Asymmetric Catalysis Hot Paper

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Enantioselective Hydrocarbamoylation of Alkenes

*Sheng Feng, Yuyang Dong, and Stephen L. Buchwald**

Abstract: The asymmetric hydroaminocarbonylation of olefins represents a straightforward approach for the synthesis of enantioenriched amides, but is hampered by the necessity to employ CO gas, often at elevated pressures. We herein describe, as an alternative, an enantioselective hydrocarbamoylation of alkenes leveraging dual copper hydride and palladium catalysis to enable the use of readily available carbamoyl chlorides as a practical carbamoylating reagent. The protocol is applicable to various types of olefins, including alkenyl arenes, terminal alkenes, and 1,1-disubstituted alkenes. Substrates containing a diverse range of functional groups as well as heterocyclic substructures undergo functionalization to provide α- and β-chiral amides in good yields and with excellent enantioselectivities.

Chiral amides are ubiquitous structural elements in pharmaceuticals, natural products, and biomolecules (Figure 1A).[1] For example, an amide substructure was present in 70 % of the top 50 selling small molecule pharmaceuticals in 2020.[2] Owing to their importance, various catalytic methods for the asymmetric synthesis of amides have been developed, including the conjugate addition[3] or reduction[4] of α,β-unsaturated amides, and α-functionalization of amides.[5] These techniques typically require the use of a pre-existing racemic or prochiral amide. Alternatively, asymmetric hydroaminocarbonylation of alkenes[6] constitutes a straightforward route to access enantioenriched amides as it allows an amide group to be directly installed onto a readily available olefin precursor. Although direct or formal intramolecular asymmetric alkene hydrocarbamoylation has been demonstrated,[7] the analogous intermolecular enantioselective hydrocarbamoylation of alkenes is less developed. Employing a high pressure of CO, Wu recently reported a Cu-catalyzed asymmetric hydroaminocarbonylation of styrene derivatives.[8a,b] An analogous Pd-catalyzed transformation was developed by Guan, although high levels of regio- and enantioselectivity were limited to styrenes.[8c] Despite these recent advances, the development of a general enantioselective hydrocarbamoylation strategy that is CO-free[9] and compatible with various types of alkenes, including vinyl arenes, vinyl heterocycles, and challenging unactivated olefins, is of considerable interest.

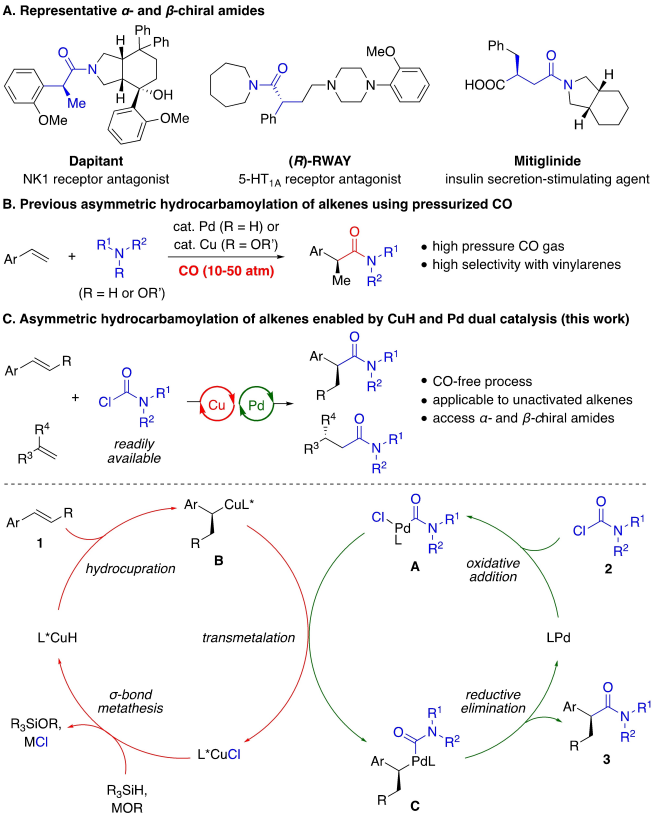


Figure 1. A) Representative biologically active molecules with chiral amide substructures. B) Previous intermolecular asymmetric hydrocarbamoylation of alkenes using pressurized CO. C) Our approach for enantioselective hydrocarbamoylation of alkenes utilizing dual CuH and Pd catalysis.

Our group and others have demonstrated that copper hydride (CuH) catalysis can enable asymmetric hydrofunctionalization of alkenes.[10] This process leverages a stereodefined organocopper intermediate, formed by enantioselective hydrocupration of alkene, to intercept various electrophiles. Based upon this precedent, we felt that widely available carbamoyl chlorides, either commercially available or prepared from the corresponding amine in one step, might obviate the need for CO in the asymmetric hydrocarbamoylation of alkenes. However, our preliminary experiments on the CuH-catalyzed alkene hydrocarbamoylation, utilizing styrene and *N*-methyl-*N*-phenylcarbamoyl

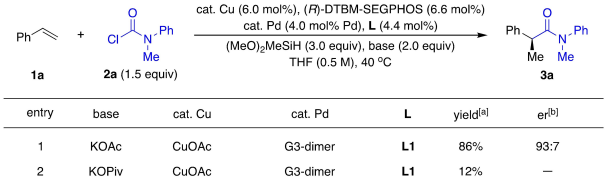
[*] S. Feng, Dr. Y. Dong, Prof. Dr. S. L. Buchwald
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
E-mail: sbuchwal@mit.edu

chloride as substrates, failed to provide the corresponding enantioenriched amide product (Scheme S1).[11]

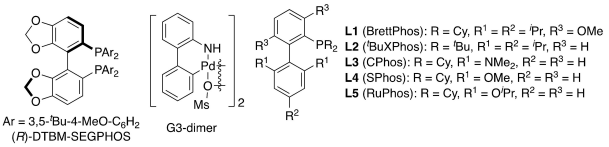
As an alternative, we envisioned that a dual CuH and Pd-catalyzed approach might enable the asymmetric hydrocarbamoylation of alkenes, in which the enantioenriched alkyl copper intermediate could undergo transmetallation with a carbamoyl Pd^{II} oxidative addition complex.[12] To date, only "prototypical" cross coupling processes, such as arylation and vinylation, have been successfully enabled by dual CuH and Pd catalysis.[13,14] In this case, initial oxidative addition of carbamoyl chloride **2** with a Pd^0 catalyst and concomitant enantioselective hydrocupration of alkene **1** would result in oxidative addition complex **A** and alkyl copper **B**. Stereospecific transmetallation would form alkyl Pd^{II} complex **C**. Intermediate **C** would undergo reductive elimination to form amide **3** and reform LPd, and the accompanying L*CuCl intermediate would react with a base and silane to regenerate the L*CuH catalyst. We felt that selection of the base would be crucial, as the use of a highly nucleophilic base might react with the carbamoyl chloride, whereas with a less nucleophilic one, regeneration of the CuH catalyst might be slowed. Moreover, the rates of the two catalytic cycles need to be well aligned to minimize undesired processes, such as racemization of **B**, reduction of carbamoyl chloride by CuH or decomposition of **A**.

We were able to identify suitable reaction conditions with styrene (**1a**) and *N*-methyl-*N*-phenylcarbamoyl chloride (**2a**) as the model substrate combination (Table 1). The ligand DTBM-SEGPHOS has facilitated numerous asymmetric CuH-catalyzed olefin hydrofunctionalization transformations,[10a] including unactivated olefins,[10c,d] and was therefore chosen as the ancillary ligand for Cu. We first examined the use of several weak bases (Table 1, entry 1–4), since a base such as NaOTMS, which has been previously employed in CuH/Pd dual catalysis protocols,[13] would likely consume the carbamoyl chloride coupling partner. The use of KOBz, in conjunction with $Cu(OAc)_2$, (*R*)-DTBM-SEGPHOS, BrettPhos Pd G3, and $(MeO)_2MeSiH$, provided the desired hydrocarbamoylation product (**3a**) in good yield and enantioselectivity. Further evaluation of different copper and palladium sources showed that the yield and enantioselectivity were slightly improved using the combination of $Cu(OAc)_2$ and $[Pd(cinnamyl)Cl]_2$ (Table 1, entry 5–7). A series of biarylphosphine ligands were then examined (Table 1, entry 7–11), revealing SPhos (**L4**) as the ideal Pd ancillary ligand. Under the optimized conditions (Table 1, entry 10), amide **3a** was obtained in 95 % yield and 97:3 er. However, when we attempted the same reaction between **1a** and diethylcarbamoyl chloride (**2b**) under the identical conditions, both the yield and enantioselectivity were considerably lower (66 % yield, 78:22 er). Since compared to **2a**, the more electron rich **2b** might undergo oxidative addition with the LPd^0 intermediate at a reduced rate. Subsequent transmetallation with intermediate **B** would also be slower, which could lead to an increased level of racemization and decomposition of **B**. After minor modifications to the reaction conditions including the base, Cu, and Pd source (Table S1),[11] the corresponding amide was formed in 80 % yield and 91:9 er. This observation also underscores the importance of matching the rates of the Cu and Pd catalytic cycles by tuning the reaction conditions.

Table 1: Optimization of the enantioselective hydrocarbamoylation of styrene.



entry	base	cat. Cu	cat. Pd	L	yield[a]	er[b]
1	KOAc	CuOAc	G3-dimer	**L1**	86%	93:7
2	KOPiv	CuOAc	G3-dimer	**L1**	12%	–
3	KOBz	CuOAc	G3-dimer	**L1**	91%	94:6
4	NaOBz	CuOAc	G3-dimer	**L1**	72%	95:5
5	KOBz	CuOAc	$Pd(OAc)_2$	**L1**	87%	95:5
6	KOBz	CuOAc	$[Pd(cinnamyl)Cl]_2$	**L1**	90%	94.5:5.5
7	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L1**	93%	94.5:5.5
8	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L2**	67%	91.5:8.5
9	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L3**	77%	95.5:4.5
10	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L4**	95%	97:3
11	KOBz	$Cu(OAc)_2$	$[Pd(cinnamyl)Cl]_2$	**L5**	87%	96.5:3.5

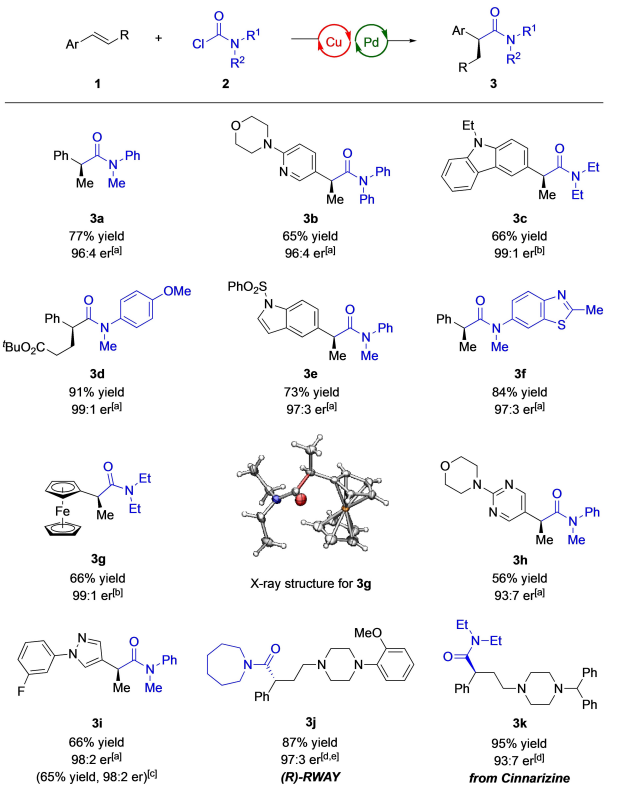


[a] Yield was determined by ^1H NMR spectroscopy of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. [b] Enantiomeric ratio was determined by SFC analysis.

Having established the reaction conditions for the asymmetric hydrocarbamoylation of vinyl arenes, we next examined the scope of the reaction (Table 2). A number of vinyl heteroarenes, both electron rich and deficient, including pyridine (**3b**), carbazole (**3c**), indole (**3e**), pyrimidine (**3h**), and pyrazole (**3i**), efficiently underwent the hydrocarbamoylation reaction to provide the corresponding amide products in good yield and excellent enantioselectivity. β-Substituted styrenes (**3d**, **3j**, **3k**) were also successful substrates in this transformation, although the reaction conditions were modified slightly for those bearing basic β-amino substituents (**3j**, **3k**) due to the moderate enantioselectivity observed under the original conditions (74:26 er for **3j**, 82:18 er for **3k**). The protocol accommodated different substituents on the nitrogen atom of carbamoyl chlorides, including methylaryl (**3a**, **3d–f**, **3h–i**), dialkyl (**3c**, **3g**, **3k**, **3j**), and diphenyl (**3b**) substructure. To demonstrate the synthetic utility of this method, we prepared (*R*)-RWAY (**3j**), a 5-HT_{1A} receptor antagonist,[15] in one step from the corresponding arylalkene in excellent yield and enantioselectivity. We were also able to obtain the enantioenriched amide derivative of Cinnarizine (**3k**), an antihistamine drug. Additionally, the absolute configuration of a ferrocene derivative **3g** was confirmed by X-ray crystallography.[16] The observed stereoselectivity of the reaction suggests a stereoretentive Cu-to-Pd transmetallation which is in accord with our previous observations (Figure 1C).[13]

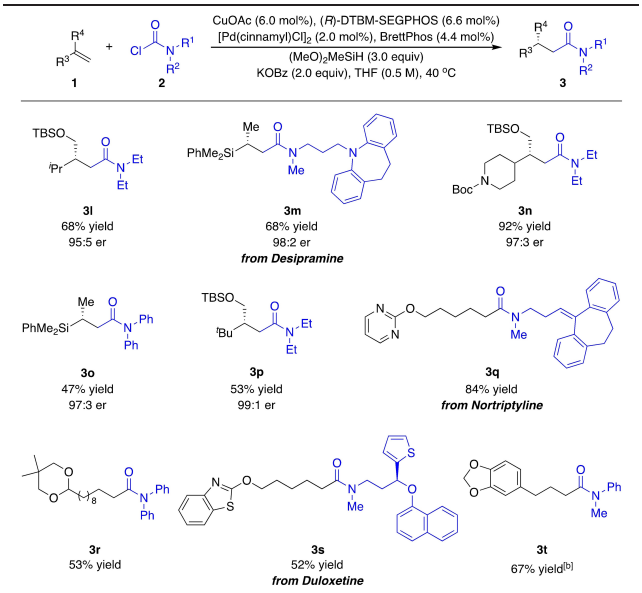
We were also interested in applying our strategy to unactivated alkenes, including 1,1-disubstituted alkenes and terminal alkenes, to access β-chiral and linear amides,

Table 2: Substrate scope for the hydrocarbamoylation of arylalkenes.



[a] Condition A: **1** (0.5 mmol, 1 equiv), **2** (1.5 equiv), $Cu(OAc)_2$ (6.0 mol%), (*R*)-DTBM-SEGPHOS (6.6 mol%), $[Pd(cinnamyl)Cl]_2$ (2.0 mol%), **L4** (4.4 mol%), KOBz (2 equiv), $(MeO)_2MeSiH$ (3 equiv), THF (0.5 M), 40°C. [b] Condition B: **1** (0.5 mmol, 1 equiv), **2** (1.5 equiv), CuOAc (6.0 mol%), (*R*)-DTBM-SEGPHOS (6.6 mol%), G3-dimer (2.0 mol%), **L1** (4.4 mol%), NaOPiv (2 equiv), $(MeO)_2MeSiH$ (3 equiv), THF (0.5 M), 40°C. [c] Isolated yields on a 1.0 mmol scale under Condition A (average of two runs). [d] Condition B, except NaOBz was used. [e] Condition B, except (*S*)-DTBM-MeO-BIPHEP was used.

Table 3: Substrate scope for the hydrocarbamoylation of unactivated olefins.[a]



[a] Condition C: **1** (0.5 mmol, 1 equiv), **2** (1.5 equiv), CuOAc (6.0 mol%), (*R*)-DTBM-SEGPHOS (6.6 mol%), $[Pd(cinnamyl)Cl]_2$ (2.0 mol%), **L1** (4.4 mol%), KOBz (2 equiv), $(MeO)_2MeSiH$ (3 equiv), THF (0.5 M), 40°C. [b] Condition C, except $Pd(OAc)_2$ (4.0 mol%), XPhos (4.4 mol%), and KOAc (2 equiv) were used instead.

respectively, via anti-Markovnikov[13c,e] hydrocarbamoylation. 1,1-disubstituted alkenes represent a challenging class of substrates in aminocarbonylation reactions due to their attenuated binding affinity towards metal hydride intermediates,[7e] and a general protocol for the intermolecular asymmetric hydroaminocarbonylation of 1,1-disubstituted alkenes remains elusive. Even for unactivated terminal olefins, only a few hydroaminocarbonylation reaction protocols are available that don't require the use of CO gas at elevated pressure.[17] In order to expand our hydrocarbamoylation protocol to unactivated alkenes, for which the hydrocupration step is more challenging compared to vinylarenes,[10c] the reaction conditions were modified by manipulating the copper source and the Pd ancillary ligand (Table S2).[11] Using the optimized conditions, 1,1-disubstituted alkenes were coupled with different carbamoyl chlorides to provide the corresponding β-chiral amides (**3l**–**3p**) in moderate to good yields and excellent enantioselectivity (Table 3). As the difference in steric demand between the geminal substituents on the olefin increases, the enantioselectivity of the reaction also improves (**3l**, **3n**, **3p**, sequentially). Additionally, amides containing a silicon-substituted β-stereogenic center (**3m**, **3o**) could be obtained by employing an alkenyl silane as substrate. The protocol is also applicable to various readily available terminal alkenes, allowing them to react efficiently with dialkyl (**3q**, **3s**), diphenyl (**3r**), and *N*-methyl-*N*-phenyl carbamoyl chlorides (**3t**). Overall, the hydrocarbamoylation reaction of unactivated alkenes was able to tolerate a broad range of heterocycles, including azepane (**3m**), piperidine (**3n**), pyrimidine (**3q**), benzothiazole (**3s**), and thiophene (**3s**). Functional groups such as acetal (**3r**, **3t**) and siloxyl (**3l**, **3n**, **3p**) were also compatible with the reaction conditions. Moreover, carbamoyl chlorides that are easily derived from several amine-containing pharmaceuticals, including Desipramine (**3m**), Nortriptyline (**3q**), and Duloxetine (**3s**), were successfully coupled with different unactivated alkenes, further demonstrating the synthetic utilities of our approach.

In summary, we have developed a highly enantioselective hydrocarbamoylation reaction of olefins utilizing readily available carbamoyl chlorides as a practical carbamoylating reagent that obviates the need for CO gas. Under mild CuH and Pd dual catalysis conditions, a broad range of alkenes, including arylalkenes, 1,1-disubstituted alkenes, and terminal olefins, were able to undergo the reaction smoothly to furnish α- and β-chiral amides bearing diverse heterocycles and functional groups. In addition, we anticipate that the use of a non-traditional carbonyl cross-coupling partner, carbamoyl chlorides, in CuH/Pd cooperative catalysis may stimulate further developments in merging CuH catalysis with other types of carbonylative cross-coupling processes.

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Conflict of Interest

S.L.B. and former coworkers receive royalties for patents held by MIT for the sale of some ligands and precatalysts used in this work.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Amides · Copper Hydride · Enantioselectivity · Hydrocarbamoylation · Palladium

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[16] Deposition Number 2157585 (for **3g**) 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.

[17] For examples on intermolecular hydrocarbamoylation of unactivated alkenes, see: a) S. Ko, H. Han, S. Chang, *Org. Lett.* **2003**, *5*, 2687–2690; b) Y. Miyazaki, Y. Yamada, Y. Nakao, T. Hiyama, *Chem. Lett.* **2012**, *41*, 298–300. For a one-pot formal hydrocarbamoylation of olefins through alkylborane intermediates, see: c) Y. Yasui, S. Tsuchida, H. Miyabe, Y. Takemoto, *J. Org. Chem.* **2007**, *72*, 5898–5900.

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