Organocatalysis **Hot Paper**

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A New Class of Organocatalysts: Sulfenate Anions**

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Abstract: *Sulfenate anions are known to act as highly reactive species in the organic arena. Now they premiere as organocatalysts. Proof of concept is offered by the sulfoxide/sulfenate-catalyzed (1–10 mol%) coupling of benzyl halides in the presence of base to generate trans-stilbenes in good to excellent yields (up to 99%). Mechanistic studies support the intermediacy of sulfenate anions, and the deprotonated sulfoxide was determined to be the resting state of the catalyst.*

In recent years, sulfenic acids and their conjugate bases, sulfenate anions (Figure 1), have gone from chemical curiosities to important intermediates in biological and synthetic chemistry.[1–5] Small-molecule sulfenic acids are highly reactive and difficult to isolate unless they are sterically protected or stabilized by hydrogen bonds.[6] Likewise, the conjugate bases of sulfenic acids, sulfenate anions, are highly reactive intermediates,[7] which have been generated and trapped in a number of organic and metal-catalyzed processes.[8] Despite their versatility, we are unaware of prior examples of small-molecule sulfenate anions that were employed as catalysts. Herein, we introduce sulfenate anions as organocatalysts and demonstrate their catalytic ability in the conversion of benzyl halides into *trans*-stilbenes.[9]

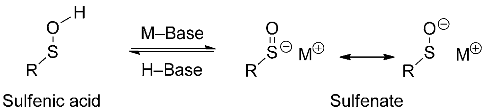
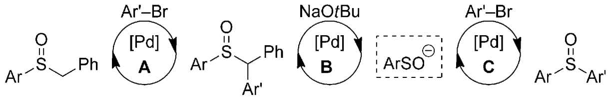
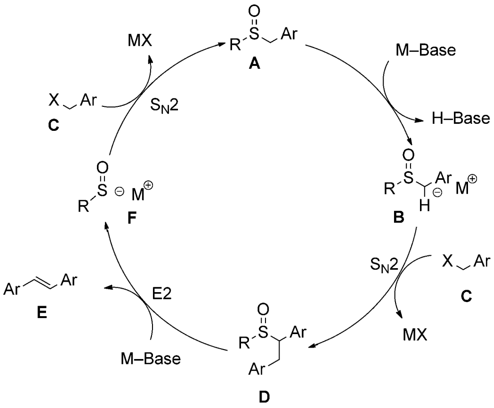


Figure 1. Sulfenic acid and its conjugate base, the sulfenate anion.

For the present work, we were inspired by our recent development of a palladium-catalyzed conversion of aryl benzyl sulfoxides into diaryl sulfoxides, wherein the palladium species drives three distinct catalytic cycles (Scheme 1).[10] The key intermediate in this process was the sulfenate anion ArSO$^-$, which was the leaving group in cycle **B** and underwent transmetalation in cycle **C**, ultimately forming a C–S bond. Based on the ability of sulfenate anions to behave as nucleophiles and leaving groups in this process, we hypothesized that sulfenate anions could be organocatalysts and set out to test this hypothesis. We proposed the sulfenate-anion-catalyzed coupling of benzyl halides to form symmetric stilbenes, which is depicted in Scheme 2.



Scheme 1. Palladium promotes the conversion of aryl benzyl sulfoxides into diaryl sulfoxides, which proceeds through three catalytic cycles; a sulfenate anion acts as the leaving group in cycle **B** and as a nucleophile in cycle **C**.



Scheme 2. Proposed mechanism of the sulfenate-anion-catalyzed coupling of benzyl halides to form symmetric stilbenes.

The starting point for our proof-of-concept reaction is benzylic sulfoxide **A** (Scheme 2). Under basic conditions, benzylic sulfoxides can be deprotonated at the α-position, and the resulting sulfoxide anion **B** reacts with the benzyl halide to generate sulfoxide **D**. Deprotonation at the β-position of **D** was envisioned to promote an E2 elimination generating *trans*-stilbene while expelling the sulfenate anion catalyst. Sulfenate anions are known to undergo nucleophilic substitution with benzyl halides,[11] regenerating sulfoxide **A** and completing the catalytic cycle. The sulfenate anion **F** is the smallest structural unit carried through this catalytic cycle.

We initiated a search for conditions for the sulfenate-anion-catalyzed synthesis of *trans*-stilbene from benzyl chloride by screening six bases, namely, LiO*t*Bu, NaO*t*Bu, KO*t*Bu, LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$, and KN(SiMe$_3$)$_2$, in the presence of benzyl phenyl sulfoxide (10 mol%) in cyclopentyl methyl ether (CPME) as the solvent at 80 °C (Table 1, entries 1–6).

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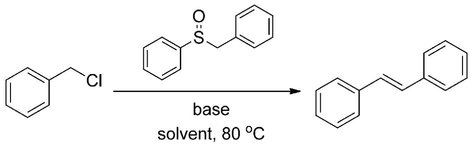
Table 1: Optimization of the formation of stilbene (**2a**) from benzyl chloride (**1a**).[a]



Entry	Base	Solvent	Catalyst [mol %]	**2a**[b] [%]
1	LiO*t*Bu	CPME	10	0
2	NaO*t*Bu	CPME	10	45
3	KO*t*Bu	CPME	10	> 98
4	$LiN(SiMe_3)_2$	CPME	10	41
5	$NaN(SiMe_3)_2$	CPME	10	51
6	$KN(SiMe_3)_2$	CPME	10	81
7	KO*t*Bu	CPME	5	100
8	KO*t*Bu	CPME	2.5	100 (95)
9	KO*t*Bu	CPME	1	74
10	KO*t*Bu	Toluene	1	57
11	KO*t*Bu	THF	1	45
12	KO*t*Bu	Dioxane	1	33
13	KO*t*Bu	DME	1	23
14	KO*t*Bu	DCE	1	0
15[c]	KO*t*Bu	CPME	2.5	88
16[d]	KO*t*Bu	CPME	2.5	14
17[e]	KO*t*Bu	CPME	2.5	92
18	KO*t*Bu	CPME	0	0

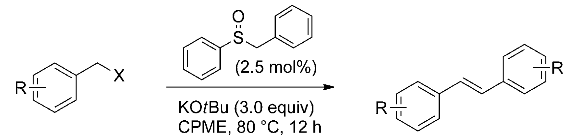
[a] Reactions conditions: **1a** (0.1 mmol, 1.0 equiv), base (3.0 equiv), 80 °C. [b] Yield determined by NMR spectroscopy using CH_2Br_2 as an internal standard. Yield of isolated product given in parentheses. [c] Base (2.0 equiv). [d] 50 °C. [e] **1a** (0.2 mmol). DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane.

Yields of stilbene **2a** as determined by ^1H NMR spectroscopy ranged from 0% (LiO*t*Bu, entry 1) to 100% (KO*t*Bu, entry 3). The use of amide bases, such as $MN(SiMe_3)_2$, led to decomposition of the starting materials (entries 4–6). Lowering the catalyst loading to 5 or 2.5 mol% of benzyl phenyl sulfoxide led to **2a** in quantitative NMR yield (entries 7 and 8). Further reduction of the catalyst loading to 1 mol% still gave a good yield (74%, entry 9). The use of five solvents under the conditions described in entry 9 gave **2a** in lower yields than with CPME (entries 10–14). Using 2.5 mol% of the sulfoxide and decreasing the amount of base to less than 3.0 equivalents or lowering the reaction temperature to below 80 °C resulted in a diminished NMR yield of **2a** (entries 15 and 16). An attempt to increase the reaction concentration from 0.1 M to 0.2 M resulted in a slightly decreased yield (92%), which is due to the formation of benzyl *tert*-butyl ether (entry 17).[12] When the reaction was conducted under the conditions of entry 8 in the absence of the sulfoxide, no stilbene was formed (entry 18). Based on the results in Table 1, our optimized conditions for sulfenate-anion-catalyzed *trans*-stilbene formation from benzyl chloride entail the use of benzyl phenyl sulfoxide (2.5 mol%) and KO*t*Bu (3.0 equiv) in CPME at 80 °C for 12 hours.

With the optimized reaction conditions in hand, the scope of the transformation was examined (Table 2). When both the benzyl chlorides and bromides were available, reactions were performed with both substrates. Benzyl chlorides were more suitable than benzyl bromides, because the latter substrates more readily undergo S_N2 reactions with the base to generate benzyl *tert*-butyl ethers. To favor the catalytic reaction and diminish the background ether formation, the sulfoxide loading was increased to 5 mol% in some cases. Benzyl chloride and bromide gave *trans*-stilbene **2a** in 95% and 81% yield, respectively. Benzyl halides with alkyl groups on the arene gave the corresponding products in reasonable to very good yields (62–92%; products **2b**, **2c**, and **2k**). More sterically hindered benzyl chloride derivatives, for example with a methyl substituent in the 2-position (**2h**, 92%) or with a naphthyl framework (**2i**, 80%), also proved to be good substrates.

Electron-rich 4-methoxybenzyl chloride was found to be a difficult substrate, providing stilbene **2d** in only 31% yield. This may be due to the decreased acidity of the benzyl sulfoxide intermediate. In contrast, substrates bearing halides gave the corresponding products in good to excellent yields (61–99%). Benzyl chlorides with fluorine substituents in the 2-, 3-, or 4-position underwent the catalytic coupling to afford stilbenes **2g**, **2l**, and **2e** in 73–89% yield. 4,4′-Dichlorostilbene (**2f**) was produced from the corresponding benzyl chloride in 99% yield, and 2,6-dichlorobenzyl chloride gave tetrachlorostilbene **2j** in 88% yield. A benzyl bromide with a trifluoromethyl substituent in the 3-position led to **2m** in 68% yield, when the amount of KO*t*Bu was decreased to 2.0 equivalents.

Table 2: Substrate scope of the sulfenate-anion-catalyzed formation of *trans*-stilbenes from benzyl halides.[a]

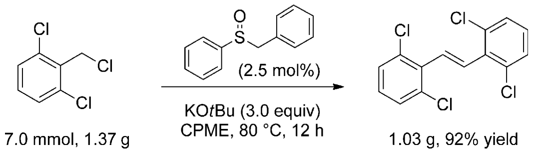


Product	R	X	Yield [%]	Product	R	X	Yield [%]
2a	H	Cl	95	**2g**	2-F	Cl	73
2a	H	Br	81	**2h**	2-Me	Cl	92
2b	4-Me	Cl	84	**2i**	1-naphthyl	Cl	80
2b	4-Me	Br	62[b]	**2j**	2,6-Cl_2	Cl	88
2c	4-*t*Bu	Br	70[b]	**2k**	3-Me	Br	75[b]
2d	4-OMe	Cl	31[b]	**2l**	3-F	Cl	89
2e	4-F	Cl	81	**2m**	3-CF_3	Br	68[c]
2e	4-F	Br	66[b]	**2n**	2-pyridyl	Cl	54[d]
2f	4-Cl	Cl	99				

[a] Reactions conditions: benzyl halide (0.1 mmol), catalyst (2.5 mol%), KO*t*Bu (0.3 mmol), CPME (1.0 mL). [b] Catalyst (5 mol%). [c] KO*t*Bu (0.2 mmol). [d] KH as the base, 110 °C for 24 hours.

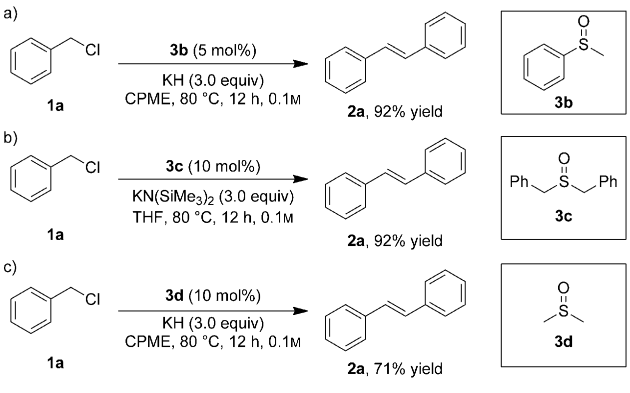
Heterocyclic stilbene derivatives exhibit interesting photophysical properties.[13] Under our standard conditions, 2-(chloromethyl)pyridine (**1n**) surprisingly did not react. When a stronger base, namely KH, was used at a higher reaction temperature (110 °C) for a longer reaction time (24 h), stilbene derivative **2n** was generated in 54% yield. Unfortunately, some base-sensitive electron-withdrawing groups, such as nitro, cyano, and trifluoromethyl substituents, were not tolerated at the 4-position of the benzyl bromide because of decomposition of the benzyl halides.

To demonstrate the scalability of this organocatalytic reaction, we performed the synthesis of **2j** on a 7.0 mmol scale with a sulfoxide loading of 2.5 mol% (Scheme 3). The *trans*-configured 2,2′,6,6′-tetrachlorostilbene was isolated in 92% yield, indicating that the reaction is scalable.



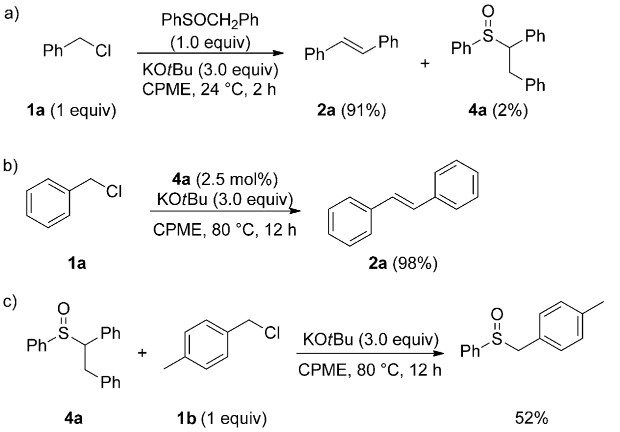
Scheme 3. Formation of 2,2′,6,6′-tetrachlorostilbene on gram scale.

Based on the mechanism proposed in Scheme 2, related precatalysts could be imagined (Scheme 4). The pK_a value of methyl phenyl sulfoxide (**3b**) is significantly higher than those of aryl benzyl sulfoxides.[14] A stronger base, such as KH, will therefore be required to generate the catalyst. The expected byproduct of catalyst formation, styrene, was observed (^{1}H NMR spectroscopy). With 5 mol% of methyl phenyl sulfoxide, stilbene was generated in 92% yield[15a] (Scheme 4a). Using 10 mol% of dibenzyl sulfoxide (**3c**), **2a** was afforded in 92% yield (Scheme 4b). Dimethyl sulfoxide (DMSO, **3d**, 10 mol%), was also a viable precatalyst, affording **2a** in 71% yield[15b] (Scheme 4c).



Scheme 4. Application of different sulfoxide catalysts.

We next set out to gain insight into the mechanism of the catalytic coupling. Upon reaction of a stoichiometric amount of benzyl phenyl sulfoxide (**3a**) with 1.0 equivalent of benzyl chloride (**1a**) under basic conditions, sulfoxide[16] **4a** was observed (2%) along with *trans*-stilbene (91%, **2a**; Scheme 5a). When independently synthesized **4a** was used as the catalyst, stilbene (**2a**) was obtained in 98% yield (Scheme 5b), suggesting that sulfoxide **4a** is an intermediate of the catalytic reaction. Furthermore, when **4a** was combined with a stoichiometric amount of 4-methylbenzyl chloride (**1b**) under the standard reaction conditions, *trans*-stilbene, 4,4′-dimethyl-*trans*-stilbene (**2b**), and 4-methylbenzyl phenyl sulfoxide (52%) were generated (Scheme 5c), suggesting that the phenylsulfenate anion is formed from **4a**. These results support the mechanism proposed in Scheme 2.



Scheme 5. Preliminary mechanistic investigations of the sulfenate-anion-catalyzed stilbene formation.

To investigate the catalyst resting state, we conducted the reaction using benzyl chloride (**1a**) at 50 °C under otherwise standard conditions. The reaction was quenched with 30 equivalents of water after 30 minutes. Benzyl phenyl sulfoxide was isolated in 87% yield, suggesting that the resting state is benzyl phenyl sulfoxide or its conjugate base. The reaction was then conducted in [D$_8$]THF and monitored by ^{1}H NMR spectroscopy. No resonances corresponding to benzyl phenyl sulfoxide were observed. Furthermore, combining benzyl phenyl sulfoxide with KO*t*Bu and monitoring the reaction by NMR spectroscopy also indicated sulfoxide deprotonation (see the Supporting Information). These results are consistent with the relative pK_a values of benzyl phenyl sulfoxide (pK_a 27.2 in DMSO) and *tert*-butanol (pK_a 32.2 in DMSO).[14] These data indicate that the deprotonated sulfoxide is the resting state of the catalyst.

To further characterize the catalyst resting state, we deprotonated benzyl phenyl sulfoxide (**3a**) with KCH_2Ph. Single crystals suitable for a crystallographic study were obtained after addition of [18]crown-6 and layering with hexanes.[17] The solid-state structure of the product, K([18]crown-6)(THF)[PhS(=O)CHPh], was determined to be monomeric with a potassium cation coordinated to both the α-carbon and oxygen atoms of the anion (Figure 2). The sp^2 nature of the benzylic carbon atom was evident from the short S–C bond of 1.691(2) Å, compared to the C–S bond length of 1.837(2) Å that was reported for the benzylic sulfoxide {2-[(NMe$_2$)CHMe]C$_6$H$_4$}S(=O)CH$_2$Ph.[18] A gas-phase DFT calculation at the B3LYP/6-31G* level of theory was performed on the [PhS(O)CHPh]$^-$ anion and the corresponding neutral sulfoxide, PhS(O)CH$_2$Ph (see the Supporting Information for details). The computed models showed a shortening of the S–C(Bn) bond by 0.166 Å and a lengthening of the S–O bond by 0.029 Å upon deprotonation. This result, together with the X-ray structure, is supportive of a multiple-bond character of the S–C(Bn) bond in the deprotonated sulfoxide anion.[19]

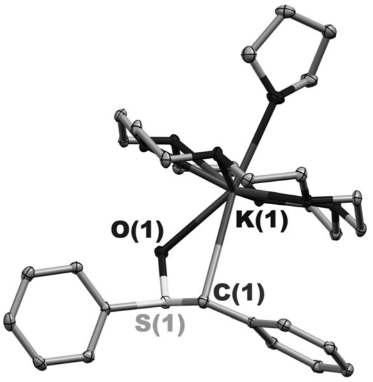


Figure 2. Crystal structure of K(18-crown-6)(THF)[PhS(=O)CHPh]. Thermal ellipsoids set at 30% probability.

In summary, we hypothesized that sulfenate anions could act as catalytic intermediates in organocatalytic reactions. This hypothesis was founded upon their ability to act as both leaving groups and nucleophiles. As a proof-of-concept reaction, we developed the base-promoted conversion of benzyl halides into *trans*-stilbenes catalyzed by sulfenate anions. Furthermore, we have shown that a variety of sulfoxide precatalysts, including DMSO, can promote this reaction at loadings of 1–10 mol%. Reactivity studies support the intermediacy of sulfenate anions and provide strong evidence that the catalyst resting state is the deprotonated sulfoxide. Based on these studies, we believe that sulfenate anions have significant potential in organocatalysis. Related reactions that are catalyzed by this novel class of catalysts are currently under investigation.

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Keywords: benzyl halides · organocatalysis · stilbenes · sulfenate anions · sulfoxides

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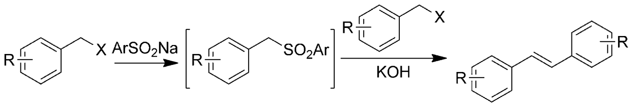

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[19] CCDC 1007043 (K([18]crown-6)(THF)[PhS(=O)CHPh]; excluding structure factors) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.