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tert-Butyl Phenyl Sulfoxide: A Traceless Sulfenate Anion Precatalyst

Mengnan Zhang,[†] Tiezheng Jia,[†] Irina K. Sagamanova,[‡] Miquel A. Pericás,[‡,§] and Patrick J. Walsh*[,†]

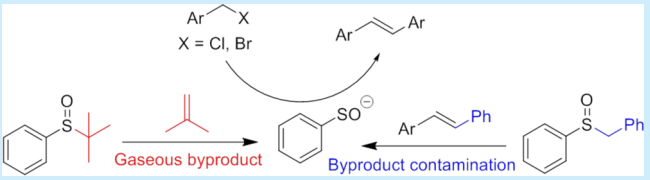
[†]Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

[‡]Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

[§]Departament de Química Organica, Universitat de Barcelona (UB), 08028 Barcelona, Spain

Supporting Information

ABSTRACT: *tert*-Butyl phenyl sulfoxide is employed as a traceless precatalyst for the generation of sulfenate anions under basic conditions and has been used to catalyze the coupling of benzyl halides to *trans*-stilbenes. The advantage of this precatalyst over previous precatalysts is that the byproduct generated on catalyst formation is a gas, facilitating product isolation in high purity. Using this second generation catalyst, a variety of *trans*-stilbenes were generated in 39−98% isolated yield.



Sulfenate anions and their conjugate acids, sulfenic acids (Figure 1), are highly reactive intermediates in biochemistry[1] and organic synthesis.[2] In organic chemistry, sulfenate anions can be trapped with alkyl halides to afford sulfoxides. We,[3] and others,[4] have recently developed methods to arylate sulfenate anions with aryl halides under palladium catalysis to afford aryl sulfoxides. Our approach (Scheme 1) begins with aryl benzyl sulfoxides, which undergo an initial α-arylation under basic conditions to generate diarylmethyl aryl sulfoxides. The palladium catalyst next promotes the cleavage of the C−S bond to liberate the sulfenate anion, which is arylated in the third catalytic cycle. In this process the sulfenate anion behaves as a leaving group in the second cycle and as a nucleophile in the third cycle.[3] Inspired by the ability of sulfenate anions to behave as both leaving groups and nucleophiles in the tricatalytic cycle in Scheme 1, we recognized their potential to act as organocatalysts. No examples of sulfenate anion catalysts were previously known.

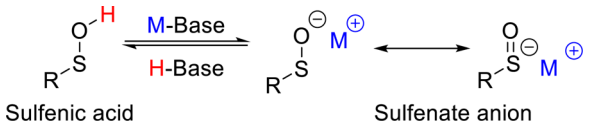
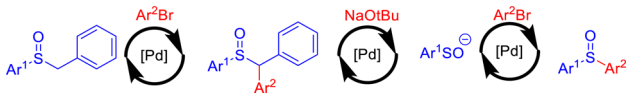


Figure 1. Sulfenic acid and its conjugate base, sulfenate anion.

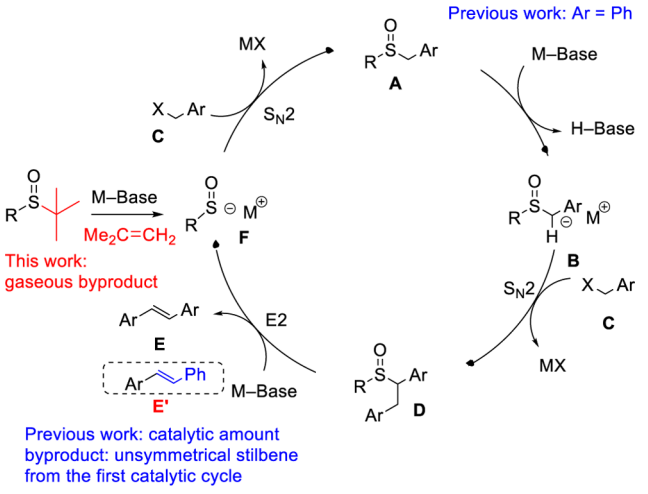
Scheme 1. Palladium Promotes the Tricatalytic Cycle with Sulfenate Anion as the Leaving Group in the Second Cycle and Nucleophile in the Third Cycle



As proof of concept, benzyl phenyl sulfoxide was applied as a precatalyst in coupling of benzyl halides to form symmetrical *trans*-stilbenes under basic conditions (Scheme 2).[5] In this process, a variety of *trans*-stilbenes could be prepared in good to excellent yields with catalyst loadings as low as 2 mol %.

The proposed mechanism for the sulfenate anion-catalyzed coupling of benzyl halides is illustrated in Scheme 2. Beginning with benzyl phenyl sulfoxide (**A**), deprotonation by KO^{t}Bu generates the anion (**B**), which was demonstrated to be the catalyst resting state. The anion **B** undergoes nucleophilic substitution with benzyl halide (**C**) to form

Scheme 2. Proposed Mechanism for Sulfenate Anion Catalyzed *trans*-Stilbene Formation from Benzyl Halides



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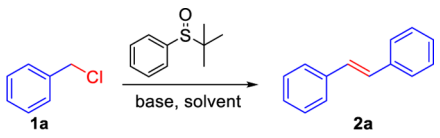
sulfoxide **D**. Deprotonation of the β-position of **D** is followed by elimination to generate the double bond in **E** with very high trans selectivity and the sulfenate anion **F**. A rather serious limitation to use of benzyl phenyl sulfoxide (**A**) as precatalyst is that the first turnover installs a phenyl group on the *trans*-stilbene. In cases where the benzylic halide (**C**) is other than benzyl chloride or bromide, the first cycle forms an unsymmetrical stilbene (PhCH=CHAr, **E′**) that is usually difficult to separate from the desired symmetric *trans*-stilbene, ArCH=CHAr (**E**). To make the sulfenate anion catalyzed synthesis of *trans*-stilbenes more attractive, we envisioned entry into the catalytic cycle at the sulfenate anion, **F**.

Herein, we report a second-generation sulfenate anion catalyst that avoids contamination of the first cycle. The precatalyst, *tert*-butyl phenyl sulfoxide, undergoes base promoted elimination to generate phenyl sulfenate anion and isobutylene as a gaseous byproduct (Scheme 2).

To explore the use of *tert*-butyl phenyl sulfoxide as precatalyst, we initially employed conditions for our catalytic coupling of benzyl chlorides using KO^{t}Bu and benzyl phenyl sulfoxide precatalyst at 80 °C for 12 h. Under these conditions, *tert*-butyl phenyl sulfoxide (2.5 mol %) afforded only 33% assay yield of *trans*-stilbene (Table 1, entry 1). The low yield was due to the reaction of benzyl chloride with KO^{t}Bu via a S_N2 process to generate benzyl *tert*-butyl ether.[6] We hypothesized that the low conversion to the desired stilbene was due to the slower E2 elimination of *tert*-butyl phenyl sulfoxide. To address this issue, we conducted the reaction in two stages. First, the precatalyst *tert*-butyl phenyl sulfoxide was heated with 3 equiv of KO^{t}Bu in CPME at 80 °C for 30 min before addition of benzyl chloride for the coupling. The assay yield of *trans*-stilbene (**2a**) increased to 43% (entry 2). Elevating the preheating temperature to 110 °C followed by cooling the reaction mixture, addition of benzyl chloride and heating to 80 °C for the coupling led to 97% assay yield of *trans*-stilbene (entry 3). Decreasing the catalyst loading to 1 mol % under otherwise identical conditions yielded 69% *trans*-stilbene (entry 4). Lowering the coupling temperature to 50 °C resulted in formation of the product with 94% assay yield (entry 5). Finally, we found that lowering the base loading to 2.0 equiv provided a slightly higher yield (96%) of *trans*-stillbene under more economical conditions (entry 6). Unfortunately, attempts to increase the reaction concentration from 0.1 to 0.2 M led to increased *tert*-butyl phenyl ether (entry 7). The assay yield remained at 96% when the coupling time was cut to 6 h (entry 8 vs 6). Further decreasing the coupling time to 4 h caused a drop in the assay yield to 88% (entry 9). Therefore, the optimized reaction conditions for *tert*-butyl phenyl sulfoxide catalyzed *trans*-stilbene formation from benzyl halides is 2.5 mol % precatalyst and 2.0 equiv of KO^{t}Bu in CPME preheated at 110 °C for 30 min, followed by addition of benzyl chloride and heating at 50 °C for 6 h.

Table 1. Optimization of Sulfenate Anion Catalyzed *trans*-Stilbene (2a) Formation from Benzyl Chloride (1a)[a]



1a 2a

entry	KO^{t}Bu (equiv)	catalyst (mol %)	temperature (°C)	time (h)	yield[b] (%)
1	3.0	2.5	80	12	33
2	3.0	2.5	80[c]	12	43
3[d]	3.0	2.5	110 → 80	12	97
4[d]	3.0	1.0	110 → 80	12	69
5[d]	3.0	2.5	110 → 50	12	94
6[d]	2.0	2.5	110 → 50	12	96
7[d,e]	2.0	2.5	110 → 50	12	90
8[d]	2.0	2.5	110 → 50	6	96 (94[f])
9[d]	2.0	2.5	110 → 50	4	88

[a]Reactions performed using 1.0 equiv of **1a** on a 0.2 mmol scale in CPME. [b]Crude yield determined by ^{1}H NMR using 0.1 mmol of CH_2Br_2 as internal standard. [c]Before benzyl chloride was added, base and precatalyst were preheated at 80 °C for 30 min. [d]Before benzyl chloride was added, base and precatalyst were preheated at 110 °C for 30 min. [e]0.4 mmol of **1a**. [f]Isolated yield.

With the optimized conditions in hand, we set out to explore the substrate scope. In general, benzyl chloride derivatives are better substrates than benzyl bromides because the latter undergo more rapid S_N2 reactions with the base to generate benzyl *tert*-butyl ethers. To compensate for the increased reactivity of benzyl bromide derivatives, 5 mol % precatalyst loading was employed with these substrates. Benzyl chloride and bromide gave *trans*-stilbene (**2a**) in 94% and 76% yield, respectively. Benzyl chlorides with substituents at para position (**2b**, **2d**, **2e**, and **2f**) were found to give higher yields at 80 °C and in some cases with 3.0 equiv of base (**1b** and **1d**) (Scheme 3). Electron-donating groups increased the pK_a of the benzylic protons of intermediates **A** and **D** (Scheme 2) making them more difficult substrates. For example, only 71% of **2b** was obtained. Substrates bearing electron withdrawing groups were better coupling partners. For example, 4,4′-difluorostilbene (**2d**), 4,4′-dichlorostilbene (**2e**), and 4,4′-dibromostilbene (**2f**) were produced in 60–97% yield. Compounds **2e** and **2f** could be easily elaborated by standard cross-coupling methods. More sterically hindered substrates, such as 2-methyl benzyl chloride (**1h**) and 1-(chloromethyl)naphthalene (**1i**), afforded **2h** and **2i** in 86% and 85% yields, respectively. Diortho-substituted 2,6-dichlorobenzyl chloride was an excellent substrate, leading to *trans*-stilbene **2j** in 98% yield. Benzyl halides substituted at the meta position with Me, F, or CF_3 group were good substrates, giving **2k**, **2l**, and **2m** in 89%, 89% and 84% yield, respectively. Heterocycle-containing stilbenes usually exhibit interesting photochemistry properties, but are more challenging to synthesize.[8] Heterocyclic 2-(chloromethyl)pyridine did not couple under our optimized conditions. Using non-nucleophilic KH, however, generated the product **2n**, but only in 39% yield.

To demonstrate the potential utility of this approach, we performed the coupling of 1-(chloromethyl)naphthalene (**1i**, 8.4 mmol, 1.48 g) to the *trans*-stilbene (**2i**) in 88% yield (Scheme 4), suggesting the reaction is scalable.

In summary, *trans*-stilbenes are widely used as industrial dyes, laser-dyes, and optoelectronic materials,[9] and significant effort has been devoted to their synthesis.[10−14] We have developed an organocatalytic method for their preparation that addresses a deficiency in our prior precatalyst, wherein a catalytic amount of an inseparable impurity was generated in

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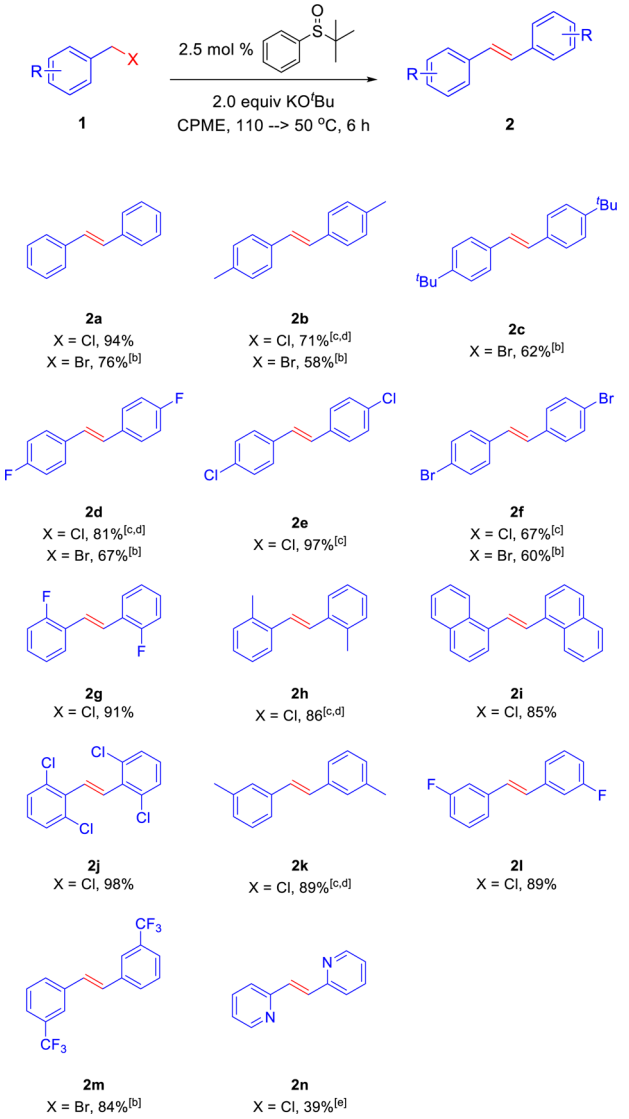
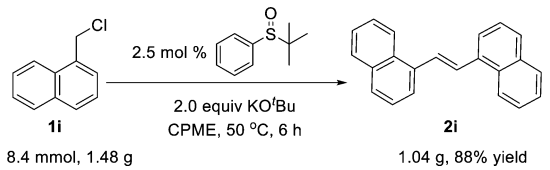
Scheme 3. Substrate Scope of Stilbene Formation from Benzyl Halides Catalyzed by Sulfenate Anions



[a]Reactions were performed using 1.0 equiv of **1** and 2.0 equiv of base on a 0.2 mmol scale. [b]5 mol % precatalyst loading. [c]80 °C. [d]3.0 equiv of KO^{t}Bu used. [e]KH used as base and reaction run for 24 h at 110 °C.

Scheme 4. *trans*-1,2-Di(α-naphthyl)ethylene Formation on Gram Scale



the first catalytic cycle. The precatalyst introduced herein, *tert*-butyl phenyl sulfoxide, undergoes base promoted E2 elimination to generate the sulfenate anion catalyst and a gaseous byproduct. Interestingly, the sulfenate anion generated under these conditions appears to survive the 110 °C precatalyst activation stage,[7] as judged by its ability to generate *trans*-stilbenes in up to 98% yield. Current efforts are focused on the application of sulfenate anion catalysts to other reactions.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pwalsh@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

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