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Cu(I)-Catalyzed Chemo- and Enantioselective Desymmetrizing C−O Bond Coupling of Acyl Radicals

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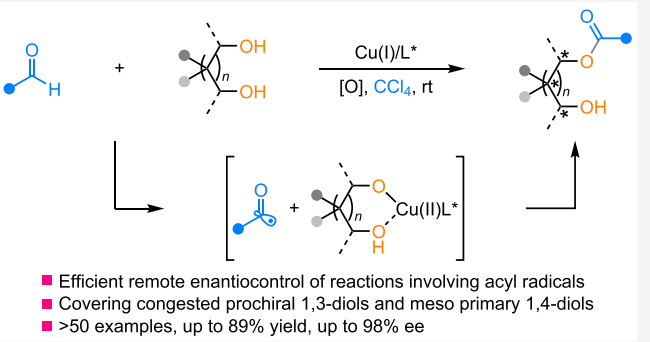
ABSTRACT: Transition-metal-catalyzed enantioselective functionalization of acyl radicals has so far not been realized, probably due to their relatively high reactivity, which renders the chemo- and stereocontrol challenging. Herein, we describe Cu(I)-catalyzed enantioselective desymmetrizing C−O bond coupling of acyl radicals. This reaction is compatible with (hetero)aryl and alkyl aldehydes and, more importantly, displays a very broad scope of challenging alcohol substrates, such as 2,2-disubstituted 1,3-diols, 2-substituted-2-chloro-1,3-diols, 2-substituted 1,2,3-triols, 2-substituted serinols, and meso primary 1,4-diols, providing enantioenriched esters characterized by challenging acyclic tetrasubstituted carbon stereocenters. Partnered by one- or two-step follow-up transformations, this reaction provides a convenient and practical strategy for the rapid preparation of chiral C3 building blocks from readily available alcohols, particularly the industrially relevant glycerol. Mechanistic studies supported the proposed C−O bond coupling of acyl radicals.



INTRODUCTION

Asymmetric radical reactions,[1] which are one of the most challenging areas of modern organic synthesis and asymmetric catalysis, provide a vital tool for preparing various enantioenriched molecules, thanks to their great functional group compatibility, high reactivity, and low steric hindrance sensitivity. Tremendous progress has been made in this field over the past few decades,[2] especially in transition-metal-catalyzed enantioselective functionalization of carbon-centered radicals (Figure 1A). Specifically, many conjugated[3] alkyl radicals, as well as some isolated ones possessing particular directing groups, have been well accommodated in a wide range of transformations with high levels of enantiocontrol.[4] For conjugated allenyl radicals, highly enantioselective cyanation and alkynylation reactions have also been achieved recently by Bao, Liu, and our group independently.[5]

By contrast, acyl radicals, which possess stabilities in between benzyl and isolated alkyl radicals,[6,7] have so far remained uninvestigated for transition-metal-catalyzed enantioselective functionalization. This is despite that acyl radicals play an integral role in organic synthesis, and their formation and application in a controlled and efficient manner have long been a goal of chemists.[7,8] In this context, among many reported methods for generating acyl radicals, the abstraction of a hydrogen atom from aldehydes represents the most convenient way because of its high atom economy and the ready availability and high stability of aldehydes.[9] However, the high reaction temperatures often required in most transition-metal-catalyzed hydrogen atom transfer (HAT) reactions of aldehydes[8d] are likely to significantly compromise the enantiodiscrimination by a chiral catalyst. A robust catalytic system that delivers sufficient reaction efficiency under mild conditions is highly preferred to achieve efficient enantiocontrol of acyl radicals. Meanwhile, many nucleophilic functionalities commonly employed for acyl radical functionalization, such as hydroxy groups, are themselves nonstereogenic in the reactions. In this sense, the planar structure of acyl groups determines that the reaction sites are most likely away from the forming stereocenter in an asymmetric reaction, which renders the stereocontrol challenging (Figure 1B).[10]

In this aspect, chemocatalytic enantioselective desymmetrizing acylation of meso and prochiral alcohols has proved to be a robust method for the convenient and rapid construction of one or multiple remote stereocenters in one step.[11,12] Although aldehydes are appealing acyl group precursors, their use in intermolecular chemocatalytic enantioselective desymmetrization of alcohols has hitherto remained rare. The only known

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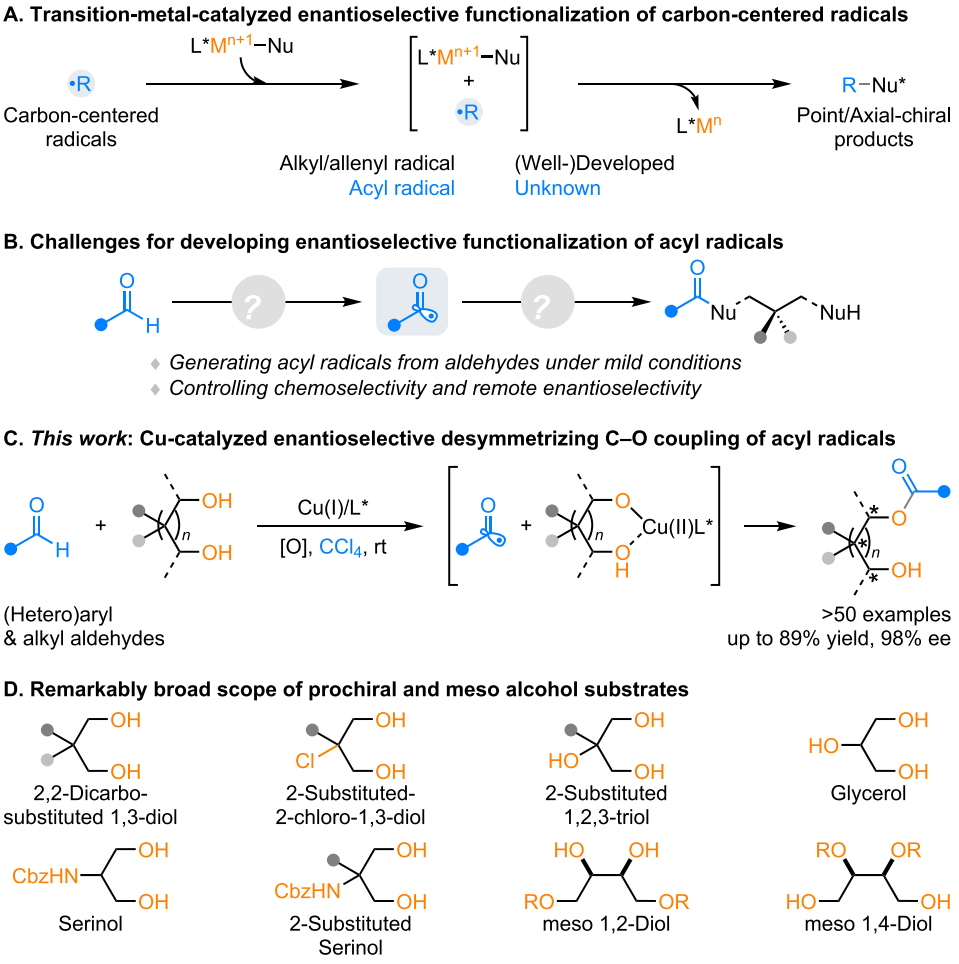

Figure 1. Motivation and development of enantioselective desymmetrizing C–O bond coupling of acyl radicals.

successful report by Chi et al. hinges on chiral N-heterocyclic carbene (NHC) catalysis in the presence of stoichiometric amounts of quinone oxidants at −45 °C.[13] Nonetheless, only 2-substituted-2-chloro-1,3-diols with aryl aldehydes have been examined in this pioneering work and thus, highly enantioselective chemocatalytic desymmetrizing acylation of a broad scope of meso and prochiral alcohols using readily available aldehydes is still highly desirable yet has thus far remained elusive.

We have a continuing interest in asymmetric reactions involving radical species,[4f,g,14] particularly for their desymmetrizing functionalization.[10,15] Based on the above knowledge and our research interest, we envisaged that our Cu(I)/multidentate anionic ligand catalytic system[14,16] would readily reduce peroxides to generate *tert*-butoxy radicals, of which the subsequent HAT with aldehydes would generate acyl radicals under mild conditions.[17] In addition, the following reactions of acyl radicals with prochiral diols bonded by chiral Cu(II) catalysts would give rise to enantioenriched esters.[12,13,17]

Herein, we describe our efforts in achieving the thus-developed Cu(I)-catalyzed enantioselective desymmetrizing C–O bond coupling of acyl radicals (Figure 1C). Aryl, heteroaryl, and alkyl aldehydes all are viable substrates for this reaction. More importantly, a range of prochiral 1,3-diols tethered by sterically congested carbons are readily accommodated by the reaction (Figure 1D), providing highly enantioenriched esters featuring synthetically challenging acyclic all-carbon,[18,19] nitrogen-,[20] oxygen-,[21] and chlorine-bearing[13a] tetrasubstituted carbon stereocenters. In addition, biomass-derived glycerol[22] and its derivative serinol[15] as well as 1,4-protected erythritol (a meso 1,2-diol)[23] are also suitable for this reaction (Figure 1D), leading to their fast valorization. Further, meso primary 1,4-diols[24] derived from erythritol are applicable to the reaction (Figure 1D). Notably, reports for the successful enantioselective desymmetrization of these prochiral 1,3-diols and meso primary 1,4-diols using chemocatalysis are scarce in the literature.[13a,15,19−22,24] A general chemocatalytic desymmetrization method exhibiting such a broad substrate scope has, to the best of our knowledge, been rare, thus constituting an excellent complementary approach to these known protocols. Upon further one- or two-step manipulations, these enantioenriched esters were readily converted to high-value-added chiral building blocks, highlighting the synthetic potential of this reaction. Our preliminary mechanistic studies supported the involvement of acyl radicals in the reaction.

RESULTS AND DISCUSSION

Reaction Development. We began our investigation by reacting 2-naphthaldehyde **A-1** with diol **S-1** in the presence of $CuBH_4(PPh_3)_2$ and the sulfonamide ligand **L1**[25] as the catalyst and **O1** as the oxidant (Table 1). Most of the initial reactions in several common solvents delivered the desired product **1** in moderate to good enantioselectivity, albeit with low conversion

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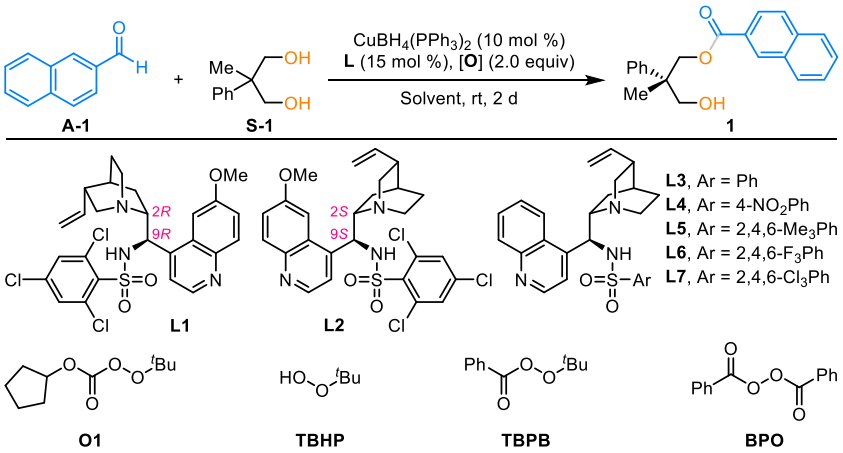
Table 1. Screening of Reaction Conditions[a]



entry	L	[O]	solvent	yield (%)	ee (%)
1	**L1**	**O1**	DCM	6[b]	80
2	**L1**	**O1**	EA	8	85
3	**L1**	**O1**	MTBE	9	61
4	**L1**	**O1**	$CHCl_3$	trace	
5	**L1**	**O1**	CCl_4	76	93
6	**L1**	TBHP[c]	CCl_4	30	38
7	**L1**	TBPB	CCl_4	17	69
8	**L1**	BPO	CCl_4	trace	
9	**L2**	**O1**	CCl_4	68	−89
10	**L3**	**O1**	CCl_4	46	−72
11	**L4**	**O1**	CCl_4	30	−73
12	**L5**	**O1**	CCl_4	67	−86
13	**L6**	**O1**	CCl_4	60	−83
14	**L7**	**O1**	CCl_4	67	−87

[a]Reaction conditions: **A-1** (0.20 mmol), **S-1** (1.5 equiv), $CuBH_4(PPh_3)_2$ (10 mol %), **L** (15 mol %), and [**O**] (2.0 equiv) in anhydrous solvent (4.0 mL) at rt for 2 days under argon. Yield was based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; ee values were based on chiral HPLC analysis. [b]The conversion was 21%. [c]TBHP (5.5 mol/L in decane).

and yield (entries 1−4). The low reaction efficiency was likely due to the nonchemoselective HAT with solvent molecules and/or β-fragmentation of *tert*-butoxy radicals[26] as well as the thus-generated secondary radicals. To our surprise, the subsequent reaction in carbon tetrachloride smoothly delivered **1** in substantially enhanced yield with excellent ee (76% yield, 93% ee, entry 5). The high reaction efficiency seemed to result from the inability of carbon tetrachloride for HAT and the good chlorine atom transfer capability of carbon tetrachloride with methyl radicals generated from the β-fragmentation of *tert*-butoxy radicals (see the Mechanistic Studies section for additional discussion). The replacement of **O1** with other oxidants such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl peroxybenzoate (TBPB), or benzoyl peroxide (BPO) uniformly led to inferior results (entries 6−8), likely as a result of the unmatched oxidation power (TBHP) or unfavored transmetalation (TBPB and BPO) or undesired catalyst decomposition (BPO). Interestingly, **L2**, which is the (2*S*,9*S*)-pseudo-enantiomer of **L1**, and its cinchonidine-derived analogue **L7** lacking the quinoline methoxy group both gave rise to only slightly diminished yield and enantioselectivity (entries 9 and 14). In addition, ligands **L5** and **L6** bearing similarly 2,4,6-trisubstituted arylsulfonyl groups delivered comparable results (entries 12 and 13) with that of **L7** (entry 14), while other ligands **L3** and **L4** lacking this structural feature provided low yield and significantly decreased enantioselectivity (entries 10 and 11). These results highlight the importance of the C2 and C9 stereocenters and the 2,4,6-trisubstituted arylsulfonyl groups in dictating the enantioselectivity. By contrast, the remaining ligand stereocenters, the quinoline methoxy group, and the electronic properties of the aforementioned 2,4,6-substituents are unimportant in this aspect. After additional condition optimization (Table S1), the optimal conditions were identified to be as follows: **A-1** (0.20 mmol), **S-1** (1.5 equiv), $CuBH_4(PPh_3)_2$ (10 mol %), **L1** (15 mol %; see Figure S1 for its X-ray structure as well as absolute configuration), and **O1** (2.0 equiv) in anhydrous carbon tetrachloride (4.0 mL) at room temperature (rt) for 2 days under argon, providing **1** in 76% yield with 93% ee.

Substrate Scope. With the optimized conditions in hand, we first examined the scope of aldehydes (Table 2). Benzaldehyde and its analogues with various substituents at different positions (ortho, meta, or para) generally exhibited high reaction efficiency and excellent enantioselectivity (**1**−**17**). Particularly, sterically encumbered aldehydes all delivered high ee values (**5**, **11**, and **16**), although the yield of **11** with the bulkiest 2-iodo substituent was low. Furthermore, heteroaromatic and alkenyl aldehydes were also compatible with the reaction conditions (**18**−**20**). Notably, a secondary aldehyde smoothly underwent the reaction to afford **21** in moderate yield with good enantioselectivity (see Scheme S1 for more results of alkyl aldehydes).

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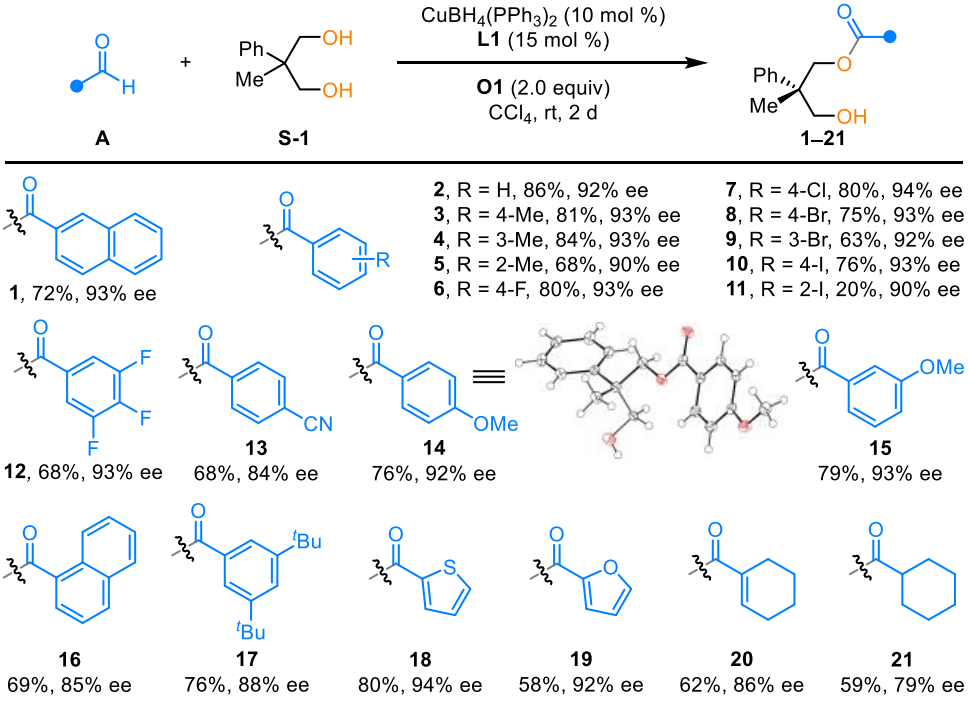
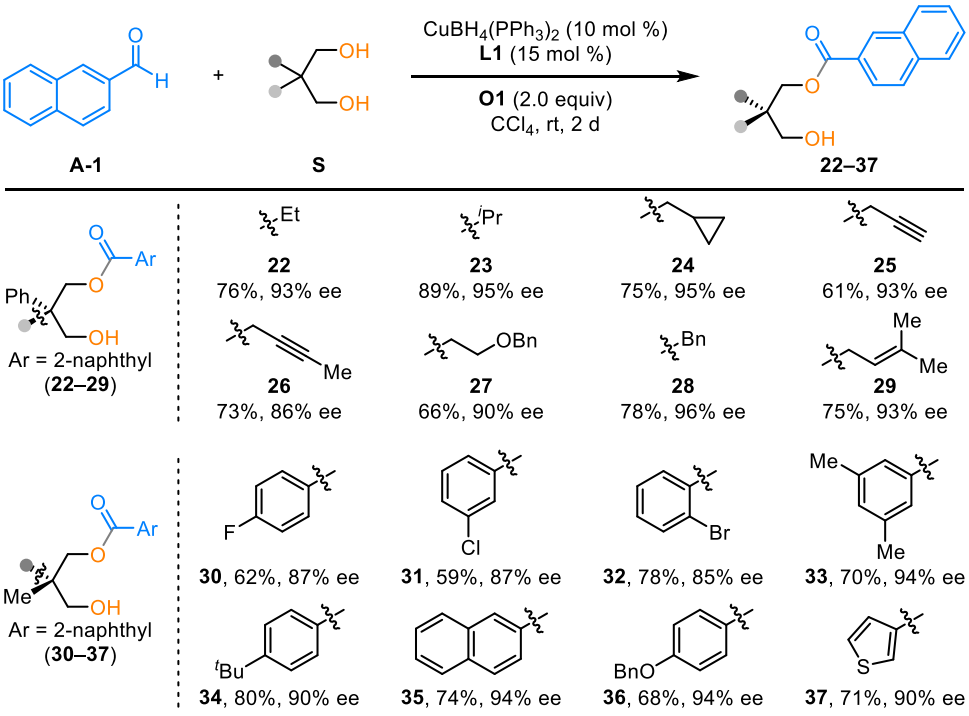
Table 2. Substrate Scope of Aldehydes[a]



[a]Reaction conditions: **A** (0.20 mmol), **S-1** (1.5 equiv), $CuBH_4(PPh_3)_2$ (10 mol %), **L1** (15 mol %), and **O1** (2.0 equiv) in anhydrous carbon tetrachloride (4.0 mL) at rt for 2 days under argon.

Table 3. Results of 2,2-Dicarbofunctionalized 1,3-Diols[a]



[a]Reaction conditions: **A-1** (0.20 mmol), **S** (0.30 mmol), $CuBH_4(PPh_3)_2$ (10 mol %), **L1** (15 mol %), and **O1** (2.0 equiv) in anhydrous carbon tetrachloride (4.0 mL) at rt for 2 days under argon.

As for the scope of 2,2-dicarbosubstituted 1,3-diols (Table 3), diverse alkyl and aryl, as well as heteroaryl groups, on the tether, were readily tolerated to provide the desired products **22**−**37** in 59−89% yield with 85−96% ee. Noteworthy is the compatibility of the reaction with alkyne (**25** and **26**) and alkene (**29**) functional groups, which are susceptible to radical reactions. In addition, the only highly enantioselective chemocatalytic desymmetrizing acylation of 2,2-dicarbosubstituted 1,3-diols with a broad substrate scope reported by Kang et al. required a very low reaction temperature (−78 °C)

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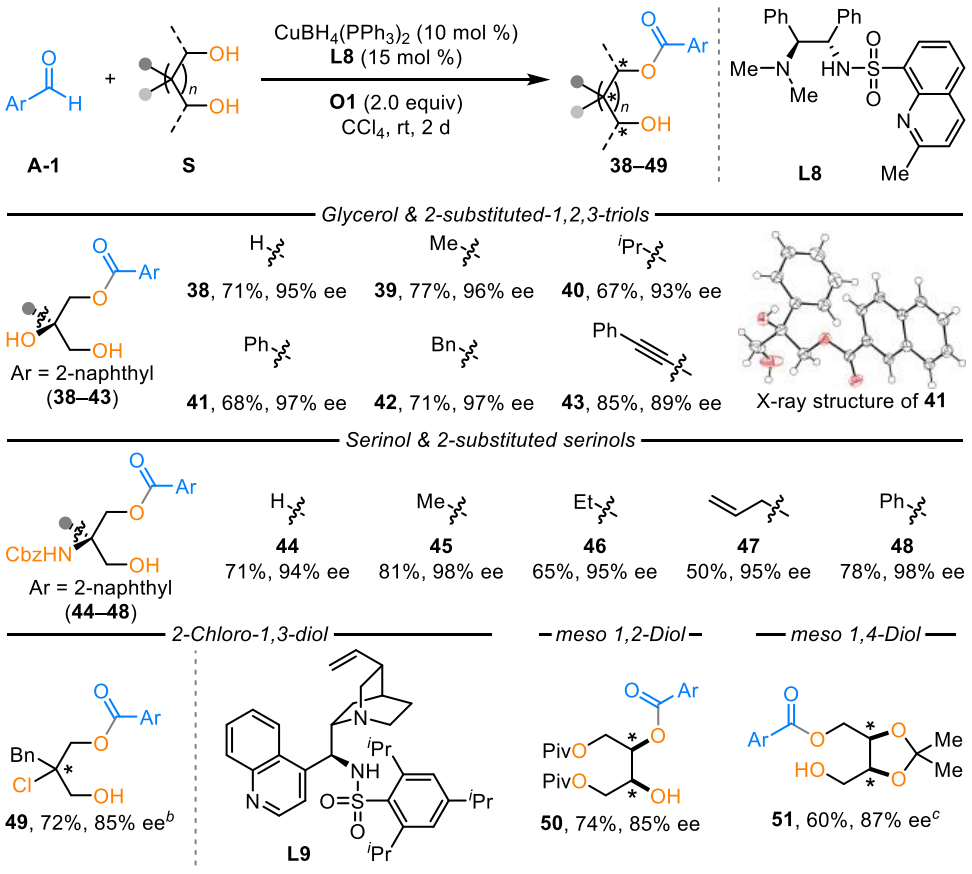
Table 4. Substrate Scopes of 1,2,3-Triols, 2-Amino-1,3-diols, 2-Substituted-2-chloro-1,3-diols, Meso 1,2-Diols, and Meso 1,4-Diols[a]



[a]Reaction conditions: **A-1** (0.20 mmol), **S** (0.30 mmol), $CuBH_4(PPh_3)_2$ (10 mol %), **L8** (15 mol %), and **O1** (2.0 equiv) in anhydrous carbon tetrachloride (4.0 mL) at rt for 2 days under argon. [b]With **L9** (15 mol %). [c]With **L1** (15 mol %). Cbz, benzyloxycarbonyl; Piv, pivaloyl.

for achieving good enantioselectivity.[19a] By contrast, our reaction proceeded at ambient conditions, thus constituting a more operationally convenient alternative approach.

In addition to the construction of chiral acyclic all-carbon quaternary stereocenters discussed above, the reaction was also rendered amenable to forging O-, N-, and Cl-bearing tetrasubstituted as well as tertiary carbon stereocenters (Table 4) upon condition reoptimization (Table S2). Accordingly, glycerol and serinol as well as their 2-substituted derivatives readily participated in the reaction with **L8**[16e] as the ligand, giving enantioenriched esters **38**−**48**. Moreover, enantioenriched tertiary chloride **49** was obtained in good yield and enantioselectivity, with **L9** as the ligand. Besides, the 1,4-protected erythritol, a formal meso 1,2-diol, was also a viable substrate for the reaction to afford **50** (see Scheme S2 for the results of *cis*-1,2-cyclohexadiol). More importantly, meso primary 1,4-diols from 2,3-protection of erythritol was applicable to the reaction, too, providing **51** with good enantioselectivity. Notably, meso primary 1,4-diols are challenging substrates for chemocatalytic enantioselective desymmetrizing acylation due to their higher nucleophilicity and longer distances between preexisting stereocenters and the reaction sites than that of meso secondary 1,4-diols.[27] Consequently, there are only two isolated case reports[24a,b] for highly enantioselective chemocatalytic desymmetrizing acylation of two meso primary 1,4-diol substrates, respectively, in the literature. Of particular note is that the convenient asymmetric desymmetrization of biomass-derived glycerol and its derivative serinol as well as erythritol embodies their fast valorization, and thus would facilitate the development of the related biomass industry.[28]

Synthetic Utility. To demonstrate the synthetic utility of this methodology, we first synthesized **38** from glycerol on a 1-mmol scale under standard conditions and observed comparable yield and enantioselectivity (Scheme 1A). We then converted **38** to enantioenriched building blocks such as acylated glycerol carbonate **52**, solketal **53**, and glycidol **54** in one step with largely retained enantiopurity. More importantly, we prepared the Cbz-protected (*S*)-*α*-methylserine **55** in two steps from **45** in 83% yield with 97% ee (Scheme 1B), thus showcasing the great potential of our reaction for expedient access to valuable *α*,*α*-disubstituted unnatural amino acid building blocks.[29] The absolute configurations of **14**, **41**, and **53** were determined to be *S*, *R*, and *R*, respectively, by X-ray structural analysis (Tables 2, 4, and Scheme 1A; see Figures S2−S4 for enlarged X-ray structures), and that of **44** was determined to be *R* by comparing the HPLC spectrum of its ester derivative with that of an authentic sample (see the Supporting Information for details). The absolute configurations of the remaining compounds were assigned by analogy.

Mechanistic Studies. Regarding the reaction mechanism, we first observed complete reaction inhibition by TEMPO or butylated hydroxytoluene (BHT), supporting the involvement

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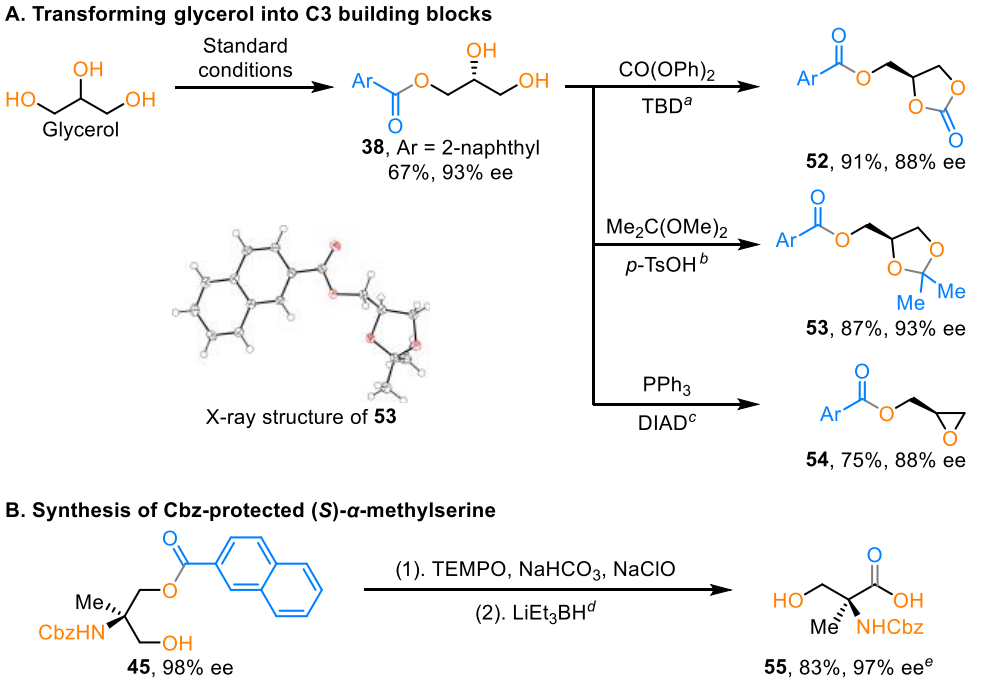
Scheme 1. Synthetic Application



[a]Reaction conditions: $CO(OPh)_2$ (1.1 equiv) and TBD (5.0 mol %) in tetrahydrofuran at rt. [b]$Me_2C(OMe)_2$ (2.0 equiv) and *p*-TsOH·H_2O (5.0 mol %) in dichloromethane at rt. [c]PPh_3 (1.05 equiv) and DIAD (1.05 equiv) in chloroform under reflux. [d](1) TEMPO (0.33 equiv), $NaHCO_3$ (5.4 equiv), aq NaClO (active chlorine 6−14%) in acetonitrile and water at rt; (2) $LiEt_3BH$ (4.5 equiv) in tetrahydrofuran at 0 °C. [e]The ee value was determined after quantitative methylation. TBD, triazabicyclodecene; Ts, toluenesulfonyl; DIAD, diisopropyl azodicarboxylate; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; aq, aqueous.

of radical species in the reaction (Scheme S3). Next, we observed the formation of **56** (see Figure S5 for its enlarged X-ray structure) from aldehyde **A-56** under the standard reaction conditions (Scheme 2A), likely indicating the formation of the corresponding acyl radical followed by intramolecular 5-exo-trig cyclization and further oxidation (Scheme S4A). By contrast, the use of aldehyde **A-57** as the substrate led to ester **57** in low yield with moderate enantioselectivity (Scheme 2B). We reasoned that the formation of **57** started with the known generation of trichloromethyl radicals from carbon tetrachloride,[30] which was next added to the terminal alkene (Scheme S4B). The resulting alkyl radical then underwent fast intramolecular 1,5-HAT followed by the enantioselective C−O coupling of the thus-formed acyl radical. Consistent with this conjecture, we observed the formation of enantioenriched **58** from **A-57** (Scheme 2C) using a known strategy[31] for inducing trifluoromethyl radicals in the absence of carbon tetrachloride as well as the subsequent alkene addition, 1,5-HAT, and acyl radical functionalization (Scheme S4C). In addition, phenylacetaldehyde did not undergo the radical C−O coupling reaction, likely due to the very fast decarbonylation of the in situ-generated phenylacetyl radicals (see Scheme S1 for details).[7] Taken together, these results supported the formation of acyl and trichloromethyl radicals and the enantioselective acyl radical C−O coupling leading to enantioenriched ester products in our reaction. Further control experiments excluded the occurrence of product kinetic resolution in the reaction (Scheme S5A and Table S3) or the possible product formation via acetal oxidation (Scheme S5B).

It is well known that acyl radicals generated from aldehydes can undergo relatively fast chlorine atom transfer with carbon tetrachloride to form corresponding acid chlorides.[32] By NMR spectroscopic analysis of the reaction mixtures, we indeed observed the formation of acid chlorides (Figure S6 and Table S4; for side products identified in the NMR spectra, see Figures S6 and S7), which were completely consumed at the end of the reaction. Nonetheless, a series of control experiments with acid chlorides in place of aldehydes confirmed that Lewis acid (Cu(I) or Cu(II))-catalyzed ionic esterification[19a,b] was unlikely operative in our reactions (Figure S8).

On the basis of these experimental results and previous reports,[17] we proposed a possible reaction mechanism, as shown in Scheme 2D. In the beginning, Cu(I) complex Cu(I)L* (**I**) and **O1** undergo a single-electron transfer process, generating the *tert*-butoxy radical and Cu(II) complex **II**. Next, **II** transforms to **III** upon ligand exchange with the alcohol substrate. On the other hand, the *tert*-butoxy radical may directly abstract a hydrogen atom from the aldehyde substrate, generating the corresponding acyl radical. Alternatively, it may also indirectly generate the acyl radical via sequential *β*-fragmentation, chlorine atom transfer with carbon tetrachloride, and HAT with the aldehyde substrate.[30,32] The thus-generated acyl radical next reacts with **III** to give rise to the enantioenriched C−O coupling product, regenerating Cu(I) complex **I** and closing the catalytic cycle. This C−O coupling likely proceeds through a radical-substitution type pathway on the basis of our preliminary theoretical studies (Figures S9−S12 and Table S5; see Figure S13 for a brief discussion on the possible enantiodiscrimination course based on this reaction mechanism).

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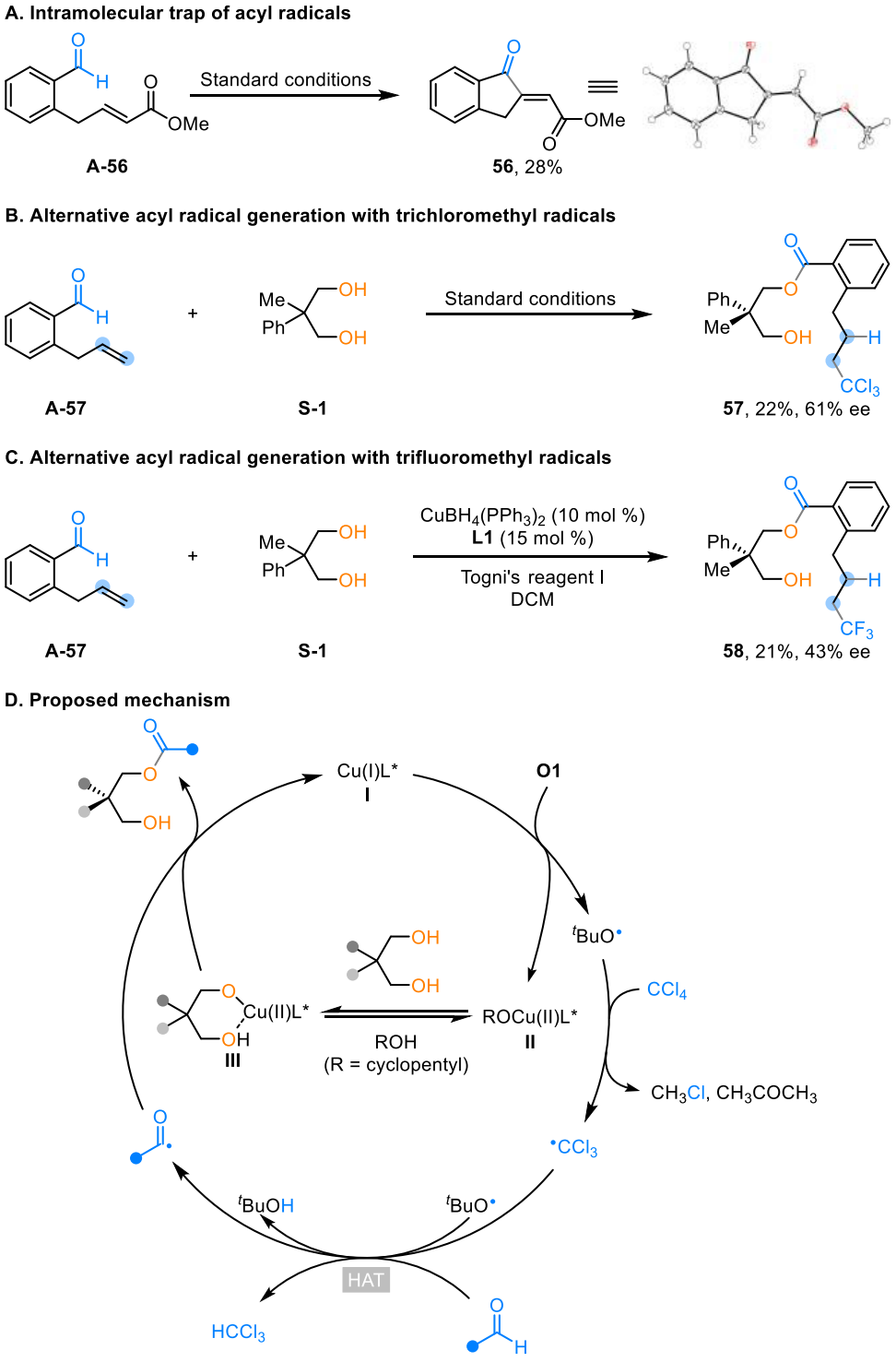
Scheme 2. Mechanistic Investigations and Proposed Mechanism



CONCLUSIONS

In summary, we have developed a copper-catalyzed enantioselective desymmetrizing radical C−O bond coupling of aldehydes with prochiral or meso alcohols. The reaction features a remarkably broad alcohol scope, covering 2,2-dicarbosubstituted 1,3-diols, 2-substituted-2-chloro-1,3-diols, 2-substituted 1,2,3-triols, 2-substituted serinols, glycerol, serinol, meso 1,2-, and 1,4-diols, of which most are challenging substrates for known chemocatalytic enantioselective desymmetrization methods. More importantly, this reaction provides a convenient and practical platform for the fast valorization of biomass industry-relevant alcohols such as glycerol and its derivative serinol as well as erythritol. Mechanistic studies support a radical reaction mechanism with the participation of carbon tetrachloride solvent. The results of this work would encourage further efforts in developing various enantioselective functionalization of acyl radicals using chiral transition-metal catalysis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c00671.

Additional experimental and theoretical results; experimental procedures; characterization of compounds; computational details; NMR spectra, and HPLC traces (PDF)

Accession Codes

CCDC 2207910−2207912 and 2207956−2207957 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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