CuH-Catalyzed Regio- and Enantioselective Hydrocarboxylation of Allenes: Towards Carboxylic Acids with Acyclic Quaternary Centers

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ABSTRACT: We report a method to prepare α-chiral carboxylic acid derivatives, including those bearing all-carbon quaternary centers, through an enantioselective CuH-catalyzed hydrocarboxylation of allenes with a commercially available fluoroformate. A broad range of heterocycles and functional groups on the allenes were tolerated in this protocol, giving enantioenriched α-quaternary and tertiary carboxylic acid derivatives in good yields with exclusive branched regioselectivity. The synthetic utility of this approach was further demonstrated by derivatization of the products to afford biologically important compounds, including the antiplatelet drug indobufen.

All-carbon quaternary stereocenters, a structural feature that can impart significant chemical and biological impact to a molecule, are critical to many synthetic and medicinal applications.[1] Consequently, catalytic and enantioselective approaches for constructing all-carbon quaternary centers, especially functionalized stereocenters, are highly desirable.[2] Carboxylic acids, a chemically versatile functional group, that can bear an α-stereogenic center often serve as useful synthetic intermediates.[3] More importantly, α-chiral carboxylic acid derivatives themselves constitute an essential class of compounds in pharmaceutical, agrochemical, and natural product arenas (Figure 1A).[4] Methods for generating enantioenriched α-chiral carboxylic acids have long been sought after.[5] Prominent synthetic strategies targeting α-chiral carboxylic acids or esters via asymmetric catalysis include hydrogenation of α,β-unsaturated carboxylic acids,[6] carbene-induced C−H insertion with diazoacetates,[7] enantioselective protonation[8] or hydrogen atom transfer[9] processes, and α-functionalization of carboxylic acid derivatives.[10-12] Nonetheless, catalytic access[13] to enantioenriched acyclic carboxylic acids or esters featuring an all-carbon α-quaternary stereocenter remains challenging.[2a-b] In this regard, common synthetic methods include allylic alkylation of geometrically pure alkenes,[14] often with superstoichiometric organometallic reagents, and α-functionalization of carboxylic acid derivatives,[11,12f] which typically necessitates a β-directing group or electron-withdrawing group (Figure 1B).

As an alternative, the hydrocarboxylation[15,16] of prochiral unsaturated substrates represents a straightforward approach for preparing carboxylic acids. Asymmetric hydrocarboxylation has typically[17] been achieved through palladium-catalyzed hydroxy- and alkoxycarbonylation processes using CO gas or a carbon monoxide surrogate.[18,19] Despite significant advances in this area, the vast majority of the methods can only synthesize α-tertiary acids or esters from vinyl arenes, and a highly enantioselective technique for the assembly of α-quaternary carboxylic acids through a hydrocarboxylation or hydroesterification of unsaturated substrates is still unknown.[17a]

Based upon our research program in copper hydride (CuH)-catalyzed asymmetric hydrofunctionalization of unsaturated substrates,[20] we sought to develop a hydrocarboxylation method for constructing enantioenriched carboxylic acids, especially α-quaternary acids. Specifically, we envisioned that a chiral organocopper species, generated in situ from the hydrocupration of an unsaturated substrate, could engage a suitable carboxylation reagent to afford enantioenriched carboxylic acids. Previously, when CO_2 was used as an electrophile in CuH-catalyzed olefin hydrofunctionalization reactions, the initially-formed silylated carboxylic acid intermediates underwent facile reduction and led to the formation of hydroxymethylene products.[21] To circumvent this reduction pathway, we targeted the CuH-catalyzed hydroesterification, as the products are unreactive under the reaction conditions and can be readily hydrolyzed to give the corresponding carboxylic acids. An ester directly attached to a leaving group is proposed as the electrophile for realizing the hydrocarboxylation process (Figure 1B). In order to obtain α-quaternary esters and acids, we sought to perform a regioselective hydrocarboxylation of allenes as the unsaturated substrate. Herein, we report a highly enantioselective CuH-catalyzed hydrocarboxylation to furnish both α-quaternary and tertiary carboxylic acid derivatives.

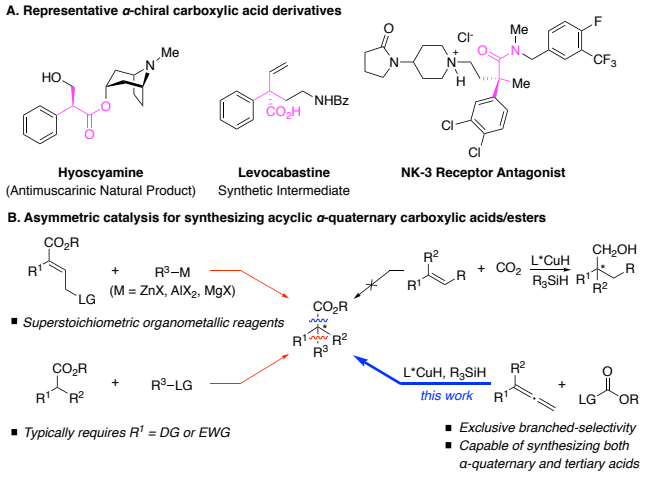
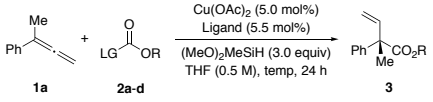


Figure 1. A. Overview of bioactive α-chiral carboxylic acid derivatives. **B.** Previous strategies and our approach to synthesize acyclic α-quaternary carboxylic acid derivatives.

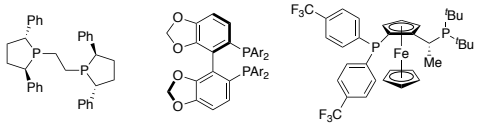
We chose 1-phenyl-1-methylallene (**1a**) as our model substrate since the branched selective hydrocarboxylation of 1-aryl-1-alkylallenes would produce valuable acyclic quaternary α-vinyl-α-aryl carboxylic acids that have been used as intermediates in the preparation of (+)-epilaurene[3d] and several pharmaceutical ingredients.[3b,14a] We began our investigation with diphenyl carbonate (**2a**) as the reagent for carboxylate introduction. A series of chiral bisphosphine ligands were evaluated in the hydrocarboxylation of **1a** with diphenyl carbonate (Table S1), and the highest level of enantioselectivity was obtained with (*R*,*R*)-Ph-BPE (**L1**). Under these conditions, the ester product was formed in 42% yield (90:10 er) exclusively as the branched isomer (Table 1, entry 1). In addition to the moderate level of enantioselectivity that was observed, the use of **2a** appeared to result in a sluggish reaction rate. We next attempted to improve the activity of electrophile by replacing **2a** with Boc_2O (**2b**) or methyl chloroformate (**2c**), which resulted in no desired hydroesterification product being formed (Table 1, entries 2−3). With **2c**, we needed an alkoxide base to regenerate LCuH from a LCuCl intermediate,[22] and we ascribed the low yield to the incompatibility between the base and methyl chloroformate. Since LCuH regeneration from LCuF complexes can proceed in the absence of a base additives,[23] we investigated the use of fluoroformates as potential carboxylation reagents. When commercially available 1-adamantyl fluoroformate (**2d**) was employed, product **3** was obtained in 83% yield (Table 1, entry 4). Upon reexamining the suitability of different ligands in reactions with **2d** (Table 1, entry 5−6, and Table S2), we found that when (*R*)-DTBM-SEGPHOS (**L2**) was used (Table 1, entry 5), the branched product was obtained as a single regioisomer in 92% yield and 99:1 er.

Table 1. Evaluation of Reaction Conditions for the CuH-Catalyzed Hydrocarboxylation of Allene[a]



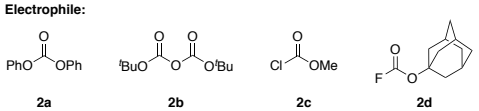
Entry	Ligand	Electrophile	Temp (°C)	Yield[b] (%)	er[c]
1	**L1**	**2a**	40	42	10:90
2	**L1**	**2b**	40	<5	-
3[d]	**L1**	**2c**	25	<5	-
4	**L1**	**2d**	25	83	13:87
5[e]	**L2**	**2d**	25	92	99:1
6[f]	**L3**	**2d**	25	77	96:4

Ligand:



(*R*,*R*)-Ph-BPE (**L1**) | Ar = 3,5-^{t}Bu-4-MeO-C_6H_2 (*R*)-DTBM-SEGPHOS (**L2**) | SL-J011-1 (**L3**)

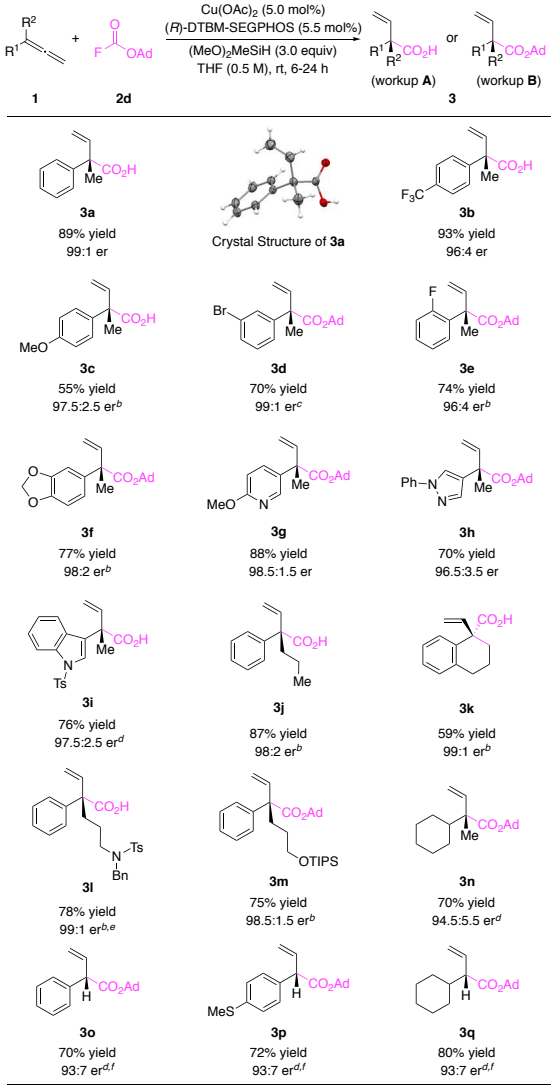
Electrophile:



2a **2b** **2c** **2d**

[a]Conditions: 0.10 mmol **2** (1.0 equiv), **1a** (2.0 equiv), copper (II) acetate (5.0 mol%), ligand (5.5 mol%), dimethoxy(methyl)silane (3.0 equiv) in THF (0.5 M). [b]Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. [c]Enantiomeric ratio was determined by SFC analysis. [d]Either LiOMe (1.1 equiv) or CsOBz (1.1 equiv) was used as an additive; **1a** (1.5 equiv) was used. [e]**1a** (1.2 equiv) was used. [f]**1a** (1.0 equiv) and **2** (1.2 equiv) were used.

Table 2. Substrate Scope for the CuH-Catalyzed Hydrocarboxylation of Allenes[a]



[a]Conditions: 0.50 mmol **2d** (1.0 equiv), **1** (1.2 equiv), copper (II) acetate (5.0 mol%), **L2** (5.5 mol%), dimethoxy(methyl)silane (3.0 equiv) in THF (0.5 M); workup **A**: NH_4F/MeOH workup followed by hydrolysis using TFA; workup **B**: NH_4F/MeOH workup; yields refer to average isolated yields of two runs; see the Supporting Information for details. [b]Reaction was carried out at 40 °C. [c]Reaction was carried out at 30 °C. [d]**L3** was used as the ligand instead. [e]**1** (1.1 equiv) was used. [f]Reaction was carried out at 0 °C in 1,2-dimethoxyethane (DME, 1.0 mL).

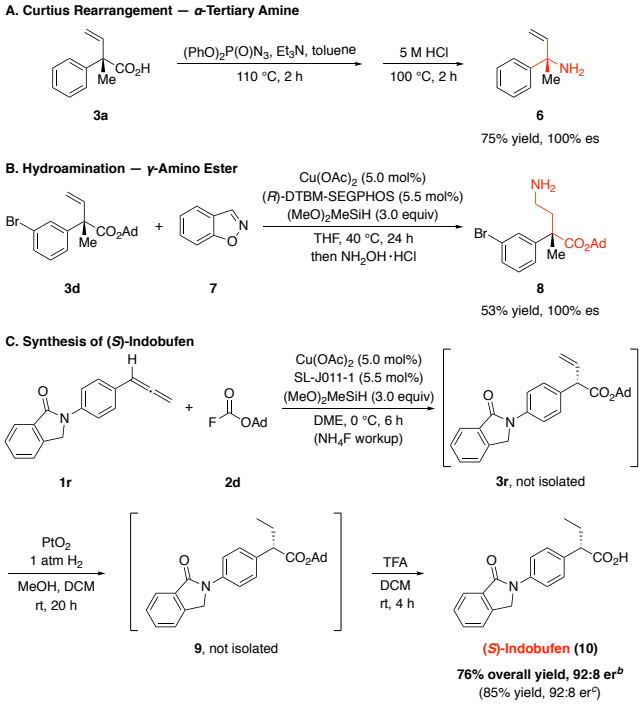
With the optimal reaction conditions identified, we first examined the substrate scope using 1,1-disubstituted allenes (Table 2). We found that a broad range of 1,1-disubstituted allenes in combination with **2d** were transformed to the desired products in good yields and with excellent enantioselectivity. Moreover, the ester products could be easily hydrolyzed to carboxylic acids in the presence of trifluoroacetic acid (TFA) in near quantitative yields. To demonstrate the feasibil-

ity of this in situ hydrolysis protocol, half of the ester products in Table 2 were isolated as carboxylic acids (**3a**–**c**, **3i**–**l**) without any purification of the intermediate esters.[24] 1-Aryl-1-alkylallenes bearing an electron-withdrawing (**3b**) and -donating group (**3c**) on the arenes were both compatible. Additionally, reactions of arenes substituted with *para*- (**3b**, **3c**), *meta*- (**3d**), and *ortho*- (**3e**) groups resulted in the formation of the products in high yields and enantioselectivity. Functional groups such as an acetal (**3f**), a sulfonamide (**3l**), and a siloxy group (**3m**) were also well tolerated. Allenes containing heterocycles, including a pyridine (**3g**) and pyrazole (**3h**), were suitable substrates for the hydrocarboxylation reaction. However, when an allene substituted with an indole (**3i**) was utilized, better results were found if ligand **L3** was used in place of **L2**. We speculate that this is due to the sterically demanding environment of the substrate that requires the use of a less bulky ligand. Allenes containing functionalized primary alkyl groups (**3j**, **3l**–**m**) as well as an exocyclic allene (**3k**) were also accommodated in this protocol. Furthermore, 1-cyclohexyl-1-methylallene (**3n**) was efficiently transformed to the hydroxycarboxylation product when ligand **L3** was employed.

We were also interested in expanding this method toward the synthesis of α-tertiary esters, which under many conditions are difficult to access in high enantioselectivity due to the easily epimerizable stereogenic center. Thus, we next examined the reaction of a monosubstituted allene, phenylallene (**1o**), under our standard reaction conditions. However, the product ester was formed with a poor level of enantioselectivity, 69.5:30.5 er (Table S4). After reevaluating the reaction parameters, the carboxylation product **3o** could be isolated in 70% yield and 93:7 er using **L3** as ligand (Table 2). A thioether-containing 1-aryl allene (**1p**) and cyclohexylallene (**1q**) were also converted to the corresponding α-tertiary esters in good yields and high enantioselectivity.

To further demonstrate the synthetic utility of our method, we examined the transformation of the hydrocarboxylation products into compounds of interest (Scheme 1). For example, chiral α-tertiary amines are found in a variety of natural products and biologically active compounds, and are difficult to access in an enantioenriched form by standard hydroamination reactions.[25] By employing a Curtius Rearrangement, we were able to convert α-quaternary carboxylic acid **3a** to α-tertiary amine **6** in a stereoretentive fashion (Scheme 1a). Additionally, we sought to apply our hydrocarboxylation products to the synthesis of enantioenriched γ-amino acid derivatives, which play an important role as γ-aminobutyric acid transaminase inhibitors and in peptide chemistry.[26] Derivatization of the resulting vinyl group in **3d**, an α-quaternary γ-amino ester **8** could be accomplished using a CuH-catalyzed hydroamination reaction[27] (Scheme 1b). We also utilized the method for the preparation of the pharmaceutical indobufen, a platelet aggregation inhibitor marketed under brand name Ibustrin.[28] (*S*)-Indobufen, previously prepared by the separation of the racemic mixture,[29c] was found to be far more potent than the (*R*)-enantiomer in terms of its antiplatelet and anti-inflammatory activities,[29] and thus an enantioselective synthetic route to (*S*)-indobufen would be of interest. In our approach, CuH-catalyzed hydrocarboxylation of allene **1r** gave ester **3r**, which underwent subsequent hydrogenation and hydrolysis to furnish (*S*)-Indobufen (**10**) in 76% overall yield and 92:8 er, without the need for any chromatographic purification.

Scheme 1. Applications of the CuH-catalyzed Hydrocarboxylation Reactions[a]



[a]See the Supporting Information for experimental details. [b]**1r** (1.0 equiv) and **2d** (1.2 equiv) were used. [c]**2d** (1.0 equiv) and **1r** (1.2 equiv) were used.

Based on previous DFT calculations on CuH-catalyzed reactions involving allenes,[30] a plausible mechanism can be proposed for this transformation, as depicted in Figure 2. An allene (**1**) first undergoes hydrocupration with a CuH catalyst to generate a rapidly equilibrating mixture of allylcopper species (**B** and **C**). The less hindered terminal allylic copper (**B**) reacts preferentially with fluoroformate **2d** through an enantiodetermining six-membered transition state (**D**), to form intermediate **E**. Subsequent collapse of the tetrahedral intermediate by β-fluoride elimination leads to the branched carboxylation product **3** and CuF. A σ-bond metathesis reaction between CuF and the silane regenerates the CuH catalyst.

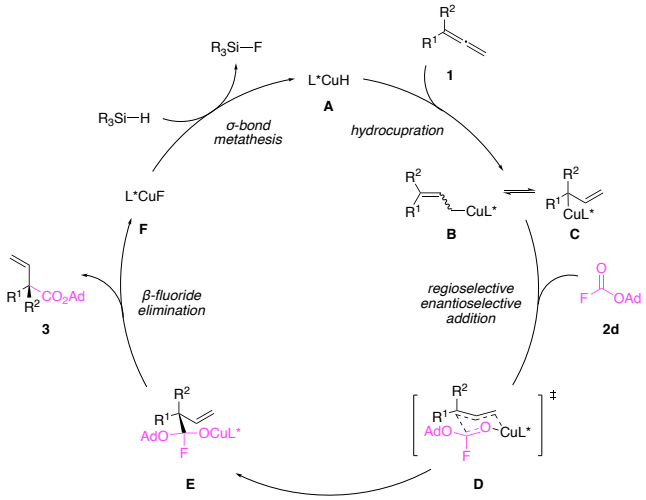


Figure 2. Proposed mechanism for the CuH-catalyzed hydrocarboxylation of allenes

In conclusion, we have developed a highly enantioselective CuH-catalyzed hydrocarboxylation to synthesize α-chiral carboxylic acids and esters, in particular α-quaternary ones. A commercially available fluoroformate was used as the carboxylation reagent to react with allenes in exclusive branched selectivity. The reaction proceeded under mild conditions and could tolerate a variety of important functional groups and heterocycles. Further derivatization of the carboxylation products provided other pharmaceutically and synthetically useful scaffolds. We anticipate that this carboxylation strategy using a fluoroformate may be extended to the discovery of other types of important asymmetric carboxylation processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data (PDF)

X-ray crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Research reported in this publication was supported by the National Institutes of Health under award number R35-GM122483. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Solvias AG is acknowledged for a generous gift of SL-J011-1. We thank Drs. Veronika Kottisch, Alexander Schuppe, and Christine Nguyen for their advice on the preparation of this manuscript. We acknowledge Dr. Peter Müller (MIT) for X-ray crystallographic analysis of **3a**. We thank the National Institutes of Health for a supplemental grant for the purchase of supercritical fluid chromatography (SFC) equipment (GM058160-17S1).

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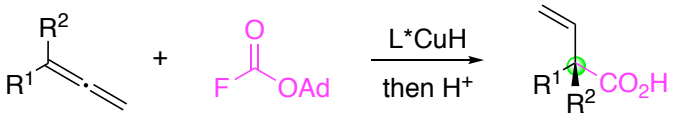

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