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VIP Synthetic Methods Very Important Paper

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

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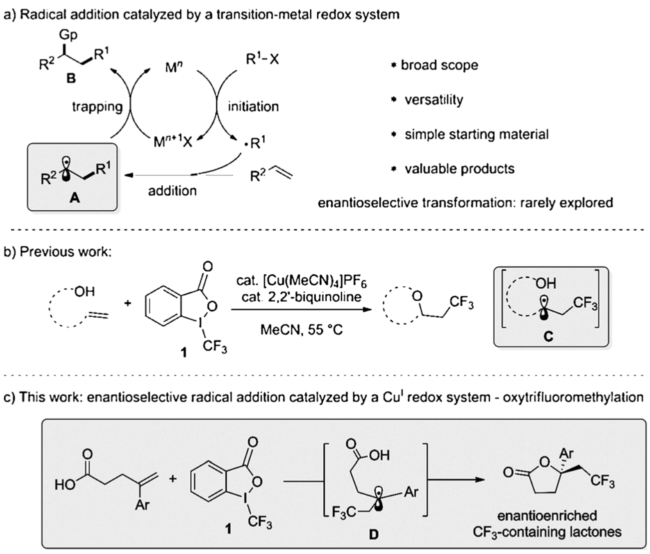
Transition-metal-catalyzed alkene difunctionalization represents a versatile and step-economical strategy for the enhancement of molecular complexity, as it accesses multiple carbon–carbon/carbon–heteroatom bonds and stereogenic centers in a single step from simple precursors.[1,2] One of the most synthetically 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 1 a), a metal-generated radical adds across the alkene to give the nascent carbon radical intermediate **A**. Subsequent functionalization of **A** gives rise to **B** while regenerating the metal catalyst. Depending on the nature of the functional group used for 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 **A**, interesting and potentially useful processes, have been rarely explored. The only disclosure is by Sonoda and co-workers and Kamigata and co-workers who reported the use of chiral rhodium and ruthenium complexes as catalysts for the atom-transfer radical addition involving carbon–halogen bond formation to afford products with 16 % *ee* and 10–40 % *ee*, respectively.[5] Our interest in developing a transition-metal-catalyzed asymmetric radical addition reaction by the enantioselective trapping of **A** originated from our recent study on the copper-catalyzed ligand-assisted oxytrifluoromethylation of alkenes.[6] This method provides efficient access to a variety of CF_3-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 by the copper-mediated trapping of the α-CF_3-alkyl radical species **C**, which is derived from the addition of CF_3 radical (Scheme 1 b).[7]



Scheme 1. Background of the methodology development.

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 **C**. 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.

Herein, we disclose the realization of this strategy in the copper-catalyzed enantioselective oxytrifluoromethylation of alkenes (Scheme 1 c). 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 $[Cu(MeCN)_4]PF_6$ combined with a series of chiral ligands. The combination of $[Cu(MeCN)_4]PF_6$ 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

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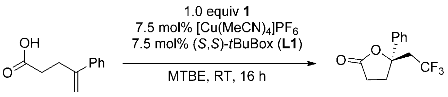
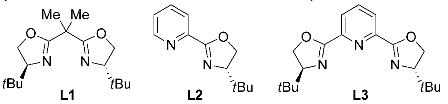
Table 1: Effect of reaction parameters on the copper-catalyzed enantioselective oxytrifluoromethylation.



2a standard conditions 3a

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_2Cl_2 instead of MTBE	84	62
6	MeOH instead of MTBE	57	36
7	CH_3CN 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 ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b] Determined by HPLC analysis using a chiral stationary phase. Tf = trifluoromethanesulfonyl.



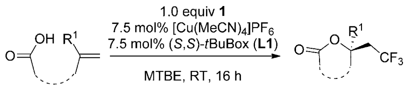
L1 L2 L3

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 result suggested the activation of **1** as an electrophile by means of Lewis acid coordination is not likely involved in the productive pathway.[11]

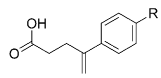
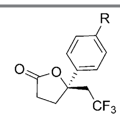
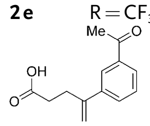
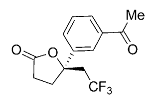
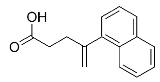
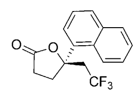
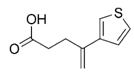
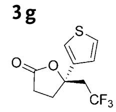
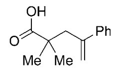
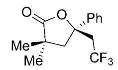
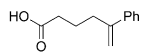
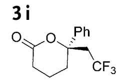
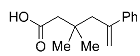
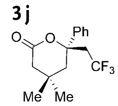
We next explored the scope of the transformation and representative examples are shown in Table 2. An array of unsaturated carboxylic acids bearing different aryl groups were found to undergo the desired transformation to give the corresponding trifluoromethylated lactones in good yields and useful enantiomeric excesses. The mild reaction 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 reaction conditions.[12]

A series of experiments was performed to test our mechanistic hypothesis (Scheme 2a). When the cyclopropane radical clock (±)-**4** was treated with **1** in the presence of the

Table 2: Copper-Catalyzed enantioselective oxytrifluoromethylation.[a]



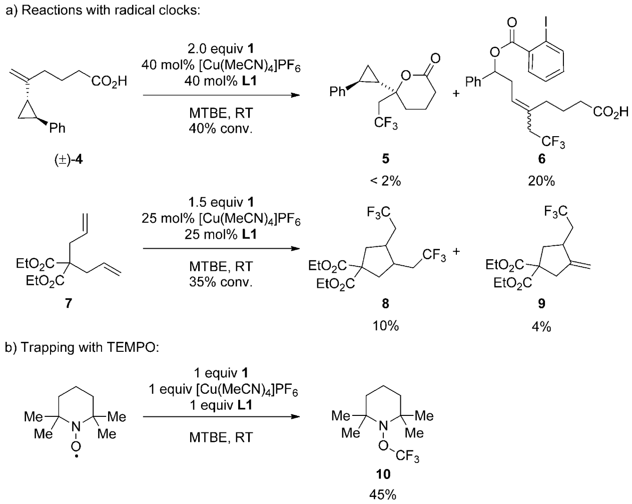
2a–k 3a–k

Entry	Substrate		Product	Yield [%][b]	*ee* [%][c]
					
1	**2a**	R = H	**3a**	88	82
2	**2b**	R = Br	**3b**	78	83
3	**2c**	R = Cl	**3c**	81	81
4	**2d**	R = F	**3d**	80	75
5	**2e**	R = CF_3	**3e**	74	81
					
6	**2f**		**3f**	78 (70)[d]	83 (98)[d]
					
7	**2g**		**3g**	44	81
					
8	**2h**		**3h**	87	74
					
9	**2i**		**3i**	72	80
					
10	**2j**		**3j**	85	81
					
11	**2k**		**3k**	85	83

[a] Reaction conditions: $[Cu(MeCN)_4]PF_6$ (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] Yields of isolated products are an average of two runs. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The product crystallized from the crude reaction mixture after work-up. For details see the Supporting Information.

catalyst system, the oxytrifluoromethylation product **5** was not detected. Instead, a complex mixture of CF_3-containing products resulting from cyclopropane ring opening was observed, the largest component of which was identified to be **6**. Further, the use of the 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-CF_3 alkyl radical intermediate (**D**; Scheme 1c). Next, the reaction between **1** and the 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 (**2l**) were synthesized and subjected to the



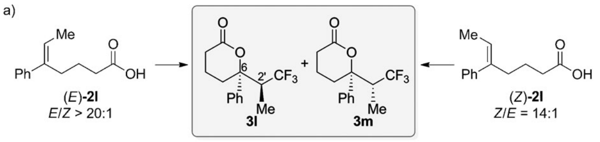
Scheme 2. a) Radical clock experiments. b) TEMPO trapping experiment.

standard reaction conditions. It was found that, regardless of the alkene geometry of the substrate, almost the same product diastereomeric ratio (**3l**/**3m** = 1:1.7), and same enantiomeric excess for each diastereomer (92 and 93 % *ee* for **3l**, 58 and 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 **3l**/*ent*-**3l**/**3m**/*ent*-**3m** to be 36:1:50:13. In terms of the CF_3-bearing stereogenic center (C2′), the ratio between the products with a 2′*R* configuration (**3m** and *ent*-**3l**) and those with a 2′*S* configuration (**3l** and *ent*-**3m**) were essentially 1:1. This observation indicated a stepwise mechanism consisting of 1) a nonstereoselective C–CF_3 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 3 b, in the first radical addition step, either (*E*)- or (*Z*)-**2l** reacts with a trifluoromethyl radical to form a C–CF_3 bond in a nonstereoselective fashion, thus furnishing a pair of enantiomeric α-CF_3-alkyl radicals **E** and **F** 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, thus providing matched/mismatched scenarios. For **E**, 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 **3l**. For its enantiomer **F**, 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*), thus leading to an enhanced selectivity (50:1) for **3m**.

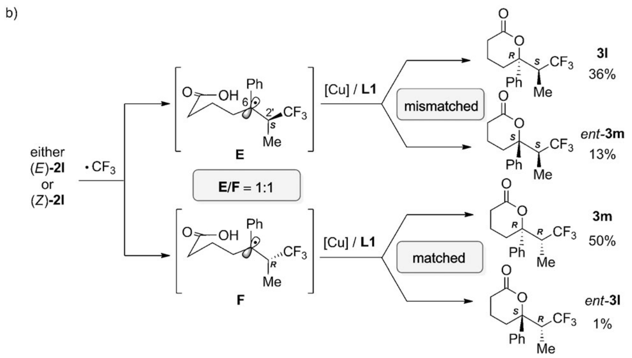
A catalytic cycle consistent with the mechanistic study discussed above is proposed (Scheme 4). A single-electron transfer between **1** and the Cu^I catalyst generates a CF_3 radical and a Cu^{II} complex. The CF_3 radical then adds across the alkene to give **D**, which undergoes enantioselective C–O bond formation mediated by the Cu^{II} species, thus affording the lactone product while regenerating the Cu^I catalyst.[16]

a)

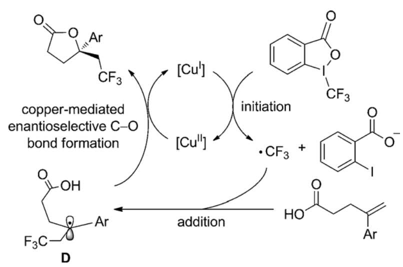


Substrate	3l Yield [%][a]	3l *ee* [%][b]	3m Yield [%][a]	3m *ee* [%][b]	d.r.[a]	Ratio of stereoisomers 3l / *ent*-3l / 3m / *ent*-3m
(*E*)-2l	28	93	47	58	1 : 1.7	36.3 : 1.3 : 49.3 : 13.1
(*Z*)-2l	24	92	40	59	1 : 1.7	35.7 : 1.5 : 49.8 : 13.0

b)



Scheme 3. a) Trisubstituted alkenes as mechanistic probes.[a] Reaction conditions: 1.2 equiv **1**, 10 mol% $[Cu(MeCN)_4]PF_6$, 10 mol% **L1**, MTBE, RT, 22 h. [a] Determined by ^{19}F NMR analysis of the crude reaction mixture. [b] Determined by HPLC analysis. b) Rationale for the product distribution observed.



Scheme 4. Mechanistic proposal.

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 CF_3-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 which 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 mL 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-(1*H*)-one **1** (Togni's reagent, 158 mg, 0.50 mmol, 1.0 equiv), and an 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 by 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/hexanes or Et_2O/hexanes) to afford the oxytrifluoromethylation product.

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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* values (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* values (around 10%).

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