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Copper-Catalyzed Carbonylative Hydroamidation of Styrenes to Branched Amides

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Abstract: Amides are one of the most ubiquitous functional groups in synthetic and medicinal chemistry. Novel and rapid synthesis of amides remains in high demand. In this communication, a general and efficient procedure for branch-selective hydroamidation of vinylarenes with hydroxyamine derivatives enabled by copper catalysis has been developed for the first time. The reaction proceeds under mild conditions and tolerates a broad range of functional groups. Applying a chiral phosphine ligand, an enantioselective variant of this transformation was achieved, affording a variety of chiral *α*-amides with excellent enantioselectivities (up to 99% *ee*) and high yields.

Amides have been identified as one of the most important structural motives since they are widely represented in natural products, pharmaceuticals and agrochemicals, as well as chemical industry (Figure 1a).[1] It is thus not surprising that efficient construction of amide bonds has received considerable interests from the synthetic community. Among numerous methods for the preparation of amides,[2] transition-metal-catalyzed hydroamidation represents a straightforward strategy for their synthesis from olefins.[3] Although Fe,[4] Co,[5] Ni,[6] and Ru[7] were used as catalyst precursors in early studies for hydroamidation, all these reactions required relatively severe conditions and resulted in fairly poor chemoselectivity. Recently, independent studies from several groups demonstrated that palladium-based catalytic systems or rhodium-based catalytic systems, which involved palladium-hydride species[8] or rhodium-hydride species[9] as the key intermediate, could address the problems of selectivity under relatively mild conditions and deliver the corresponding amides in good yields (Figure 1b). Based on the importance of amides, developing novel and efficient strategies for hydroamidation using earth-abundant catalysts and readily available starting materials under mild conditions for the synthesis of amides is still highly desirable.

Among the transition metal catalysts, copper catalysts are attractive with several advantages including abundant availability, being non-expensive, less toxic, etc. However, compared with the other metal catalysts, copper is much less explored in carbonylation chemistry.[10,11] To the best of our knowledge, there is no report been published on successfully applying copper catalysts in hydroamidation of alkenes under CO atmosphere. Inspired by the recent work on copper-catalyzed hydroamination of alkenes,[12] we hypothesized that Cu-H catalysis could serve as a platform for synthesizing branched amides. Specifically, in the presence of silane, [(L)Cu-X] could generate an active [(L)Cu-H] species, which would subsequently insert olefins and produce alkyl copper intermediates. After oxidative addition of hydroxylamine derivative followed by CO insertion reductive elimination delivers the desired branched amides (Figure 1c). On the other hand, compared to asymmetric hydroformylation,[13] hydroesterification,[14] and hydroxycarbonylation,[15] the asymmetric hydroamidation of alkenes under CO atmosphere is much more challenging.

Herein, we report for the first time the development of a general and efficient copper catalyst for the hydroamidation of vinylarenes with hydroxyamine derivatives, giving selectively branched amides. The chiral α-amides were also obtained with high *ees* by using a chiral phosphine ligand (Figure 1d).

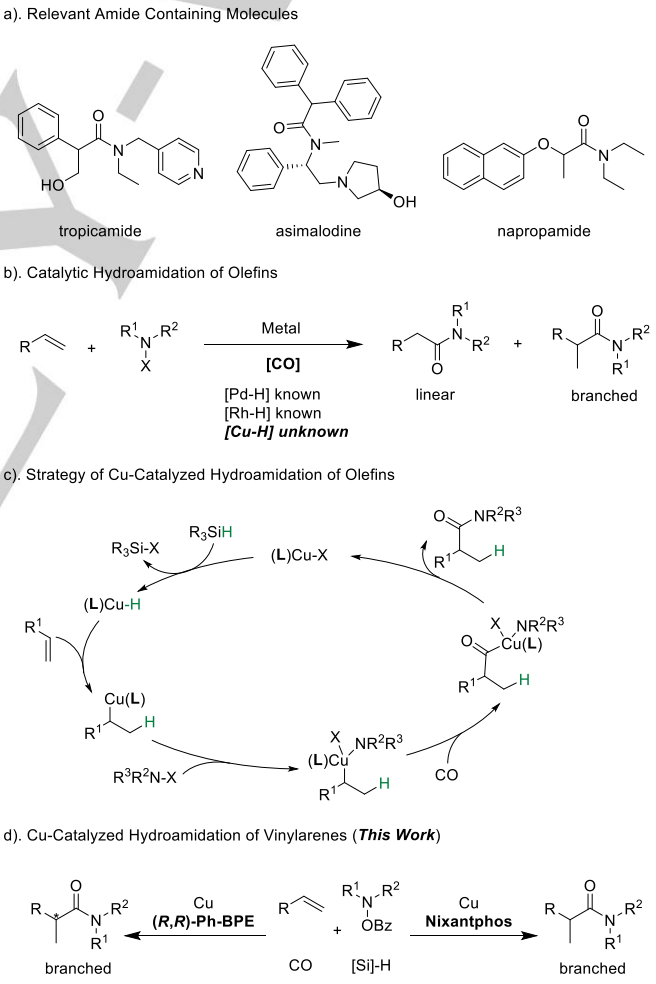

Figure 1. a) Relevant amide containing molecules. b) Catalytic hydroamidation of olefins. c) Strategy of Cu-catalyzed hydroamidation of olefins. d) Cu-catalyzed hydroamidation of olefins (this work).

To begin the investigation, we started by optimizing a model reaction using styrene **1a** (1.5 equiv) and hydroxylamine

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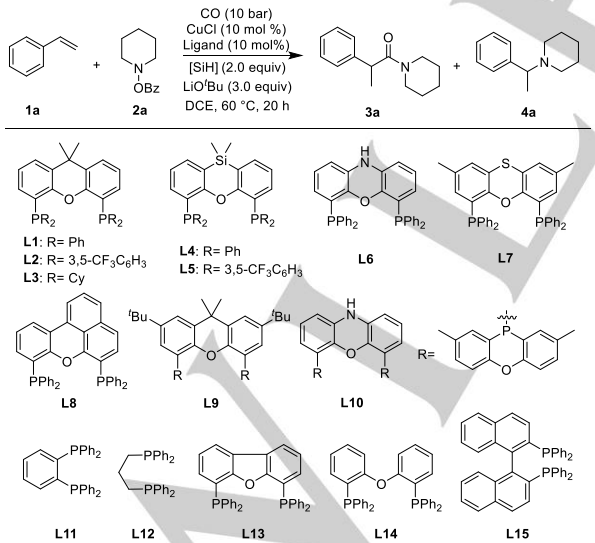
derivative **2a** (1.0 equiv) as substrates, CuCl as the metal catalyst, Xantphos (**L1**) as the ligand and LiO^tBu as the base under CO (10 bar) atmosphere. As shown in Table **1** (entries 1-7), a survey of representative silanes at 60 °C in DCE (1,2-dichloroethane) showed that $MePhSiH_2$ as the hydride source could afford the desired product branched amide **3a** in 56% GC yield, albeit the direct C-N coupling product **4a** was also generated in 10% yield (entry 3). Then different Xantphos-type ligands were tested. Xantphos with different substituents, such as **L2**, **L3** (Cy-Xantphos), only gave **3a** in trace amount (entries 8-9). Meanwhile, Xantphos-type ligands with different bite angles, such as Sixantphos (**L4**, **L5**), Nixantphos (**L6**), Thixantphos (**L7**), Benzoxantphos (**L8**) were applied in the reaction (entries 10-14), the results indicated that Nixantphos with a larger bite angle was the optimal ligand and provided the desired product **3a** in 63% yield (entry 12; Figure 2).[16] Nixantphos with phenoxaphosphine substituents (**L10**, entry 16) could also deliver **3a** in 44% yield. Using other commonly used phosphorus ligands (**L11-L15**) did not give the desired product (entries 17-21). From the relation between yields and bite angle, it implies that tetrahedral complex stabilization by the phosphine ligand was important here (Figure 2). Notably, the yield of **3a** could be further improved to 72 % by decreasing temperature to 50 °C, and only trace amount of **4a** was detected (entry 22). Notably, *tert*-butoxy(methyl)(phenyl)silane can be detected as end reaction product. Moreover, the catalyst system can be reused (See Supporting information). After the original reaction, all reagents except copper and ligand were added and 67% yield of **3a** can be obtained in the second round. To see if radical intermediate was involved during the process, 2 equivalents of radical scavengers were added into our model system under the optimal conditions, the yield of **3a** decreased (BHT = 19%; α-phenylstyrene = 56%). This result implies might exist radical intermediate. More studies are under progress to illustrate the reaction mechanism.

Table 1. Optimization of the Reaction Conditions.[a]



Entry	Silane	Ligand	Bite Angle	Yield **3a** (%)	Yield **4a** (%)
1	Et_3SiH	**L1**	111	0	0
2	$(EtO)_2MeSiH$	**L1**	111	39	6
3	$MePhSiH_2$	**L1**	111	56	10
4	Ph_2SiH_2	**L1**	111	34	6
5	Et_2SiH_2	**L1**	111	45	7
6	Ph_3SiH	**L1**	111	27	trace
7	PMHS	**L1**	111	7	trace
8	$MePhSiH_2$	**L2**		trace	0
9	$MePhSiH_2$	**L3**		trace	0
10	$MePhSiH_2$	**L4**	109	0	0
11	$MePhSiH_2$	**L5**		0	0
12	$MePhSiH_2$	**L6**	114	63	2
13	$MePhSiH_2$	**L7**	110	37	6
14	$MePhSiH_2$	**L8**	120	25	trace
15	$MePhSiH_2$	**L9**		9	trace
16	$MePhSiH_2$	**L10**		44	7
17	$MePhSiH_2$	**L11**	83	0	0
18	$MePhSiH_2$	**L12**	91	0	0
19	$MePhSiH_2$	**L13**	131	0	0
20	$MePhSiH_2$	**L14**	102	0	0
21	$MePhSiH_2$	**L15**	92	0	0
22[c]	$MePhSiH_2$	**L6**	114	72 (70)[b]	trace

[a] Standard conditions: **1a** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), [SiH] (0.4 mmol, 2.0 equiv), CuCl (10 mol%), Ligand (10 mol%), LiO^tBu (0.6 mmol, 3.0 equiv), CO (10 bar), DCE (1.0 mL), 60 °C, 20 h; Yields are determined by GC analysis using hexadecane as internal standard. [b] Isolated yield. [c] Under 50 °C.

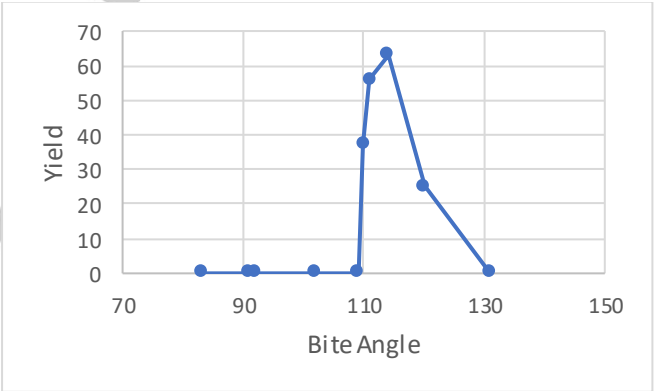


Figure 2. Relation between bite angle and yield of **3a**.

With the optimal conditions in hand, we initially investigated the scope of vinylarenes in the reactions with **2a** (Scheme 1). Styrene bearing different electron-donating or electron-withdrawing group at the *para* position were successfully converted into the branched amides **3a-3h** in moderate to good yields (51-83%). The *ortho*-substituted (*o*-OBn) and *meta*-substituted (*m*-Me, *m*-F) styrenes were also converted well (**3i-3k**). Functionalizable styrenes bearing a butene or bis(pinacolato)boron at the *meta*- position reacted effectively to give **3i** and **3m** in 71% and 63% yields, respectively. Moreover, di- and tri-substituted styrenes also reacted smoothly to furnish the desired products (**3n**, **3o**). 1-vinylnaphthalene, 2-vinylnaphthalene, 5-vinylbenzo[*d*][1,3]dioxole and 5-vinylbenzo[b]thiophene and 2-vinylthiophene were also

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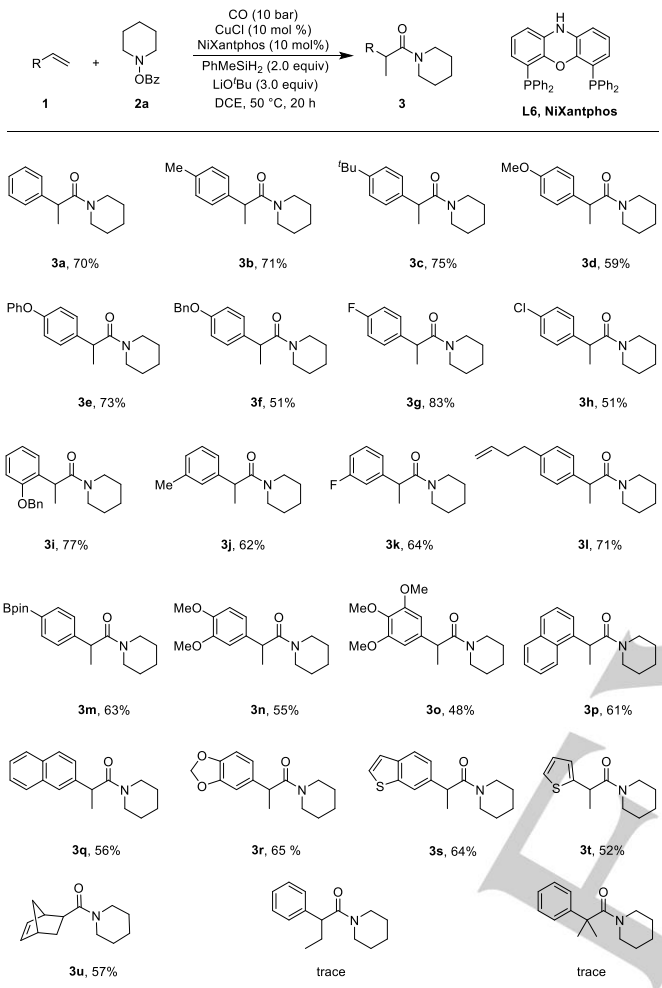
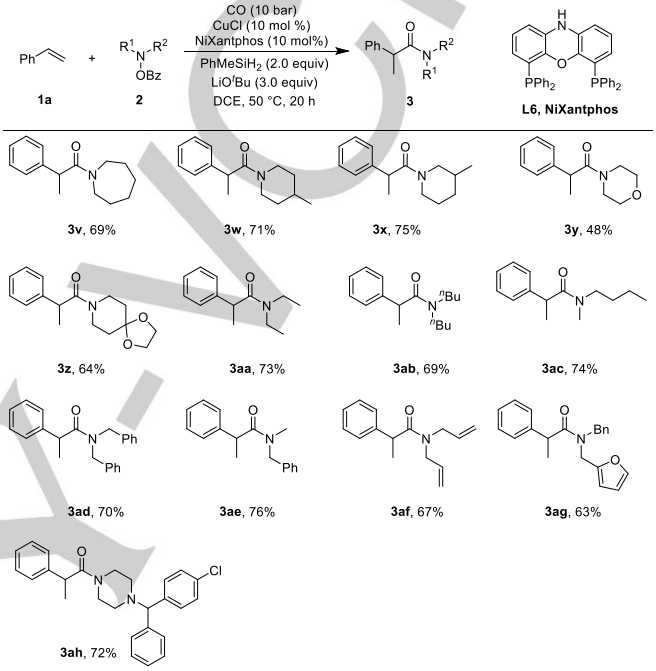
converted efficiently in the reaction (**3p**-**3t**). Surprisingly, the bicyclic strained alkene could also provide **3u** in 57% yield. However, only trace of the desired products could be detected when using *α*-substituted styrene and *β*-substituted styrene as the substrates.



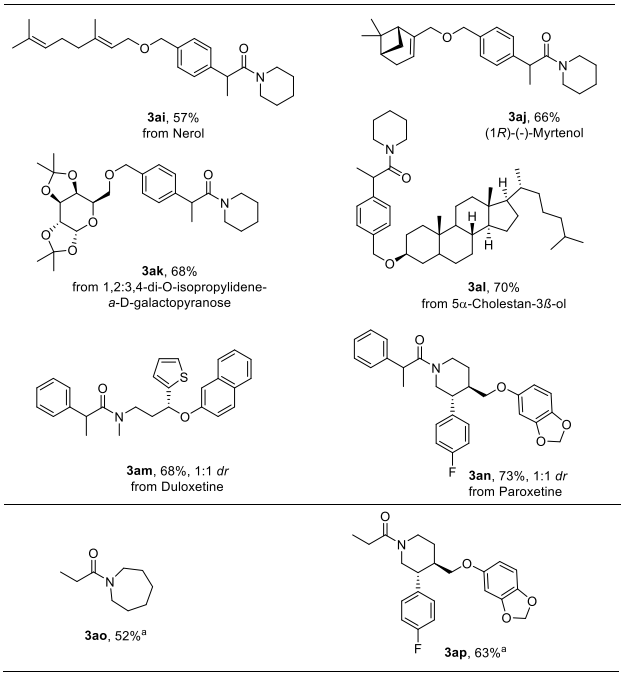
Scheme 1. Substrate scope of vinylarenes. Reaction conditions: **1** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), $MePhSiH_2$ (0.4 mmol, 2.0 equiv), CuCl (10 mol%), Nixantphos (10 mol%), LiO^tBu (0.6 mmol, 3.0 equiv), CO (10 bar), DCE (1.0 mL), 50 °C, 20 h, isolated yields.

The compatibility of this catalytic system with a variety of hydroxylamine derivative electrophiles was then examined (Scheme 2). Cyclic dialkyl (**3v-3z**), acyclic dialkyl (**3aa-3ac**), dibenzyl (**3ad**) and alkylbenzylamine-based electrophiles (**3ae**) were all suitable partners, delivering the corresponding branched amides in good yields. Moreover, *N*, *N*-diallylamine provided the desired product **3af** in 67% isolated yield. Additionally, substrates bearing heterocyclic motifs, including furan (**3ag**) and piperazine (**3ah**), could also be accommodated, providing the hydroamidated products in good yields.

To demonstrate the potential applications, late-stage modification of pharmaceutical derivatives and natural products were investigated (Scheme 3). More specifically, styrenes bearing carbon-carbon double bonds, such as Nerol and (*R*)-Myrtenol, gave the corresponding products **3ai** and **3aj** in 57% and 66% yields, respectively. Applying *α*-D-galactopyranose and 5*α*-Cholestan-3*β*-ol derived styrenes as the reactants afforded the desired products **3ak** and **3al** in good yields. Furthermore, Duloxetine and Paroxetine-based hydroxylamine derivative electrophiles participated in this transformation efficiently to provide the modified pharmaceutical products **3am** and **3an** in high yields with 1:1 *dr*. Ethene gas can applied as well and moderate yields of the corresponding products (**3ao**, **3ap**) were isolated under standard conditions.



Scheme 2. Substrate scope of hydroxyamine derivatives. Reaction conditions: **1** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), $MePhSiH_2$ (0.4 mmol, 2.0 equiv), CuCl (10 mol%), Nixantphos (10 mol%), LiO^tBu (0.6 mmol, 3.0 equiv), CO (10 atm), DCE (1.0 mL), 50 °C, 20 h, isolated yields.



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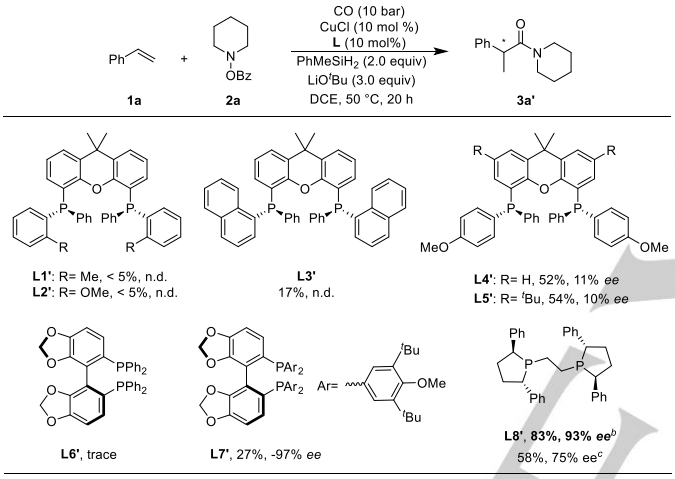
Scheme 3. Substrate scope of complex molecules and ethene. Reaction conditions: **1** (0.3 mmol, 1.5 equiv), **2** (0.2 mmol, 1.0 equiv), $MePhSiH_2$ (0.4 mmol, 2.0 equiv), CuCl (10 mol%), Nixantphos (10 mol%), LiO^tBu (0.6 mmol, 3.0 equiv), CO (10 bar), DCE (1.0 mL), 50 °C, 20 h, isolated yields, *ee*s are determined by chiral-phase HPLC. [a] ethene gas (2 bar) was used instead of styrenes.

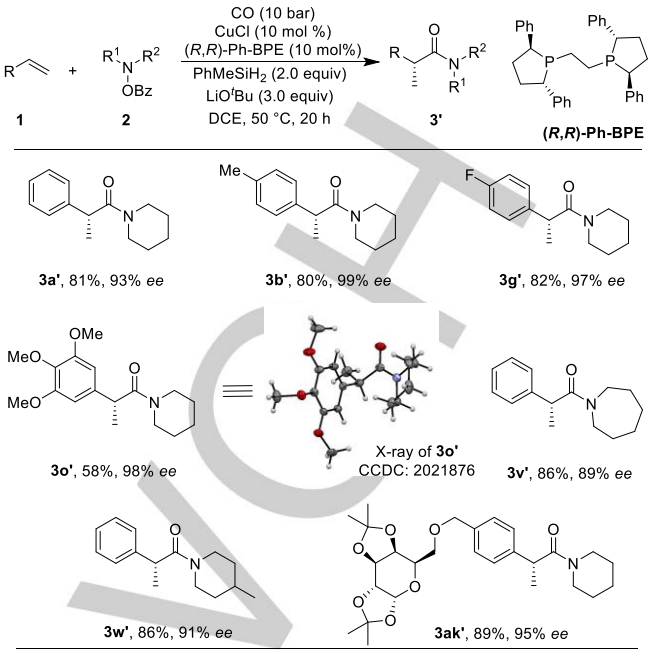
We subsequently set out to develop an enantioselective variant of this Cu-catalyzed hydroamidation by using chiral ligands (Table 2). Unfortunately, P-chirogenic Xantphos ligands (**L1'-L5'**)[17] were ineffective here. (*S*)-Segphos (**L6'**) only gave trace of **3a'**, bulky (*S*)-DTBM-Segphos (**L7'**) gave the desired product in 27% yield, albeit with an excellent enantioselectivity. Then we identified a combination of CuCl and (*R*,*R*)-Ph-BPE (**L8'**) to be optimal in view of the yield and enantioselectivity, and the desired **3a'** was isolated in 83% yield with 93% *ee*.

Table 2. Optimization Studies for Cu-Catalyzed Enantioselective Hydroamidation of **1a** with **2a**.[a]



[a] Standard conditions: **1a** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), $MePhSiH_2$ (0.4 mmol, 2.0 equiv), CuCl (10 mol%), Ligand (10 mol%), LiOtBu (0.6 mmol, 3.0 equiv), CO (10 bar), DCE (1.0 mL), 50 °C, 20 h; Yields are determined by GC analysis using hexadecane as internal standard; *Ee*s are determined by chiral-phase HPLC. n.d. = not determined. [b] Isolated yield. [c] $Cu(OAc)_2$ instead of CuCl.

The scope of the enantioselective Cu-catalyzed hydroamidation of vinylarenes was tested subsequently (Scheme 4). Overall, both styrenes and hydroxyamine derivatives worked well under the asymmetric catalytic system, leading to the corresponding α-chiral amides in high yields with excellent enantioselectivities. The absolute configuration of **3a'** was determined to be *R* by comparing its optical rotation with **(*R*)-3a**,[18] and the configuration of the other compounds described in this work are assigned in analogy to **3a'**.



Scheme 4. Substrate scope of enantioselective Cu-catalyzed hydroamidation. Reaction conditions: **1** (0.3 mmol, 1.5 equiv), **2** (0.2 mmol, 1.0 equiv), $MePhSiH_2$ (0.4 mmol, 2.0 equiv), CuCl (10 mol%), (*R*,*R*)-Ph-BPE (10 mol%), LiO^tBu (0.6 mmol, 3.0 equiv), CO (10 bar), DCE (1.0 mL), 50 °C, 20 h, isolated yields, *ee*s are determined by chiral-phase HPLC.

In summary, we have developed the first Cu-catalyzed hydroamidation of vinylarenes with hydroxyamine derivatives to produce a variety of amides with excellent regioselectivities. The method displays broad functional group tolerance and proceeds under mild conditions. An enantioselective Cu-catalyzed hydroamidation of vinylarenes has been also developed successfully by using (*R*,*R*)-Ph-BPE as the chiral phosphine ligand. The asymmetric variant of this transformation allows for the synthesis of α-chiral amides in good yields with excellent enantioselectivities (up to 99% *ee*). We believe this highly branch-selective hydroamidation presented in the study provides a new strategy to enantioselectively forged amide bonds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: hydroamidation • copper • amides • carbonylation • enantioselectivity

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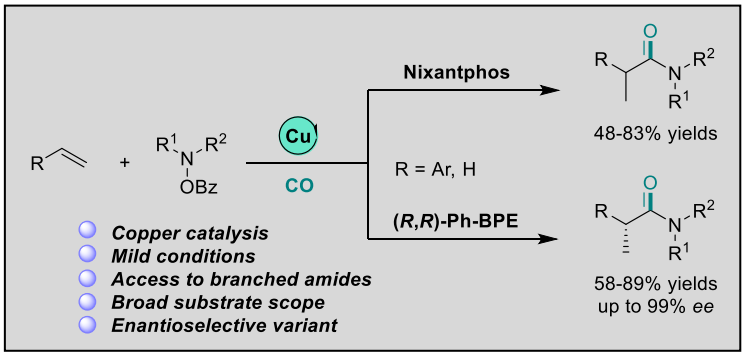

The first Cu-catalyzed hydroamidation of vinylarenes with hydroxyamine derivatives has been developed. The method displays broad functional group tolerance and proceeds under mild conditions, allowing for the synthesis of branched amides. The asymmetric variant of this transformation was also achieved by applying (*R,R*)-Ph-BPE as the ligand, delivering the *α*-chiral amides in good yields with excellent enantioselectivities (up to 99% *ee*).