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Nondirected Copper-Catalyzed Sulfoxidations of Benzylic C−H Bonds

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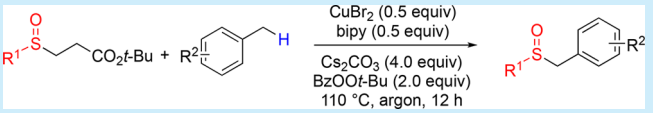
Supporting Information

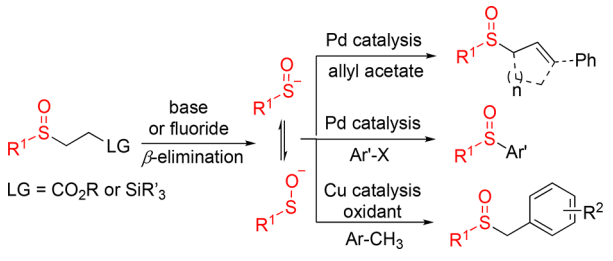
ABSTRACT: A copper-catalyzed sulfoxidation of benzylic C−H bonds by nondirected oxidative C(sp^3)-H activation was developed. The process proceeds via sulfenate anions, which are generated by base-triggered elimination of β-sulfinyl esters and benzyl radicals. The functional group tolerance is high, and the product yields are good.



Methylarenes are inexpensive and readily available starting materials used as solvents, industrial feedstocks, and gasoline components. In synthesis, they are attractive for the preparation of complex molecules, including pharmaceuticals, agrochemicals, polymers, and commodity chemicals.[1] In recent years, multifarious catalytic methods have been developed for direct transformations of benzylic C−H bonds into C−C,[2] C−N,[3] C−O,[4] and C−F bonds.[5] In contrast, examples of constructing C(sp^3)−S bonds in this manner are rare, represented by the report of Qing and co-workers, who found copper-catalyzed trifluoromethylthiolations of benzylic sp^3 C−H bonds with a combination of $AgSCF_3$ and KCl as the trifluoromethylthiol source.[6] Appreciating the extraordinary value of sulfoxides as building blocks in organic synthesis, chiral auxiliaries, and ligands in transition-metal-catalyzed reactions[7] and recognizing their multiple applications as active ingredient in pharmaceuticals and crop protecting agents,[8] we set high priorities in developing a sulfoxide synthesis by C(sp^3)−S bond formation through C−H bond activation.[9] The realization of this concept is described here.

In recent years, the use of aryl sulfenate anions ($ArSO^-$) has become an attractive alternative for accessing sulfoxides.[10,11] Palladium-catalyzed C−S couplings proved particularly effective in such reactions,[11] as, for example, shown by Poli, Madec, Walsh, and others, who demonstrated allylic alkylations and arylations of aryl sulfenate anions (Scheme 1, top and middle). In general, those transformations were initiated by β-elimination of the corresponding β-sulfinyl ester or silane triggered by base or fluoride ions. Coupling partners were allyl acetates and aryl halides, respectively. So far, reactions between sulfenate anions and hydrocarbons have remained unreported. We have now discovered a copper catalysis filling this gap that allows the preparation of sulfoxides by couplings of in situ generated sulfenate anions with oxidatively activated methylarenes (Scheme 1, bottom).

Scheme 1. Metal-Catalyzed Coupling Reactions of Sulfenate Anions Generated by β-Elimination



For the initial experiments, β-sulfinyl ester **1a** and toluene (**2a**) were chosen as representative starting materials. The latter compound was used in large excess (100-fold) as it had a dual role being both reagent and solvent. β-Elimination of **1a** upon addition of Cs_2CO_3 was expected to generate the corresponding *p*-tolyl sulfenate anion, which was hypothesized to react with the benzyl radical obtained by copper-catalyzed oxidation of **2a** with a *tert*-butyl perbenzoate (**A**, **B**, or **C**). The expected product was benzyl *p*-tolyl sulfoxide (**3aa**). The results are presented in Table 1.

A brief screening of copper salts (with **A** as oxidant) identified $CuBr_2$ as the most effective catalyst leading to sulfoxide **3aa** in 49% yield (Table 1, entries 1−4). Using CF_3-substituted *tert*-butylperoxy benzoates **B** and **C** instead of **A** as oxidant had negative effects on the yield of **3aa** (Table 1, entries 4−6). Increasing the amount of $CuBr_2$ from 0.4 equiv to 0.5 equiv raised the yield of **3aa** to 60% (Table 1, entry 7). Finally, applying triphenylphosphine, 2,2-bipyridine (bipy), and 1,10-phenanthroline (phen) as additives (Table 1, entries 8−10) revealed bipy to be superior over the other two compounds allowing to isolate **3aa** in 80% yield.

Next, the substrate scope with respect to the β-sulfinyl esters **1** was examined. Toluene (**2a**) was kept as reaction partner. The results are summarized in Scheme 2.

In general, all couplings proceeded well providing the corresponding benzyl sulfoxide in yields ranging from 35% to 82%. The best results were obtained in formations of aryl benzyl sulfoxides (**3aa**-**3la**), which were isolated in an average yield of 72% (for all 12 products). Neither electronic nor steric effects induced by substituents on the arene significantly affected the yields. Noteworthy, halo groups were tolerated as

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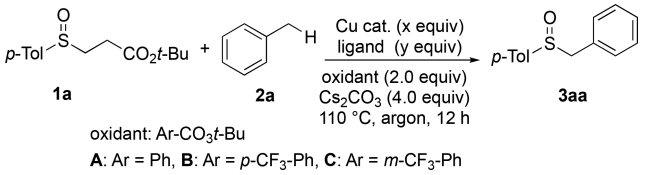
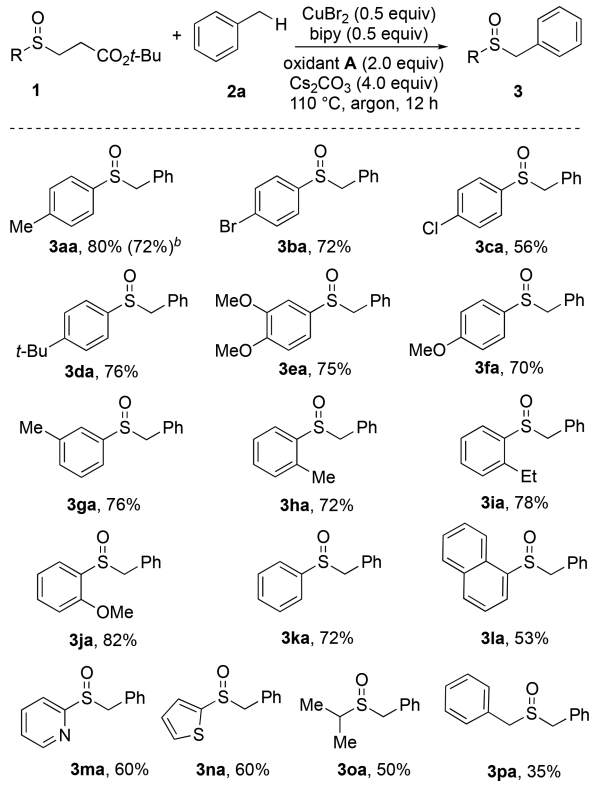
Table 1. Development of Optimal Reaction Conditions[a]



entry	Cu cat.	x	ligand[b]	y	oxidant	yield (%)
1	CuTc[c]	0.4			A	30
2	CuBr	0.4			A	43
3	$CuCl_2$	0.4			A	45
4	$CuBr_2$	0.4			A	49
5	$CuBr_2$	0.4			B	33
6	$CuBr_2$	0.4			C	26
7	$CuBr_2$	0.5			A	60
8	$CuBr_2$	0.5	PPh_3	0.5	A	60
9	$CuBr_2$	0.5	bipy	0.5	A	80
10	$CuBr_2$	0.5	phen	0.5	A	53

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (20.0 mmol), Cu cat., ligand, oxidant (0.4 mmol), Cs_2CO_3 (0.8 mmol), 110 °C, 12 h, under argon. [b]bipy = 2,2′-bipyridine, phen = 1,10-phenanthroline. [c]Tc = thiophene-2-carboxylate.

Scheme 2. Substrate Scope for β-Sulfinyl Ester 1 using Toluene (2a) as Reaction Partner[a]



[a]Performed on a 0.2 mmol scale (for **1a**) with a 100-fold excess of toluene (**2a**). [b]In parentheses: Use of 1.0 mmol of **1a**.

revealed by the formations of **3ba** and **3ca**, which were isolated in 72% and 56% yield, respectively. Representing heterocyclic systems, 2-pyridinyl- and 2-thiophenyl-containing sulfoxides **3ma** and **3na** were prepared. Their yields of only 60% could be an indication of a hampering effect by metal coordination through the multiple heteroatoms in the starting materials and products. The relatively low yields of 50% and 35% for benzyl isopropyl sulfoxide (**3oa**) and dibenzyl sulfoxide (**3pa**), respectively, might be due to competing oxidative processes and radical formations at the branched aliphatic and benzyl sulfur substitutents.

In the subsequent set of reactions, toluene (**2a**) was substituted by other methyl arenes. β-Sulfinyl ester **1a** served as coupling partner. The reaction conditions were kept as optimized before (Table 1, entry 9). Figure 1 shows the results.

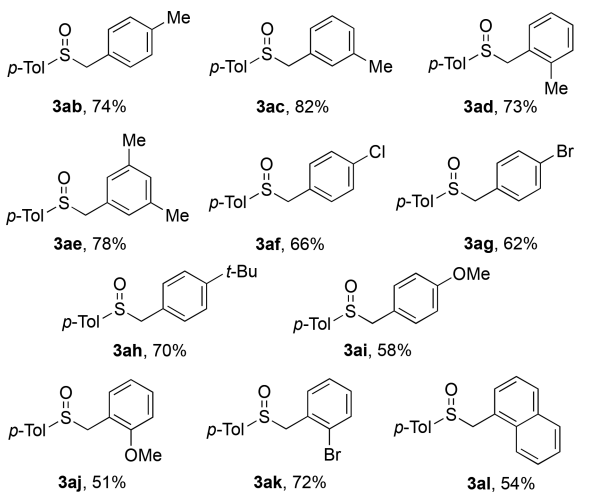
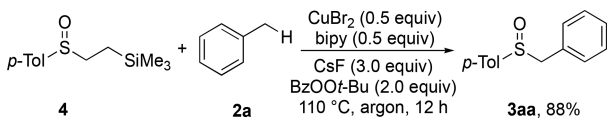


Figure 1. Substrate scope for methyl arenes with β-sulfinyl ester **1a**.

Also this screening revealed a high tolerance toward electronic and steric effects induced by substituents. For example, all three isomers of xylene gave similar yields of the corresponding sulfoxides with *meta*-xylene being the best [(*p*-)**3ab**: 74%, (*m*-)**3ac**: 82%, and (*o*-)**3ad**: 73%]. Subjecting halo-containing methyl arenes to the reaction with **1a** led to products **3af**, **3ag**, and **3ak**. In this case, the *ortho*-substituted derivative performed best providing **3ak** in 72% yield. Isomers **3af** and **3ag** with *para*-halo groups were only formed in 66% and 62% yield, respectively. 1-Methylnaphthalene furnished sulfoxide **3al** in 54% yield.

Recently, Walsh and co-workers described the use of aryl/alkyl 2-(trimethylsilyl)ethyl sulfoxides[12] as precursors of sulfenate anions in palladium-catalyzed arylation reactions.[11j,k] Those couplings were initiated by fluoride-triggered β-eliminations. Using this strategy in the aforementioned benzylic C−H sulfoxidation allowed the reaction of toluene (**2a**) with trimethyl[2-(*p*-tolylsulfinyl)ethyl)]- silane (**4**) providing sulfoxide **3aa** in 88% yield (Scheme 3).

Scheme 3. Sulfoxidation of Toluene (2a) with β-Trimethylsilyl Sulfoxide 4



With respect to the mechanism (Scheme 4), we suggest a reaction path with two key intermediates - a benzyl radical (**I**) and a sulfenate anion (**II**). In this scenario, **I** is generated from the methyl arene by hydrogen abstraction with *tert*-butoxide radical, which is formed by an electron-transfer process from copper to *tert*-butyl perbenzoate and subsequent elimination of

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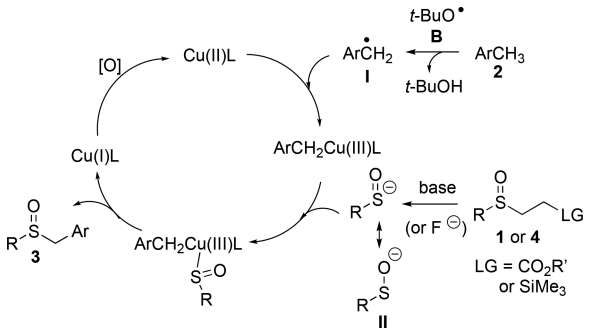
Scheme 4. Proposed Mechanism



tert-butoxide. Intermediate **II** results from the corresponding β-sulfinyl ester or silane, which undergoes β-elimination upon treatment with base or fluoride. Both **I** and **II** assemble at copper by addition and ligand exchange.[13−16] Reductive elimination leads to the observed product **3** and a copper species of lower oxidation state. Reoxidation of the latter regenerates the initial copper complex thereby closing the catalytic cycle.

In summary, we developed a copper-catalyzed sulfoxidation of benzylic sp^3 C−H bonds. The reaction enables the synthesis of a wide range of functionalized benzyl sulfoxides using inexpensive, readily available methylarenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00615.

General experimental procedure and characterization details (PDF)

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Notes

The authors declare no competing financial interest.

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(15) As shown in Scheme 4, we hypothesize that the catalytic cycle involves copper species with three oxidation states (+I, + II, and + III). However, other scenarios, which do not involve all of the aforementioned oxidation states at copper, are also possible.

(16) During the preparation of this manuscript, the synthesis of sulfinamides by copper-catalyzed amidations of sulfenate anions derived from *β*-sulfinyl esters was reported. A direct interaction between the sulfenate anion and the copper catalyst was suggested there as well. See: Dai, Q.; Zhang, J. *Adv. Synth. Catal.* **2018**, DOI: 10.1002/adsc.201701510.

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