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CuH-Catalyzed Asymmetric Reductive Amidation of α,β-Unsaturated Carboxylic Acids

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02064 Read Online

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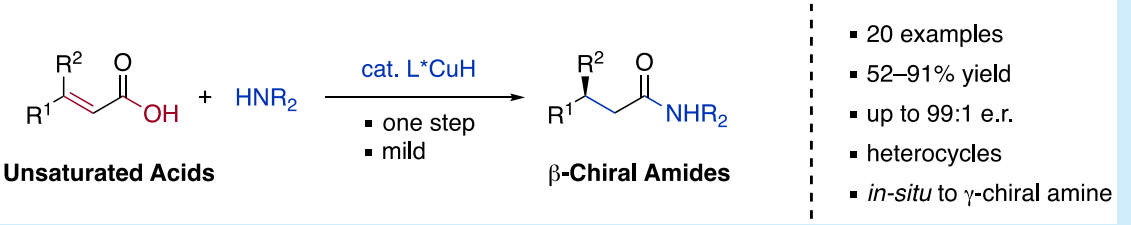

ABSTRACT: The direct enantioselective copper hydride (CuH)-catalyzed synthesis of β-chiral amides from α,β-unsaturated carboxylic acids and secondary amines under mild reaction conditions is reported. The method utilizes readily accessible carboxylic acids and tolerates a variety of functional groups in the β-position including several heteroarenes. A subsequent iridium-catalyzed reduction to γ-chiral amines can be performed in the same flask without purification of the intermediate amides.

Amides are an integral part of the backbone of all biological systems, as well as important elements of many pharmaceutical agents. Consequently, amide bond formation is of great importance in organic chemistry and methods for the direct catalytic amidation of carboxylic acids under mild conditions are highly desirable.[1] In addition, β-chiral amides are found in many natural products and are considered to be important pharmacophores.[2] Furthermore, this substructure can be regarded as a useful intermediate for the synthesis of additional pharmaceutically relevant molecules, such as γ-chiral amines.[3]

The synthesis of amides bearing stereogenic centers at the β-position generally requires multiple steps.[4] Currently available strategies include copper-catalyzed asymmetric conjugate additions,[5] asymmetric conjugate reductions,[6] and transition-metal-catalyzed hydrogenation reactions[7] of unsaturated carbonyl compounds (Figure 1A). Each of these approaches requires a final amidation reaction, typically involving the use of stoichiometric coupling reagents.[8]

The enantioselective CuH-catalyzed 1,4-reduction of unsaturated esters,[9] in which a chiral bisphosphine-ligated CuH-species is generated by a hydrosilane as a stoichiometric reducing agent can be used to asymmetrically reduce a variety of α,β-unsaturated alkenes under mild reaction conditions.[10] The analogous reduction of lactams has been successfully implemented;[11] however, acyclic amides are not reduced under CuH-catalysis conditions. In general, the alternative access to β-chiral amides via direct enantioselective conjugate transformation of unsaturated amides is more challenging due to their lower reactivity compared to other Michael acceptors.[12]

Despite these advances that have been made in the preparation of β-chiral amides, a general approach that enables the catalytic amidation of carboxylic acids and the formation of a stereogenic center in a single operation under mild conditions would allow the expedited synthesis of substructures found in many biologically active molecules. Our group recently reported the direct asymmetric CuH-catalyzed hydroacylation[13] and 1,4-reduction[14] of α,β-unsaturated carboxylic acids to generate α-chiral ketones (Figure 1B). Mechanistic investigations suggested that these reactions may proceed through a ketene intermediate. Thus, we considered whether this ketene might be intercepted by an exogenous nucleophile, rather than undergoing reaction with LCuH or LCuR. Specifically, whether by performing the 1,4-reduction reaction in the presence of an amine nucleophile might allow for the formation of an amide product with a chiral center at the β-position (Figure 1C).

When we attempted such a reaction using secondary amines as nucleophiles, we indeed observed clean conversion of α,β-unsaturated acid substrates (**1**) to the desired β-chiral amides (**3**, Figure 2).[15] Optimization revealed that several β,β-disubstituted unsaturated carboxylic acids were effectively converted using low quantities of the precatalyst mixture (*S*)-CuCatMix[16] (see Supporting Information (SI) for details). The use of dimethoxy(methyl)silane (DMMS) as the hydride source permitted efficient amidation at room temperature in

Received: June 22, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02064
Org. Lett. XXXX, XXX, XXX−XXX

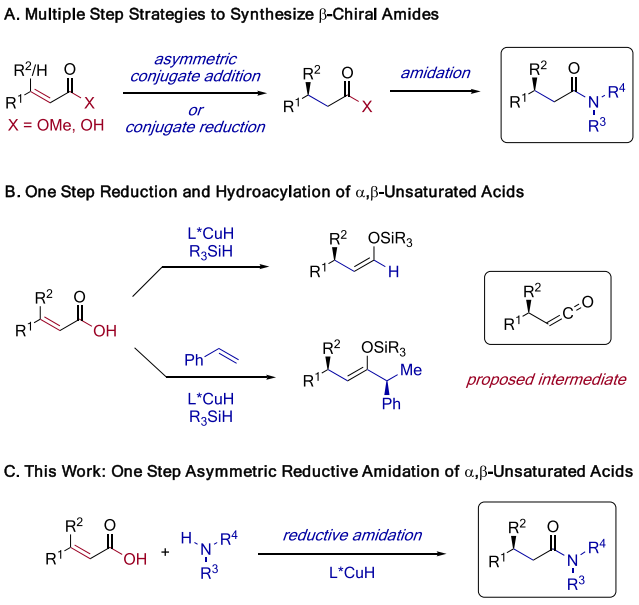

Figure 1. (A) Common multistep strategies to synthesize β-chiral amides from unsaturated carbonyls. (B) CuH-catalyzed silyl ester formation and 1,4-reduction allows the reduction and hydroacylation of unsaturated carboxylic acids presumably via ketene intermediates. (C) The direct formation of β-chiral amides in one step from unsaturated carboxylic acids (this work).

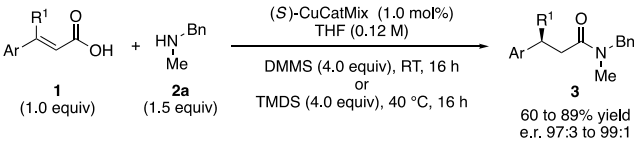

Figure 2. Preliminary screen of CuH catalyzed reductive coupling reactions of α,β-unsaturated acids and a secondary amine. (*S*)-CuCatMix = $Cu(OAc)_2$, (*S*)-DTBM-SEGPHOS, PPh_3 (1:1.1:1.1 ratio, precomplexed, air-stable free-flowing powder). Silanes: Dimethoxy(methyl)silane (DMMS) or 1,1,3,3-tetramethyldisiloxane (TMDS).

THF, while with 1,1,3,3-tetramethyldisiloxane (TMDS)[17] similar conversions were observed at 40 °C.

Next, we examined the substrate scope for the direct CuH-catalyzed amidation reaction at 1.0 mmol scale. Using either of the optimized protocols, DMMS at rt or TMDS at 40 °C, amide **3a** was obtained in similar yields and stereoselectivity (Figure 3). Product **3b**, which is structurally similar to recently investigated Ubiquitin-specific protease 7 inhibitors,[2a] could be prepared directly from unprotected 4-hydroxypiperidine. In this case, the procedure employing TMDS at 40 °C was found to be superior.

The reaction of (*E*)-3-phenylbut-2-enoic acid with α-disubstituted and chiral (*S*)-(−)-*N*,α-dimethylbenzyl-amine gave amide **3c** in a yield of 61% and with excellent stereoselectivity. Reactions involving tetrazole- or quinoline/diamine-containing acids gave similar yields with high enantiomeric ratio (**3d** and **3e**). A ferrocene substituted acid, as well as α,β-unsaturated carboxylic acids bearing heterocycles including pyrimidine, indole, pyrazole, pyrrole, benzothiazole, and dimethylthiazole, at the β-position was efficiently coupled with different amines in good to excellent yields and with high enantioselectivity (**3g**–**l**). In addition, an alkyl chloride in β-position was well-tolerated under the reaction conditions, although diminished enantioselectivity was observed (**3m**).

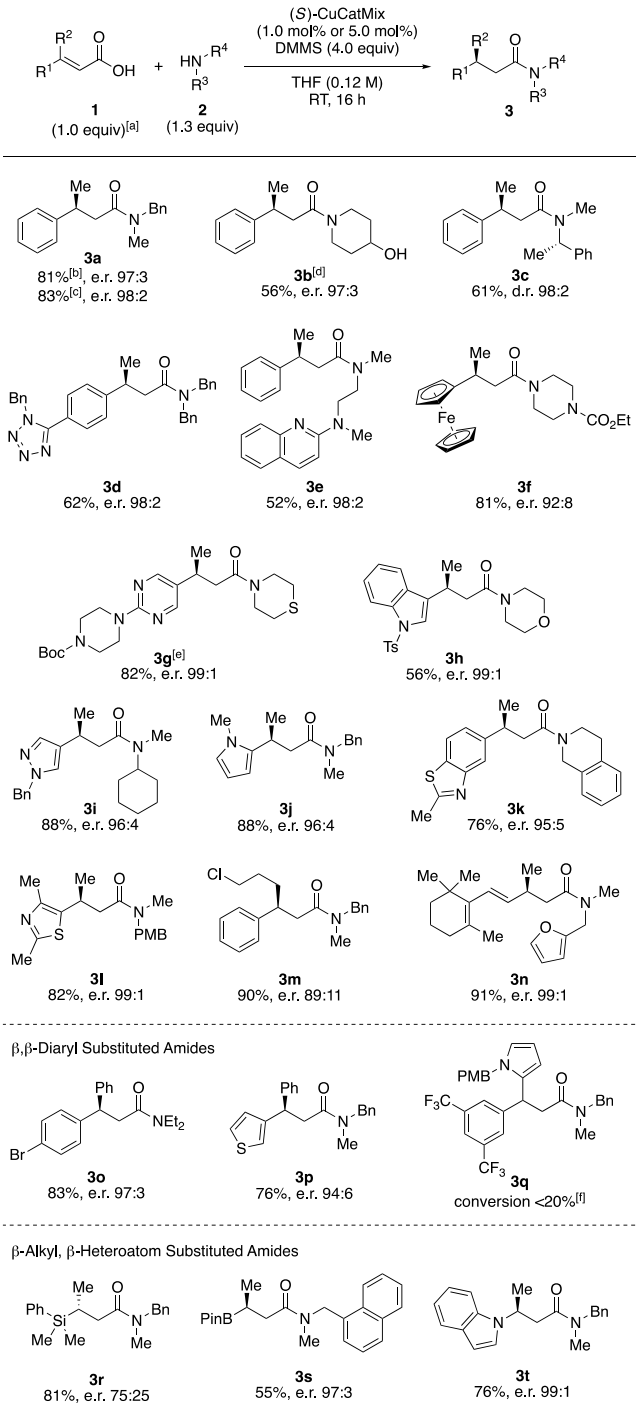

Figure 3. Scope of the CuH catalyzed reductive amidation of β,β-disubstituted α,β-unsaturated carboxylic acids with secondary amines. [a]Reaction performed with 1.0 mmol of carboxylic acid and 5.0 mol % (*S*)-CuCatMix. Reported yields are isolated yields and are the average of two runs. Enantiomeric ratios were determined by SFC. [b]Reaction performed with 1.0 mol % (*S*)-CuCatMix. [c]Reaction performed with TMDS at 40 °C and 1.0 mol % (*S*)-CuCatMix. [d]Reaction performed with TMDS at 40 °C and at a concentration of 0.06 M, followed by deprotection with TBAF. [e]Reaction performed at a concentration of 0.06 M. [f]Low conversions were observed with ortho-substituted substrates. Conversion determined by ^{1}H NMR on 0.10 mmol scale (see SI for more examples).

https://dx.doi.org/10.1021/acs.orglett.0c02064
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Moreover, the β-alkenyl β-alkyl acid derived from β-ionone could be coupled with a furan-containing amine (**3n**). The procedure for the β-(hetero)aryl,β-alkyl-substituted substrates also worked well for β,β-diaryl substituted acids. In particular, acids containing a bromoarene and a thiophene were efficiently converted to the desired products (**3o** and **3p**). However, under these conditions, only low conversions were observed for the reactions of more sterically hindered acids (see **3q** and SI for more structures), as well as using sterically hindered amines such as diisopropylamine. We also examined substrates with heteroatoms at the β-position. Silane **3r** was obtained in good yield from the corresponding *Z*-olefin, although with diminished enantiopurity (75:25). In contrast, boronic ester **3s** and *N*-substituted indole **3t** were obtained with excellent levels of enantiomeric purity. In the cases of more complex substrates, including nitrogen-rich heterocycles and functional group containing amines, a 5 mol % catalyst loading was employed to ensure full conversion of the unsaturated carboxylic acids.

Based on recent work of transition-metal-catalyzed reduction of amides to enamines and amines with hydrosilanes,[18] we also saw an opportunity to develop a one-pot synthesis of γ-chiral amines based on our reaction (Figure 4). Amines with

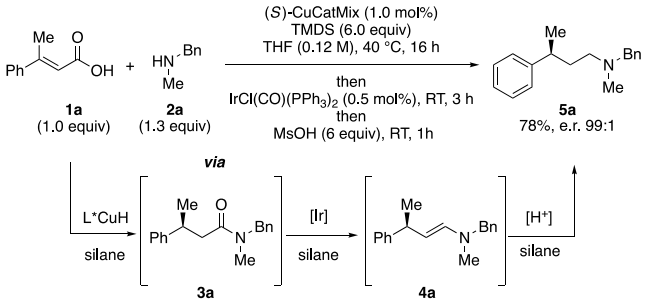

Figure 4. One-pot synthesis of γ-chiral amines.

stereocenters in the γ-position are frequently encountered structural components in bioactive molecules.[19] However, these remote stereocenters are in general challenging to form directly and are usually installed in a stepwise process from a β-chiral aldehyde followed by reductive amination reactions.[14] After a CuH-catalyzed reductive amidation reaction, 0.5 mol % $IrCl(CO)(PPh_3)_2$ (Vaska's complex) was added to the crude reaction mixture, upon which the enamine **4a** was efficiently formed. Subsequent addition of methanesulfonic acid (MsOH) induced further reduction, presumably via iminium ion formation, delivering γ-chiral amine **5a** in excellent yield and enantiomeric ratio.

We next investigated some aspects of the mechanism of Cu catalyzed reductive amidation of α,β-unsaturated acids (Figure 5). Based on our previous investigations, we considered path A as a possibility, in which the CuH-catalyzed 1,4-reduction of a silyl ester delivers a copper enolate that could eliminate to a ketene intermediate. Addition of the amine to the ketene would then give the observed β-chiral amide product. An alternative mechanism is illustrated as path B, involving the direct amidation of the intermediate silyl ester,[20] followed by conjugate reduction of the resulting unsaturated amide.

Several experiments in THF-d_8 were performed and analyzed by ^{1}H NMR spectroscopy. To identify and characterize the silyl ester intermediates, (*E*)-3-phenyl-but-2-enoic acid (**1a**), 0.5 mol % of (*S*)-CuCatMix, and 1 equiv of DMMS were

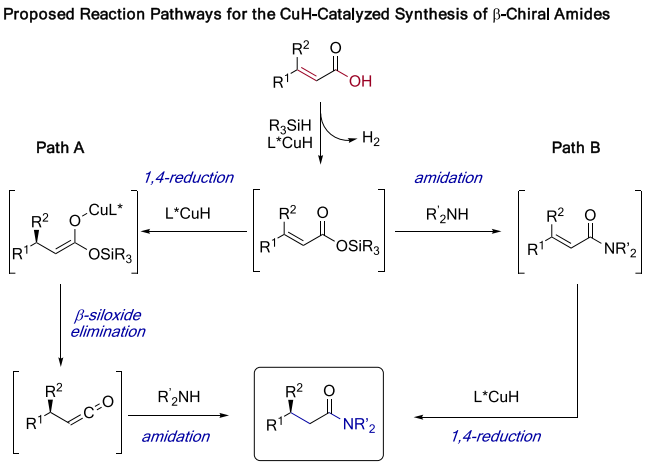

Figure 5. Two reaction pathways are considered after initial silylation of the carboxylic acid.

combined. Full conversion to a mixture of silylated intermediates **6a**, **6b**, and **6c** (Figure 6A) in a ratio of 4:1:1 was observed after 60 h. Furthermore, neither 1,4-reduction of the activated silyl esters nor interconversion between the intermediates was observed.

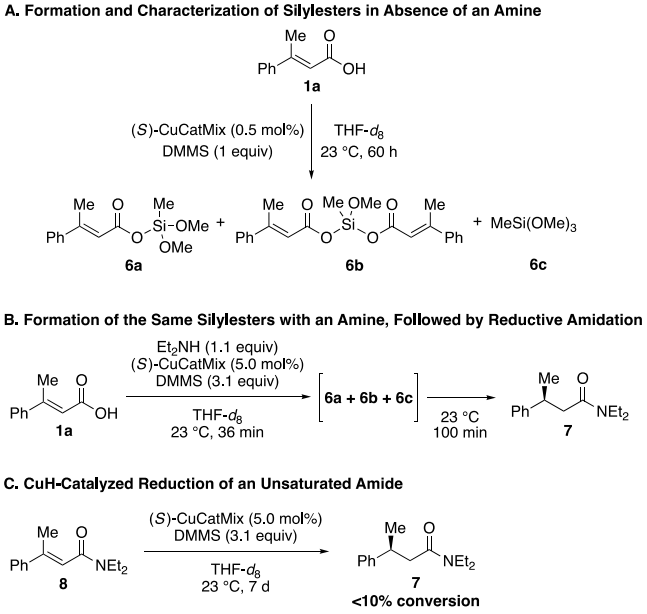

Figure 6. (A) Intermediary silyl ester intermediates identified and characterized by NMR spectroscopy and high-resolution mass spectrometry. (B) The CuH-catalyzed amidation was monitored by ^{1}H NMR-spectroscopy. (C) The CuH-catalyzed reduction of an unsaturated amide is not efficient under the described conditions.

Next, we monitored reactions using the conditions described in Figure 3 (Figure 6B), using acid **1a** and Et_2NH as model substrates. Initially, the same silylated intermediates (**6a**, **6b**, **6c**) as observed previously were formed, although their generation was accelerated (36 min vs 60 h), possibly by the presence of the basic amine.[21] After complete consumption of the acid, first the more activated[22] dimeric intermediate **6b** is converted to product **7**, followed by the conversion of monomer **6a**. No other intermediates resulting from 1,4-

https://dx.doi.org/10.1021/acs.orglett.0c02064
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reduction, such as Cu-enolates or ketenes, were observed. Furthermore, the unsaturated amide **8** was not detected.

When we independently prepared and isolated unsaturated amide **8** and subjected it to the standard reaction conditions, less than 10% of **7** was observed, even with a 7 day reaction time, suggesting that path B plays at most a minor role (Figure 6C) in the CuH-catalyzed asymmetric reductive amidation of unsaturated carboxylic acids.

In conclusion, we have developed a one-step CuH-catalyzed method to access β-chiral amides starting from readily available unsaturated carboxylic acids. The mild reaction conditions tolerate various functional groups and heterocycles. Subsequent one-pot reduction with Vaska's complex allowed the direct reduction to form γ-chiral amines. The formation and consumption of reaction intermediates was monitored, and several silyl ester intermediates were identified.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02064.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research reported in this publication was supported by the National Institutes of Health (R35-GM122483). The content of this communication solely reflects the research and opinion of the authors and does not necessarily represent the official views of the NIH. A.L. thanks the Swiss National Science Foundation (SNSF) for a postdoctoral fellowship (P2BSP2_174978). Y.Z. thanks Bristol-Myers Squibb for support through a fellowship. We thank the National Institutes of Health for a supplemental grant (R01-GM058160-17S1) for the purchase of supercritical fluid chromatography (SFC) equipment. We thank Dr. Walter Massefski (MIT) for assistance with NMR spectroscopy. We thank Drs. Richard Liu (MIT), Scott McCann (MIT), Christine Nguyen (MIT), and Alexander Schuppe (MIT) for their advice on the preparation of this manuscript.

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https://dx.doi.org/10.1021/acs.orglett.0c02064
Org. Lett. XXXX, XXX, XXX−XXX