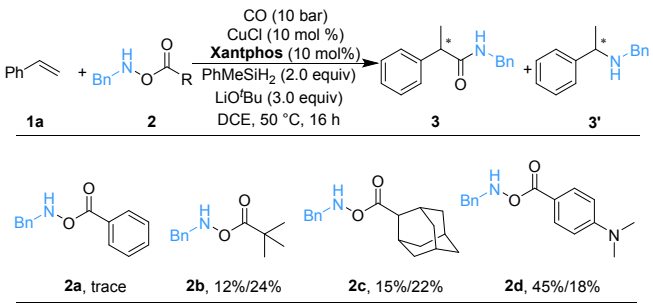


Figure 1. a) Traditional hydroaminocarbonylation. b) Cu-catalyzed hydroaminocarbonylation: synthesis of branched tertiary amides. c) Selective molecules with a secondary amide motif. d) Synthesis of α-chiral secondary amides and α,β-unsaturated secondary amides (this work).

Results and discussion

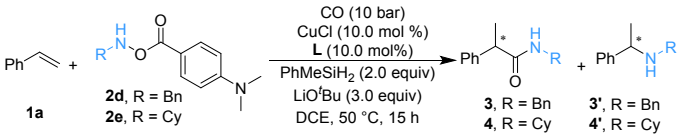
We began our work by studying the reaction between styrene **1a** (1.2 equiv) and *O*-benzoyl-*N*-benzylhydroxylamine **2a** [BnN(H)OBz, 1.0 equiv] utilizing our previously reported conditions (Table 1). Unfortunately, only trace of the desired secondary amide **3** can be detected. We reasoned that this result might be caused by the poor stability of amine transfer reagent **2a**, the rapid nonproductive consumption of **2a** by LCuH diminished the yield. Thus, we tested different amine transfer reagents for this hydroaminocarbonylation under the same conditions. The results were summarized in Scheme 1, we found that the use of **2d**, an amine transfer reagent bearing a 4-(dimethylamino)benzoate group, delivered the desired secondary amide **3** in the highest yield, albeit the direct C-N coupling product **3'** was also generated in 18% yield.

Table 1. Screening of amine transfer reagents.[a]

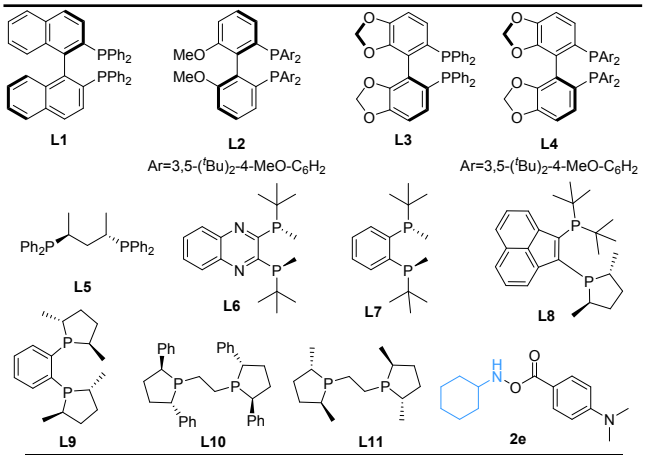


[a] Standard conditions: **1a** (0.12 mmol, 1.5 equiv), **2** (0.1 mmol, 1.0 equiv), [SiH] (0.2 mmol, 2.0 equiv), CuCl (10 mol%), Ligand (10 mol%), LiO^{t}Bu (0.3 mmol, 3.0 equiv), CO (10 bar), DCE (0.5 mL), 50 °C, 16 h; Yields are determined by GC analysis using hexadecane as internal standard.

Table 2. Optimization of the Reaction Conditions.[a]



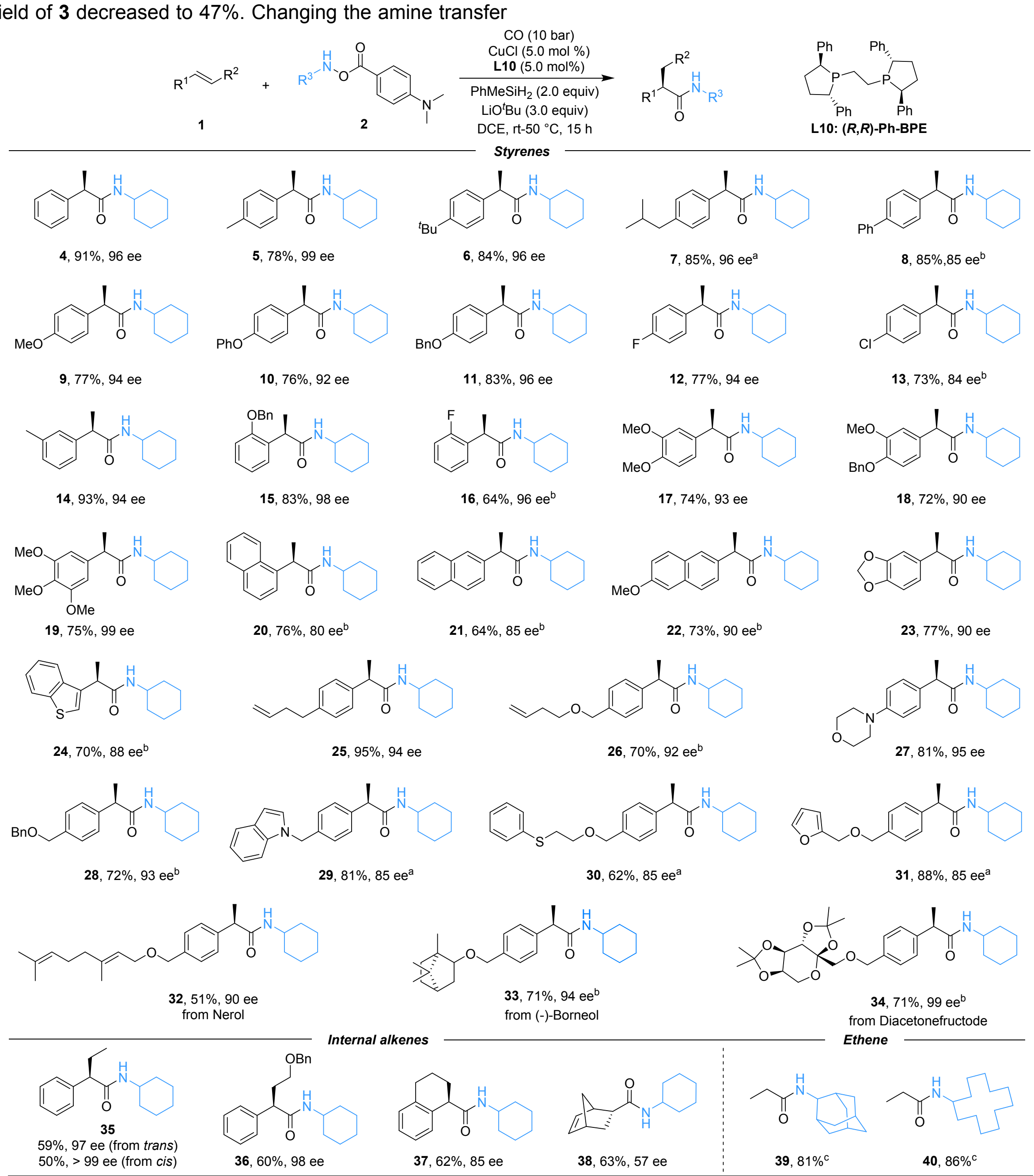
Entry	2	Ligand	Yield (%)	ee (%)
1	2d	**L1-L3**	trace (**3/3'**)	/
2	2d	**L4**	8/6 (**3/3'**)	n.d
3	2d	**L5**	10/7 (**3/3'**)	n.d
4	2d	**L6**	14/2 (**3/3'**)	73 (**3**)
5	2d	**L7**	trace (**3/3'**)	/
6	2d	**L8**	trace (**3/3'**)	/
7	2d	**L9**	trace (**3/3'**)	/
8	2d	**L10**	62/9 (**3/3'**)	99 (**3**)
9	2d	**L11**	trace (**3/3'**)	/
10[b]	2e	**L10**	89/trace (**4/4'**)	95 (**4**)
11[bc]	2e	**L10**	91/trace (**4/4'**)	96 (**4**)
12[bcd]	2e	**L10**	83/trace (**4/4'**)	96 (**4**)



[a] Standard conditions: **1a** (0.12 mmol, 1.2 equiv), **2d** (0.1 mmol, 1.0 equiv), [SiH] (0.2 mmol, 2.0 equiv), CuCl (10 mol%), Ligand (10 mol%), LiO^{t}Bu (0.3 mmol, 3.0 equiv), CO (10 bar), DCE (0.5 mL), 50 °C, 15 h; Yields are determined by GC analysis using hexadecane as internal standard. *Ee* values are determined by chiral-phase HPLC. n.d. = not determined. [b] Using **2e** as substrate, isolated yield. [c] CuCl (5 mol%), Ligand (5 mol%). [d] rt (room temperature, 26 °C).

After determined the best amine transfer reagent **2d**, we started to investigate the reaction by using chiral ligands for constructing α-chiral secondary amides. As shown in Table 2, chiral ligands **L1**-**L3** only gave a trace amount of product **3**. Bulky (*S*)-DTBM-Segphos (**L4**) and (*S,S*)-BDPP (**L5**) delivered the desired product in very low yields. The use of (*S,S*)-QuinoxP* **L6** leads to 14% yield of the desired product **3** with moderate enantioselectivity (Table 2, entry 4, 73 ee). (*S,S*)-BenzP* (**L7**), **L8**, (*R,R*)-Me-DuPhos (**L9**), and (*S,S*)-Me-BPE (**L11**) were ineffective for this reaction.

Fortunately, using (*R*,*R*)-Ph-BPE (**L10**) as the ligand provided **3** in 62% yield with excellent enantioselectivity (Table 2, entry 8, 99 ee). From these results, especially compare with result between L9-L11, we believe the bite angle and the basicity of the ligand applied are crucial for the success of this transformation. Then different kinds of silanes were tested, low or no yield of product **3** was formed when Et_3SiH, PMHS, or $(EtO)_2MeSiH$ was applied. Excellent ee of the carbonylated product can be obtained when Ph_2SiH_2 was used, but the yield of **3** decreased to 47%. Changing the amine transfer reagent **2d** to **2e**, the desired product **4** can be afforded in 89% yield with 95 ee (Table 2, entry 10). Notably, the yield of **4** would not be diminished by decreasing the catalyst loading to 5.0 mol%, and trace of **4'** was detected (Table 2, entry 11, 91% yield, 96 ee). Surprisingly, lowering the temperature to room temperature (26 °C), the reaction still could proceed well, giving product **4** in 83% yield (Table 2, entry 12, 96 ee).



Scheme 1. Substrate scope of alkenes. Standard conditions: **1** (0.12 mmol, 1.2 equiv), **2** (0.1 mmol, 1.0 equiv), $MePhSiH_2$ (0.2 mmol, 2.0 equiv), CuCl (5.0 mol%), **L10** (5.0 mol%), LiO^tBu (0.3 mmol, 3.0 equiv), CO (10 bar), DCE (0.5 mL), 50 °C, 15 h, isolated yields. *ee* values are determined by chiral-phase HPLC. [a] 40 °C. [b] rt (room temperature, 26 °C). [c] Ethene gas (2 bar) was used instead of styrenes.

After identification of the optimal conditions, we next investigated the generality of this asymmetric Cu-catalyzed hydroaminocarbonylation reaction. The reaction efficiency was first evaluated under the optimal reaction conditions with the scope of alkenes. As shown in Scheme 1, styrenes bearing different electron-donating or electron-withdrawing groups at the *para* position were successfully converted into the α-chiral secondary amides **4-13** in high yields and excellent enantiomeric ratios (73-91% yield, 85-99 ee). *Meta*-F, *meta*-Me, and *ortho*-OBn-substituted styrenes gave the corresponding products **14-16** in 64-93% yields and 94-98 ee values, thus indicating that the reaction is insensitive

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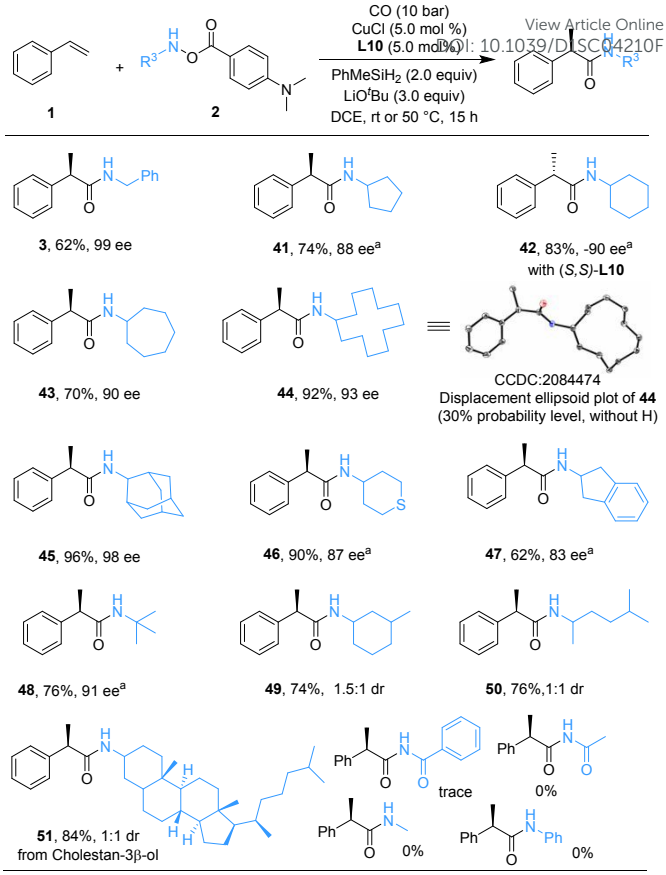
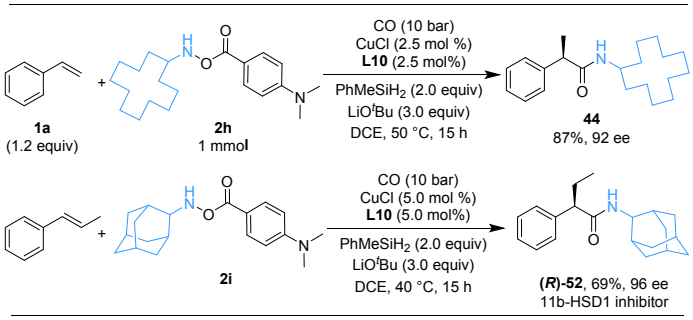
to the steric of the styrenes. Di- and tri-substituted styrenes were also proceeded smoothly to generate the desired products **17-20** with high enantioselectivities (72-75% yield, 90-99 ee). To our delight, 1-vinylnaphthalene, 2-vinylnaphthalene, 2-methoxy-6-vinylnaphthalene, 5-vinylbenzo[*d*][*1,3*]dioxole, and 5-vinylbenzo[*b*]thiophene converted efficiently in the reaction even at room temperature (**20-24**, 64-77% yield, 80-90 ee). Gratifyingly, excellent enantiomeric ratios were observed even by using functionalized styrenes as the coupling partners (**25-31**, 62-95% yield, 85-95 ee). Moreover, the late-stage functionalization of bioactive molecules has been investigated. Nerol, (-)-Borneol, and Diacetonefructose derived styrenes were all reacted well, generating the corresponding secondary amides in good yields and high er values (**32-34**, 51-71% yield, 90-99 ee). Furthermore, internal styrenes were also proved to be compatible under the catalytic system; *trans*-*β*-methylstyrene afforded product **35** in 59% yield with 97 ee, *cis*-*β*-methylstyrene gave **35** in 50% yield with >99 ee, product **36** can be delivered in good yield and excellent enantioselectivity (60% yield, 97 ee). When 1,2-dihydronaphthalene was employed, the desired product **37** was isolated in 62% yield with 93:7 er. The bicyclic strained alkene could also provide **38** in 63% yield but with moderate enantioselectivity (57 ee). Meanwhile, ethene gas can be applied as well and high yields of the corresponding products (**39**, **40**) were isolated under standard conditions，which further demonstrated the generality of the reaction. However, no desired product could be detected when the other aliphatic alkenes were tested, but the decomposition of the hydroxylamine starting material.

We then turned our attention to the compatibility of hydroxylamine electrophiles and were pleased to find a broad substrate scope. The reactivities of various mono alkyl-substituted amine transfer reagents were investigated for the synthesis of α-chiral secondary amides (Scheme 2). We observed that cyclic amine sources were tolerated with five-, seven-, and even twelve-membered rings, affording the desired products **41**, **43**, and **44** with high yields and excellent enantioselectivities (70-92% yield, 88-93 ee). The absolute configuration of **44** was confirmed by X-ray crystallographic analysis,[19] and the configuration of the other compounds described in this work was assigned in analogy to **44**. The (*S*)-configuration product **42** can be obtained in 83% yield (-90 ee) by using (*S,S*)-Ph-BPE. In the current system, amine transfer reagents were well tolerated regardless of the bulky adamantyl group (**45**), heterocyclic group (**46**), and indanyl group (**47**). Amine transfer reagent with a tertiary alkyl group substituent was a competent substrate, delivering product **48** in good yield and enantioselectivity (76% yield, 91 ee). Additionally, desired products **49**-**51** can be also isolated in 74%-84% yields with indicated diastereomeric ratio (dr) values. In these cases, there are *ee* values, but we been not able to measure the value. Additionally, several other examples of substrates were prepared and tested as well, but very low or no desired product could be detected. This might be due to the decreased stability of the corresponding amine substrates. The attempting to prepare substrate related with aniline derivate failed.



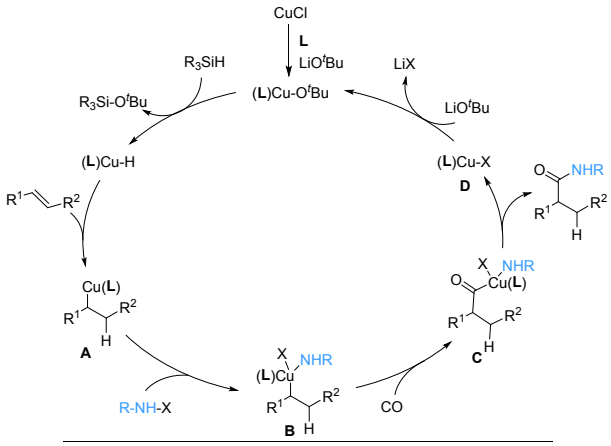
Scheme 2. Substrate scope of hydroxylamines. Reaction conditions: **1** (0.12 mmol, 1.2 equiv), **2** (0.1 mmol, 1.0 equiv), $MePhSiH_2$ (0.2 mmol, 2.0 equiv), CuCl (5.0 mol%), **L10** (5.0 mol%), LiO^tBu (0.3 mmol, 3.0 equiv), CO (10 bar), DCE (0.5 mL), 50 °C, 15 h, isolated yields; *ee* values are determined by chiral-phase HPLC, diastereoselectivities determined by ^1H NMR analysis. [a] rt (room temperature, 26 °C).

Table 3. Scale-up reaction and the synthesis of 52[a]



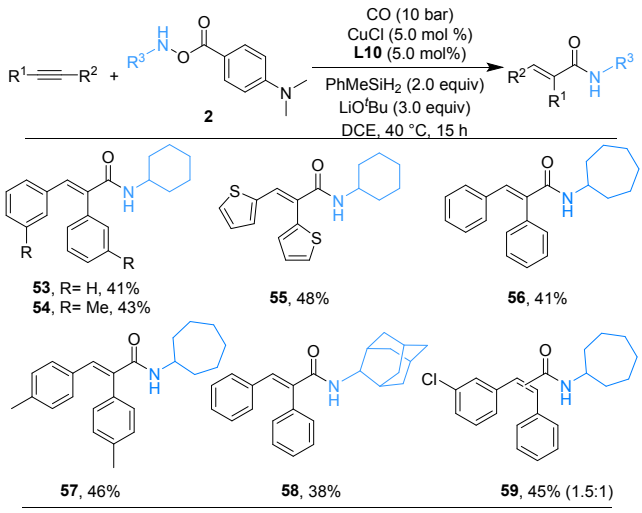
[a] Isolated yield, *ee* values are determined by chiral-phase HPLC.

As a demonstration of the robustness and practicality of this method, the hydroaminocarbonylation process could be easily conducted on 1.0 mmol scale with styrene and hydroxylamine electrophiles **2h** (Table 3, eq 1). Using reduced catalyst loading, 2.5 mol% CuCl and (*R*,*R*)-Ph-BPE-phos, **44** could be synthesized in 87% isolated yield with high stereoselectivity (92 ee). Furthermore, the (***R***)-**52** product (**52** is a 11b-HSD1 inhibitor)[18b] can also be obtained easily in 69% yield and 96 ee by using *trans*-*β*-methylstyrene and **2i** under standard conditions (Table 3, eq 2).



Scheme 3. Proposed catalytic cycle.

The reaction mechanism is proposed according to previous literature (Scheme 3).[16, 20] Initial formation of (L)CuO^{t}Bu from Cu(I), ligand, and LiO^{t}Bu, followed by reaction with [Si]H, generates an active copper hydride species (L)Cu-H. Subsequently, (L)Cu-H insertion into alkene provides alkylcopper intermediates **A**. After oxidative addition with electrophile hydroxylamine, the intermediates **B** formed, which underwent CO insertion to give the intermediates **C**. Then, reductive elimination occurs to deliver the desired product, together with a (L)Cu-X complex **D**. Finally, ligand exchange with LiO^{t}Bu regenerates the (L)CuO^{t}Bu species for the next catalytic cycle.



Scheme 4. Substrate scope of alkynes. Reaction conditions: alkynes (0.1 mmol, 1.0 equiv), **2** (0.12 mmol, 1.2 equiv), MePhSiH$_2$ (0.2 mmol, 2.0 equiv), CuCl (5.0 mol%), **L10** (5.0 mol%), LiO^{t}Bu (0.3 mmol, 3.0 equiv), CO (10 bar), DCE (0.5 mL), 40 °C, 15 h, isolated yields.

Alkynes are synthetically versatile and useful starting materials, because they can be prepared by a range of strategies.[21] In addition, the potential reactivity of the two π-bonds increases their flexibility in multistep reaction sequences. Naturally, we then applied alkynes as substrate under a similar catalytic system. A series of desired α,β-unsaturated secondary amide can be successfully delivered in moderate yields (**53-59**) as we anticipated and, as shown in Scheme 4, the products were produced as single geometric isomers.

Conclusions

In conclusion, we have developed a copper-catalyzed regioselective and enantioselective intermolecular hydroaminocarbonylation of alkenes with electrophilic hydroxylamines. Electrophilic amine transfer reagent possesses a 4-(dimethylamino)benzoate group was the key to this process. The use of these reagents enabled the development of a general method to directly convert styrenes and even challenging β-substituted styrenes to α-chiral secondary amides. The method displays broad functional group tolerance and proceeds under very mild conditions, producing the desired α-chiral secondary amides in high yields with excellent enantioselectivities (up to >99 ee). We believe this Cu-catalyzed enantioselective synthesis of α-chiral secondary amides provided a new idea in the study of asymmetric hydroaminocarbonylation. Furthermore, alkynes were also compatible substrates bearing in this catalytic system, giving the corresponding α,β-unsaturated secondary amide products.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 a) W. B. Motherwell, *Appl. Organomet. Chem.* 2000, **14**, 170-170; b) D. B. G. Williams, M. L. Shaw, M. J. Green, C. W. Holzapfel, *Angew. Chem. Int. Ed.* 2008, *47*, 560-563; c) A. Brennführer, H. Neumann, M. Beller, *ChemCatChem* 2009, **1**, 28-41; d) R. Franke, D. Selent, A. Börner, *Chem. Rev.* 2012, **112**, 5675-5732; e) M. Amézquita-Valencia, H. Alper, *J. Org. Chem.* 2016, **81**, 3860-3867; f) K. Dong, X. Fang, S. Gülak, R. Franke, A. Spannenberg, H. Neumann, R. Jackstell, M. Beller, *Nat. Comm.* 2017, **8**, 1-7; g) H. Matsubara, T. Kawamoto, T. Fukuyama, I. Ryu, *Acc. Chem. Res.* 2018, **51**, 2023-2035; h) J.-B. Peng, F.-P. Wu, X.-F. Wu, *Chem. Rev.* 2019, **119**, 2090-2127; i) X. Wang, B. Wang, X. Yin, W. Yu, Y. Liao, J. Ye, M. Wang, L. Hu, J. Liao, *Angew. Chem. Int. Ed.* 2019, **58**, 12264-12270; j) J. Yang, J. Liu, H. Neumann, R. Franke, R. Jackstell, M. Beller, *Science* 2019, **366**, 1514.
2 a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* 2013, **113**, 1-35; b) X.-F. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann, M. Beller, *Acc. Chem. Res.* 2014, **47**, 1041-1053; c) J. Liu, C. Schneider, J. Yang, Z. Wei, H. Jiao, R. Franke, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* 2021, **60**, 371-379.
3 A. Striegler, J. Weber, *J. Prakt. Chem.* 1965, **29**, 281-295.
4 a) P. Pino, P. Paleari, *Gazz. Chim. Ital.* 1951, **81**, 64; b) P. Pino, R. Magri, *Chim. Ind.* 1952, **34**, 511; c) S. I. Lee, S. U. Son, Y. K. Chung, *Chem. Commun.* 2002, 1310-1311.
5 W. Reppe, H. Main, *Chem. Abstr.* 1953, **47**, 5428.

6 Y. Tsuji, T. Ohsumi, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* 1986, **309**, 333-344.

7 a) X. Fang, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* 2013, **52**, 14089-14093; b) H. Li, K. Dong, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* 2015, **54**, 10239-10243; c) J. Liu, H. Li, A. Spannenberg, R. Franke, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* 2016, **55**, 13544-13548.

8 C. Jiménez-Rodriguez, A. A. Núñez-Magro, T. Seidensticker, G. R. Eastham, M. R. L. Furst, D. J. Cole-Hamilton, *Catal. Sci. Technol.* 2014, **4**, 2332-2339.

9 H. Liu, N. Yan, P. J. Dyson, *Chem. Commun*. 2014, **50**, 7848-7851.

10 a) G. Zhang, B. Gao, H. Huang, *Angew. Chem. Int. Ed.* 2015, **54**, 7657-7661; b) Y. Hu, Z. Shen, H. Huang, *ACS Catal.* 2016, **6**, 6785-6789; c) J. Zhu, B. Gao, H. Huang, *Org. Biomol. Chem.* 2017, **15**, 2910-2913; d) B. Gao, G. Zhang, X. Zhou, H. Huang, *Chem. Sci.* 2018, **9**, 380-386; e) J. Li, S. Wang, S. Zou, H. Huang, *Commun. Chem.* 2019, **2**, 14.

11 T. Xu, F. Sha, H. Alper, *J. Am. Chem. Soc.* 2016, **138**, 6629-6635.

12 For selected examples for Rh-catalyzed hydroamination, see: a) A. Behr, D. Levikov, E. Nürenberg, *Catal. Sci. Technol.* 2015, **5**, 2783-2787; b) K. Dong, X. Fang, R. Jackstell, G. Laurenczy, Y. Li, M. Beller, *J. Am. Chem. Soc.* 2015, **137**, 6053-6058.

13 Y.-H. Yao, H.-Y. Yang, M. Chen, F. Wu, X.-X. Xu, Z.-H. Guan, *J. Am. Chem. Soc.* 2021, **143**, 85-91.

14 H.-Y. Yang, Y.-H. Yao, M. Chen, Z.-H. Ren, Z.-H. Guan, *J. Am. Chem. Soc.* 2021, **143**, 7298-7305.

15 a) T. Suzuki, Y. Uozumi, M. Shibasaki, *J. Chem. Soc., Chem. Commun.* 1991, 1593-1595; b) Y. Yan, X. Zhang, X. Zhang, *J. Am. Chem. Soc.* 2006, **128**, 16058-16061; c) C. Godard, B. K. Muñoz, A. Ruiz, C. Claver, *Dalton Trans.* 2008, 853-860; d) B. Yang, Y. Qiu, T. Jiang, W. D. Wulff, X. Yin, C. Zhu, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* 2017, **56**, 4535-4539; e) M. Chen, X. Wang, P. Yang, X. Kou, Z.-H. Ren, Z.-H. Guan, *Angew. Chem. Int. Ed.* 2020, **59**, 12199-12205; f) D. M. Hood, R. A. Johnson, A. E. Carpenter, J. M. Younker, D. J. Vinyard, G. G. Stanley, *Science* 2020, **367**, 542-548.

16 a) C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* 2008, **108**, 2916-2927; b) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* 2013, **52**, 10830-10834; c) S.-L. Shi, S. L. Buchwald, *Nat. Chem.* 2015, **7**, 38-44; d) D. Niu, S. L. Buchwald, *J. Am. Chem. Soc.* 2015, **137**, 9716-9721; e) R. Y. Liu, S. L. Buchwald, *Acc. Chem. Res.* 2020, **53**, 1229-1243; f) L.-J. Cheng, N. P. Mankad, *J. Am. Chem. Soc.* 2017, **139**, 10200-10203; g) L.-J. Cheng, S. M. Islam, N. P. Mankad, *J. Am. Chem. Soc.* 2018, **140**, 1159-1164.

17 Y. Yuan, F.-P. Wu, C. Schünemann, J. Holz, P. C. J. Kamer, X.-F. Wu, *Angew. Chem. Int. Ed.* 2020, **59**, 22441-22445.

18 a) A. Greenberg, C. M. Breneman, J. F. Liebman, *The amide linkage: Structural significance in chemistry, biochemistry, and materials science*, John Wiley & Sons, 2002; b) N. A. Magnus, T. M. Braden, J. Y. Buser, A. C. DeBaillie, P. C. Heath, C. P. Ley, J. R. Remacle, D. L. Varie, T. M. Wilson, *Org. Process Res. Dev.* 2012, **16**, 830-835; c) O. Uchikawa, K. Fukatsu, R. Tokunoh, M. Kawada, K. Matsumoto, Y. Imai, S. Hinuma, K. Kato, H. Nishikawa, K. Hirai, M. Miyamoto, S. Ohkawa, *J. Med. Chem.* 2002, **45**, 4222-4239; d) JANSSEN PHARMACEUTICA N.V. - WO2004/56744, 2004, A1; e) S. Duquesne, D. Destoumieux-Garzón, J. Peduzzi, S. Rebuffat, *Nat. Prod. Rep.* 2007, **24**, 708-734; f) D. J. Greenblatt, J. S. Harmatz, A. Karim, *J. Clin. Pharmacol.* 2007, **47**, 485-496; g) E. A. Ilardi, A. Zakarian, *Chem. Asian J.* 2011, **6**, 2260-2263; h) D. Fiorito, Y. Liu, C. Besnard, C. Mazet, *J. Am. Chem. Soc.* 2020, **142**, 623-632.

19 Deposition Numbers 2084474 (for **44**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures. The absolute configuration was assigned as *R* which is consistent with the determined Flack parameter [0.01(12)].

20 a) T. Tsuda, T. Hashimoto, T. Saegusa, *J. Am. Chem. Soc.* 1972, **94**, 658-659; b) T. H. Lemmen, G. V. Goeden, J. C. Huffman, R. L. Geerts, K. G. Caulton, *Inorg. Chem.* 1990, **29**, 3680-3685.

21 a) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* 2009, **351**, 963-983; b) D. Habrant, V. Rauhala, A. M. P. Koskinen, *Chem. Soc. Rev.* 2010, **39**, 2007-2017; c) R. Chinchilla, C. Nájera, *Chem. Soc. Rev.* 2011, **40**, 5084-5121.