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Copper-Catalyzed Stereospecific C−S Coupling Reaction of Enantioenriched Tertiary Benzylic Amines via in Situ Activation with Methyl Triflate

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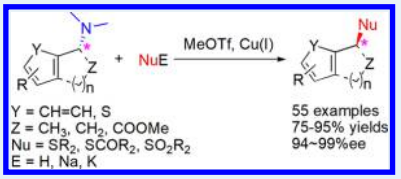
Supporting Information

ABSTRACT: A one-pot protocol for the synthesis of highly enantiopure benzylic thioethers, thioacetates, and sulfones (94−99% ee) via a ligand-free, copper-catalyzed stereospecific C−S coupling reaction of thiols and enantioenriched tertiary benzylic amines via in situ activation by methyl triflate is developed. Various enantioenriched tertiary benzylic amines, including 1-arylalkylamines, 1-tetrahydronaphthylethylamine, heterocyclic amines (e.g., 1-(thiophen-2-yl)ethanamine), and amino acid esters containing a benzylamine moiety, are highly efficient substrates, and their chirality is efficiently transferred to the products (94−99% ee). The absolute configurations of the products are predictable and follow the pattern of S_N2-type substitutions; an inversion of the absolute configuration of the tertiary amines occurs during the C−S coupling reaction. Not only are various alkene-, arene-, and heteroarenethiols suitable for this C−S coupling reaction but also potassium thioacetate and sodium phenylsulfinate are as well. A plausible mechanism was proposed on the basis of the experimental results.



KEYWORDS: *copper, tertiary benzylic amines, benzylic thioethers, chirality, cross coupling, methyl triflate, mechanism*

INTRODUCTION

There are a number of sulfur-containing bioactive natural products and pharmaceutical agents,[1−4] including β-lactam and sulfonamide antibiotics, penicillamine, selective COX-II inhibitors, H2-receptor antagonists,[5] pyrimidine thionucleosides,[6] and immunoconjugates.[7]

More interestingly, optically active benzylic sulfides exhibit excellent biological activities. For example, popular pharmaceutical products and naturally occurring compounds such as montelukast,[8] cardizem (diltiazem),[9] eflucimibe,[10] and mPEES-1 inhibitors[11,12] contain a chiral center bearing a carbon−sulfur bond (Figure 1).

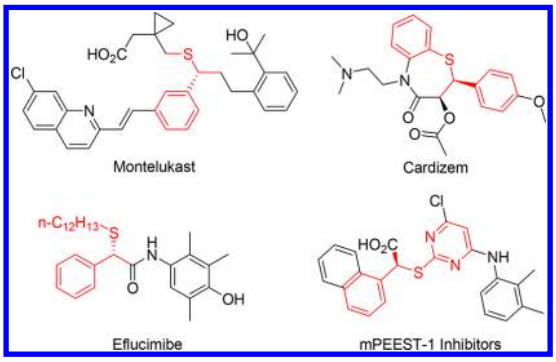


Figure 1. Several typical drugs with chiral benzylic thioether moieties.

There are many methods for the preparation of thioethers,[13−17] but fewer synthetic approaches exist for the preparation of highly enantioenriched benzylic sulfides with a benzylic chiral center. Enantioenriched benzylic thioethers are mainly synthesized via the following methods. (1) Enantioenriched benzylic alcohols can be activated with MsCl[18] and Ph_2PCl[19] and then replaced with thiol salts via S_N2 substitution, which may suffer from low enantiopurities and reaction efficiencies.[20] (2) Lewis acids can catalyze S_N2-type substitutions of enantioenriched benzylic alcohols, which give products with very low ee values (8−15% ee).[21] (3) Iridium and palladium can catalyze asymmetric allylic thioetherifications,[22−26] which need expensive transition-metal catalysts and toxic and expensive chiral ligands. (4) Asymmetric thiolation of sulfonyl indoles can be used to synthesize 3-*sec*-sulfur-substituted indoles, which is limited by its narrow substrate scope.[27,28] (5) Asymmetric trifluoromethylthiolation can be carried out through an enantioselective Doyle−Kirmse reaction with expensive rhodium catalysts, and the reaction may require explosive diazo esters.[29] (6) Nucleophilic substitution of enantioenriched tertiary benzylic amines can be achieved via in situ activation with benzyne, which results in 90−99% ee (Scheme 1).[30]

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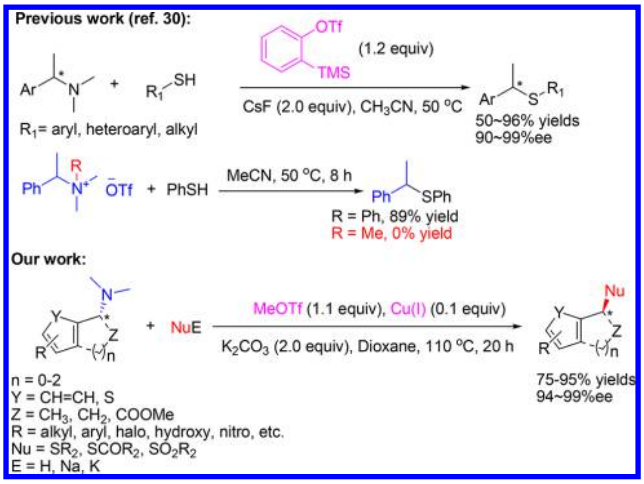
Scheme 1. Synthetic Methods for the Preparation of Enantioenriched Benzylic Thioethers



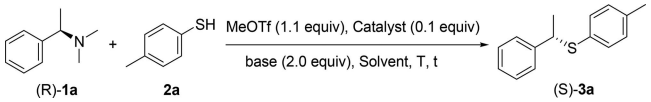
The last method has some outstanding advantages. For example, (1) highly enantiopure tertiary benzylic amines are readily available, (2) in comparison with chiral amine-derived diazonium compounds,[31] diazotates,[32] or pyridinium salts[33] or after the introduction of electron-withdrawing groups to their amino groups,[31,34−36] tertiary benzylic amines are much more able to transfer their chirality into the products (90−99% ee), and (3) through the in situ activation with benzyne, tertiary benzylic amines can be converted to ammonium triflates, which may produce enantioenriched benzylic thioethers via nucleophilic substitution. However, this protocol is not applicable to quaternary benzylic trimethylammonium salts or tertiary benzylic amines with in situ activation by the much less expensive methyl triflate,[30] which is much less reactive. In addition, some deficiencies still exist with this method; for example, some substrates produce products in yields as low as 50%.

Enantioenriched quaternary ammonium salts or tertiary benzylic amines that are activated by methyl triflate can be substituted by an electrochemically generated phosphide[37] and undergo nickel-catalyzed cross couplings with boron reagents (Scheme 1).[38−41] Inspired by related studies and based on our ongoing studies on coupling reactions,[42−46] we envisioned that tertiary benzylic amines activated in situ by methyl triflate will react with thiols only if an appropriate catalyst is used.

Initially, we adopted (*R*)-*N*,*N*-dimethyl-1-phenylethylamine ((R)-**1a**) as the tertiary benzylic amine and methyl triflate as the in situ activator to react with *p*-methylthiophenol (**2a**) under argon. On the basis of common Ullman coupling reaction conditions, we adopted CuI as the catalyst and K_2CO_3 as the base for our initial studies on this reaction. This reaction did proceed but gave a low yield (Table 1, entry 1). CuBr and CuCl also gave low yields (entries 2 and 3). Fortunately, tetrakis(acetonitrile)copper(I) hexafluorophosphate afforded a much higher yield (58%, entry 4). The two cupric salts $Cu(OTf)_2$ and $Cu(OAc)_2$ gave even poorer results (entries 5 and 6). $Ni(OAc)_2{\cdot}4H_2O$ showed good catalytic activity in the nickel-catalyzed borylation of benzylic ammonium salts.[38−41] However, it gave a lower yield in this reaction than was achieved with $Cu(CH_3CN)_4PF_6$ (entry 7).

Interestingly, when the reaction was performed in air, that is, all the starting materials were placed in a test tube with a ground-glass mouth, the vessel was sealed with a rubber stopper, and the air was not exchanged for inert gas, the vessel was put in a preheated oil bath to begin the reaction; amazingly, the yield was approximately the same (Table 1, entry 8). For convenience, these reactions were then performed in air.

Table 1. Optimization of the Conditions of the Copper-Catalyzed Cross Coupling between (*R*)-1a and 2a[a,b]



entry	catalyst	base	solvent	temp (°C)	yield (%)
1[c]	CuI	K_2CO_3	DMSO	100	25
2[c]	CuBr	K_2CO_3	DMSO	100	30
3[c]	CuCl	K_2CO_3	DMSO	100	10
4[c]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	DMSO	100	58
5[c]	$Cu(OTf)_2$	K_2CO_3	DMSO	100	<10
6[c]	$Cu(OAc)_2$	K_2CO_3	DMSO	100	trace
7[c]	$Ni(OAc)_2{\cdot}4H_2O$	K_2CO_3	DMSO	100	45
8	$Cu(CH_3CN)_4PF_6$	K_2CO_3	DMSO	100	57
9[d]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	toluene	100	27
10[d]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	THF	100	60
11[d]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	100	80
12[d]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	DMF	100	trace
13[d]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	60	40
14[d]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	80	66
15[d]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	110	94
16[d]	$Cu(CH_3CN)_4PF_6$	NaOAc	dioxane	110	10
17[d]	$Cu(CH_3CN)_4PF_6$	^tBuOK	dioxane	110	20
18[d]	$Cu(CH_3CN)_4PF_6$	CsF	dioxane	110	80
19[d]	$Cu(CH_3CN)_4PF_6$	$CsCO_3$	dioxane	110	87
20[d]	$Cu(CH_3CN)_4PF_6$	K_3PO_4	dioxane	110	85
21[e]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	110	94
22[f]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	110	60
23[g]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	110	72
24[h]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	110	50
25[i]	$Cu(CH_3CN)_4PF_6$	K_2CO_3	dioxane	110	0
26	$Cu(CH_3CN)_4PF_6$		dioxane	110	0
27		K_2CO_3	dioxane	110	0

[a]Unless otherwise noted, the reactions were carried out with 1.0 mmol of **1**, 1.0 mmol of **2**, 0.1 mmol of catalyst, and 2.0 mmol of base in 3 mL of solvent for 20 h in a sealed test tube with a ground-glass mouth in air. [b]Yields correspond to isolated products. [c]Under an argon atmosphere. [d]2.0 mmol of **2a** was used. [e]3.0 mmol of **2a** was used. [f]The reaction time was 6 h. [g]The reaction time was 12 h. [h]0.05 mmol of catalyst was used. [i]Bidentate amine ligands, including *N*,*N*′-dimethylethylenediamine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, and 1,10-phenanthroline, were used.

Next, we began to screen solvents. The experimental results indicate that dioxane was the best solvent for this reaction, as it gave the desired product (*S*)-**3a** in 80% yield (Table 1, entries 10−12). Then, the reaction temperature was evaluated. The reaction conducted at 60 °C gave **3a** in a low yield (40%, entry 13). When the temperature was increased to 110 °C, the yield reached as high as 94% (entry 15). The investigation of bases showed that K_2CO_3 was the most effective base for this reaction (entries 16−20 vs entry 15).

An increase of **2a** to 3 equiv resulted in nearly the same yield (Table 1, entry 21 vs entry 15), and a portion of *p*-methylthiophenol **2a** tended to be converted to the disulfide; therefore, 2 equiv of **2a** was adopted. An examination of the reaction time showed that the reaction yields increased with

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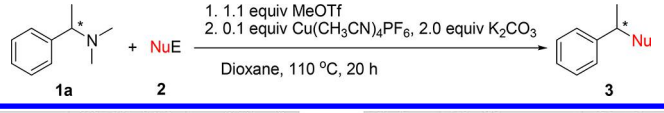
Table 2. Scope of the Copper-Catalyzed Cross Coupling between *N,N*-Dimethyl-1-phenylethylamine (1a) and Various Thiols or Organic Sulfur Salts 2[a,b]



Entry	NuE	Product	Yield (%)	ee (% ee)
1	**2a**	(±)-**3a**	94	--
2	**2a**	(S)-**3a**	93	97
3	**2a**	(R)-**3a**	91	98
4	**2b**	(±)-**3b**	81	--
5	**2b**	(R)-**3b**	82	95
6	**2c**	(±)-**3c**	84	--
7	**2c**	(S)-**3c**	86	97
8	**2d**	(±)-**3d**	85	--
9	**2d**	(S)-**3d**	84	98
10	**2d**	(R)-**3d**	87	97
11	**2e**	(±)-**3e**	84	--
12	**2e**	(R)-**3e**	86	99
13	**2f**	(±)-**3f**	80	--
14	**2f**	(S)-**3f**	82	99
15	**2g**	(±)-**3g**	85	--
16	**2g**	(S)-**3g**	83	96
17	**2h**	(±)-**3h**	70	--
18	**2h**	(R)-**3h**	75	98
19	**2i**	(±)-**3i**	78	--
20	**2i**	(S)-**3i**	80	98
21	**2j**	(±)-**3j**	78	--
22	**2j**	(R)-**3j**	75	98
23	**2k**	(±)-**3k**	77	--
24	**2k**	(R)-**3k**	78	98
25	**2m**	(±)-**3m**	86	--
26	**2m**	(S)-**3m**	89	99
27	**2n**	(±)-**3n**	87	--
28	**2n**	(S)-**3n**	89	96
29	**2o**	(±)-**3o**	82	--
30	**2o**	(R)-**3o**	85	99
31	**2p**	(±)-**3p**	89	--
32	**2p**	(S)-**3p**	85	95
33	**2q**	(±)-**3q**	89	--
34	**2q**	(S)-**3q**	87	98
35	**2r**	(±)-**3r**	88	--
36	**2r**	(S)-**3r**	84	95

[a]Reaction conditions: 1.0 mmol of **1a**, 2.0 mmol of **2**, 0.1 mmol of $Cu(CH_3CN)_4PF_6$, and 2.0 mmol of K_2CO_3 in 3 mL of dioxane, 110 °C, 20 h, in air. [b]Yields presented are of isolated products.

increasing time (entries 15 and 22−23), but reaction times of more than 20 h were unnecessary. A decrease in the catalyst loading of $Cu(CH_3CN)_4PF_6$ to 5 mol % resulted in only 50% yield (entry 24).

Generally, ligands are beneficial for reactions, as they stabilize the central metal ion of the catalysts. Oddly, this reaction did not proceed when several bidentate amine ligands, such as *N,N′*-dimethylethylenediamine, *N,N,N′,N′*-tetramethylethylenediamine, and 1,10-phenanthroline, were added to the reaction mixture (Table 1, entry 25). No product was formed in the absence of either catalyst or base (entries 26 and 27).

With the optimized reaction conditions in hand, various arenethiols were evaluated in the C−S coupling reaction with racemic and enantioenriched (*R*)- and/or (*S*)- *N,N*-dimethyl-1-phenylethylamine (**1a**) with in situ activation by methyl triflate (Table 2).

There is an interesting phenomenon shown by the data in Table 2: that is, all of the *R* forms of the tertiary benzylic amines gave the *S* forms of the thioethers and vice versa. It seems that the methyl triflate activated, copper-catalyzed coupling reaction occurs via an S_N2-type substitution: that is, the chiral configurations of the tertiary benzylic amines were completely inverted during the C−S coupling reaction. Moreover, the inverted chirality is highly stereospecific: namely, nearly no racemization occurs during any of the transformations. All of the thioethers were obtained in 95−

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99% ee from commercially available enantioenriched *N*,*N*-dimethyl-1-phenylethylamine (the enantiopurity of this chiral reagent was not determined).

All *p*-, *m*-, and *o*-methylthiophenols were examined. All of them gave the desired benzylic thioethers with excellent enantiopurity and high yields (Table 2, entries 1−7), and steric hindrance from the ortho substituent did not decrease the yield of product **3a**. Both enantiomers of the thioethers could be obtained (entries 2 and 3). Yields of the racemic and enantioenriched products were generally the same (entry 1 vs entries 2 and 3).

More importantly, various halogen substituents on thiophenol were well tolerated in this C−S coupling (Table 2, entries 8−18). Furthermore, no homocoupling of the halogen-substituted thiophenols occurred, despite the fact that each halogen-substituted thiophenol held both an electrophilic halogen group and a nucleophilic sulfhydryl group. Except for 2,4-dichlorothiophenol, which provided a moderate yield (entries 17 and 18), all thiophenols afforded fairly high yields of more than 80%.

Next, various heteroaryl thiols were investigated (Table 2, entries 19−24). All of these coupling reactions offered fairly good yields and extremely high ee values.

In the reported benzyne-activated nucleophilic substitution, a simple ethanethiol was examined and afforded 50% yield and 92% ee,[30] which means that alkanethiols are not suitable substrates for this protocol. Surprisingly, for our copper-catalyzed, methyl triflate activated method, not only simple alkyl thiols (Table 2, entries 25−30) but also ethyl mercaptoacetate (entries 33 and 34) produced the desired thioethers with extremely high enantiopurities (up to 99% ee) and yields (82−89%) that were comparable to those obtained with arenethiols.

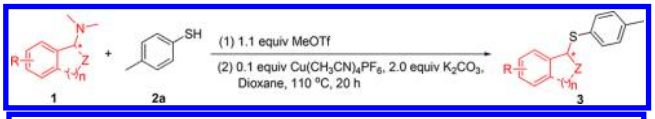
Potassium thioacetate also provided the enantioenriched benzylic thioacetate with 98% ee and 87% yield via the expected C−S coupling process (Table 2, entries 33 and 34). Sodium tolylsulfinate produced a chiral benzylic sulfone with excellent enantiopurity and high yield (entries 35 and 36).

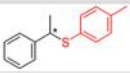
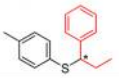
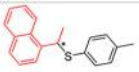
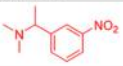
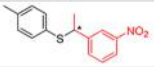
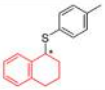
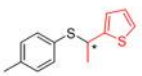
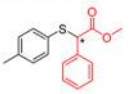
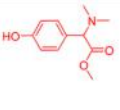
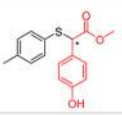
Via in situ activation by methyl triflate, the copper(I)-catalyzed C−S cross-coupling reaction of a series of enantioenriched tertiary benzylic amines **1a**−**h** and *p*-toluenethiol (**2a**) successfully afforded the desired absolute-configuration-inverted benzylic thioethers in good yields (83−94%) and with excellent enantiopurities (94−99% ee) (Table 3, entries 1−22).

When the benzylic methyl group of *N*,*N*-dimethyl 1-phenylethylamine (**1a**) was replaced with an ethyl group (**1b**) or when the phenyl group of **1a** was replaced with a 1-naphthyl group (**1c**), the corresponding products were generated in lower yields of approximately 50% via the benzyne activation method.[21] To our delight, in our copper(I)-catalyzed protocol, **1b** (Table 3, entries 4−6) and **1c** (entries 7−9) provided the corresponding products in high yields and enantiopurities comparable to those for **1a** (entries 1−3). *N*,*N*-Dimethyl-1-(3-nitrophenyl)ethylamine (**1d**), with a strong electron-withdrawing nitro group, also provided good results (entries 10 and 11).

It is worth mentioning that the benzyne-activated protocol was not suitable for the reaction of valuable *N*,*N*-dimethyl 1-tetrahydronaphthylethylamine (**1e**).[30] However, the methyl triflate activated, copper(I)-catalyzed approach afforded a nearly perfect reaction with high yields and extremely high enantiopurities of 97−99% ee (Table 3, entries 13 and 14).

Table 3. Scope of the Copper-Catalyzed Cross Coupling between Various Tertiary Benzylic Amines 1 and *p*-Methylbenzenethiol (2a)[a,b]



Entry	1	Product	Yield (%)	ee (%ee)
				
1	(±)-**1a**	(±)-**3a**	94	--
2	(R)-**1a**	(S)-**3a**	93	97
3	(S)-**1a**	(R)-**3a**	91	98
				
4	(±)-**1b**	(±)-**3s**	90	--
5	(R)-**1b**	(S)-**3s**	89	98
6	(S)-**1b**	(R)-**3s**	92	98
				
7	(±)-**1c**	(±)-**3t**	90	--
8	(R)-**1c**	(S)-**3t**	91	98
9	(S)-**1c**	(R)-**3t**	90	98
				
10	(±)-**1d**	(±)-**3u**	87	--
11	(S)-**1d**	(R)-**3u**	89	99
				
12	(±)-**1e**	(±)-**3v**	91	--
13	(R)-**1e**	(S)-**3v**	91	97
14	(S)-**1e**	(R)-**3v**	93	99
				
15	(±)-**1f**	(±)-**3w**	83	--
16	(S)-**1f**	(R)-**3w**	85	94
				
17	(±)-**1g**	(±)-**3x**	90	--
18	(R)-**1g**	(S)-**3x**	90	99
19	(S)-**1g**	(R)-**3x**	88	98
				
20	(±)-**1h**	(±)-**3y**	86	--
21	(R)-**1h**	(S)-**3y**	86	99
22	(S)-**1h**	(R)-**3y**	85	97

[a]Reaction conditions: 1.0 mmol of **1a**, 2.0 mmol of **2**, 0.1 mmol of $Cu(CH_3CN)_4PF_6$, and 2.0 mmol of K_2CO_3, 3 mL of dioxane, 110 °C, 20 h, in air. [b]Yields presented are of isolated products.

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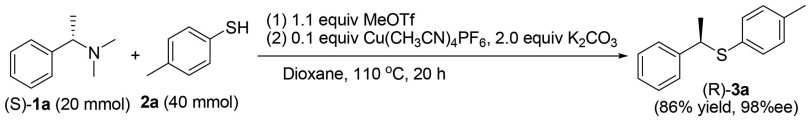
Scheme 2. Larger Scale Reaction



Although highly enantioenriched 1-heteroarylethyl thioethers are not common, they show promise as a class of valuable building blocks for medicinal chemistry. Heteroatoms, especially sulfur, in heterocyclic moieties may interfere in coupling reactions. Luckily, the thiophenyl group did not hamper the C−S coupling reaction of (*S*)-*N*,*N*-dimethyl-1-(thiophen-2-yl)ethanamine (Table 3, entries 15 and 16). Given the heterocyclic benzylic amine substrate, the 85% yield and 94% ee achieved in this reaction are quite pleasing (entry 16).

Amino acids are the basic building blocks of peptides, proteins, and enzymes. Most natural amino acids have high enantiopurities and are relatively inexpensive members of the chiral pool. *N*,*N*-Dimethyl amino acid esters were not tested in the benzyne-activated protocol.[30] Given the value and ready accessibility of chiral amino acids, phenylglycine methyl ester and *p*-hydroxyphenylglycine methyl ester were evaluated in the methyl triflate activated, copper-catalyzed C−S coupling reaction. It has been reported that enantiopure (*R*)-*N*,*N*-dimethyl phenylglycine methyl ester gave a completely racemic C−C coupling product in a Pd-catalyzed C−C coupling reaction with arylboronic acid at 80 °C.[47] However, amazingly, the copper-catalyzed C−S coupling reaction afforded the C−S coupling products with extremely high enantiopurities of 98−99% ee (Table 3, entries 17−19). Importantly, the hydroxyl group of *N*,*N*-dimethyl *p*-hydroxyphenylglycine methyl ester did not disturb the C−S coupling reaction of the tertiary benzylic amines. The C−S coupling reaction of *p*-hydroxyphenylglycine methyl ester provided yields and enantiopurities comparable to those achieved with phenylglycine methyl ester (entries 20−22). This discovery confirms that it is possible to use natural, inexpensive, and readily available chiral amino acids in this protocol.

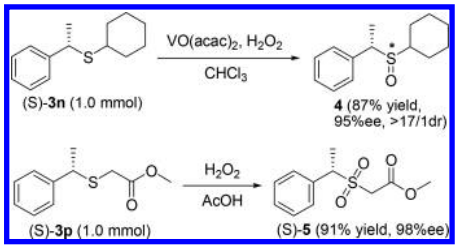
To verify the effectiveness of this reaction platform, a larger scale reaction was conducted (Scheme 2). A 20 mmol scale reaction provided the corresponding product in 86% yield and 98% ee, demonstrating that this method has potential applications in industrial chemical production.

Chiral sulfoxides and sulfones are not only a diverse group of bioactive substances[1−4] but also an important class of chiral catalysts and chiral ligands used in organic synthesis.[1−4] To further demonstrate the applicability of this method, two (**3n**,**p**) of the synthesized thioethers were diastereoselectively converted to sulfoxide **4** (note: the absolute configuration of the sulfinyl moiety was not determined) with 95% ee and >17/1 dr and chiral sulfone ((*S*)-**5**) with 98% ee, respectively (Scheme 3), which demonstrates the important potential of this method for industrial production.

To explore the reaction mechanism, three control experiments were conducted (Scheme 4).

First, we found that the reaction of quaternary ammonium salt **8** with *p*-toluenethiol (**2a**) under the same experimental conditions efficiently provided desired the target product **3** (eq 1 in Scheme 4), which suggests that tertiary benzylic amines are efficiently transformed into their corresponding quaternary ammonium salts during the reaction.

Scheme 3. Reaction Expansion by Functional Group Transformation



Next, in the Pd-catalyzed C−C coupling reaction of benzylic quaternary ammonium salts and arylboronic acids, styrene was obtained via elimination from the benzylic quaternary ammonium salts.[47] Thus, we tried the reaction of *p*-toluenethiol (**2a**) and styrene (**11**) to verify whether this C−S coupling reaction involves the addition of styrene. The experimental result shows that almost no target product **3** was obtained, and the main product was the disulfide **7** (eq 2 in Scheme 4). From this result we can speculate that the quaternary ammonium salts are not transformed into olefins in the reaction and that this C−S coupling reaction did not involve styrenes.

Third, we performed an experiment in which TEMPO was added to the standard conditions to verify whether this reaction involved a free radical. **3a** was obtained in 82% yield, which is comparable to the model reaction (eq 3 in Scheme 4). This means that TEMPO does not obviously influence the conversion; therefore, a single-electron-transfer mechanism can be excluded from the reaction mechanism.

The results of the control experiments suggest that this reaction is a metal complex catalyzed cross-coupling reaction and that copper(I) serves as the metal center of the catalyst complex. A few papers have reported that copper(I) may be converted to copper(III) during oxidative addition processes.[48−50] We adopted ESI-mass spectrometry to determine the structure of the copper catalyst intermediate in the oxidative addition step.

The sample preparation for mass spectrometry was as follows. Under argon, the benzylic quaternary ammonium salt $Cu(CH_3CN)_4PF_6$ and THF were heated at 60 °C for 20 h. Then, the reaction mixture was cooled to room temperature, and the THF was removed on a rotary evaporator. The resulting residue was dissolved in acetonitrile to afford the mass spectrometry sample. The ESI-mass spectrum in the positive ion mode showed two peaks (164 and 477 Da) (see the Supporting Information). The 164 Da peak corresponded to *N*,*N*,*N*-trimethyl-1-phenylethanaminium ($C_{11}H_{18}N^+$) from *N*,*N*,*N*-trimethyl-1-phenylethanaminium triflate (**8**; Scheme 5). The 477 Da peak is from the unusual five-coordinated complex cation $[(C_8H_9)Cu(CH_3CN)(THF)(NMe_3)(OTf)]^+$ (**9**) (Scheme 5), which is from the copper source ($Cu(CH_3CN)_4PF_6$), THF, and ammonium triflate **8**, which provides $N(CH_3)_3$, OTf^-, and 1-phenylethyl cation ($[C_8H_9]^+$) as a stable cation.

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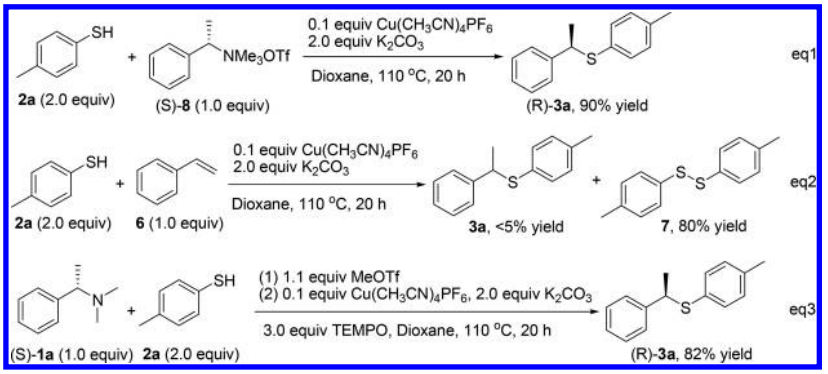
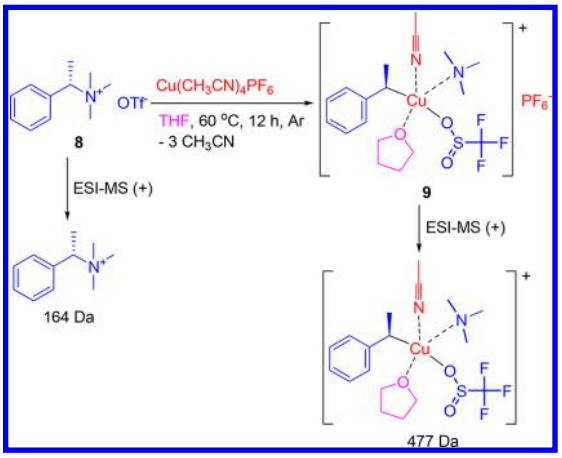
Scheme 4. Control Experiments

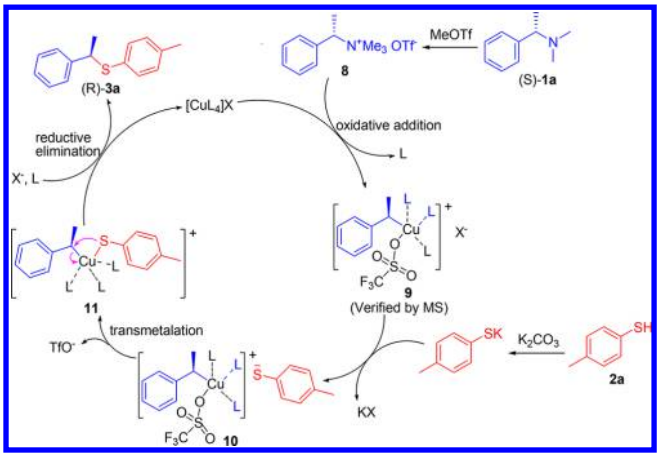


Scheme 5. ESI-MS of the Mixture of $Cu(CH_3CN)_4PF_6$ and *N,N,N*-Trimethyl-1-phenylethanaminium Triflate (8) in THF



On the basis of the above experimental results and previous relevant studies, a reasonable mechanism for the C−S coupling reaction is proposed, as shown in Scheme 6. First, (*S*)-*N,N*-dimethyl-1-phenylethylamine (**1a**) rapidly reacts with methyl triflate to form a quaternary benzylic ammonium salt ((*S*)-**8**) as an electrophilic reagent, which was verified by Watson's report[38] and our experiments. The oxidative addition of the copper(I) compound (e.g., $Cu(CH_3CN)_4PF_6$) and **8** occurs via a similar S_N2-type reaction: that is, the copper(I) species attacks the quaternary ammonium salt (**8**) from the back of the ammonium group, breaking the C−N bond. The released trimethylamine probably coordinates with the copper, and thus, an unusual five-coordinated copper(III) intermediate ((*R*)-**9**) with the reverse absolute configuration is formed, and the structure of this complex was verified by ESI-mass spectrometry (Scheme 6 and the Supporting Information). In the presence of the weak base K_2CO_3, *p*-toluenethiol (**2a**) is converted into potassium thiolate, which is exchanged with the hexafluorophosphate anion in the outer sphere to afford copper(III) intermediate (*R*)-**10**. Then, the thiolate anion attacks the inner sphere of the copper(III) species to expel an X^- ion to form a copper(III) intermediate ((*R*)-**11**) during the transmetalation. Copper-mediated bond reconstruction in the complex (*R*)-**11** completely retains the chirality of the benzylic carbon during the transfer. Intramolecular electron transfer of the complex intermediate (*R*)-**11** during the reductive elimination results in the formation of the desired product (*R*)-**3a**. When (*R*)-**3a** is expelled from the catalytic species, the copper(I) catalyst is regenerated, turning over the catalytic cycle.

Scheme 6. Plausible Mechanism[a]



[a]L = solvent (CH_3CN, THF, 1,4-dioxane), $N(CH_3)_3$, etc.; X = PF^{6-}, OTf^-.

This mechanism may clarify the experimental observations. For example, the presence of bidentate amine ligands including *N,N′*-dimethylethylenediamine, *N,N,N′,N′*-tetramethylethylenediamine, and 1,10-phenanthroline completely inhibited this reaction. To explain this, we conjecture that a bidentate amine ligand and $Cu(CH_3CN)_4PF_6$ will form a strong coordination complex: that is, the two Cu−N bonds formed to the bidentate amine ligand molecule are much shorter than those to the two acetonitrile molecules. The two shorter Cu−N bonds make formation of the five-coordinated copper complex (**9**) impossible: namely, the copper complex with a bidentate amine ligand only permits four coordination sites. There are not enough coordinate sites to accommodate *N,N,N*-trimethyl-1-phenylethanaminium triflate (**8**) and subsequent dissociation into intermediate **9** during the oxidative addition.

CONCLUSIONS

In summary, an efficient one-pot method for the synthesis of highly enantiopure benzylic thioethers, thioacetates, and sulfones (94−99% ee) was developed via a ligand-free copper-catalyzed C−S cross-coupling reaction between (hetero)arene- and alkanethiols and enantioenriched tertiary benzylic amines via in situ activation by methyl triflate. These enantioenriched benzylic amines include 1-arylalkylamines, 1-tetrahydronaphthylethylamine, heterocyclic amines (e.g., 1-(thiophen-2-yl)ethanamine), and amino acid esters containing

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a benzylamine moiety (e.g., phenylglycine ester and 4-hydroxyphenylglycine ester). Moreover, this protocol is applicable to large-scale synthesis. The highly enantiopure thioethers can easily be transformed into sulfoxides with high diastereoselectivity (95% ee, >17/1 dr) and sulfones with high enantiopurity (98% ee). Because these reactions can be performed in air, this protocol is a simple, operationally easy, and effective strategy for the synthesis of various chiral compounds containing C−S bonds. Moreover, a plausible mechanism is proposed on the basis of the experimental data, and this mechanism can be used to explain various experimental observations in the ligand-free copper-catalyzed C−S coupling reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b03032.

Experimental details and chemical compound information (PDF)

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Notes

The authors declare no competing financial interest.

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