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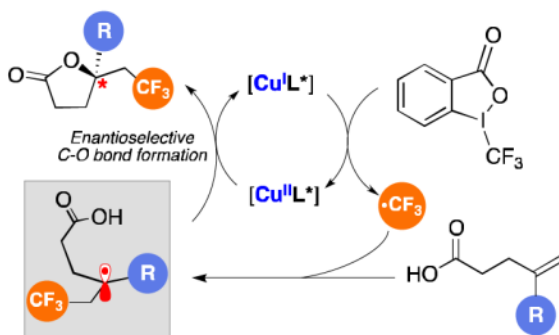
Enantioselective Functionalization of Radical Intermediates in Redox Catalysis: Copper-Catalyzed Asymmetric Oxytrifluoromethylation of Alkenes**

Rong Zhu and Prof. Dr. Stephen L. Buchwald

Department of Chemistry, Room 18-490, Massachusetts Institute of Technology, Cambridge, MA 02139 (USA)

Stephen L. Buchwald: sbuchwal@mit.edu

Abstract



A method for the efficient enantioselective oxytrifluoromethylation of alkenes has been developed using a copper catalyst system. Mechanistic studies are consistent with a metal-catalyzed redox radical addition mechanism, in which a C–O bond is formed via the copper-mediated enantioselective trapping of a prochiral alkyl radical intermediate derived from the initial trifluoromethyl radical addition.

Keywords

difunctionalization; radical; copper; asymmetric catalysis; trifluoromethylation

Transition metal-catalyzed alkene difunctionalization represents a versatile and step-economical strategy for the enhancement of molecular complexity, as it accesses multiple carbon–carbon/carbon–heteroatom bonds and stereogenic centers in a single step from simple precursors.^[1,2] One of the most synthetically important transformations of this class is the radical addition of alkenes catalyzed by a transition metal redox system.^[3] In a typical catalytic cycle (Scheme 1a), a metal-generated radical adds across the alkene to give nascent carbon radical intermediate **I**. Subsequent functionalization of **I** gives rise to **II** while regenerating the metal catalyst. Depending on the nature of the functional group used for

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Correspondence to: Stephen L. Buchwald, sbuchwal@mit.edu.

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trapping, a C–X (X = halogen), C–O, C–N or C–C bond can be incorporated.^[4] In contrast to numerous reports on reactions that afford racemic products, catalyst-controlled enantioselective functionalizations of **I**, interesting and potentially useful processes, have been rarely explored. The only disclosure is by Sonoda and Kamigata who reported the use of chiral rhodium and ruthenium complexes as catalysts for the atom transfer radical addition involving carbon–halogen bond formation affording products with 16% ee and 10–40% ee, respectively.^[5] Our interest in developing a transition metal-catalyzed asymmetric radical addition reaction via the enantioselective trapping of **I** originated from our recent study on the copper-catalyzed ligand-assisted oxytrifluoromethylation of alkenes.^[6] This method provides efficient access to a variety of CF₃-containing building blocks such as lactones, cyclic ethers and epoxides. A redox radical addition mechanism was proposed for this transformation, in which a C–O bond was formed via the copper-mediated trapping of an α -CF₃-alkyl radical species **III** derived from the addition of CF₃ radical (Scheme 1b).^[7]

During the course of our study, the use of a bidentate pyridine-based ligand was found to facilitate the C–O bond formation step. This ligand effect prompted us to explore the possibility of achieving asymmetric catalysis in this system by means of enantioselectively trapping the putative intermediate **III**. This strategy represents a mechanistically unique approach to enantioselective C–O bond formation via a radical intermediate. Given the wide range of difunctionalization reactions such radical intermediates can participate in and the lack of methods for exploiting their reactivity in enantioselective transformations, we believed that the study of this transformation could have a significant impact in the broader context of transition metal redox catalysis.

In this report, we disclose the realization of this strategy in the copper-catalyzed enantioselective oxytrifluoromethylation of alkenes. Mechanistic investigations are consistent with a metal-catalyzed redox radical addition mechanism, featuring the enantioselective functionalization of an alkyl radical intermediate.

We began our study by examining the reaction of 4-phenyl-4-pentenoic acid (**2a**) with Togni's reagent (**1**)^[8] in the presence of a catalytic amount of Cu(MeCN)₄PF₆ combined with a series of chiral ligands. The combination of Cu(MeCN)₄PF₆ and (*S,S*)-*t*BuBox (**L1**) in methyl *tert*-butyl ether (MTBE) at room temperature furnished the oxytrifluoromethylation product **3a** in 85% yield and 81% ee (Table 1, entry 1). The enantioselectivity showed a significant dependence on the solvent, following the trend: ethereal solvents > ethyl acetate > chloroalkane solvents > alcohol solvents > acetonitrile (entries 4–7). Next, the use of a cationic copper(I) precatalyst was found necessary for the desired reaction to take place. Copper(I) iodide was incapable of catalyzing the desired transformation, while the use of copper(I) chloride provided a substantial amount of **3a** with slight selectivity for the opposite enantiomer (entries 8 and 9).^[9] The reaction could not be catalyzed by a cationic copper(II) salt (entry 10).^[10] In addition, two Lewis acids were tested and **3a** was detected in neither of these cases (entries 11 and 12). This suggested the activation of **1** as an electrophile by means of Lewis acid coordination is not likely involved in the productive pathway.^[11]

We next explored the scope of the transformation and representative examples are shown in table 2. An array of unsaturated carboxylic acids bearing different aryl groups were found to undergo the desired transformation to give the corresponding trifluoromethylated lactones in good yields and useful enantiomeric excesses. The mild conditions were compatible with a number of functional groups including aryl halides (table 2, entries 2–4) and ketones (entry 6). An electron-deficient aryl substituent (entry 5) and a 3-thiophenyl substituent (entry 8) on the alkene were also tolerated. The incorporation of a geminal dimethyl group showed little effect on the yield or enantiomeric excess realized (entries 9 and 11). Incomplete

conversion of the starting material and a diminished yield of product was observed when the sterically demanding 1-naphthyl substituent was present, even though a good level of enantiomeric excess was still observed (entry 7). It was found that both γ - and δ -lactones (entries 10 and 11) were accessible under the standard conditions.^[12]

A series of experiments was performed to test our mechanistic hypothesis (Scheme 2a). When cyclopropane radical clock **4** was treated with **1** in the presence of the catalyst system, the oxytrifluoromethylation product **5** was not detected. Instead, a complex mixture of CF₃-containing products resulting from cyclopropane ring opening was observed, the largest component of which was identified to be **6**. Further, the use of diallyl malonate **7** as substrate provided two 5-*exo*-cyclization products, **8** and **9**.^[13] These observations are consistent with a mechanism involving an α -CF₃-alkyl radical intermediate **IV** (Scheme 1c). Next, the reaction between **1** and a radical scavenger TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) in the presence of the catalyst system afforded the trifluoromethyl-trapping adduct **10** in 45% yield (Scheme 2b).^[14]

A study of the reaction of trisubstituted alkene substrates provided further insight into the reaction mechanism. As shown in Scheme 3a, both geometric isomers of 5-phenyl-5-heptenoic acid (**2I**) were synthesized and subjected to the standard reaction conditions respectively. It was found that, regardless of the alkene geometry of the substrate, almost the same product diastereomeric ratio (**3I** : **3m** = 1:1.7), and same enantiomeric excess for each diastereomer (92–93% ee for **3I**, 58–59% ee for **3m**) were obtained. This observation excluded a Wacker-like oxycupration mechanism for the C–O bond formation process.^[15] Next, from these results we were able to calculate the ratio of the four stereoisomers **3I** : *ent*-**3I** : **3m** : *ent*-**3m** to be 36:1:50:13. In terms of the CF₃-bearing stereogenic center (C2'), the ratio between the products with a 2'*R* configuration (**3m** and *ent*-**3I**) and those with a 2'*S* configuration (**3I** and *ent*-**3m**) was essentially 1:1. This observation indicated a stepwise mechanism consist of (1) a non-stereoselective C–CF₃ bond-forming step and (2) a diastereoselective C–O bond-forming step, which explains the stereoisomer ratio obtained as illustrated below.

As shown in Scheme 3b, in the first radical addition step, either (*E*)- or (*Z*)-**2I** reacts with a trifluoromethyl radical to form a C–CF₃ bond in a non-stereoselective fashion, furnishing a pair of enantiomeric α -CF₃-alkyl radicals **V** and **VI** in a ratio close to 1:1. In the C–O bond-forming step, both the copper catalyst system and the already established stereogenic center at the 2' position come into play, providing matched/mismatched scenarios. For **V**, the catalyst-controlled selectivity (6*R* over 6*S*) contradicts the substrate-controlled selectivity (6*S*, 2'*S* over 6*R*, 2'*S*), therefore affording a diminished selectivity (36:13) for the catalyst-controlled product **3I**. For its enantiomer **VI**, the catalyst-controlled selectivity (6*R* over 6*S*) is reinforced by the substrate-controlled selectivity (6*R*, 2'*R* over 6*S*, 2'*R*), leading to an enhanced selectivity (50:1) for **3m**.

A catalytic cycle consistent with the mechanistic study discussed above is proposed (Scheme 4). A single-electron-transfer between **1** and the Cu(I) catalyst generates a CF₃ radical and a Cu(II) complex. The CF₃ radical then adds across the alkene to give **IV**, which undergoes enantioselective C–O bond formation mediated by the Cu(II) species, affording the lactone product while regenerating the Cu(I) catalyst.^[16]

In conclusion, we have developed a simple and mild method for the efficient enantioselective oxytrifluoromethylation of alkenes using a copper-based catalyst system. This method delivers a set of enantioenriched CF₃-containing lactones with good functional group compatibility. Evidence was found in support of a redox radical addition mechanism, in which a C–O bond is enantioselectively formed via a carbon radical intermediate. This

method provides a novel approach to enantioselective C–O bond formation that can potentially be applied to a range of transition metal-catalyzed radical difunctionalization reactions. We are continuing work to expand the scope of this copper-catalyzed enantioselective difunctionalization strategy.

Experimental Section

An oven-dried 25 test tube equipped with a Teflon-coated magnetic stir bar was charged with tetrakis(acetonitrile)copper(I) hexafluorophosphate (14 mg, 0.0375 mmol, 0.075 equiv), 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (11 mg, 0.0375 mmol, 0.075 equiv.), 1-trifluoromethyl-1,2-benziodoxol-3-(*IH*)-one **1** (Togni's reagent, 158 mg, 0.50 mmol, 1.0 equiv) and unsaturated carboxylic acid (0.50 mmol, 1.0 equiv). The tube was sealed with a Teflon screw-cap-septum. The vessel was then briefly evacuated and backfilled with argon (this sequence was repeated a total of three times). Anhydrous methyl *tert*-butyl ether (10 mL) was added to the tube via syringe to afford a blue mixture. The reaction mixture was stirred at room temperature (25 °C) for 16 h. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (12 mL). The aqueous layer was separated and extracted with diethyl ether (4 mL×3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (EtOAc/hexane or Et₂O/hexane) to afford the oxytrifluoromethylation product.

Supplementary Material

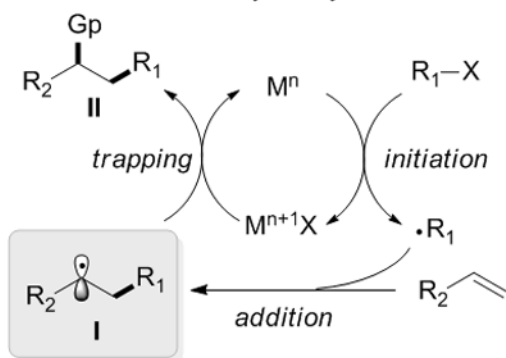
Refer to Web version on PubMed Central for supplementary material.

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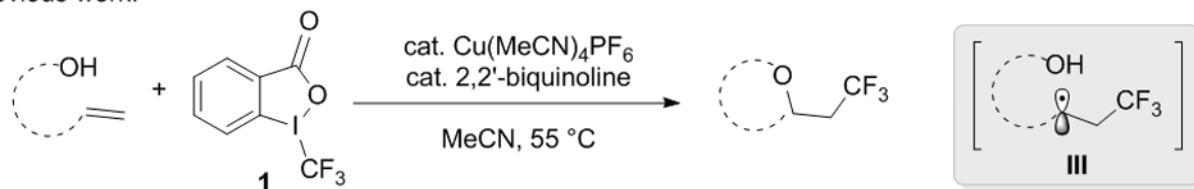
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9. Using other cationic copper(I) precatalysts, such as (CuOTf)₂•C₆H₆ or CuCl + AgBF₄, gave similar results as in Table 1, entry 1. Cu(MeCN)₄PF₆ was preferred because of its relative air- and moisture-insensitivity that allows for easy bench-top set-up.
10. Recent representative examples of Cu-catalyzed transformations involving arylodonium salts: Cahard E, Bremeyer N, Gaunt MJ. *Angew Chem Int Ed.* 2013; 52:9284. Phipps RJ, McMurray L, Ritter S, Duong HA, Gaunt MJ. *J Am Chem Soc.* 2012; 134:10773. [PubMed: 22712572] Zhu S, MacMillan DWC. *J Am Chem Soc.* 2012; 134:10815. [PubMed: 22716914] Kieffer ME, Chuang KV, Reisman SE. *J Am Chem Soc.* 2013; 135:5557. [PubMed: 23540731]
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12. a) The reactions of substrates containing 1,1-dialkylsubstituted alkene groups in place of styrene derivatives gave good yields (50%–90%) and low ee's (15%–40%). b) In preliminary experiments, substrates containing an alcohol group in place of the carboxylic acid group did not undergo the similar oxytrifluoromethylation reaction. c) In preliminary experiments, the intermolecular oxytrifluoromethylation of simple styrene derivatives gave low ee's (around 10%).
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16. The details of this enantioselective C–O bond formation step are unclear at this point. Three possible scenarios have been proposed: a) single-electron-oxidation of **III** to the corresponding carbocation by the Cu(II) complex, followed by nucleophilic trapping; b) single-electron-oxidation of **III** by the Cu(II) complex and nucleophilic trapping occurring simultaneously in a concerted transition state; c) recombination of **III** and the Cu(II) complex to afford an alkyl Cu(III) complex, which reductively eliminates to give the C–O bond.

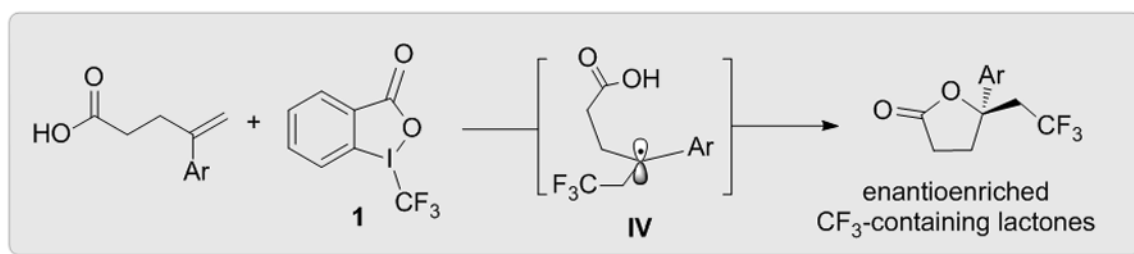
(a) Radical addition catalyzed by a transition metal redox system

*f* broad scope*f* versatility*f* simple starting material*f* valuable products**enantioselective transformation: rarely explored**

(b) Previous work:

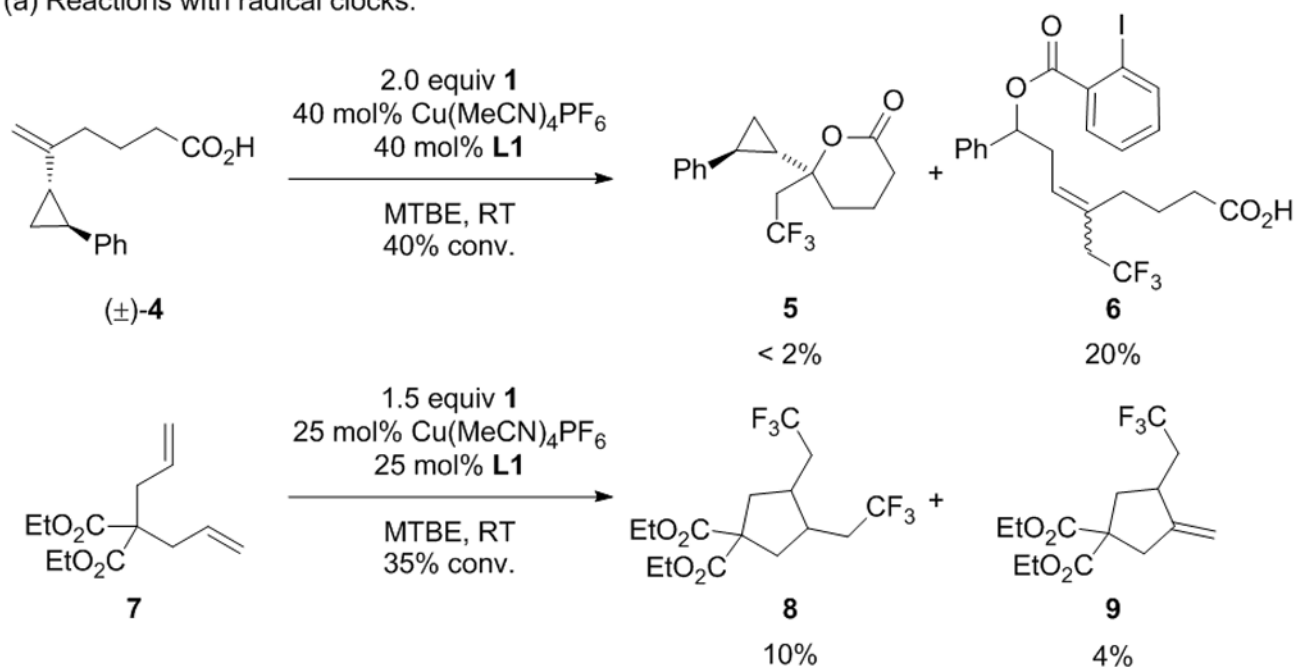


(c) This work: enantioselective radical addition catalyzed by a Cu(I) redox system - oxytrifluoromethylation

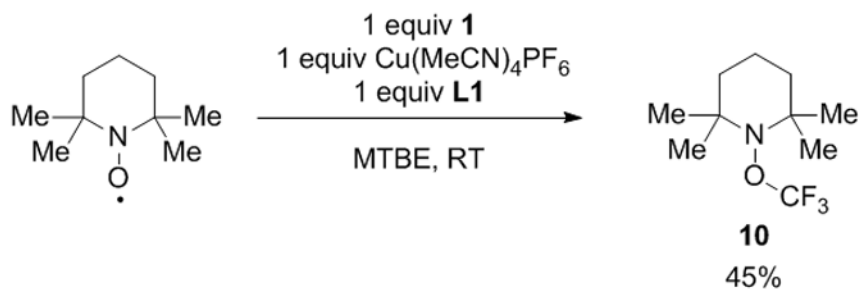


Scheme 1.
Background of the methodology development.

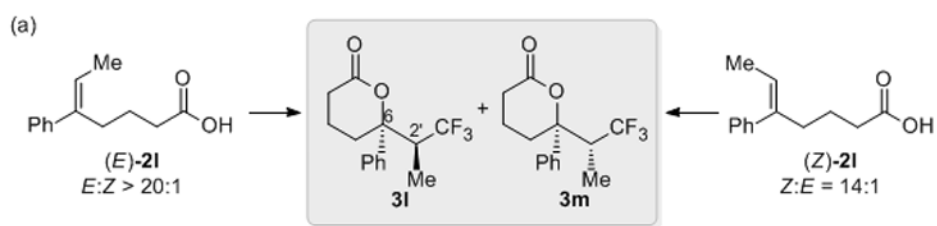
(a) Reactions with radical clocks:



(b) Trapping with TEMPO:

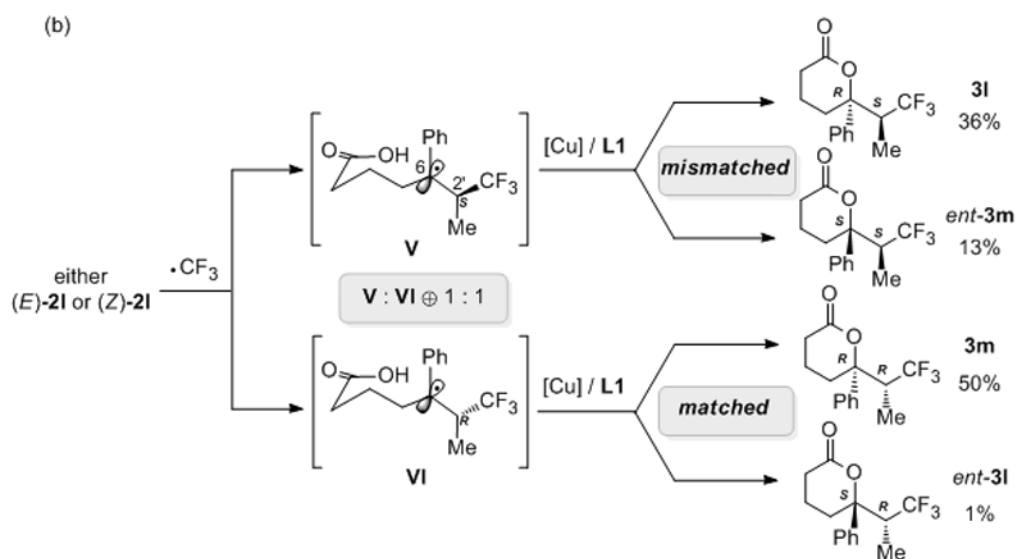
**Scheme 2.**

(a) Radical clock experiments. (b) TEMPO trapping experiment.



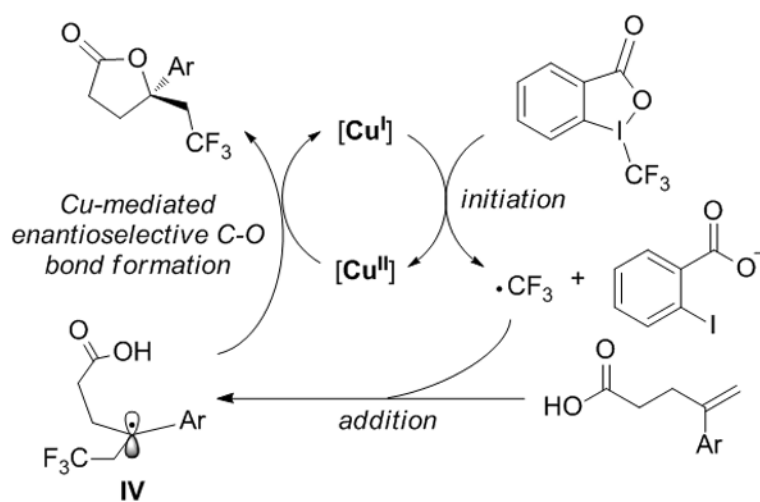
substrate	3I		3m		d.r. ^[b]	ratio of stereoisomers 3I : ent-3I : 3m : ent-3m
	yield [%] ^[b]	ee [%] ^[c]	yield [%] ^[b]	ee [%] ^[c]		
(E)-2I	28	93	47	58	1 : 1.7	36.3 : 1.3 : 49.3 : 13.1
(Z)-2I	24	92	40	59	1 : 1.7	35.7 : 1.5 : 49.8 : 13.0

[a] Reaction conditions: 1.2 equiv **1**, 10 mol% Cu(MeCN)₄PF₆, 10 mol% **L1**, MTBE, RT, 22 h. [b] Determined by ¹⁹F NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis.



Scheme 3.

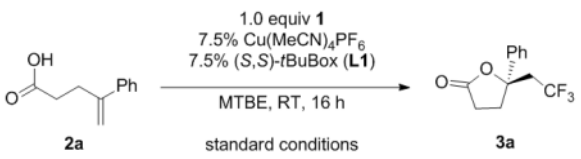
(a) Trisubstituted alkenes as mechanistic probes.^[a] (b) Rationale for the product distribution observed.



Scheme 4.
Mechanistic proposal.

Table 1

Effect of reaction parameters on the copper-catalyzed enantioselective oxytrifluoromethylation.



Entry	change from standard conditions	Yield [%] ^[a]	ee [%] ^[b]
1	none	85	81
2	L2 instead of L1	< 2	n.d.
3	L3 instead of L1	< 2	n.d.
4	EtOAc instead of MTBE	82	71
5	CH ₂ Cl ₂ instead of MTBE	84	62
6	MeOH instead of MTBE	57	36
7	CH ₃ CN instead of MTBE	80	4
8	CuI instead of Cu(MeCN) ₄ PF ₆	< 2	n.d.
9	CuCl instead of Cu(MeCN) ₄ PF ₆	66	-21
10	Cu(OTf) ₂ instead of Cu(MeCN) ₄ PF ₆	< 2	n.d.
11	Zn(OTf) ₂ instead of Cu(MeCN) ₄ PF ₆	< 2	n.d.
12	Sc(OTf) ₃ instead of Cu(MeCN) ₄ PF ₆	< 2	n.d.

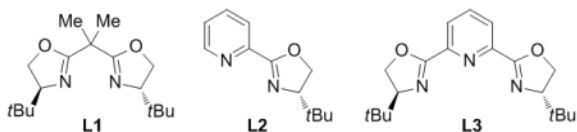
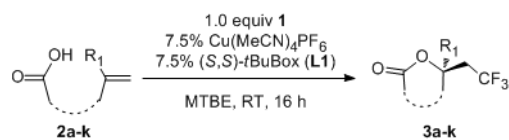
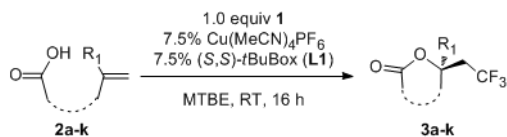
^[a]Determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard.^[b]Determined by chiral HPLC analysis.

Table 2

Copper-Catalyzed enantioselective oxytrifluoromethylation.^[a]

Entry	Substrate	Product	Yield [%] ^[b]	ee [%] ^[c]
1	R = H 2a	3a	88	82
2	R = Br 2b	3b	78	83
3	R = Cl 2c	3c	81	81
4	R = F 2d	3d	80	75
5	R = CF ₃ 2e	3e	74	81
6			78 (70) ^[d]	83 (98) ^[d]
7			44	81
8			87	74
9			72	80
10			85	81



Entry	Substrate	Product	Yield [%] ^[b]	ee [%] ^[c]
11	<p style="text-align: center;">2k</p>	<p style="text-align: center;">3k</p>	85	83

^[a] Reaction conditions: Cu(MeCN)₄PF₆ (7.5 mol %), **L1** (7.5 mol %), **1** (1.0 equiv), **2** (0.50 mmol, 1.0 equiv) in 10 mL MTBE at 25 °C for 16 h.

^[b] Isolated yields, average of two runs.

^[c] Determined by chiral HPLC analysis.

^[d] The product crystallized from the crude reaction mixture after work-up. For details see the supporting information.