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Versatile Enantioselective Synthesis of Functionalized Lactones via Copper-Catalyzed Radical Oxyfunctionalization of Alkenes

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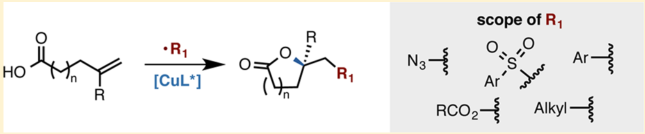
Supporting Information

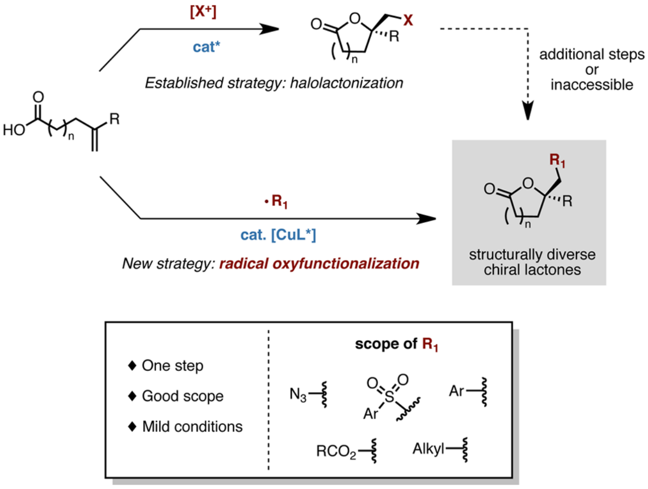
ABSTRACT: A versatile method for the rapid synthesis of diverse enantiomerically enriched lactones has been developed based on Cu-catalyzed enantioselective radical oxyfunctionalization of alkenes. The scope of this strategy encompasses a series of enantioselective difunctionalization reactions: oxyazidation, oxysulfonylation, oxyarylation, diacyloxylation, and oxyalkylation. These reactions provide straightforward access to a wide range of useful chiral lactone building blocks containing tetrasubstituted stereogenic centers, which are hard to access traditionally.



INTRODUCTION

Chiral γ- and δ-lactones are valuable compounds that are not only found in a large number of biologically active natural and unnatural molecules but also serve as versatile synthetic intermediates en route to many related architectures such as chiral tetrahydrofuran, tetrahydropyran, and hydroxycarboxylic acid derivatives.[1] Among the numerous efforts toward efficient catalytic asymmetric syntheses of γ- and δ-lactones from achiral precursors, the direct cyclization of unsaturated carboxylic acids in the presence of an electrophile is an attractive approach due to the ready availability of the starting materials and the simultaneous incorporation of a second useful functional group.[2,3] In particular, elegant solutions have been recently devised for enantioselective halolactonization reactions, delivering halogenated γ- and δ-lactones in high yields with good enantioselectivity.[4,5] However, successful examples of enantioselective lactonization are thus far largely limited to the use of electrophilic halogen electrophiles. While chiral halolactones themselves are certainly useful, subsequent steps are required to convert the alkyl halides in these compounds into a more diverse array of functional groups. Moreover, many useful functional groups, such as an aryl group, are difficult to access from the alkyl halides generated using this approach. In order to access a broader scope of structurally diverse chiral lactones in a step-economical and versatile fashion, a new strategy allowing the use of other electrophiles is required (Scheme 1).

Scheme 1. Catalytic Enantioselective Synthesis of Functionalized Lactones from Alkenes



We envisioned a new synthesis of chiral lactones incorporating the features discussed above based on a strategy that we recently established during the investigation of the copper-catalyzed enantioselective oxytrifluoromethylation reaction.[6] We found that the tandem CF_3 radical addition/enantioselective C−O bond forming lactonization of unsaturated carboxylic acid substrates could be achieved efficiently in one step. Given the intrinsic versatility associated with the stepwise nature of this radical addition/interception mechanism, we were interested in applying this strategy to the use of a broad range of other radical species for enantioselective lactonization reactions, which would afford products that require multiple synthetic steps or are hard to access traditionally.

A simplified generic catalytic cycle proposed is depicted in Scheme 2. Initial reaction between the Cu(I) catalyst and the radical source R_1−X (**1**) would generate a Cu(II) species and a radical $^{\bullet}R_1$. This radical would then add to the alkene substrate **2**, affording a tertiary alkyl radical intermediate **I**. Finally, the enantioselective C−O bond forming process of **I** mediated by the Cu(II) complex would furnish the lactone product **3** and regenerate the Cu(I) species. Herein, we report a series of copper-catalyzed enantioselective lactonization reactions enabled by the radical oxyfunctionalization of alkenes, including oxyazidation (R_1 = N_3−), oxysulfonylation (R_1 = $ArSO_2$−),

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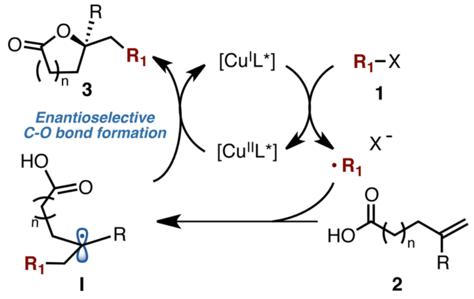
Scheme 2. Proposed Generic Catalytic Cycle



oxyarylation (R_1 = Ar−), diacyloxylation (R_1 = RCO_2−), and oxyalkylation (R_1 = alkyl). Some mechanistic features of this type of reactions are also discussed in the last part.

■ RESULTS AND DISCUSSION

Reaction Scope. We first applied this general strategy to the catalytic enantioselective alkene oxyazidation reaction (R_1 = N_3) that would give rise to chiral azidolactones.[7,8] This transformation would yield a straightforward yet rarely explored approach to enantiomerically enriched 1,2-aminoalcohol derivatives, which are useful synthetic building blocks and are found in many biologically relevant compounds.[9] To evaluate the proposed transformation, a combination of two simple commercially available reagents, (diacetoxyiodo)benzene as the oxidant and trimethylsilyl azide as the azidyl radical precursor (eq 1) is used to react with 4-phenyl-4-pentenoic acid (**2a**).[10] It

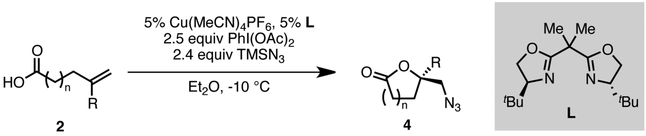
$$PhI(OAc)_2 + TMSN_3 \xrightarrow{Cu(I) \curvearrowright Cu(II)} PhI + TMSOAc + AcO^- + \cdot N_3 \qquad (1)$$

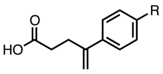
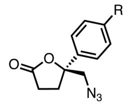
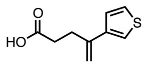
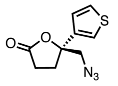
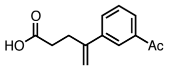
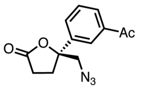
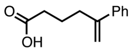
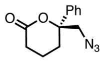
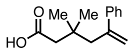
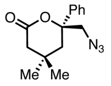
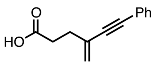
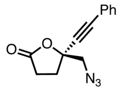
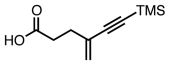
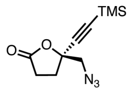
was found that in the presence of a catalytic amount of $Cu(MeCN)_4PF_6$ and (*S*,*S*)-^{t}BuBox (**L**), the desired oxyazidation product **4a** could be obtained in 63% yield and 89% ee (Table 1, entry 1). The use of preformed azidoiodine(III) reagents did not yield a detectable amount of desired product.[11]

We next explored the scope of this transformation, and representative examples are summarized in Table 1. A series of unsaturated carboxylic acids bearing different aryl substituents on the alkene were found to undergo the desired oxyazidation reaction to afford the corresponding azidolactones in good enantioselectivity (**4a**−**j**). Electron-neutral and -deficient aryl substituents were well tolerated (**4a**−**e**), while slightly lower enantioselectivity was observed with substrates containing a very electron-rich *p*-methoxyphenyl substituent (**4f**). The mild reaction conditions were compatible with a range of functional groups including aryl halides (**4b**, **4c**), nitriles (**4d**), ketones (**4h**), and 3-thiophenyl groups (**4g**). In addition, both *γ*- and *δ*-lactones (**4i**, **4j**) proved accessible under the standard reaction conditions. The incorporation of a geminal dimethyl group in the substrate showed little effect on the enantioselectivity obtained.

We next sought to apply this protocol to substrates without a styrenyl unit (**2k** and **2l**). Substrates containing a 1,3-enyne structure are especially interesting because further transformation of the alkyne group in the product would give access to a more diverse class of structures. It was found that the oxyazidation of these substrates proceeded smoothly to furnish the enantiomerically enriched lactone product in moderate yields and moderate to good enantiomeric excesses (**4k**, **4l**). Notably, a silyl protecting group on the alkyne was tolerated, which allows for further elaboration of the product (**4l**).[12]

Table 1. Cu-Catalyzed Enantioselective Alkene Oxyazidation[a]

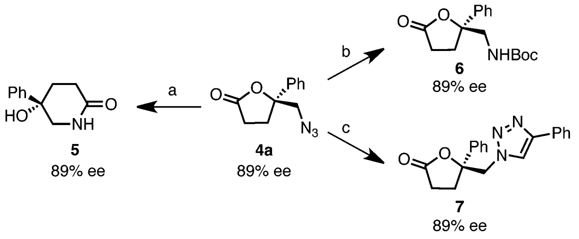


Entry	Substrate		Product	Yield [%][b]	ee [%][c]
					
1	R = H	2a	4a	63	89
2	R = Br	2b	4b	55	89
3	R = Cl	2c	4c	56	89
4	R = CN	2d	4d	50	90
5[e]	R = CF_3	2e	4e	46	91
6	R = OMe	2f	4f	68	75
7[d]	 2g		 4g	69	82
8[e]	 2h		 4h	53	90
9	 2i		 4i	62	89
10	 2j		 4j	68	92
11[e]	 2k		 4k	50	72
12[e,f]	 2l		 4l	44	82

[a] Reaction conditions: $Cu(MeCN)_4PF_6$ (5 mol %), **L** (5 mol %), **2** (0.50 mmol, 1.0 equiv), $PhI(OAc)_2$ (2.5 equiv), $TMSN_3$ (2.4 equiv), in 30 mL of Et_2O at −10 °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] Additional 2,6-di-*tert*-butylpyridine (1.1 equiv) was added. [e] $Cu(MeCN)_4PF_6$ (8 mol %) and **L** (8 mol %) was used. [f] The enantiomeric excess was determined by HPLC analysis of the derivatized product, see the Supporting Information.

The azide group in the lactone product can be easily converted to a number of useful nitrogen-containing functional groups in good yields (Scheme 3). For example, palladium-

Scheme 3. Derivatization of the Oxyazidation Product 4a[a]

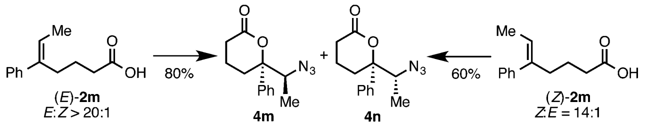


[a]Reaction conditions: (a) Pd/C, H_2 (balloon), MeOH, RT; then DMAP (10 mol %), RT, 78%; (b) Pd/C, H_2 (balloon), Boc_2O, THF, RT, 88%; (c) sodium ascorbate (0.8 equiv), $CuSO_4{\cdot}5H_2O$ (0.4 equiv), phenylacetylene (1.1 equiv), ${}^tBuOH/H_2O$, RT, 96%.

catalyzed hydrogenation of lactone **4a** in methanol afforded chiral tertiary alcohol-containing *δ*-lactam **5** via an azide reduction/translactamization cascade. Conversely, hydrogenation of **4a** in the presence of di-*tert*-butyl dicarbonate furnished the Boc-protected aminolactone **6**. The azide group could also undergo [3 + 2] cycloaddition with phenylacetylene to give a triazole derivative **7**. No erosion of enantiomeric excess was observed in any of these cases.

To provide further evidence for our mechanistic hypothesis, oxyazidation reactions with trisubstituted alkene substrates were examined. As shown in Scheme 4, both geometric isomers of 5-phenyl-5-heptenoic acid ((*E*)- and (*Z*)-**2m**) were synthesized and subjected to the standard reaction conditions. It was found that, regardless of the alkene geometry of the substrate (*E* or *Z*), the same product diastereomeric ratio (**4m**/**4n** = 10:1) and same enantiomeric excess for each diastereomer were obtained (**4m**, 11% and 12% ee; **4n**, 93% and 93% ee). This observation was consistent with the radical addition type mechanism proposed in Scheme 2.[6a,13]

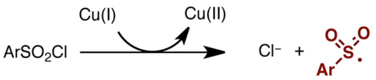
Scheme 4. Cu-Catalyzed Oxyazidation of Trisubstituted Alkenes[a]



substrate	d.r.[b]	4m ee [%][b]	4n ee [%][b]	ratio of stereoisomers 4m : *ent*-4m : 4n : *ent*-4n
(*E*)-2m	10 : 1	12	93	51.1 : 40.0 : 8.6 : 0.3
(*Z*)-2m	10 : 1	11	93	50.6 : 40.3 : 8.8 : 0.3

[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol %), **L** (10 mol %), **2m** (0.10 mmol, 1.0 equiv), $PhI(OAc)_2$ (2.5 equiv), $TMSN_3$ (2.4 equiv), in 6 mL of Et_2O at −10 °C for 16 h. [b]Determined by HPLC analysis using a chiral stationary phase.

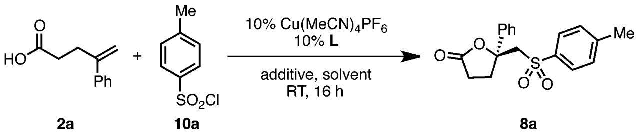
With these results in hand, the copper-catalyzed enantioselective oxysulfonylation involving the addition of a sulfonyl radical was next examined.[14] This transformation would furnish enantiomerically enriched *β*-hydroxyl sulfone derivatives, which are found in many biologically relevant molecules.[15] Compounds containing this structure are also frequently used as intermediates in the synthesis of a variety of natural products.[16] Traditional means of preparation of chiral *β*-hydroxysulfones typically involves the asymmetric reduction of *β*-ketosulfones,[17] which does not provide access to *β*-sulfonyl tertiary alcohol derivatives. We hypothesized that these could be accessed via our enantioselective oxyfunctionalization strategy in combination with the generation of a sulfonyl radical from arylsulfonyl chlorides (eq 2).[18]



(2)

To test this hypothesis, we studied the reaction of **2a** with tosyl chloride (**10a**) in the presence of Cu(I) catalyst and **L** (Table 2). Our initial attempt, carried out in ethyl acetate, provided the oxysulfonylation product **8a** in 12% yield and 28% ee (entry 1). It was found that the yield of **8a** could be improved by the addition of a base to neutralize the HCl generated during the reaction (entry 2). We reasoned that the enantioselectivity might be adversely affected by the chloride ion generated from the reduction of tosyl chloride. Based on this hypothesis, the reaction was carried out in the presence of silver acetate as both an acid and a chloride scavenger, and a significant increase in yield and enantioselectivity was observed (entry 3). After evaluation of a series of silver salts, the use of silver carbonate was determined to provide the optimal results, leading to an excellent yield of the desired product with over 70% ee (entry 4). The use of methyl *tert*-butyl ether or ethyl ether as the solvent was found to provide inferior results compared with that when ethyl acetate was utilized with regard to both the yield and enantioselectivity (entry 5 and 6).

Table 2. Selected Optimizations for the Cu-Catalyzed Enantioselective Alkene Oxysulfonylation[a]



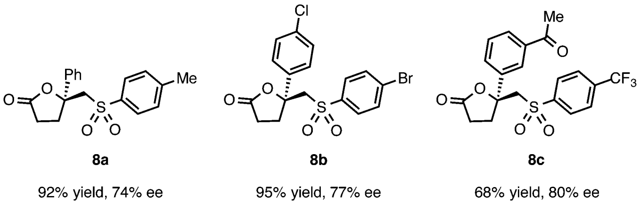
entry	base	solvent	yield [%][b]	ee [%][c]
1	None	EtOAc	12	28
2	NaOAc (1.1 equiv)	EtOAc	37	18
3	AgOAc (1.1 equiv)	EtOAc	62	74
4	Ag_2CO_3 (0.55 equiv)	EtOAc	95	74
5	Ag_2CO_3 (0.55 equiv)	MTBE	31	66
6	Ag_2CO_3 (0.55 equiv)	Et_2O	48	38

[a]Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol %), **L** (10 mol %), **2a** (0.10 mmol, 1.0 equiv), tosyl chloride (1.1 equiv), base (*x* equiv), in 2 mL of solvent at RT for 16 h. [b]The yields were determined by ^1H NMR spectroscopic analysis using a internal standard. [c]The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

Representative examples of the enantioselective oxysulfonylation process are shown in Scheme 5. In general, this method delivers enantiomerically enriched sulfonyl-substituted lactones in good to high yields and good enantioselectivity. The ready availability of arylsulfonyl chlorides allows quick access to chiral building blocks containing a diverse array of arylsulfonyl groups using this method.

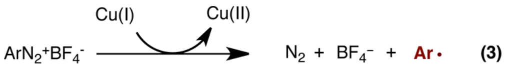
Next, we sought to expand the scope of this method further to include not only C−heteroatom but also C−C bond formation, such as C−aromatic carbon bond formation. Transition metal-catalyzed processes to effect this transformation have been the subject of intense study, due to their potential applications in synthetic chemistry.[19] To date, however, limited success has been achieved on the development of an enantioselective version of this type of transformation.[20]

Scheme 5. Examples of the Cu-Catalyzed Enantioselective Oxysulfonylation[a]



[a] Reaction conditions: Cu(MeCN)$_4$PF$_6$ (10 mol %), **L** (10 mol %), **2** (0.50 mmol, 1.0 equiv), arylsulfonyl chloride (1.1 equiv), silver carbonate (0.60 equiv), in 8 mL of ethyl acetate at RT for 16 h. Yields are of isolated products (average of two runs). The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

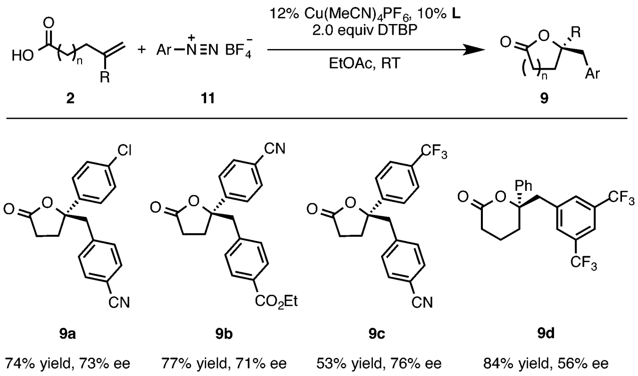
We felt that the merger of our copper-catalyzed strategy and the classic Meerwein arylation conditions using aryl diazonium salts (eq 3) would be a viable means to develop an enantioselective process.[21,19d,e]



$$\mathrm{ArN_2{}^+BF_4{}^-} \xrightarrow{\mathrm{Cu(I)}\ \to\ \mathrm{Cu(II)}} \mathrm{N_2 + BF_4{}^- + Ar\bullet} \qquad (3)$$

It was found that in the presence of the copper chiral catalyst and 2,6-di-^{t}Bupyridine (DTBP) as an acid scavenger, a series of unsaturated carboxylic acids bearing electron-neutral and -deficient aryl groups reacted with aryl diazonium salts to furnish the desired oxyarylation products in good yields with moderate to good enantioselectivity (Scheme 6, **9a**–**9d**). A number of common functional groups were found to be compatible with the reaction conditions, such as an aryl chloride (**9a**), an ethyl benzoate (**9b**), and a nitrile group (**9c**). In addition, a δ-unsaturated carboxylic acid afforded the corresponding aryl-substituted δ-lactone in good yield, albeit with a lower ee (**9d**).

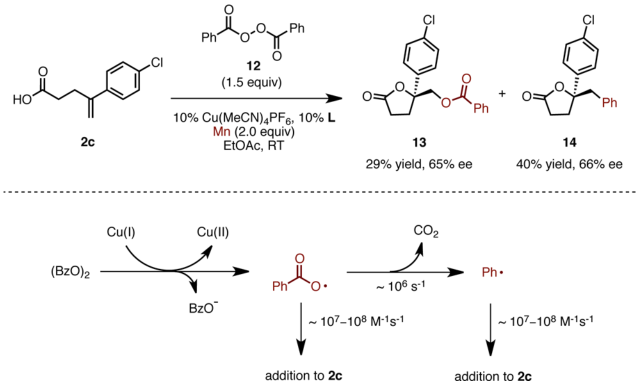
Scheme 6. Examples of the Cu-Catalyzed Enantioselective Oxyarylation[a]



[a] Reaction conditions: Cu(MeCN)$_4$PF$_6$ (12 mol %), **L** (10 mol %), **2** (0.50 mmol, 1.0 equiv), aryl diazonium tetrafluoroborate (2.0 equiv), 2,6-di-^{t}Bupyridine (2.0 equiv), in 8 mL of ethyl acetate at RT for 16 h. Yields are of isolated products (average of two runs). The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

In addition to nitrogen-, sulfur-, and carbon-centered radicals, we also wanted to explore the use of oxygen-centered radicals in a Cu-catalyzed enantioselective oxyfunctionalization reaction. Peroxides are readily available precursors for the generation of oxygen-centered radicals. However, the reduction of peroxides by Cu(I) tends to be so rapid that a relatively high concentration of radical species is quickly built up. This leads to significant amount of unproductive radical−radical termination processes as a termination event, leaving the copper catalyst in the Cu(II) oxidation state and resulting in a low conversion of the alkene. We therefore sought to use a mild reducing agent to expedite the reduction of the Cu(II) species back to Cu(I). As shown in Scheme 7, good conversion was achieved when **2c** was treated with dibenzoyl peroxide (**12**) in the presence of the chiral catalyst and manganese(0). Two lactone products were formed in this process: the diacyloxylation product **13** (29% yield, 65% ee) from benzoyloxyl radical addition and the oxyarylation product **14** (40% yield, 66% ee) from the addition of a phenyl radical presumably derived from the decarboxylation of the original benzoyloxyl radical. The rate constants of the addition of aroyloxyl radicals to styrenes typically lie in the range between 10^7 to 10^8 M^{-1} s^{-1}, while the ones for the decarboxylation processes have been determined to be ca. 10^6 s^{-1}.[22] Therefore, comparable rates for the two competing pathways are expected at the concentration of substrate (~0.05 M), consistent with the product distribution observed.

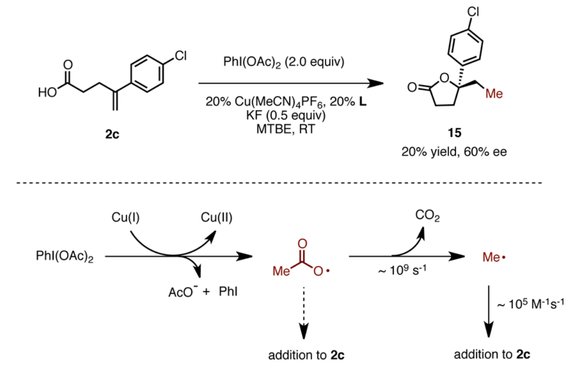
Scheme 7. Cu-Catalyzed Radical Diacyloxylation and Decarboxylative Oxyalkylation



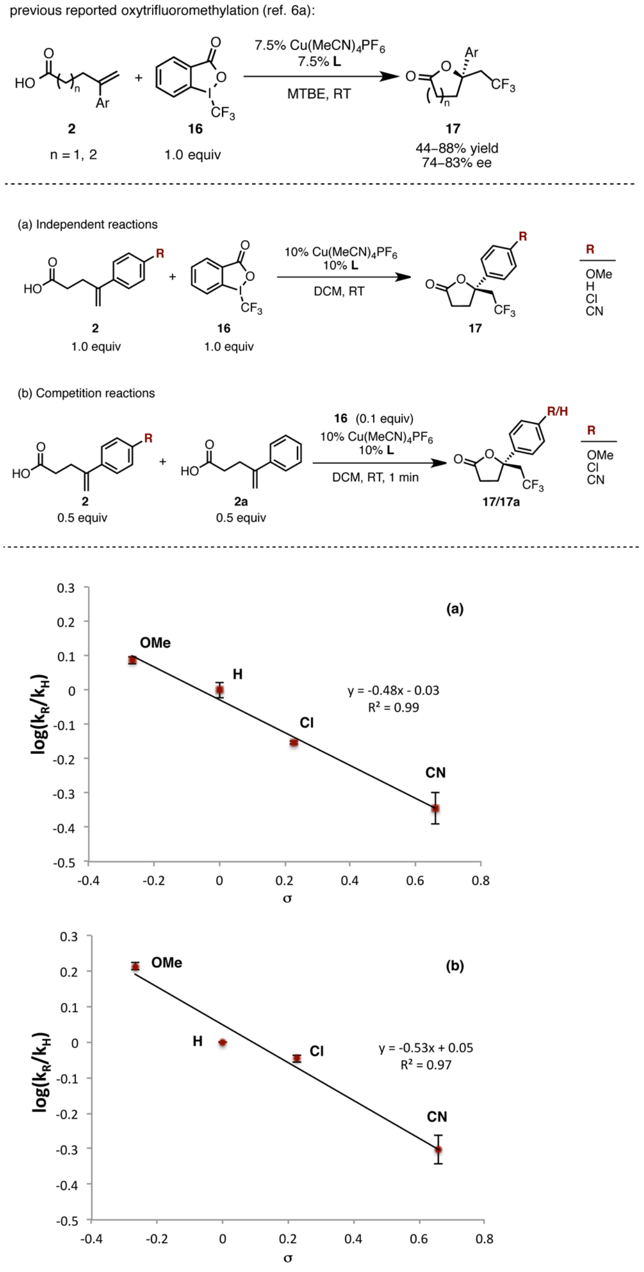
The decarboxylation of an alkyl carbonyloxyl radical to generate the corresponding alkyl radical is much more rapid than that of its aryl analogues ($k \approx 10^9$ s^{-1}), which provides a viable method to generate alkyl radicals under conditions that are compatible with our method.[23] As such, we found that a methyl radical could be generated from PhI(OAc)$_2$ and utilized in the copper-catalyzed enantioselective oxyfunctionalization reaction. As shown in Scheme 8, the reaction of **2c** and PhI(OAc)$_2$ produced oxymethylation product **15** in 20% yield and 60% ee. No acetoxyl radical addition product was observed as expected. The low yield obtained might be attributable to the sluggish addition of the methyl radical ($k \approx 10^5$ M^{-1} s^{-1}) to **2c**.[24]

Mechanistic Considerations. To gain further mechanistic insight into these copper-catalyzed enantioselective radical oxyfunctionalization reactions, the oxytrifluoromethylation reaction of **2** was selected as a model system for study. A Hammett study was performed to probe the electronic effects of the substrate alkene on the reaction rate (Scheme 9). Relative reaction rate measurements by independent reactions (Scheme 9a) and one-pot competition experiments (Scheme 9b) yielded similar small negative ρ values (−0.48 and −0.53

Scheme 8. Cu-Catalyzed Radical Oxyalkylation



Scheme 9. Hammett Plot of Oxytrifluoromethylation Reaction



respectively). This indicated that a small partial positive charge develops in the transition state of the turnover-limiting step, a feature that is consistent with the polar effect expected for the addition of an electrophilic CF_3 radical onto the alkene.[25]

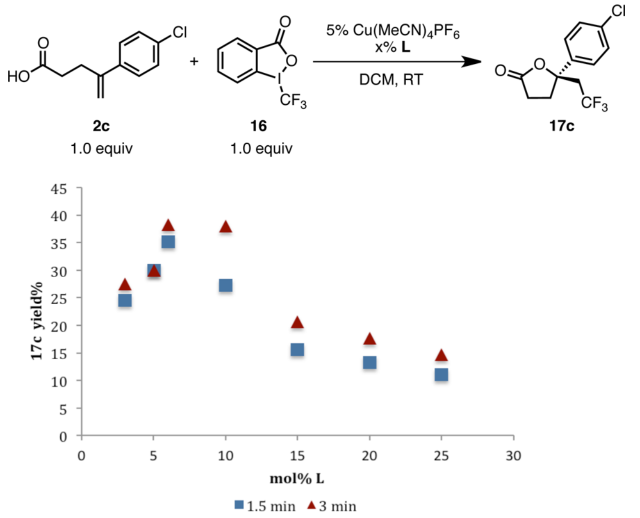
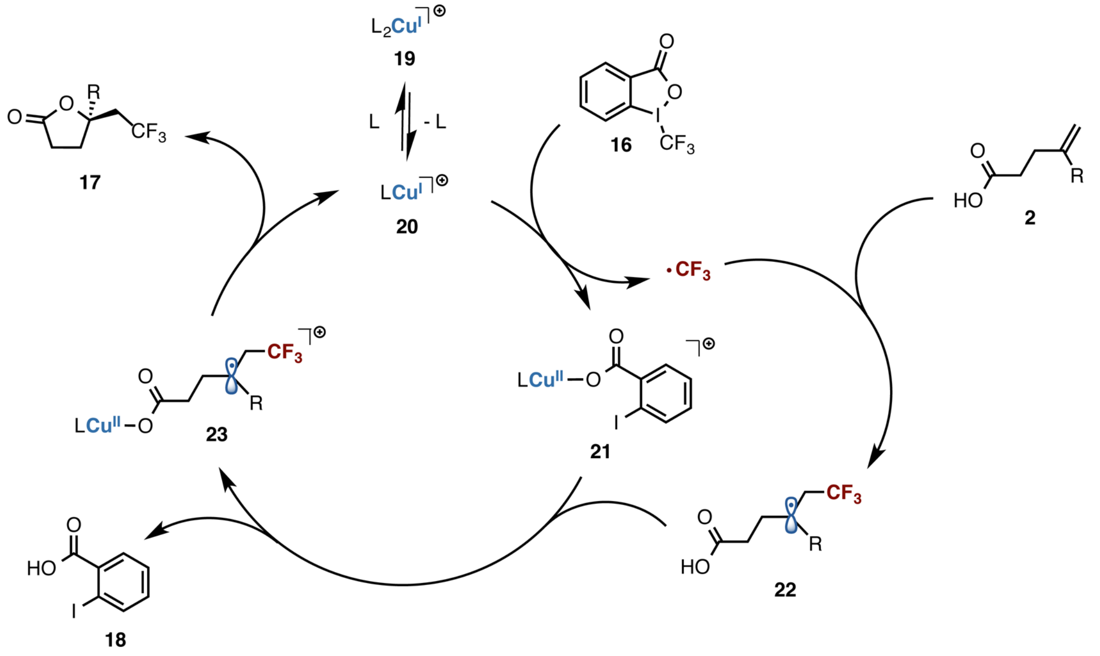


Figure 1. Effect of ligand stoichiometry on reaction rate. Reaction conditions: $Cu(MeCN)_4PF_6$ (10 mol %), **L** (x mol %), **2c** (0.10 mmol, 1.0 equiv), **16** (1.0 equiv), in 1.2 mL of CH_2Cl_2 at RT. Yields were determined by ^{19}F NMR spectroscopy.

The relationship of the relative stoichiometry of ligand and metal on reaction rate was also investigated. Conversion to product at 1.5 and 3 min was determined using a fixed quantity of $Cu(MeCN)_4PF_6$ (10 mol %) while the amount of **L** was varied. As shown in Figure 1, when [**L**]/[Cu] < 1, higher [**L**] increased the initial reaction rate; in contrast higher [**L**] resulted in reaction inhibition when [**L**]/[Cu] ≥ 1. On the basis of these results, we deduced that active catalyst incorporates only one **L**, while the 2:1 complex $[CuL_2]^{x+}$ is an off-cycle species.[26] In addition, we noted that although greater initial rates were obtained with [**L**]/[Cu] < 1, these reactions stopped at low conversion of the substrate. In contrast, more persistent turnovers were observed in the cases where [**L**]/[Cu] ≥ 1. This suggests that the $[CuL]^{x+}$ species is somewhat unstable; the use of excess ligand helps ameliorate this.[27] Thus, there is a balance between stability and reactivity.

A possible catalytic cycle that is consistent with all the mechanistic data we have accorded is depicted in Scheme 10. An equilibrium likely exists between the monoligated complex $[CuL]^+$ (**20**) and bis-ligated complex $[CuL_2]^+$ (**19**). Intermediate **20** would react with **16** to afford a Cu(II) carboxylate complex **21**, as well as a CF_3 radical. The turnover-limiting step likely involves the irreversible addition of the CF_3 radical onto the alkene, which generates the tertiary radical **22**. Since it was found that the enantioselectivity is insensitive to the structural change in the backbone of the reagent **16** and no C−O bond formation product derived from 2-iodobenzoate was detected in any of the cases investigated, we postulate that tricoordinate complex **23** is ultimately formed from the reaction between **21** and **22**. Complex **23** undergoes the enantioselective C−O bond forming step to furnish the oxytrifluoromethylation product **17** and regenerate the Cu(I) catalyst. Although $^\bullet R_1$ and X^- differ in these cases (see Scheme 2), we anticipate that the related oxyazidation, oxysulfonylation,

Scheme 10. Proposed Catalytic Cycle for the Enantioselective Oxytrifluoromethylation Reaction



oxyarylation, diacyloxylation, and oxyalkylation reactions proceed via similar mechanisms.

The nature of the enantiodetermining C–O bond forming step is intriguing but hard to probe experimentally because it likely proceeds through unobservable transient intermediates. However, the classic asymmetric Kharasch oxidation reaction via allylic radical intermediates derived from cyclic alkenes catalyzed by Cu-chiral bisoxazoline complexes has been well documented in the literature, where a pericyclic rearrangement from a distorted square planar allyl-Cu(III) carboxylate intermediate has been proposed to account for the C–O bond formation.[28] Although such pericyclic rearrangement pathway is not viable for the tertiary alkyl radicals involved in this study, it is nevertheless reasonable to consider an addition/reductive elimination pathway via a Cu(III) intermediate based on these precedents.[28b,29,30]

As shown in Scheme 11, we propose that the enantiodetermining C–O bond formation from tricoordinate Cu(II) carboxylate complex **24** might occur through (1) Cu–C bond formation between Cu(II) center and the prochiral alkyl radical and (2) C–O bond forming reductive elimination of the resulting Cu(III) complex. Since the reductive elimination from the Cu(III) center is generally considered to be a rapid process, it is likely that the radical addition to Cu(II) is the enantiodetermining step, through which two diastereomeric Cu(III) complexes **II** and **III** are produced and undergo reductive elimination with retention of the configurations.[28b] Possible transition states for the Cu–C bond form leading to **II** and **III** are depicted. A distorted square planar geometry is likely adopted by the copper complex. The SOMO interacting with the copper atom is likely close to perpendicular to the benzene plane due to the stabilization offered by delocalization. In general, these two transition states are energetically differentiated by the orientations of the aryl and alkyl groups. The transition state in which the aryl group occupies the pseudoequatorial position (leading to **II**) should be favored on steric grounds and is consistent with the observed sense on enantioinduction.[31]

This model can be used to qualitatively explain the significantly lower reactivity and enantioselectivity obtained by the use of copper halides as precatalysts instead of the cationic salt $Cu(MeCN)_4PF_6$. The halide group is likely to occupy a coordination site at the copper atom throughout the entire catalytic cycle. The relatively small size of a halide group as opposed to a carboxylate ligand would still allow the combination between the tetracoordinated Cu(II) center and the tertiary alkyl radical to occur without prior ligand dissociation. However, this additional ligand would slow down the process due to the added steric hindrance and, more importantly, change the geometry of the transition state dramatically as the radical might be forced to approach the copper atom from the direction of *z*-axis. This is also in line with the increased yield and enantioselectivity observed in the oxysulfonylation reaction with Ag(I) salts as additives, where copper(II)-chloride complex is formed in situ by the reaction with arylsulfonyl chlorides (Table 2).

■ CONCLUSION

We have developed a general and versatile method for the catalytic enantioselective oxyfunctionalization of alkenes based on a Cu-mediated enantioselective C–O bond forming process of prochiral alkyl radical intermediates. A wide range of radicals were found to participate in this type of reaction, including azidyl, arylsulfonyl, aryl, acyloxyl, and alkyl radicals. This method provides rapid access to a broad spectrum of interesting enantiomerically enriched lactones through tandem C–N/C–O, C–S/C–O, $C–C_{aryl/alkyl}$/C–O, or C–O/C–O bond formation, in good yields and useful enantiomeric excesses in most instances with good functional group compatibility. Kinetic data are consistent with the radical addition of alkene being the turnover-limiting step. A model for the transition state of the enantiodetermining step is proposed based on a hypothesis involving an alkyl radical–Cu(II) combination and subsequent reductive elimination.

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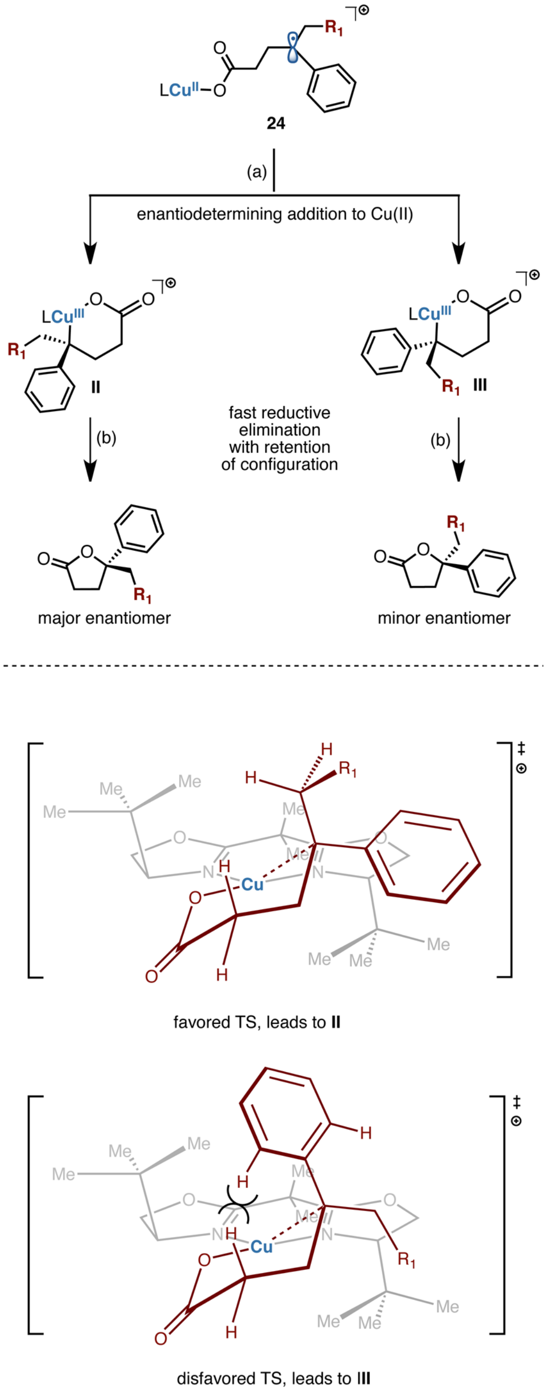
Scheme 11. Possible Pathways for the Enantioselective C−O Bond Forming Process



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization, and spectra data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04821.

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Notes

The authors declare no competing financial interest.

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(13) (a) The different diastereoselectivities observed for oxytrifluoromethylation (favors Ph/Me "syn") and oxyazidation (favors Ph/Me "anti") reactions might be attributable to the difference between the size of a trifluoromethyl group (CF_3 > Me > H) and that of an azido group (Me > N_3 > H). (b) Some additional evidence including the result from radical clock experiments was also found consistent with the mechanism proposed in Scheme 2. See Supporting Information for details.

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