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B_2cat_2-Mediated Reduction of Sulfoxides to Sulfides

Fumiya Takahashi,[a] Keisuke Nogi,*[a] and Hideki Yorimitsu*[a]

[a] F. Takahashi, Dr. K. Nogi, Prof. Dr. H. Yorimitsu
Department of Chemistry
Graduate School of Science, Kyoto University
Sakyo-ku, Kyoto 606-8502, Japan
http://kuchem.kyoto-u.ac.jp/orgchem/
E-mail: knogi@kuchem.kyoto-u.ac.jp; yori@kuchem.kyoto-u.ac.jp

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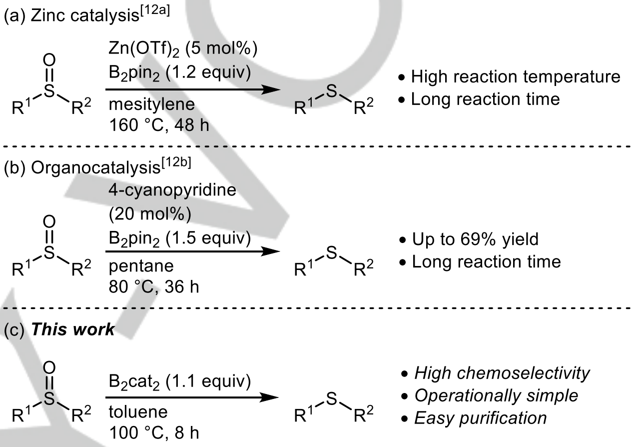
Abstract: An efficient and operationally simple method for the reduction of sulfoxides to sulfides has been developed using bis(catecholato)diboron (B_2cat_2) as a reducing agent. The present method accommodates various functional groups which are generally prone to reduction: halides, alkynes, carbonyls, nitriles, and heterocycles are totally intact, and only sulfoxide moieties undergo reduction chemoselectively. Moreover, the remaining diboron and the resulting boron-containing wastes are readily removable, the practicality of this protocol being thus demonstrated.

Organosulfur compounds have occupied important positions as bioactive entities, functional materials, and useful building blocks or reagents in organic synthesis.[1] Among organosulfur compounds, sulfoxides have attracted attention of synthetic chemists because of the unique reactivity as is seen in Swern oxidation[2] and Pummerer-type reactions.[3] Besides these classical reactions, sulfoxides are also utilized in asymmetric transformations as chiral auxiliaries.[4] Moreover, owing to the coordination ability to transition metals, sulfoxides promote catalytic C−H functionalizations as directing groups.[5] After these reactions, the sulfoxide moiety can be removed, which often accompanies the reduction of sulfoxides to sulfides and subsequent desulfurization. From that perspective, reduction of sulfoxides to sulfides is a simple yet important process in organic synthesis.[6] Although there are many reports on reduction of sulfoxides by means of metal hydrides[7] or low-valent transition metals,[8] these reactions intrinsically suffer from competing reduction of other functionalities such as carbonyls. Sulfur(II) coumpounds[9] and phosphines[10] are also known to promote the reduction of sulfoxides, but they often encounter purification problems. In the former case, separation of the resulting sulfide products from the remaining sulfur(II) reductants such as thiols and sulfides can be problematic. The latter faces the formation of phosphine oxides as byproducts that are tedious to remove. Efficient methods achieving good functional group tolerance and facile purification of the products are of high demand.

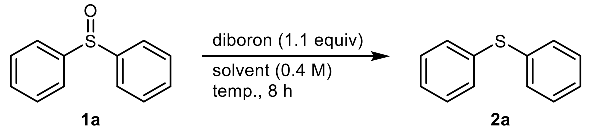


Scheme 1. Reduction of sulfoxides using diboron reagents

Recently we have been interested in the development of reductive transformations using diboron reagents.[11] During our investigation, we found that sulfoxides were reduced to the corresponding sulfides by means of diborons. Although there are two reports on the reduction of sulfoxides with bis(pinacolato)diboron (B_2pin_2) as a deoxygenating reagent,[12] catalysts, long reaction time, and/or high reaction temperature are required (Scheme 1a and 1b). Herein, we report an efficient and operationally simple method for the chemoselective reduction of sulfoxides to sulfides (Scheme 1c). The use of stable yet fairly reactive bis(catecholato)diboron (B_2cat_2) allowed additive- and catalyst-free reduction of high efficiency.[13]–[15]

By employing diphenyl sulfoxide (**1a**) as a model substrate, we conducted optimization of the reaction conditions (Table 1). First, reaction temperature was examined. At 60 °C or 80 °C, **1a** was not fully consumed even with prolonged reaction time (entries 1−3). Full conversion of **1a** was accomplished at 100 °C to afford the corresponding sulfide **2a** quantitatively (entry 4). Next, we investigated the effect of solvents. As with toluene, the use of non-polar solvents such as octane achieved a high conversion (entry 5). On the other hand, coordinating solvents such as DMF and 1,4-dioxane were less effective for the reduction (entries 6 and 7). The employment of B_2cat_2 was indispensable; the yield of **2a** significantly dropped with less Lewis acidic B_2pin_2 and bis(neopentyl glycolato)diboron (B_2nep_2) (entries 8 and 9). The screening of solvents and diboron reagents indicates that coordination of the oxygen atom of sulfoxide to the boron atom of diboron would be important, and the use of coordinating solvents or less Lewis acidic diboron reagents[16] would thus decrease the yield (See Scheme 3 for mechanistic discussions).

Table 1. Optimization study



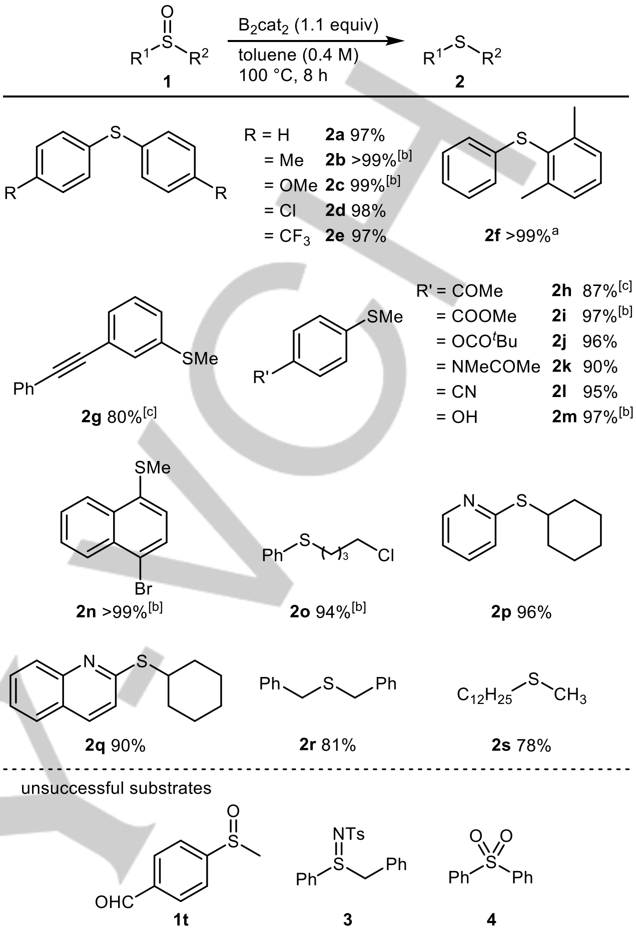
entry	temp.	diboron	solvent	yield (%)[a]
1	60 °C	B_2cat_2	toluene	54
2	80 °C	B_2cat_2	toluene	65
3[b]	80 °C	B_2cat_2	toluene	88
4	100 °C	B_2cat_2	toluene	100 (97)[c]
5	100 °C	B_2cat_2	octane	95
6	100 °C	B_2cat_2	DMF	80
7	100 °C	B_2cat_2	1,4-dioxane	65
8	100 °C	B_2pin_2	toluene	10
9	100 °C	B_2nep_2	toluene	27

[a] Determined by GC with tridecane as an internal standard. [b] For 29 h. [c] Isolated yield.

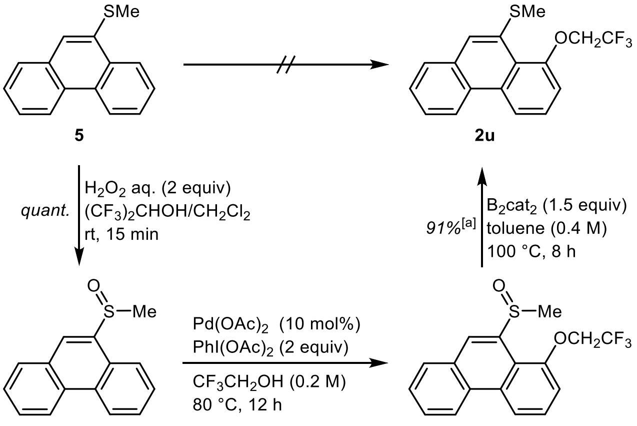
Having optimized reaction conditions (Table 1, entry 4), we next investigated the reaction scope. Various diaryl sulfoxides **1a−1e** possessing electron-donating or -withdrawing groups afforded the corresponding sulfides **2a−2e** in excellent yields. Sterically hindered *ortho*-substituted diaryl sulfoxide **1f** could be reduced quantitatively. It is worth noting that the present reduction method accommodates a wide range of functional groups which are potentially reducible. For example, halogen (**2d** and **2n**), alkyne (**2g**), ketone (**2h**), ester (**2i** and **2j**), amide (**2k**), and nitrile (**2l**) were intact during the reaction, and the sulfoxide moieties were reduced chemoselectively. Moreover, a non-protected phenolic hydroxy group of **2m** was well-tolerated. Surprisingly, the C(sp^3)−Cl bond in **1o**, which is significantly susceptible to reductive conditions, was totally inert under the reaction conditions. In addition, heteroaryl sulfoxides **1p** and **1q** successfully underwent the reaction to furnish **2p** and **2q** in excellent yields. Not only aryl sulfoxides but also dialkyl sulfoxides **1r** and **1s** were applicable to the present reaction. Unfortunately, formyl-substituted sulfoxide **1t** and sulfilimine **3** gave complex product mixtures. Sulfone **4** did not undergo the reaction and was fully recovered. Of note, in some cases in Table 2, purification by column chromatography was not necessary. Simple filtration with a pad of alumina successfully removed the remaining B_2cat_2 and byproduct $(catB)_2O$[17] to afford analytically pure products **2** (See Experimental Section for details).

By means of the present method, we attempted formal C8-selective C−H alkoxylation of 9-(methylsulfanyl)phenanthrene (**5**) (Scheme 2). Because the sulfanyl moiety is readily oxidized, oxidative C−H functionalization of **5** is difficult. However, sulfoxide **6** prepared from **5** uneventfully underwent C8-selective C−H alkoxylation[5f] to afford **1u** in 83% yield. Finally, the present reduction was applied to **1u** to furnish **2u** in 91% yield.

Table 2. Scope with respect to sulfoxides[a]



[a] Reaction conditions: **1** (0.50 mmol), B_2cat_2 (0.55 mmol), toluene (1.2 mL), at 100 °C under air for 8 h. [b] Analytically pure products were obtained without purification by column chromatography. [c] 1.5 equiv of B_2cat_2 were used.



Scheme 2. Formal C8-selective C−H alkoxylation of 9-(methylsulfanyl)phenanthrene (**5**). [a] Analytically pure product was obtained without purification by column chromatography.

In order to gain mechanistic insights, we plotted time profiles of the reduction of several diaryl sulfoxides. Figure 1 indicates that electron-rich sulfoxides reacted faster than electron-poor ones. This implies that the easier the complexation of a sulfoxide to a diboron is, the faster the reaction proceeds.

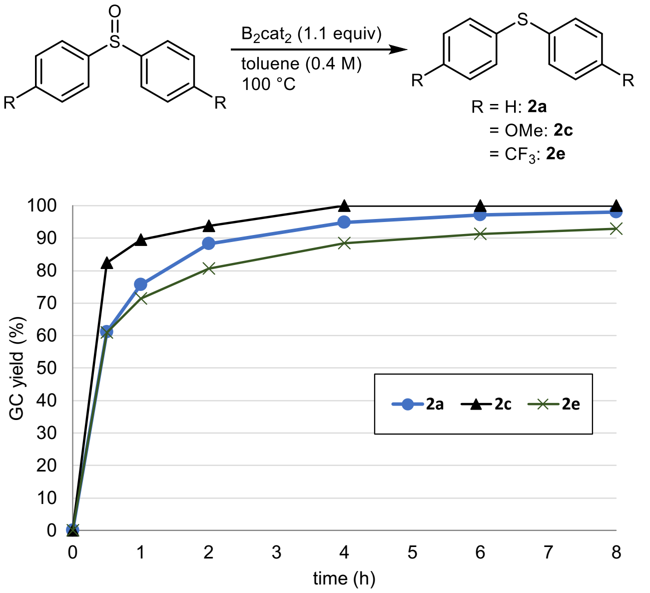
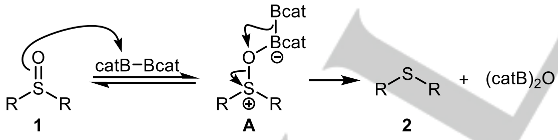


Figure 1. Reaction time profile according to the *para*-substituents on diaryl sulfoxides

As is shown in Scheme 3, the reaction would be initiated with reversible coordination of the oxygen atom of **1** to the boron atom of B_2cat_2 to generate intermediate **A**. Subsequently, 1,2-migration of the terminal boryl moiety to the oxygen would give reduction product **2** accompanied by the formation of $(catB)_2O$.[15a] To facilitate the formation of **A**, the use of B_2cat_2, more Lewis acidic than B_2pin_2 and B_2nep_2, would be vital. Given the time profile depicted in Figure 1, electron-rich sulfoxides would shift the equilibrium toward **A**, which resulted in acceleration of the reaction.



Scheme 3. A possible mechanism.

In conclusion, we have developed an efficient and operationally simple method for reduction of sulfoxides to sulfides with B_2cat_2 as a reducing agent. This user-friendly protocol is characterized by high functional group tolerance and easy purification process.

Experimental Section

General procedure for the reduction of sulfoxides **1**

A 10-mL reaction tube was charged with sulfoxide **1** (0.50 mmol), B_2cat_2 (0.13 g, 0.55 mmol), and toluene (1.2 mL) under air. The resulting mixture was stirred at 100 °C for 8 h. The mixture was directly passed through a pad of alumina (8.8 g, ϕ = 22 mm, H = 25 mm) with ethyl acetate (20 mL) as an eluent, and concentrated under reduced pressure to give product **2**. If necessary, purification was done by column chromatography on silica gel (hexane/ethyl acetate).

Acknowledgements

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Keywords: Bis(catecholato)diboron • Chemoselective • Reduction • Sulfide • Sulfoxide

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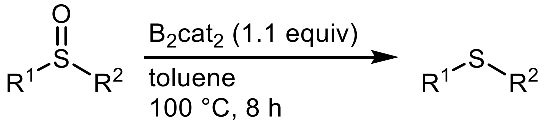
Entry for the Table of Contents

Key Topic: Chemoselective Reduction



- *High chemoselectivity*
- *Operationally simple*
- *Easy purification*

An efficient and operationally simple method for the reduction of sulfoxides to sulfides using bis(catecholato)diboron as a reducing agent is described. This user-friendly protocol is characterized by high functional group tolerance and easy purification process.

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