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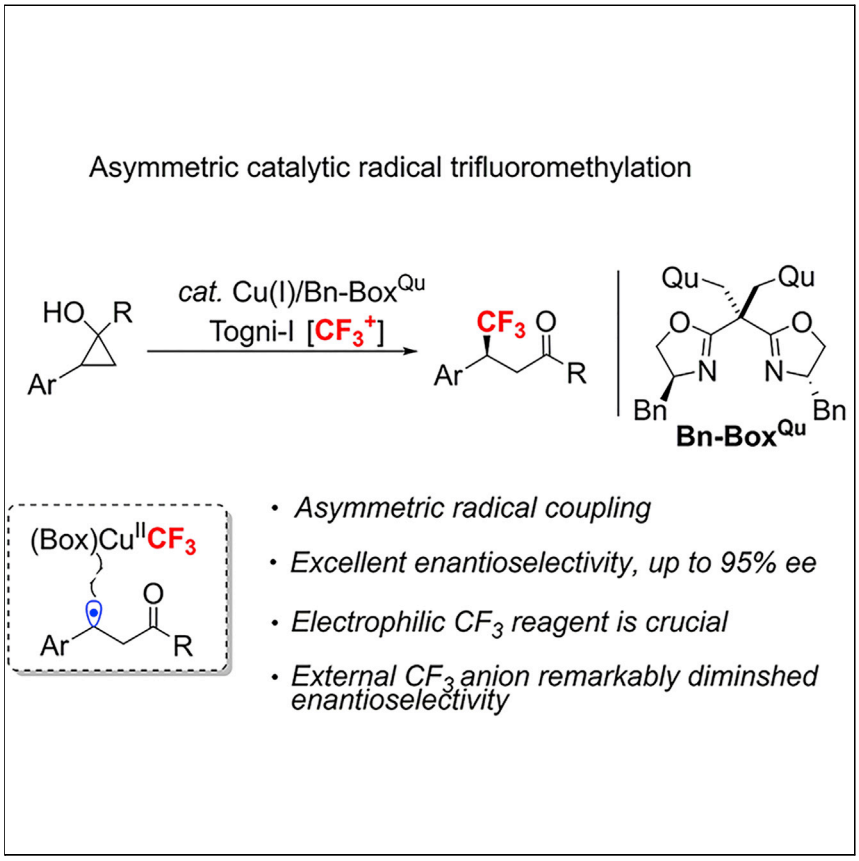
Enantioselective Copper-Catalyzed Trifluoromethylation of Benzylic Radicals via Ring Opening of Cyclopropanols



The asymmetric trifluoromethylation of aryl-substituted cyclopropanols via a radical ring-opening pathway is reported herein, which provides an easy and straightforward access to structurally diverse β-CF_3 ketones in good yields and excellent enantioselectivities under very mild conditions. Critical to the success of the copper-catalyzed radical relay is that a benzylic radical intermediate can be enantioselectively trapped by reactive (L*)$Cu^{II}CF_3$. In addition, a novel quinolinyl-containing bisoxazoline ligand plays a significant role in the asymmetric trifluoromethylation.

Chao Jiang, Lei Wang, Honggang Zhang, Pinhong Chen, Yin-Long Guo, Guosheng Liu

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HIGHLIGHTS

Asymmetric catalytic radical trifluoromethylation

Novel quinolinyl-containing bisoxazoline ligand

Electrophilic CF_3 reagent is crucial to the reaction

External CF_3 anion remarkably diminished enantioselectivity

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Enantioselective Copper-Catalyzed Trifluoromethylation of Benzylic Radicals via Ring Opening of Cyclopropanols

Chao Jiang,[1] Lei Wang,[1] Honggang Zhang,[1] Pinhong Chen,[1] Yin-Long Guo,[1] and Guosheng Liu[1,2,3,*]

SUMMARY

The asymmetric trifluoromethylation of aryl-substituted cyclopropanols via a radical ring-opening pathway is reported herein, which provides an easy and straightforward access to structurally diverse β-CF_3 ketones in good yields and excellent enantioselectivities under very mild conditions. Critical to the success of the copper-catalyzed radical relay is that a benzylic radical intermediate can be enantioselectively trapped by reactive (L*)$Cu^{II}CF_3$. In addition, a novel quinolinyl-containing bisoxazoline ligand plays a significant role in the asymmetric trifluoromethylation.

INTRODUCTION

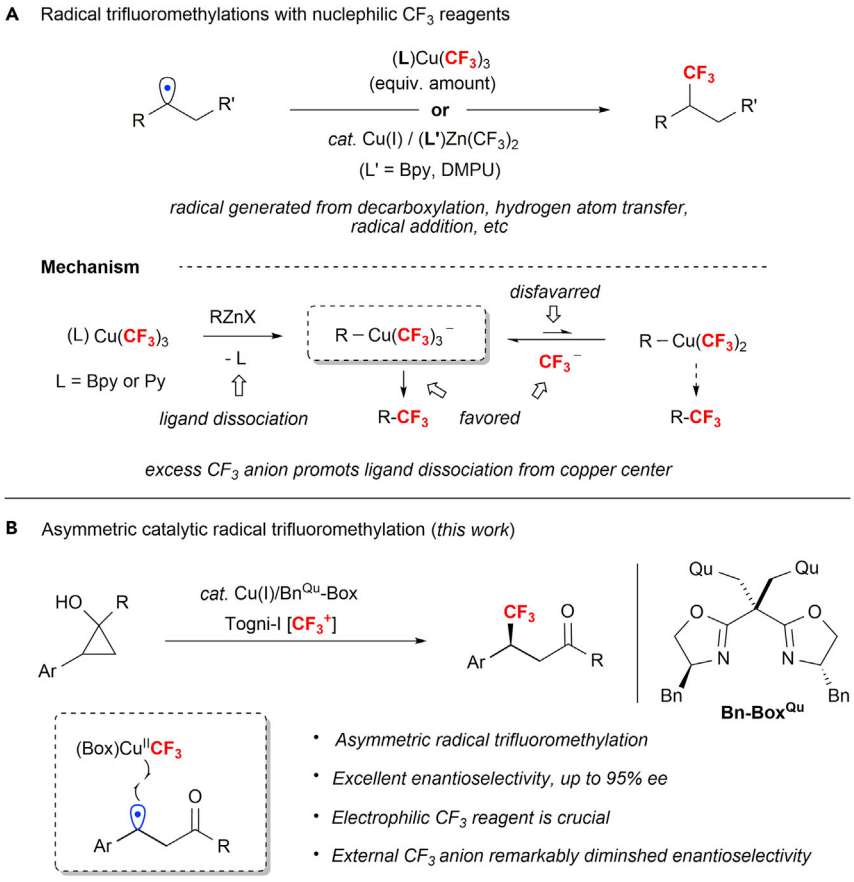
The incorporation of trifluoromethyl (CF_3) groups into biologically active molecules has a significant effect on their physical and biological properties, such as lipophilicity, metabolic stability, and bioavailability.[1,2] Particularly, optically pure CF_3-containing organic compounds have been broadly utilized as pharmaceuticals and agrochemicals.[3] Therefore, considerable effort has been devoted to the development of asymmetric trifluoromethylations during the last decade.[4–7] Despite advances, the asymmetric trifluoromethylation mainly relied on asymmetric nucleophilic and electrophilic trifluoromethylations, which are limited to the synthesis of enantiomerically enriched CF_3-substituted alcohols and ketones, respectively.[8–10] In contrast, the asymmetric trifluoromethylation of carbon-centered radicals is extremely difficult owing to highly reactive radical species. So far, there are no reports of asymmetric radical trifluoromethylations to date.

Distinct from the extensive studies on CF_3 radical addition to alkenes,[11–13] an alternative method for the trifluoromethylation of the carbon-centered radicals has recently received much attention and serves as an attractive tool to introduce the CF_3 group into organic molecules. For instance, as shown in Scheme 1A, Li and co-workers reported a series of Cu-mediated radical trifluoromethylation reactions by using a stoichiometric amount of Cu(III) species [(Bpy)Cu$(CF_3)_3$].[14,15] Copper-mediated C–H bond trifluoromethylation reactions with the same (Bpy)Cu$(CF_3)_3$ reagent were also developed by the groups of Liu[16] an Cook[17] independently. Additionally, copper-catalyzed radical trifluoromethylation reactions were demonstrated by using (L)Zn$(CF_3)_2$ (L = Bpy or DMPU) (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) as effective nucleophilic CF_3 reagents.[18–20]

As our ongoing research interest in asymmetric radical transformations (ATRs), we have recently developed a copper-catalyzed radical relay strategy for the enantioselective cyanation[21–23] and arylation,[24,25] where the benzylic radical was enantioselectively trapped by (Box)Cu$(CN)_2$ or (Box)Cu-Ar species.[26–29] Inspired by the recent

The Bigger Picture

The incorporation of trifluoromethyl (CF_3) groups into biologically active molecules has a significant effect on their physical and biological properties, and optically pure CF_3-containing organic molecules broadly exist in pharmaceuticals and agricultural chemicals. Thus, exploration of efficient asymmetric trifluoromethylation methods is sought after. Recently, radical trifluoromethylation coupling emerged as one of most efficient methods for the synthesis of CF_3-containing molecules, but asymmetric variants remain a formidable challenge. In this article, a copper-catalyzed asymmetric trifluoromethylation of cyclopropanols via a radical relay process is disclosed using a chiral ligand Bn-Box^{Qu}. The reaction enables the synthesis of diverse, optically pure β-CF_3 ketones efficiently, which can serve as versatile building blocks for the synthesis of an (*R*)–CF_3-modified analog of the drug cinacalcet.



Scheme 1. Copper-Mediated or -Catalyzed Radical Trifluoromethylation
Qu, quinolinyl.

progress on the radical trifluoromethylation,[14–20] we envisioned that the asymmetric trifluoromethylation of secondary alkyl radicals forging chiral C–CF_3 bonds might be possible by introducing chiral ligands.

Initially, we investigated the asymmetric trifluoromethylations of benzylic C–H bonds and styrenes using a nucleophilic CF_3 reagent (e.g., TMSCF_3) instead of TMSCN (trimethylsilyl cyanide) under our previously reported conditions.[21] Unfortunately, these reactions failed to give the desired products in an enantioselective manner. Recently, the mechanistic studies from the Liu group[30] revealed that ligands readily dissociated from a copper center in the reactions of (L)$_n$Cu(CF_3)$_3$ (L, Bpy or Py) with alkylzinc reagents. Subsequently, the resulting RCu(CF_3)$_3$ underwent direct reductive elimination to form R–CF_3 bonds. On the contrary, the CF_3 anion is extremely difficult to disassociate from the copper center,[30,31] indicating that the CF_3 anion exhibited a stronger binding to the copper center (Scheme 1A, bottom), which is similar to the effect of cyanides on the asymmetric cyanation of benzylic radicals.[21] Therefore, the excess amount of CF_3 anion could potentially promote the ligand dissociation from the copper center, making the asymmetric radical trifluoromethylation extremely difficult.

In order to avoid the detrimental effect of excessive CF_3 anions, we turned our attention to surveying electrophilic trifluoromethylating reagents.[32,33] Over the last decade, the ring opening of cyclopropanols proceeding through a radical process

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to generate a key carbon-centered radical intermediate has been well-established, especially in the presence of high-valent metal species.[34–40] With this model reaction, we communicate herein the asymmetric radical trifluoromethylation reaction, where the benzylic radical was generated by the copper-catalyzed radical ring opening of aryl-substituted cyclopropanols.[41–43] Notably, the Togni-I CF_3^+ reagent was employed as an electrophilic CF_3 source, avoiding the presence of excess amounts of CF_3 anion. In addition, a novel bisoxazoline (Box) ligand bearing two quinolinyl moieties plays a key role in both the reaction efficiency and enantioselectivity (Scheme 1B).

RESULTS AND DISCUSSION

To test the possibility of the asymmetric radical trifluoromethylation, the radical ring opening of cyclopropanols was used as a model reaction. We examined the reaction of cyclopropanol **1a** with Togni-I reagent in MeOH at 0°C for 12 h, in the presence of 10 mol % $Cu(MeCN)_4PF_6$ and 12 mol % bisoxazoline (Box) **L1** as the catalyst. To our delight, the reaction provided the desired trifluoromethylation product **2a** in 36% yield, albeit with a very low enantioselectivity (7% ee). Encouraged by this result, a series of different Box ligands were then investigated as shown in Scheme 2A (Table S1). The ligand **L2**, bearing gem-methyl and benzyl groups, yielded the product **2a** with 22% ee; replacing the methyl group with an ethyl group (**L3**) led to remarkably increased enantioselectivity (60% ee). The ligand **L4**, with gem-ethyl and pyridyl methylene ($PyCH_2$) groups, gave the product **2a** in a better yield (40%) but with a lower enantioselectivity (26% ee); in comparison, introducing a quinolinyl methylene ($QuCH_2$) group into the ligand **L5** resulted in a much better enantioselectivity (64% ee).

Moreover, the enantioselectivity could be further improved to 81% ee by introducing gem-di$QuCH_2$ groups into the ligand **L6**. Solvent screening revealed that, in a mixture of MeOH and $CHCl_3$, the reaction gave the product **2a** in slightly better enantioselectivity (86% ee). In addition, performing the reaction at −10°C could further increase the enantioselectivity (up to 91% ee). While all the above-mentioned reactions gave the product **2a** in only low to moderate yields, increasing the loading of catalyst was highly beneficial to the reaction efficiency; the reaction using 20 mol % Cu(I) and 24 mol % Box **L6** delivered the product **2a** in 68% yield with 93% ee, and even better yields (74%) and higher enantioselectivity (95% ee) were obtained using 30 mol % Cu(I) and 36 mol % **L6**.

In order to elucidate the roles of the quinolinyl moiety in **L6**, we prepared the ligand **L7** bearing $QuCH_2$ and $NpCH_2$ groups and **L8** bearing gem-di$NpCH_2$ groups. The reaction using **L7** afforded product **2a** in a 50% yield with 92% ee, while **L8** resulted in a significantly diminished yield (16%) with very low enantioselectivity (5% ee). These control experiments suggested that the $QuCH_2$ group plays an important role in the enantioselective trifluoromethylation reaction.

Inspired by our previous studies, a $(L^*)Cu^{II}$-CF_3 complex was proposed to act as a key intermediate for the radical coupling reactions (Scheme 1B). Thus, we assumed that analyzing the structures of $(L^*)CuBr_2$ (L* = **L6** or **L8**) complexes should provide more information for the enantioselective control. However, we failed to get any crystals of these complexes; instead, complexes (**L9**)$CuBr_2$ and (**L10**)$CuBr_2$ (**L9** and **L10** are derived from 1-amino-2-indanol) were unambiguously identified as a twisted square planar geometry by X-ray crystallography. The general trend in enantioselectivity of the reactions using **L9** and **L10** is similar to that of the reactions using **L6** and **L8**

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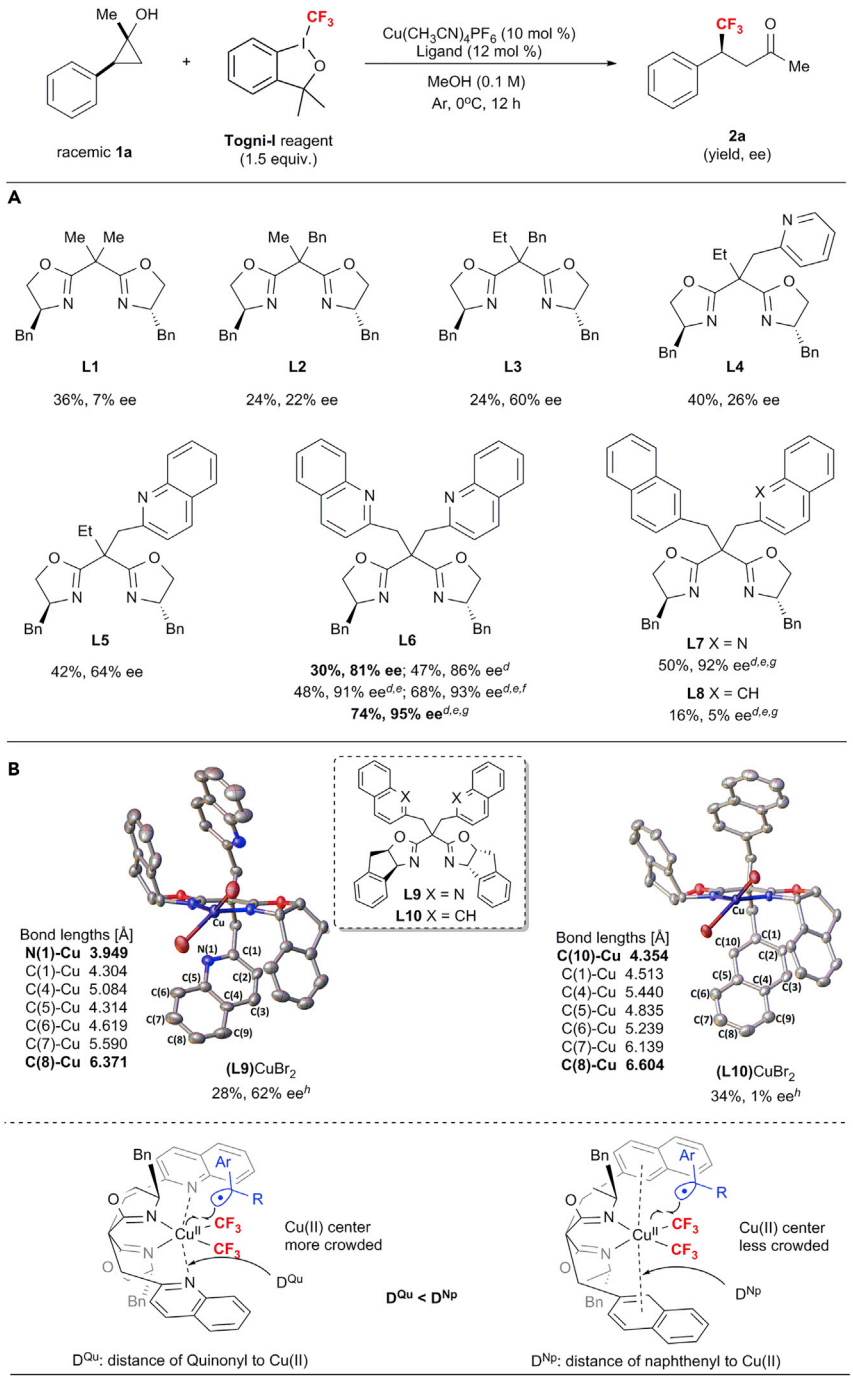

Scheme 2. Optimization of the Reaction Conditions

[a]Reaction was run on a 0.1 mmol scale.[b]^{19}F-NMR yield with CF_3-DMAc as an internal standard.[c]The ee values were determined by HPLC on a chiral stationary phase.[d]$CHCl_3/CH_3OH$ (v/v = 7:3).[e]Reaction at −10°C.[f]Cu(I) catalyst (20 mol %) and ligand (24 mol %).[g]Cu(I) catalyst (30 mol %) and ligand (36 mol %).[h]$Cu(CH_3CN)_4PF_6$ (30 mol %) and **L9** or **L10** (36 mol %) in $CHCl_3/CH_3OH$ (v/v = 7:3) at −10°C.

(Scheme 2B, top). Notably, the binding geometry of quinolinyl with Cu in (**L9**)$CuBr_2$ is remarkably different than that of naphthyl with Cu in (**L10**)$CuBr_2$, in that a weak interaction between quinoline and the copper center makes a more crowded geometry

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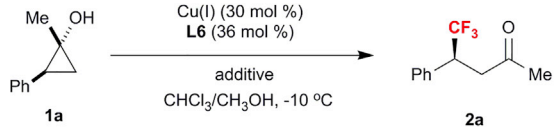


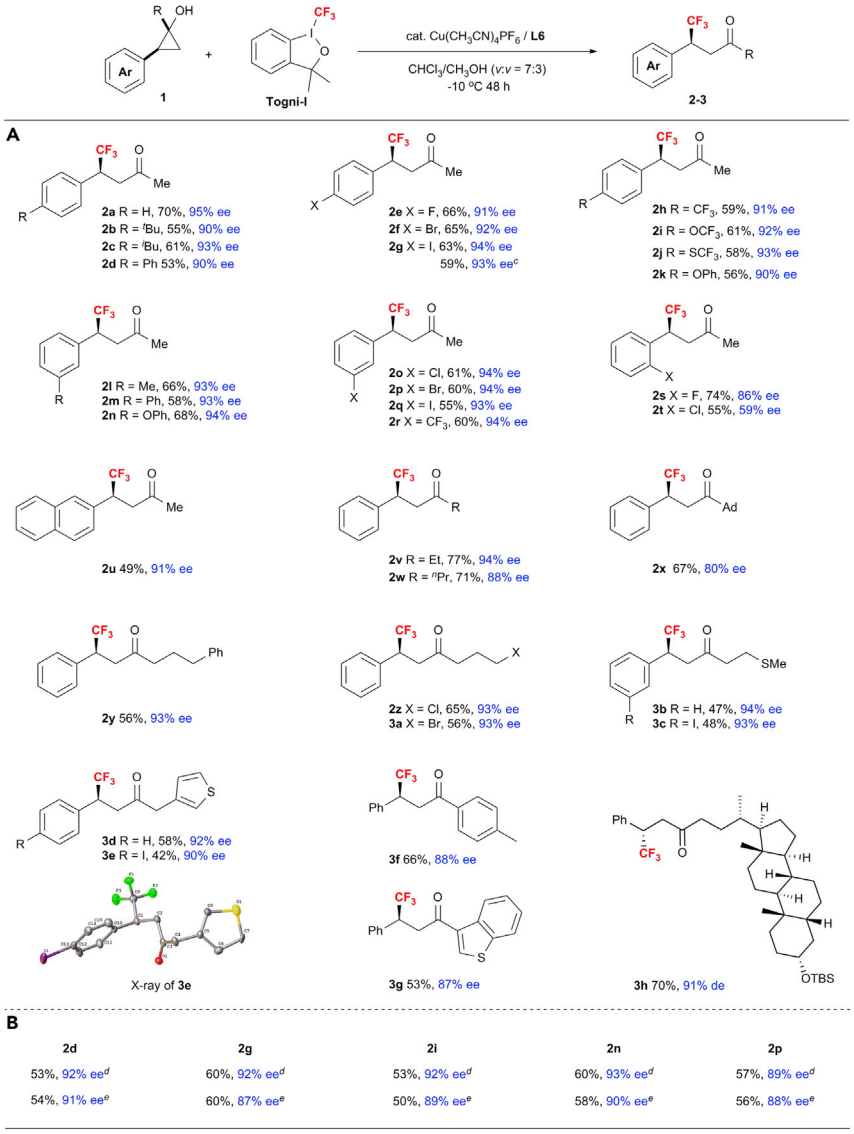
additive (equiv.)	none	$(DMPU)_2Zn(CF_3)_2$ (0.3)	$TMSCF_3$/CsF	
			(0.3 / 0.3)	(0.5 / 0.5)
2a yield (ee)	70% (95% ee)	42% (47% ee)	18% (43% ee)	12% (12% ee)

Scheme 3. The Effect of CF_3 Anion

around the copper center in (**L9**)$CuBr_2$ than (**L10**)$CuBr_2$, accounting for higher enantioselectivities in the benzylic radical-trapping step (Scheme 2B, bottom).

To clarify the effect of excess CF_3 anions on the enantioselectivity, external nucleophilic CF_3 reagents, such as $(DMPU)_2Zn(CF_3)_2$, $TMSCF_3$/CsF were added to the standard reaction conditions. In comparison to the standard conditions, shown in Scheme 3 (Table S5), the enantiomeric excess of **2a** dramatically decreased, whereas the higher concentration of free CF_3^- from $TMSCF_3$ gave an even lower ee value than that of $(DMPU)_2Zn(CF_3)_2$. This observation is consistent with our hypothesis that excess CF_3 anions exhibit a negative effect on the asymmetric trifluoromethylation, owing to the competitive coordination to the copper center and the resulting dissociation of **L6**.

With the optimized reaction conditions in hand, we then explored the substrate scope of the asymmetric trifluoromethylation reaction (Scheme 4A). The reaction tolerated a wide array of functional groups with different electronic nature on the benzene ring of substrate **1**. For example, introducing different groups, such as alkyl, aryl, halogen, CF_3, SCF_3, OCF_3, and ether at the C4 or C3 position on the benzene ring furnished the corresponding β-CF_3 ketones **2a–2r** in good yields (53%–70%) with excellent enantioselectivities (87%–94% ee). However, ortho-substituted substrates yielded the desired products **2s** and **2t** in good yields with moderate to good enantioselectivities (86% ee for **2s** and 59% ee for **2t**). In addition, the aryl framework was extended to a naphthalene-derived system (**2u**, 49% yield and 91% ee). Moreover, substituents adjacent to the hydroxyl group in aryl-substituted cyclopropanols **1** can be various alkyl and aryl groups, and all these substrates gave the desired products **2v–3g** in moderate to good yields (42%–77%) with good to excellent enantioselectivity (80%–94% ee). In addition, various functional groups, such as a halogen, thioether, or thiophene on the alkyl chain were tolerated under our current conditions. The absolute configuration of (*S*)-**3e** was determined by X-ray. More importantly, the reaction of a substrate derived from lithocholic acid also proceeded smoothly to afford the desired product **3h** in a 70% yield with excellent diastereoselectivity (91% de). To demonstrate the scalability of our method, the asymmetric trifluoromethylation was performed on a gram scale to give 1.22 g of the product **2g** without loss of reaction yields and enantioselectivity (59% yield, 93% ee). Moreover, when the catalyst loading decreased to 20 mol % or 15 mol %, the reaction also proceeded smoothly to give the desired products (**2d**, **2g**, **2i**, **2n**, and **2p**) with the same or slightly diminished yields and/or selectivities (Scheme 4B). Unfortunately, reactions of 2-alkylcyclopropanols provided the desired trifluoromethylation products with poor enantioselectivity, presumably owing to the involvement of unstable transient alkyl-substituted carbon-centered radicals, which



Scheme 4. Substrate Scope

[a]Reaction conditions: **1** (0.2 mmol), Togni-I (0.3 mmol), $Cu(CH_3CN)_4PF_6$ (30 mol %), **L6** (36 mol %) in 2.0 mL $CHCl_3$/MeOH (v/v = 7:3) at −10°C.[b]Isolated yield and enantiomeric excess (ee) were determined by HPLC on a chiral stationary phase.[c]6.0 mmol scale (**2g** 1.22 g).[d]$Cu(CH_3CN)_4PF_6$ (20 mol %), **L6** (24 mol %).[e]$Cu(CH_3CN)_4PF_6$ (15 mol %), **L6** (18 mol %).

is unable to be trapped enantioselectively by the chiral copper(II) intermediate at the moment.

Finally, the compatibility of functional groups and heteroarenes was surveyed by subjecting various additives into the standard reaction conditions of **1a**. As shown in Scheme 5, excellent functional group compatibility was observed. For instance, various functional groups, such as ester **A1**, phenol **A2**, aldehyde **A3**, pyridine-N-oxide **A4**, amine **A5**, nitrile **A6**, and amides **A7** and **A8**, were well tolerated, which nearly had no effect on both reactivity and enantioselectivity of the standard reaction. Moreover, these additives were remained in the catalytic system with good to excellent levels of mass balance. In addition, similar results were also observed in the cases

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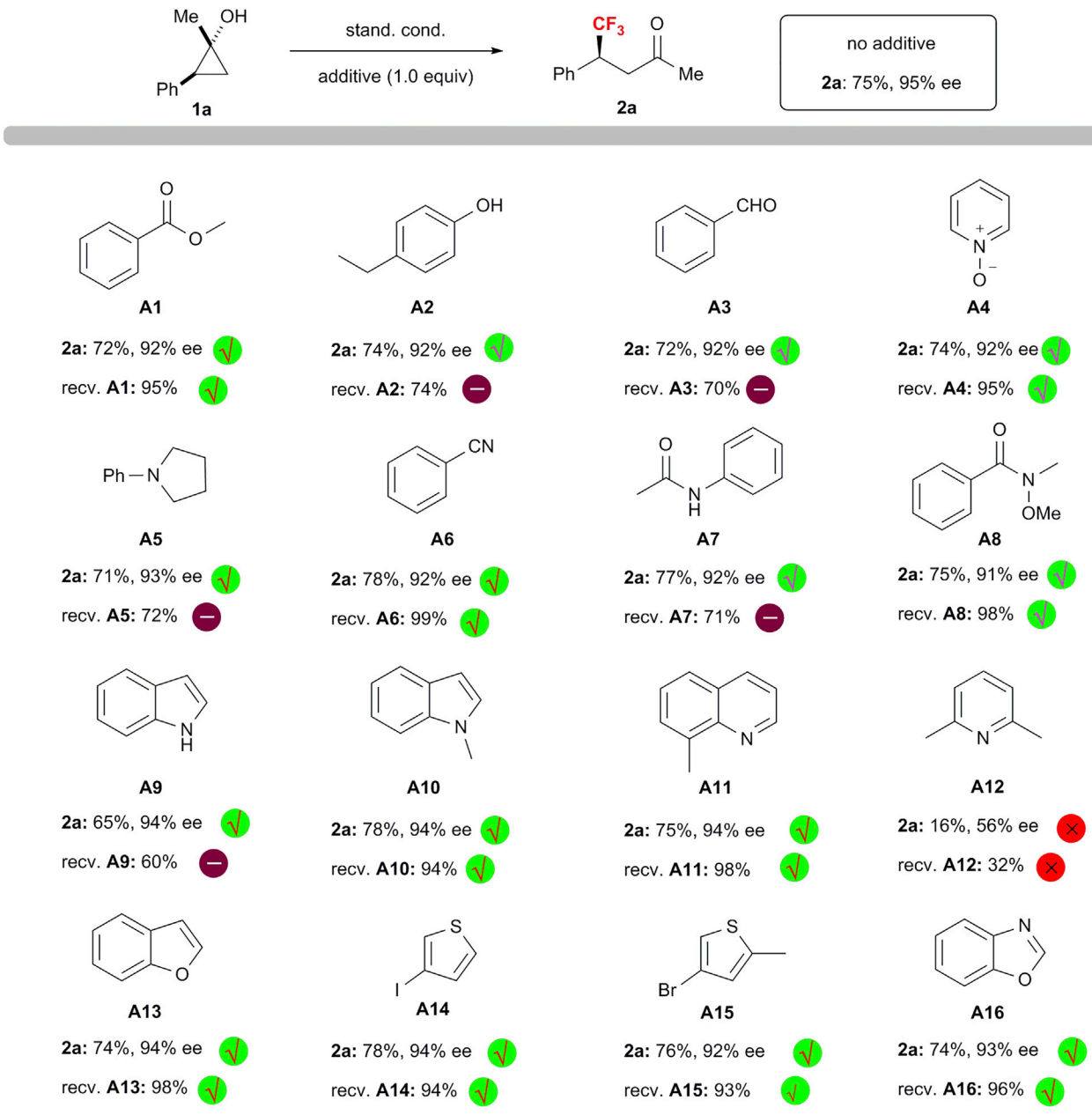

Scheme 5. Functional-Group Tolerance

[a]Reaction was run on a 0.1 mmol scale.[b]^{19}F-NMR yield with CF_3-DMAc as an internal standard and the ee values were determined by HPLC on a chiral stationary phase.[c]GC yield.
recv, recovered additives.

of indoles **A9** and **A10**, quinoline **A11**, benzofuran **A13**, thiophenes **A14** and **A15**, and benzoxazole **A16**, and all of additives were survived very well except for free indole **A9**. However, pyridine **A12** proved to have a detrimental effect on the reaction.

Transformation and Application

To showcase the synthetic utility of our method, further transformations of the enantiomerically enriched β-CF_3 ketones were surveyed (Scheme 6). For example, **2g**

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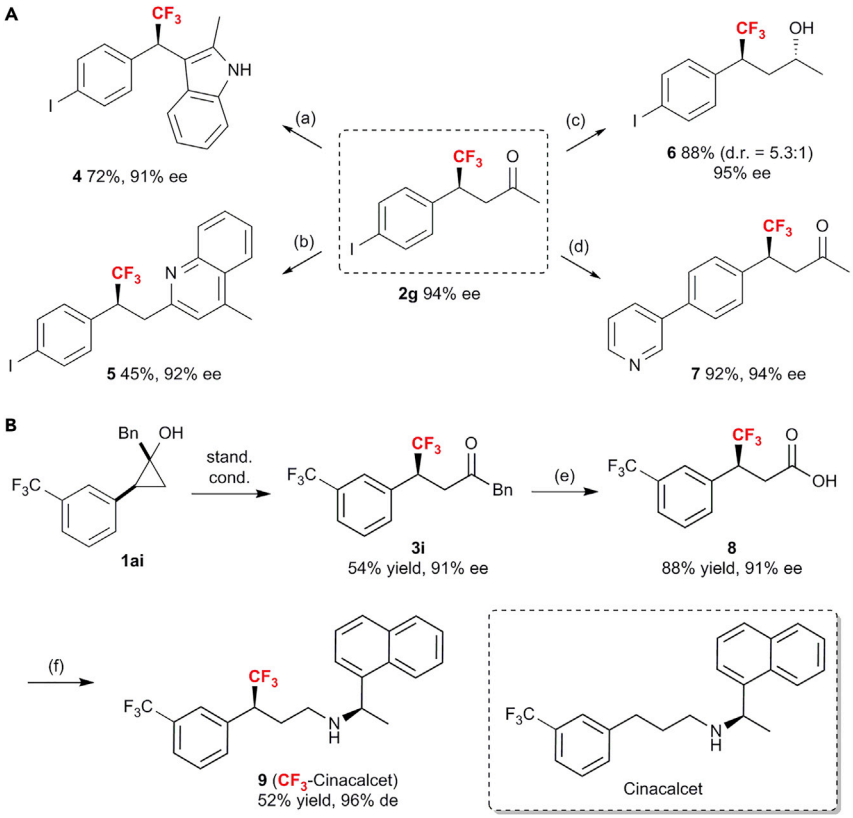

Scheme 6. Synthetic Applications

Reaction conditions:

(A) $PhNHNH_2$, HOAc.

(B) Propylphosphonic anhydride, 2-amino-acetophenone in DMF.

(C) *cat.* (*S*)-CBS, $BH_3{\cdot}SMe_2$.

(D) *cat.* $Pd(PPh_3)_4$, 3-Pyridylboronic acid, K_2CO_3 in dioxane/H_2O.

(E) (1) TFA, *m*-CPBA in DCM; (2) Pd/C, H_2 in THF.

(F) (1) $(COCl)_2$, (*R*)-1-(1-naphthyl)ethylamine in DCM; (2) BH_3 in THF.

could be readily converted into indole **4** in a 72% yield with 91% ee and quinoline **5** in a 45% yield with 92% ee. The ketone moiety was reduced to give an optically pure β-CF_3 alcohol **6** in a 88% yield with a 5.3:1 dr ratio by using (*S*)-CBS as the catalyst, and two isomers were separated by silica column. In addition, **2g** was converted into **7** via a cross-coupling reaction. Furthermore, our present asymmetric trifluoromethylation reaction was applied to the synthesis of an (*R*)-CF_3-modified analog of cinacalcet, a drug for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and hypocalcemia.[44] The trifluoromethylation product **3i** (91% ee) underwent sequential Baeyer-Villiger oxidation and hydrogenation to yield β-CF_3 acid **8** in a 88% yield without the loss of optical purity. Compound **8** was further converted into CF_3-modified cinacalcet **9** through a condensation and reduction sequence in a 52% overall yield with a 96% de, providing an opportunity to survey the fluorine effects on the biologically active cinacalcet.

To provide more insight into the possible radical reaction mechanism, several control experiments were conducted. When α,β-unsaturated ketone **10** was subjected to the reaction of **1v** under the standard conditions, only the ring-opened product **2v** was obtained in a 53% yield with 93% ee, ruling out the possible asymmetric

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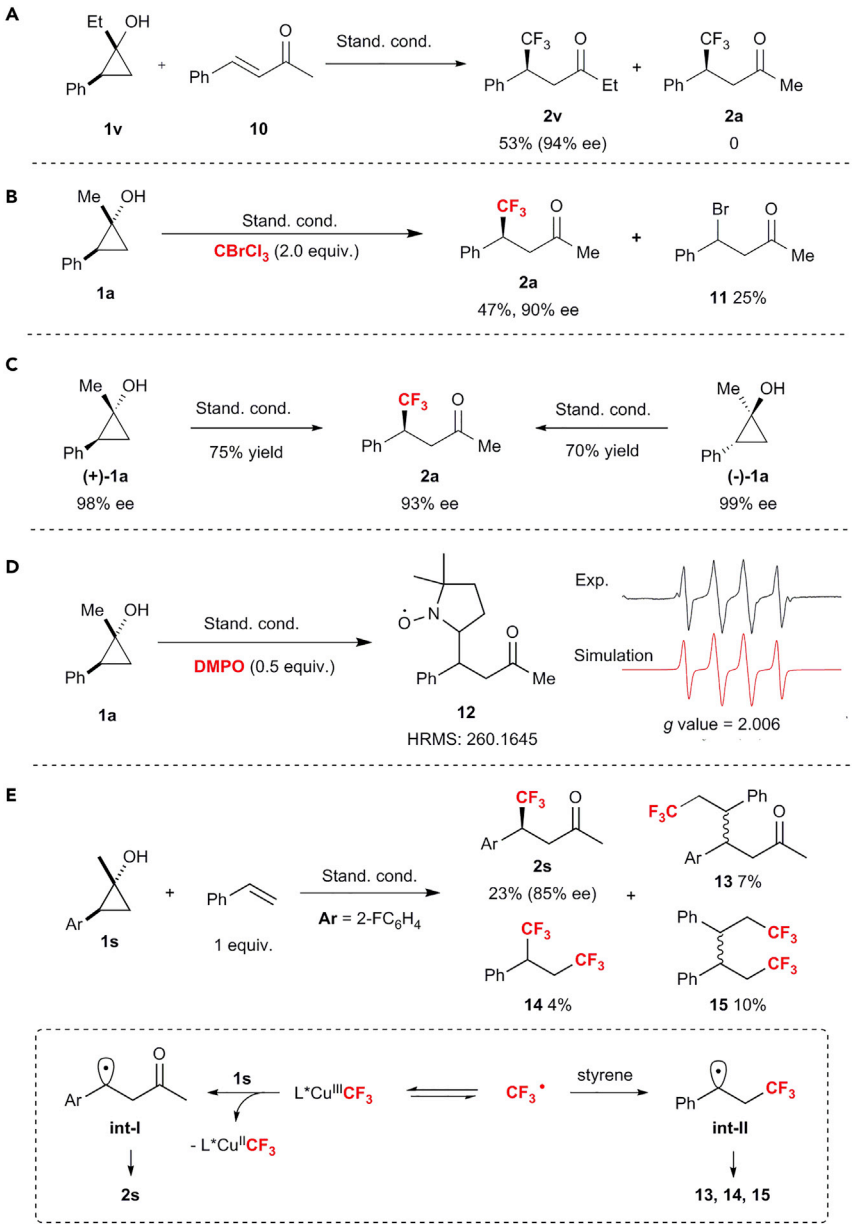


Scheme 7. Mechanistic Studies

Michael addition pathway (Schemes 7A and S1). By adding 2 equiv of $CBrCl_3$ as a radical scavenger to the model reaction, the bromination product **11** was produced in 25% yield (Schemes 7B and S2). In addition, reactions of two opposite enantiomers, (+)-**1a** and (−)-**1a**, delivered the same enantiomer **2a** in similar yields with the same enantioselectivity (93% ee) (Schemes 7C and S3). These observations suggested that the benzylic radical was involved in the asymmetric trifluoromethylation reaction. In fact, the benzylic radical was also trapped by DMPO (5,5-dimethyl-1-pyrroline N-oxide), and the resulting more stable radical **12** was detected by EPR (electron paramagnetic resonance) and high resolution mass spectrometry, which also demonstrated the involvement of the benzylic radical (Schemes 7D and S4; Figure S1). Moreover, when 1 equiv of styrene was subjected to the reaction of **1s** under

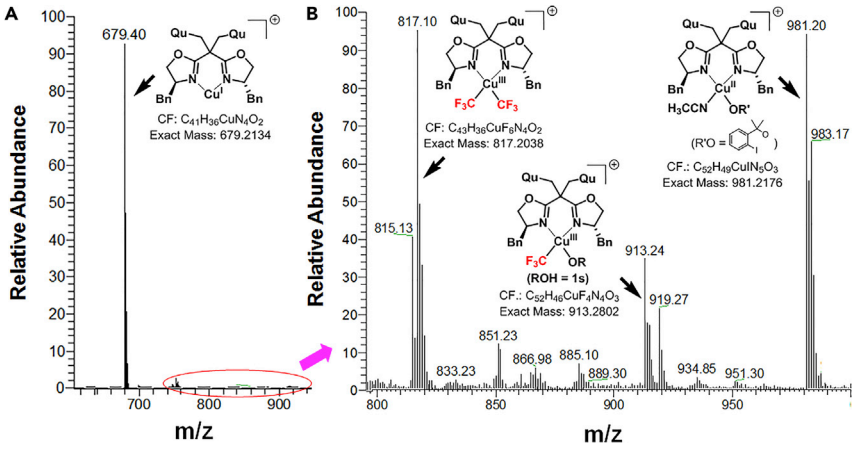
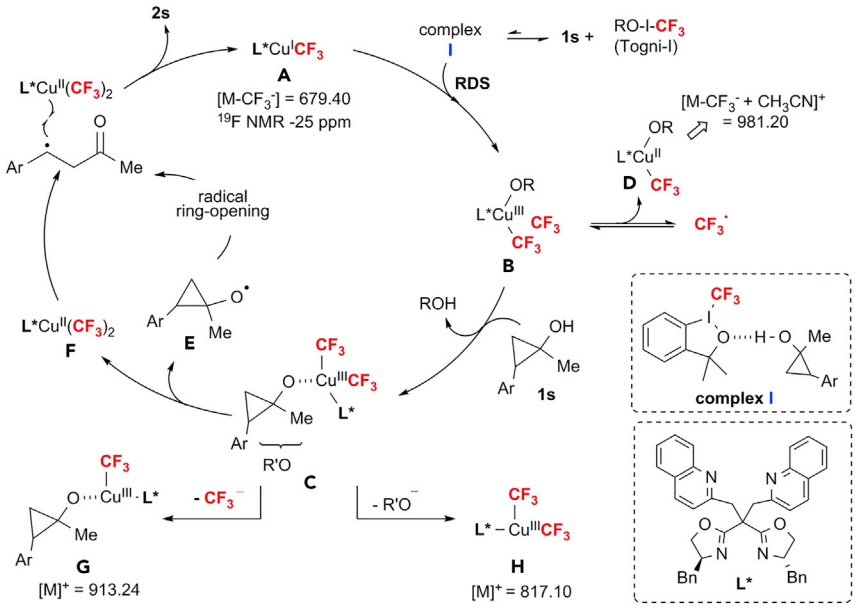


Figure 1. Reaction of 1s Monitored by Mass Spectrometry *In Situ*
Qu, quinolinyl; CF, chemical formula.

the standard conditions, besides the ring-opening trifluoromethylation product **2s**, the radical addition product **14** and the benzylic radical self- and cross-coupling products **13** and **15** were also observed (Schemes 7E and S5). We reasoned that the initial oxidation of L*Cu(I) with Togni-I led to the formation of a (L*)$Cu^{III}CF_3$ species. Then, homolytic cleavage of Cu^{III}-CF_3 bonds occurred to generate a CF_3 radical, followed by radical addition to the styrene, leading to the formation of **13–15** (right). However, in the absence of styrene, the (L*)$Cu^{III}CF_3$ complex reacted with **1s** to generate a benzylic radical int-I via a radical ring-opening pathway, resulting in the formation of trifluoromethylated product **2s** (left).

We also analyzed a crude mixture of the reaction of **1s** by mass spectrometry *in situ* (Figures 1 and S3). A peak of 679.40 (*m/z*), assigned to (**L6**)Cu(I), was observed as the predominant species in the solution, indicating that the oxidation of (**L6**)Cu(I) with Togni-I might be the rate-determining step (Figure 1A). Moreover, the ^{19}F NMR (nuclear magnetic resonance) spectrum of the reaction mixture showed a signal at −25 ppm, which is consistent with the data of $Cu^{I}CF_3$ reported in the literature (see Figure S4).[45] Furthermore, there are two peaks of 817.10 (*m/z*) and 913.24 (*m/z*) (Figure 1B) obtained in the mixture, which could be derived from the same key (**L6**)Cu(III) species **C** bearing two CF_3 and cyclopropanoxide after losing a CF_3 anion (**G**) and propropanoxide (**H**), respectively (Scheme 8). Finally, a peak of 981.20 (*m/z*) (Figure 1B) assigned to (**L6**)Cu(II) species **D** generated from the (L*)Cu(III) species **B** by losing CF_3 radical (Scheme 8) was also observed. Moreover, the MS spectrum showed a much stronger signal at 679.40 (*m/z*) and very weak signals at 817.10 (*m/z*), 913.24 (*m/z*), and 981.20 (*m/z*) (Figure 1A), indicating that the concentration of $Cu^{I}CF_3$ species **A** is much higher than those of Cu(III) species **B** and **C**. This observation revealed that the oxidation of Cu(I) species **A** to Cu(III) species **B** possibly contributes to the rate-determining step. This conclusion is also supported by additional kinetic studies: the reaction exhibited a first order dependence on the concentration of the copper catalyst [Cu(I)/**L6** = 1:1.2] and the saturated dependence on both Togni-I and cyclopropanol substrate (for details, see Figures S7–S9).

Based on these studies, a proposed mechanism is described in Scheme 8. Initially, the oxidation of Cu^{I} with Togni-I-containing complex **I** as the rate-determining step (for details, see Figures S5 and S10) yielded a Cu(III) intermediate **B**, which subsequently reacted with cyclopropanols **1** to give a complex **C**. Homolytic cleavage of Cu^{III}–O



Scheme 8. Proposed Mechanism

bonds in complex **C** led to the formation of a (L*)$Cu^{II}(CF_3)_2$ species **F** and an alkoxide radical **E**. Fast radical ring opening of the alkoxide radical **E** formed a benzylic radical, which was enantioselectively trapped by the (L*)$Cu^{II}(CF_3)_2$ species **F** via a possible Cu(III) intermediate, affording the final enantioenriched trifluoromethylation.

Conclusion

In conclusion, we have developed a copper-catalyzed enantioselective oxidative trifluoromethylation of aryl-substituted cyclopropanols via copper-catalyzed radical relay, which provides an efficient and straightforward access to β-CF_3 ketones in good yields with good to excellent enantioselectivity. Further mechanistic studies and new asymmetric radical trifluoromethylations are ongoing in our laboratory.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Guosheng Liu (gliu@mail.sioc.ac.cn).

Materials Availability

This study did not generate new unique reagents.

Data and Code Availability

The crystallography data have been deposited at the Cambridge Crystallographic Data Center (CCDC) as CCDC: 1956334 (3e), 1956335 [(L9)$CuBr_2$], and 1956336 [(L10)$CuBr_2$] and can be obtained free of charge from www.ccdc.cam.ac.uk/getstructures.

Full experimental procedures are provided in the Supplemental Information.

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SUPPLEMENTAL INFORMATION

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AUTHOR CONTRIBUTIONS

C.J. and H.Z. conducted the experiments. L.W. and Y.-L.G. conducted the MS spectrum experiments. C.J. and G.L. designed the experiments and analyzed the data. G.L. and P.C. wrote the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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