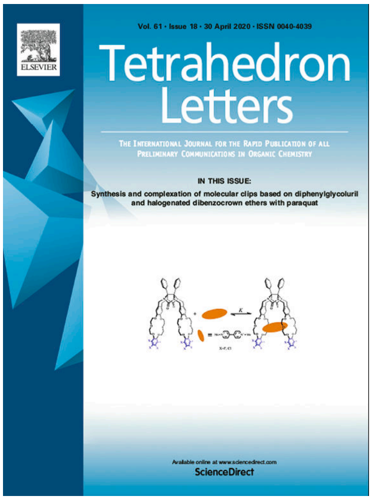

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Cu_2O-catalyzed C-S coupling of quaternary ammonium salts and sodium alkane-/arene-sulfinates

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ABSTRACT

A new protocol for the synthesis of (enantioenriched) benzylic sulfones *via* the Cu_2O-catalyzed C-S bond cross coupling of alkane-/arene-sulfinates and (enantioenriched) benzylic quaternary ammonium salts has been developed. The product benzylic sulfones were obtained in good to high yields (75-96%). Chiral arylmethyl sulfones with high enantiomeric excess (90-94% ee) were also synthesized in the presence of Cu_2O and 1,1'-bis-(diphenylphosphino)ferrocene (dppf).

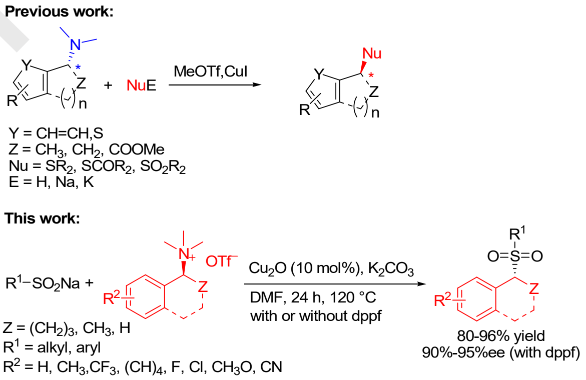
Introduction

Many therapeutically interesting compounds contain sulfone motifs, such as Dapsone [1], and the non-steroidal antiandrogen Casodex [2]. Sulfones also find extensive applications in organic and drug synthesis. For example, primary alkyl aryl sulfones can be converted into the corresponding carboxylic acids in good to excellent yields *via* double deprotonation and exposure to atmospheric oxygen [3]; sulfones were used in the preparation of various γ-alkylidene butenolides [4]; and halogenation of the α-position of sulfones afforded α-halo sulfones [5].

Sulfones are typically prepared by oxidizing sulfides [6]; however, this is often accompanied by the formation of sulfoxide by-products. In recent years, H_2O_2 [7] and oxygen [8] have been utilized as oxidants to synthesize sulfones from thioethers. Sulfones have also been obtained *via* the cross coupling of halogenated arenes with sodium sulfinate [9].

Recently (enantioenriched) quaternary ammonium salts or tertiary benzylic amines that are activated *in situ* by methyl triflate were reported as a novel class of electrophiles and coupled with various nucleophiles, such as boron reagents [10], thiols [11], amines [12], and phosphates [13] *via* C-N cleavage. Inspired by related studies and based on our ongoing studies on carbon-heteroatom coupling reactions [14], herein we report the Cu_2O-catalyzed C-S bond cross coupling of (enantioenriched) quaternary ammonium salts and sodium sulfinates *via* C-N bond cleavage (Scheme 1).

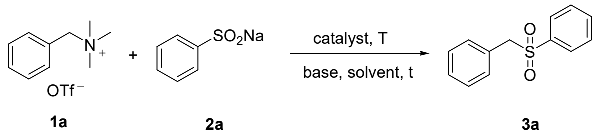
In comparison with amine-derived pyridinium salts [11], diazonium compounds [15] or diazotates [16], highly enantiopure benzylic quaternary ammonium salts are readily available, and the various chiral sulfone products obtained by our method have excellent ee values (90-95%ee).



Scheme 1. Synthesis of (enantioenriched) sulfones.

Initially, the reaction of *N,N*-dimethyl(phenyl)methanamine and methyl triflate afforded its corresponding quaternary ammonium salt (**1a**). The cross coupling reaction of quaternary ammonium salt (**1a**) and sodium phenylsulfinate (**2a**) under various conditions was then investigated (Table 1). In the presence of $Cu(MeCN)_4PF_6$ (10 mol%) and K_2CO_3 (1.0 eq.), the coupling reaction gave the targeted C-S bond coupling product **3a** in good yield (72%, Table 1, Entry 1). Next, the examination of other catalysts and the control reaction without a transition metal catalyst showed that Cu_2O was also a suitable catalyst (Entries 3 vs 1-7). Cu_2O was selected because it is less expensive than $Cu(MeCN)_4PF_6$ and can be recycled. DMF was found to be the best solvent after the screening of several common solvents (Entries 11 vs 3, 8-10). Increasing the amount of substrate **2a** to 2.0 mmol afforded a much high a stronger base was determined to be unnecessary (Entries 14 vs 12). Increasing the temperature to 120 ºC gave the best result of 95% yield (Entries 15 vs 12 and 16).

Table 1. Optimization of the reaction conditions.[a]

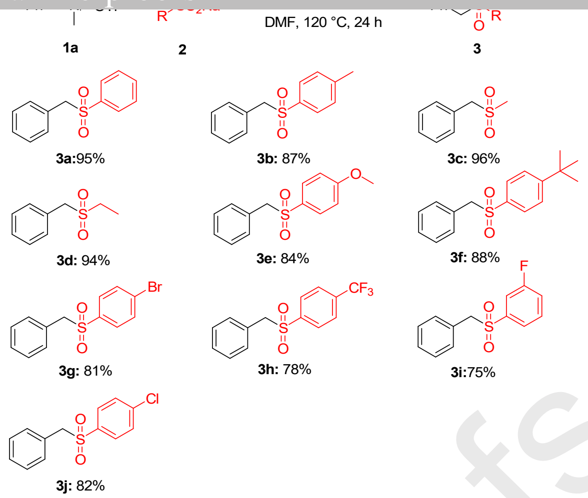


Entry	Catalyst	Base	Solvent	Temp (ºC)	Yield **3a** (%)[b]
1	$Cu(MeCN)_4PF_6$	K_2CO_3	1,4-dioxane	110	72
2	CuI	K_2CO_3	1,4-dioxane	110	20
3	Cu_2O	K_2CO_3	1,4-dioxane	110	62
4	$FeCl_3$	K_2CO_3	1,4-dioxane	110	trace
5	$NiCl_2$	K_2CO_3	1,4-dioxane	110	26
6	$CuCl_2$	K_2CO_3	1,4-dioxane	110	trace
7 [c]	---	K_2CO_3	DMF	120	trace
8	Cu_2O	K_2CO_3	MeCN	80	trace
9	Cu_2O	K_2CO_3	THF	60	trace
10	Cu_2O	K_2CO_3	H_2O	100	trace
11	Cu_2O	K_2CO_3	DMF	110	75
12 [c]	Cu_2O	K_2CO_3	DMF	110	86
13 [d]	Cu_2O	K_2CO_3	DMF	110	84
14 [c]	Cu_2O	t-BuOK	DMF	110	75
15 [c]	**Cu_2O**	**K_2CO_3**	**DMF**	**120**	**95**
16 [c]	Cu_2O	K_2CO_3	DMF	150	92

[a] Reagents and conditions: Unless otherwise noted, the reactions were carried out with 1.0 mmol of **1a**, 1.0 mmol of **2a**, 0.1 mmol of catalyst and 1.0 mmol of base, in 5 mL of solvent for 24 h in a sealed test tube with a standard ground mouth. [b] Isolated yield. [c] **2a** (2.0 mmol) was used. [d] **2a** (3.0 mmol) was used.

With the optimized conditions in hand, various sodium arene/alkanesulfinates (**2**) were reacted with benzyl quaternary ammonium salt **1a** (Table 2). Both alkane- and arene-sulfinates gave the desired sulfones in good to excellent yields. Sodium alkanesulfinates, including methane- and ethane-sulfinates afforded similar yields as that of sodium benzenesulfinate (**3c** and **3d** vs **3a**). Both electron-donating and electron-withdrawing groups on the sodium benzenesulfinates were not beneficial to this coupling reaction. Additionally, electron-withdrawing groups on the sodium benzenesulfinates decreased the yields more than electron-donating groups (**3b**, **3e**, **3f** vs **3g-3j**).

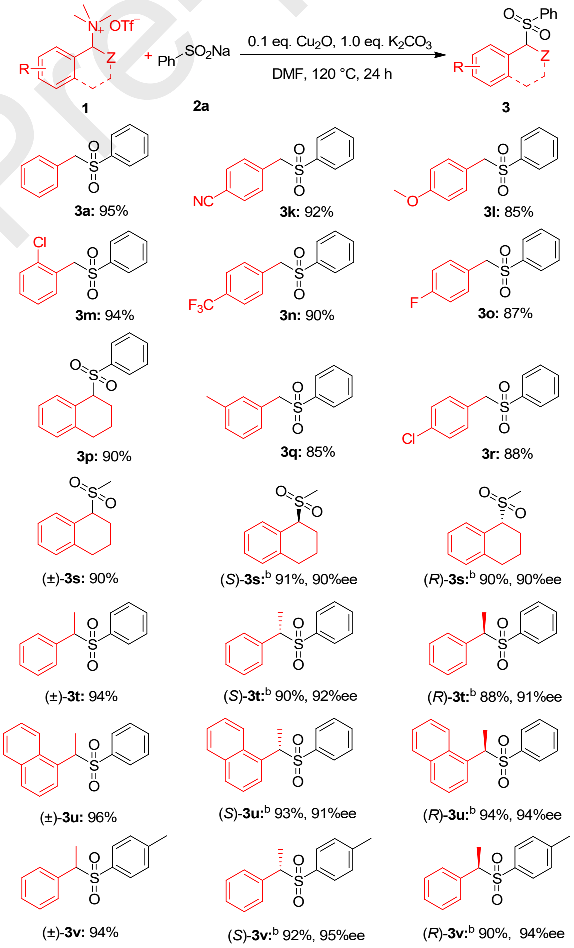
Table 2. Scope of the sodium sulfinates.[a]



[a] Reagents and conditions: 1.0 mmol **1a**, 2.0 mmol **2**, 0.1 mmol Cu_2O and 1.0 mmol K_2CO_3, in 5 mL DMF, 120 °C, 24 h. Isolated yield.

Next, the reactions of various quaternary ammonium salts (**1**) with sodium benzenesulfinate (**2a**) were evaluated (Table 3). Overall, the C-S coupling reactions proceeded smoothly and provided the desired products in high to excellent yields (**3a** and **3k-3v**).

Table 3. Scope of the quaternary ammonium salts.[a]



[a] Reagents and conditions: 1.0 mmol **1**, 2.0 mmol **2a**, 0.1 mmol Cu_2O and 1.0 mmol K_2CO_3, in 5 mL DMF, 120 °C, 24 h. Isolated yield. [b] DPPF (0.1 equiv) as ligand.

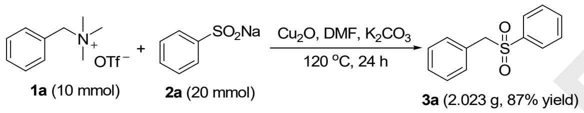
Both electron-withdrawing and electron-donating groups on the benzene ring of the quaternary ammonium salts afforded high yields, and the position of the functional group has no obvious effect (**3m**, **3r**).

Furthermore, these reaction conditions tolerated a wide vari

methoxy (**3l**), cyano (**3k**), fluoro (**3o**), trifluoromethyl (**3n**), and chloro (**3m**, **3r**).

Disappointingly, enantioenriched quaternary ammonium salts only provided racemic products under the optimized conditions. Fortunately, racemization was inhibited when 1,1′-ferrocenediyl-bis(diphenylphosphine) (dppf) was added as a ligand. For example, (*R*)- and (*S*)-1-phenylethanamines from Aladdin reagent company have enantiopurities of 94.1% and 94.6%, respectively (for HPLC traces, see the ESI), and their corresponding (*S*)- and (*R*)-benzylic sulfone products **3t** have enantiopurities of 92% and 91%, respectively. As a result, all of the enantioenriched benzylic quaternary ammonium salts which were synthesized from commercially available enantioenriched benzylic amines possessed high enantiopurities of 90-95% ((*S*)- and (*R*)-**3s**, **3t**, **3u**, **3v**).

This reaction shows an interesting phenomenon: *R* forms of the enantioenriched benzylic amine-derived chiral quaternary ammonium salts gave the *S* form of the sulfones and vice versa. For example, the (*R*)-1-phenylethylamine-derived quaternary ammonium salt afforded (*S*)-**3v**, which was verified *via* comparison with the chiral HPLC trace and specific rotation of previously reported (*S*)-**3v** [11]. It appears that the copper-catalyzed C-S bond coupling reaction occurs *via* a S_N2 type substitution, and thus the absolute configurations of the chiral quaternary ammonium salts reverse during the C-S bond coupling reaction.



Scheme 2. Gram-scale reaction.

In order to verify the scale-up possibility of this reaction, a gram-scale reaction was performed. A ten-mmol-scale reaction provided the corresponding product in 87% yield (Scheme 2).

In summary, an efficient method was developed for the synthesis of (enantioenriched) benzylic sulfones *via* the Cu_2O-catalyzed C-S bond cross coupling reaction of (enantioenriched) benzylic quaternary ammonium salts and sodium alkane-/arene-sulfinates. Enantioenriched sulfones were obtained in excellent enantiopurities using dppf as a ligand.

Acknowledgments

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