DOI: 10.1002/cctc.201402817

A New Role for Sulfenate Anions: Organocatalysis

Adrian L. Schwan^{*[a]}

Organocatalysis is now commonplace as a means to create carbon–carbon bonds in an efficient, green and stereoselective manner, all in the absence of transition metals. The number of research contributions outlining organocatalyst use has undergone an astounding increase in recent years.^[1]

A major factor in the emergence and growth of this field has been the imagination and resourcefulness of researchers, traits that brought them to envision, source and exploit a broad collection of structural motifs to act as catalysts.^[2] Similarly, the number of reactions that have been re-examined under the lens of organocatalysis is remarkable.

To add to the vast number of past contributions, it is time to introduce a new player in the field. Walsh and co-workers have unveiled the sulfenate anion as an organocatalyst for the conversion of benzyl halides to symmetrically substituted stilbenes.^[3]

The sulfenate anion is the conjugate base of a sulfenic acid (Figure 1).^[4] Both of these entities have a reputation for being transient and their isolation is possible but only if the com-



Figure 1. Structures of a general sulfenic acid and its conjugate base.

pound possesses certain structural features.^[5] Access to transient sulfenates is usually by chemically induced release from a stable sulfoxide. Sulfenates are prochiral and have been probed for their chemical reactivity,^[4] organometallic chemistry^[6] and nucleophilic chemistry,^[7] the latter primarily taking the form of alkylation at sulfur to provide sulfoxide. Recent work has focussed on enantio-^[8,9] and diastereoselective sulfoxide formation.^[10]

The sulfenic acid has a pK_a of about 6–7, making the sulfenate a reasonable leaving group. This feature and the sulfenate's nucleophilicity were viewed as an ideal combination for participation in a catalytic cycle involving C–S bond formation and C–S bond cleavage as "bookend" reactions to a C–C bond forming process.^[3] The proposed catalytic cycle is outlined in Scheme 1, in which the sulfenate anion could be harnessed to facilitate carbon–carbon bond formation before its re-release into solution. The reactive nature of the sulfenate demands

[a] Prof. Dr. A. L. Schwan
Department of Chemistry
University of Guelph
Guelph, Ontario, N1G 2W1 (Canada)
E-mail: schwan@uoguelph.ca



hemPu

Scheme 1. Catalytic cycle for the sulfenate-mediated conversion of benzyl halides to *trans*-stilbenes.

that it should be introduced as a precatalyst and this is achieved in the sequence through the use of a sulfoxide (1). Deprotonation at the α position to the sulfoxide and benzylation of the anionic carbon with benzyl halide **2** creates a sulfinylsubstituted 1,2-diarylethane (**3**), which undergoes base-mediated bimolecular elimination to form stilbene product **4**, while simultaneously generating sulfenate (**5**). The sulfenate is alkylated by the stoichiometric benzyl halide (**2**) to regenerate simple sulfoxide (**1**) and complete the cycle.

With this plan in mind, the Walsh group embarked on a series of experiments to achieve the chemistry and then optimize the reaction conditions.^[3] Benzyl phenyl sulfoxide was chosen as sulfoxide 1 and was employed initially in a 10 mol% loading. With cyclopentyl methyl ether (CPME) as solvent and benzyl chloride as the substrate, a series of butoxide and hexamethyldisilazide bases were screened. Potassium *tert*-butoxide proved very effective, delivering styrene in over 98% yield. Additional optimization was characterized by variation of solvent, precatalyst loading, reaction temperature and relative amounts of benzyl halide substrate vs. potassium *tert*-butoxide. These efforts resulted in 1.0 equivalent of benzyl chloride (0.1 mmol, 0.1 molar in CPME) with 3.0 equivalents potassium *tert*-butoxide at 80 °C for 12 h as the optimized conditions.

Given these reaction conditions, the authors sought to explore the breadth of the chemistry.^[3] The effectiveness of the protocol for a series of symmetrically substituted *trans*-stilbenes is outlined in Table 1. The table also provides evidence that benzyl chlorides are more effective than benzyl bromides. This is surprising in light of the frequent use of benzyl bromides for capturing sulfenates. Speculation on this is that the benzyl chlorides are more competitive alkylating agents and more stable under the higher temperature conditions of this protocol.

Table 1. Scope of phenyl sulfenate-catalyzed stilbene formation. ^[a] O Image: Comparison of the strength					
R	х	Yield [%]	R	х	Yield [%]
Н	CI	95	2-F	CI	73
н	Br	81	2-Me	Cl	92
4-Me	Cl	84	1-naphthyl	Cl	80
4-Me	Br	62 ^[b]	2,6-Cl ₂	CI	88
4-tBu	Br	70 ^[b]	3-Me	Br	75 ^[b]
4-OMe	Cl	31 ^[b]	3-F	CI	89
4-F	Cl	81	3-CF ₃	Br	68 ^[c]
4-F	Br	66 ^[b]	2-pyridyl	Cl	54 ^[c]
4-Cl	Cl	99			
[a] Reaction conditions as indicated in the text. [b] 5 mol% precatalyst loading. [c] Base identity and/or reaction conditions changed.					

Generally, reaction yields were within the 50–99% range. The lone exception (31%) was when the aryl unit was *para*methoxybenzyl, a group that may negatively affect the deprotonation step. 2,2',6,6'-Tetrachlorostilbene was formed in 88% yield on the 0.1 mmol-scale. This reaction was chosen to evaluate the scalability of the protocol. If 1.37 g (7.0 mmol) of 2,6-dichlorobenzyl chloride were subjected to the optimized reaction conditions, 92% yield of the corresponding stilbene was obtained.

All of the aforementioned experiments were performed by using benzyl phenyl sulfoxide as a precatalyst (Scheme 1, Ar = Ph). However, upon recognition of the role played by this compound, other sulfoxides were also reasoned to be suitable precatalysts and were tested for their fit with the chemistry. Acknowledging that methyl phenyl sulfoxide is less acidic, yet possesses the requisite features, it was tested with potassium hydride. Performing the reaction with 5 mol% methyl phenyl sulfoxide and benzyl chloride as the substrate delivered stilbene in 92% yield. Similarly, dibenzyl sulfoxide (10 mol%) facilitated the conversion of benzyl chloride to stilbene in 92% with 3 equivalents of potassium bis(trimethylsilyl)amide in THF. DMSO also served as a suitable precatalyst, albeit with reduced efficiency. Use of 10 mol % DMSO with 3 equivalents of potassium hydride and benzyl chloride in CPME gave stilbene in 72% yield.

Although the outcomes of the chemistry were consistent with the proposed catalytic cycle, the authors nonetheless sought to gather other supportive evidence.^[3] For instance, the butoxide-mediated reaction of equimolar amounts of benzyl chloride (**2**, X = Cl) and benzyl phenyl sulfoxide (**1**, R = Ar = Ph) gave stilbene in 91% yield and afforded 2% of 1,2-diphenyl-1-(phenylsulfinyl)ethane (**3**, R = Ar = Ph). In another experiment, much like those outlined in the preceding paragraph seeking other sources of sulfenate, sulfoxide **3** (R = Ar = Ph) was shown to be an effective precatalyst; it simply entered the catalytic cycle at a different stage. In that experiment, the use of stan-

dard conditions and 2.5 mol % **3** (R=Ar=Ph) afforded stilbene in 98% yield. It was also demonstrated through a crossoverlike experiment that sulfoxide **3** (R=Ar=Ph) was an efficient source of sulfenate.

To establish the catalyst resting state, the reaction conditions were replicated but at 50 °C. The reaction was quenched with water after 30 min to reveal an 87% yield of benzyl phenyl sulfoxide (1, R = Ar = Ph), indicating that either the sulfoxide or its anion was the resting state. However, running the reaction in [D₈]THF to allow ¹H NMR analysis did not reveal any benzyl phenyl sulfoxide. An additional experiment indicated that potassium *tert*-butoxide was able to deprotonate benzyl phenyl sulfoxide in organic solution, prompting the conclusion that the anion of benzyl phenyl sulfoxide was the resting state in this catalytic cycle.

Given that outcome, Walsh and co-workers sought to isolate the potassium anion of benzyl phenyl sulfoxide.^[3] This was achieved by deprotonation with KCH₂Ph and the subsequent addition of [18]crown-6 to facilitate crystal formation. Although not vital to the message of the paper, the X-ray structure and allied DFT calculations identified structural differences between the neutral sulfoxide and its α -sulfinyl carbanion.

The history of sulfenate chemistry borders on being esoteric, with some contributions garnering interest from the broader organic chemistry community. Recent research, and in particular the current Walsh paper,^[3] have given the sulfenate anion a new cause. The chemistry celebrates the unique character of sulfenates and assembles their properties with those of sulfoxides into a single catalytic cycle, demonstrating what is believed to be the first use of a sulfenate in catalysis. More importantly, the work leads the charge of sulfenate chemistry towards mainstream usage in organic chemistry.

Keywords: carbanions • organocatalysis • reaction mechanisms • stilbenes • sulfur

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Received: October 13, 2014 Published online on

ChemCatChem 0000, 00, 1-3

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HIGHLIGHTS

