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# 1,3-Benzodithiole-1,1,3,3-tetraoxide (BDT) as a versatile methylation reagent in catalytic enantioselective Michael addition reaction with enals

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ABSTRACT

A protocol of an organocatalytic highly enantioselective conjugate addition of nucleophilic BDT to enals has been developed and the versatile Michael adducts serve as useful building blocks for a variety of organic transformations.



Chiral methyl unit is one of the most important organic groups widely distributed in natural products, drugs and various chiral chemical products and intermediates. Asymmetric methods to construct methyl moiety include α- or β-alkylation of carbonyl compounds with chiral auxiliaries,[1] enantioselective protonation at α-position of carbonyl compounds,[2] asymmetric hydrogenation of double bond with $H_2$/metal/ligand method,[3] resolution of racemic alcohol with lipase[4] and conjugate addition of methyl metal to electron-deficient olefins.[5] Recently, organocatalytic asymmetric transfer hydrogenation of β-branched α-, β-unsaturated aldehydes or nitroolefins with Hantzsch ester as 'H' source was proved to be an efficient method for the synthesis of chiral β-alkyl aldehydes or nitroalkanes.[6] However, the examples of organocatalytic direct Michael addition of methyl group or its precursor to α-, β-unsaturated aldehydes remain elusive.[7]

Recently, sulfones have received much attention in the synthetic communities. The sulfonyl moiety in products can be conveniently converted into various useful functionalities, and accordingly vinyl sulfones[8] and α-substituted sulfones[9] have been widely used as electrophiles and nucleophiles in a variety of organic transformations. Very recently, we, Moyano and Rios, Kim, Cordova and Shibata groups independently reported the Michael addition of fluorobis(phenylsulfonyl)methane to α-, β-unsaturated carbonyls with high enantioselectivities for the preparation of monofluoromethyl compounds (Fig. 1).[10] In our continuing effort on expanding the viable synthetic strategy, we envision that the use of the unsubstituted

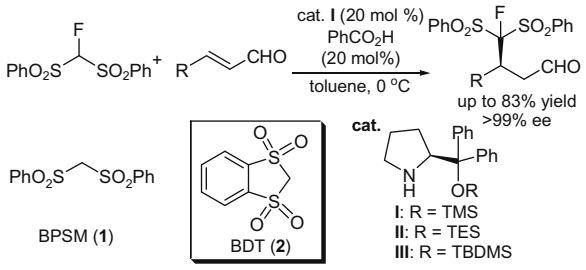


**Figure 1.** Nucleophilic bissulfonylmethanes.

bis(phenylsulfonyl)methane is more valuable. It is believed that a variety of electrophiles can be introduced. Therefore, the strategy is particularly attractive in medicinal chemistry and drug discovery with the ease of making analogues.

However, as demonstrated in our early studies, the reaction between bis(phenylsulfonyl)methane (BPSM) (**1**) and 4-nitrocinnamaldehyde gave only a trace amount (<5% yield) of Michael adduct.[10a] The same outcome was observed by Ruano and Alemán group in similar studies.[11] Only β-alkyl substituted α-, β-unsaturated aldehydes effectively participate in the organocatalytic Michael reaction. We surmise that this may result from the steric hindrance and low reactivity of methylene moiety in bis(phenylsulfonyl)methane. To generate a more reactive sulfonyl-derived methylene species, we believe that a rigid cyclic structure such as 1,3-benzodithiole-1,1,3,3-tetraoxide (BDT, **2**) could be a useful reagent for the direct conjugate addition process. To our knowledge, although this reagent was reported more than 10 years ago,

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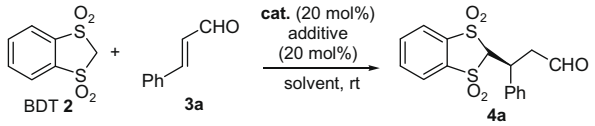
it has rarely been used in the organic synthesis.[12] Herein, we wish to report our discovery of BDT as an efficient nucleophile in the direct Michael addition to various substituted enals including aromatic systems with good to excellent enantioselectivities and in moderate to high yields.[13] Moreover, the viable Michael adducts can be used for further synthetic elaborations to conveniently be transformed to new functionalities.

We initially examined the Michael reaction of BDT (**2**) and cinnamaldehyde **3a** in the presence of diphenylprolinol silyl ether **I** (20 mol %) in toluene at rt. To our delight, even when no base was added, the reaction proceeded smoothly to provide the desired product **4a** in 78% yield and with 94% ee after 72 h (Table 1, entry 1), indicating that indeed the methylene moiety in BDT is much more active. Further investigation of the reaction medium revealed that the reaction was tolerated by various solvents. Good to high enantioselectivities and moderate to excellent yields were obtained in most of the solvents screened (entries 2–8). The best result was achieved when *t*-BuOMe was used (86% yield and 96% ee) (entry 8). Survey of catalysts identified the bulky TBDMS catalyst **III** as the best promoter by improving the ee value to excellent level without sacrificing the yield (entry 10 vs entry 8). Reducing the loading of **3a** from 1.5 equiv to 1.2 equiv gave similar results, but longer reaction time was needed (entry 11). The effect of additives on the reaction was also probed. Surprisingly, the basic additive NaOAc hindered the reaction significantly, giving only 43% yield even after 5 d (entry 12). In contrast, benzoic acid accelerated the process dramatically to generate improved yield albeit with slightly decreased enantioselectivity (96% yield and 97% ee) (entry 13). Finally, decreasing the catalyst loading from 20 mol % to 10 mol % and simultaneously reducing the volume of solvent from 0.8 mL to 0.4 mL gave the same results (Table 1, entry 14 vs entry 13). It is noteworthy that adduct **4a** can easily precipitate from *t*-BuOMe to give highly pure product without column chromatography. To demonstrate the advantage of our methodology, 1.0 mmol scale of BDT was applied under the optimal reaction conditions as described in Table 1, (entry 14). After 72 h, 4.0 mL of hexane was added into the reaction mixture, stirred for another 20 min and then filtered; the solid was washed with 10 mL of *t*-BuOMe/hexane (1/1) to afford pure **4a** as a white solid in 84% yield. Lowering the catalyst loading to 5 mol % required a long reaction time as well (60 h), even at higher temperature (40 °C) with slight drop in both yield (91%) and ee (93%) (entry 15). It should be noted that the enantiomeric excess found by us was enriched in this simple purification process. The ee of the crude product was determined to be 97%, while the purified product by filtration was reached to 99%.

With optimal reaction conditions in hand, we then explored the scope of Michael addition of BDT to a wide range of α-, β-unsaturated aldehydes. As shown in Table 2, a number of cinnamaldehydes bearing electron-donating and electron-withdrawing substituents were successfully applied in the Michael reaction with BDT. The corresponding aldehyde products **4a–k** were successfully isolated with very high enantioselectivities (93–98% ee) and in good to excellent yields (63–98%) (entries 1–11). In some cases, toluene instead of *t*-BuOMe is the better solvent for the reaction (entries 5–11). Furthermore, heteroaromatic and alkyl enals could also effectively engage in the conjugate addition process with high efficiency (entries 12–14). Although no single solvent was suitable for the alkyl enals, the use of a mixture of toluene and THF was optimal (entries 13–14). The absolute configuration of the Michael adducts was determined to be *S* by single-crystal X-ray analysis of corresponding alcohol **5** derived from **4c** (Fig. 2).[14]

Finally, to demonstrate the synthetic utility of the Michael adducts **4**, a series of organic transformations were performed. Reduction of the aldehyde **4a** gave an alcohol **6**. Then direct reductive removal of the phenylsulfonyl group of compound **6** using a modified protocol activated Mg (0) in the presence of $Bu_4N^+Br^-$

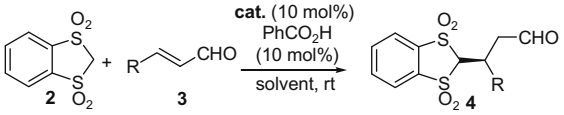
**Table 1**
Optimization of the reaction conditions[a]




| Entry | Cat. | Solvent | Additive | *t* (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **I** | Toluene | None | 72 | 78 | 94 |
| 2 | **I** | $CH_2Cl_2$ | None | 43 | 79 | 86 |
| 3 | **I** | EtOH | None | 36 | 98 | 83 |
| 4 | **I** | EtOAc | None | 60 | 77 | 90 |
| 5 | **I** | $Et_2O$ | None | 36 | 81 | 95 |
| 6 | **I** | THF | None | 83 | 63 | 93 |
| 7 | **I** | DME | None | 83 | 58 | 91 |
| 8 | **I** | *t*-BuOMe | None | 40 | 86 | 96 |
| 9 | **II** | *t*-BuOMe | None | 40 | 83 | 97 |
| 10 | **III** | *t*-BuOMe | None | 72 | 83 | 99 |
| 11[d] | **III** | *t*-BuOMe | None | 120 | 86 | 99 |
| 12[d] | **III** | *t*-BuOMe | NaOAc | 120 | 43 | — |
| 13[d] | **III** | *t*-BuOMe | $PhCO_2H$ | 72 | 96 | 97 |
| **14**[e] | **III** | ***t*-BuOMe** | **$PhCO_2H$** | **72** | **95** | **97** |
| 15[f] | **III** | *t*-BuOMe | $PhCO_2H$ | 60 | 91 | 93 |

[a] Unless stated otherwise, the reaction was carried out with **3a** (0.15 mmol), **2** (0.10 mmol), catalyst (0.02 mmol) and additive (0.02 mmol) in 0.8 mL of solvent at rt for a specified time. The mixture was then directly purified by silica gel chromatography.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralpak IB) by converting to corresponding alcohol.
[d] 0.12 mmol of **3a** used.
[e] Reaction conditions: **3a** (0.12 mmol), **2** (0.10 mmol), catalyst **III** (0.01 mmol) and $PhCO_2H$ (0.01 mmol) in 0.4 mL of *t*-BuOMe at rt.
[f] 5 mol % **III** used at 40 °C.

**Table 2**
Scope of Michael addition of BDT (**2**) to α-, β-unsaturated aldehydes (**3**)[a]




| Entry | R | Cat. | Solvent | *t* (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | Ph, **4a** | **III** | *t*-BuOMe | 72 | 95 | 97 |
| 2 | 4-$FC_6H_4$, **4b** | **III** | *t*-BuOMe | 120 | 70 | 94 |
| 3 | 4-$ClC_6H_4$, **4c** | **III** | *t*-BuOMe | 72 | 68 | 96 |
| 4 | 4-$BrC_6H_4$, **4d** | **III** | *t*-BuOMe | 72 | 90 | 94 |
| 5 | 4-$CNC_6H_4$, **4e** | **III** | Toluene | 96 | 87 | 98 |
| 6 | 4-$NO_2C_6H_4$, **4f** | **III** | Toluene | 43 | 85 | 98 |
| 7[d] | 4-$MeC_6H_4$, **4g** | **I** | Toluene | 68 | 71 | 93 |
| 8[e] | 4-$MeOC_6H_4$, **4h** | **III** | Toluene | 34 | 98 | 96 |
| 9[d] | 3-$FC_6H_4$, **4i** | **III** | Toluene | 120 | 72 | 95 |
| 10 | 3-$NO_2C_6H_4$, **4j** | **III** | Toluene | 115 | 76 | 98 |
| 11[d] | 2-$FC_6H_4$, **4k** | **I** | Toluene | 72 | 63 | 94 |
| 12[d,e] | 2-Furanyl, **4l** | **I** | Toluene | 72 | 76 | 84 |
| 13[d,e,f] | Me, **4m** | **III** | Toluene/THF (1/1, v/v) | 35 | 95 | 88 |
| 14[d,e,f] | Et, **4n** | **III** | Toluene/THF (1/1, v/v) | 135 | 73 | 92 |

[a] Unless stated otherwise, the reaction was carried out with **3** (0.18 mmol), **2** (0.15 mmol), catalyst (0.015 mmol) and $PhCO_2H$ (0.015 mmol) in 0.6 mL of solvent at rt for a specified time. The mixture was then directly purified by silica gel chromatography.
[b] Isolated yield.
[c] ee was determined by HPLC analysis (Chiralpak IA, IB or IC) of corresponding alcohol of **4**.
[d] 20 mol % catalyst used.
[e] No $PhCO_2H$ used.
[f] Two equivalents of aldehyde used.

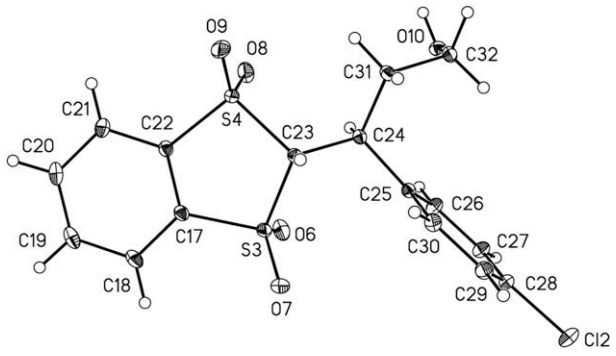
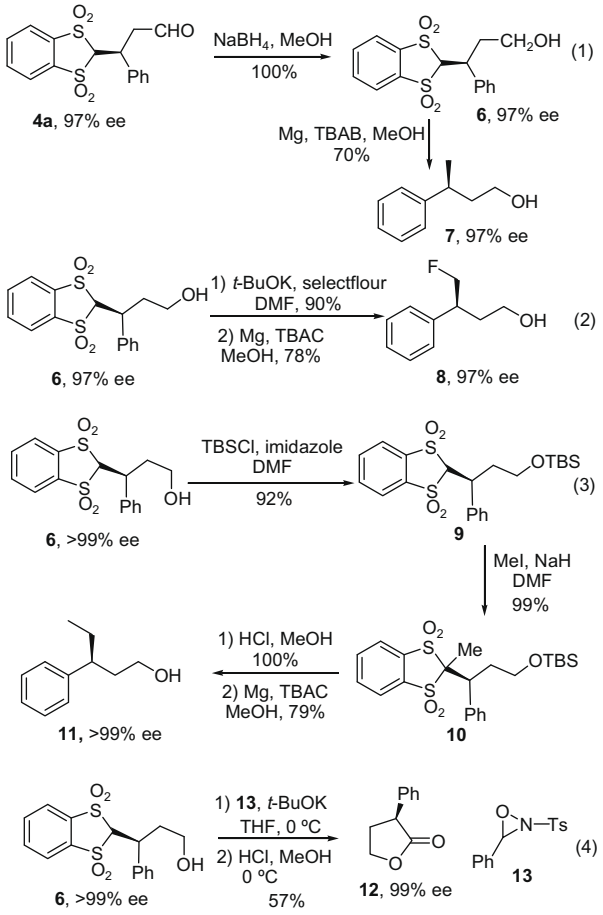



**Figure 2.** X-ray crystallographic structure **5**.

or $Cl^-$ (TBAB or TBAC) in MeOH provided 3-methyl phenylpropanol in a good yield (Eq. 1). It is noteworthy that without TBAB or TBAC, a low yield for the cleavage of phenylsulfonyl group was obtained. Treatment of compound **6** with selectfluor and *t*-BuOK in DMF was followed by reductive removal of the phenylsulfonyl group to afford monofluoromethylated product **8** (Eq. 2). Moreover, a methyl group can be introduced readily to lead to 3-ethyl compound **11** (Eq. 3). Finally, the treatment of the sulfone **6** with oxidant oxaziridine **11** in the presence of *t*-BuOK followed by lactonization afforded synthetically valuable chiral lactone **12** (Eq. 4).[15] Significantly, no racemization was observed in all cases.




In conclusion, we have developed a new nucleophilic reagent BDT for the direct organoctalytic asymmetric Michael addition to a wide range of α-, β-unsaturated aldehydes with good to excellent ee's and in good to excellent yields. The process features the simple filtration without column chromatography to afford products in good yield and with enriched enantioselectivity. These features render the process particularly attractive for a large-scale synthesis. Furthermore, the viable phenylsulfonyl group in Michael adducts can be easily converted into a variety of new functionalities. Further investigations of this versatile reagent in new organic transformations are currently underway in our laboratory and will be reported in due course.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.102.

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13. During the preparation of this manuscript, a similar approach is reported by Palomo and co-workers: Landa, A.; Puente, Á.; Santos, J. I.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2009**, *15*, 11954.

14. CCDC 749599 contains the Supplementary data for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk.
15. A possible reaction pathway for the transformation is: oxidation of the bissulfonyl moiety to a carboxylic acid by oxaziridine **13** is followed by lactonization to give lactone **12**. The chemistry is developed based on the works by Davis, F. A.; Jenkins, R., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, *19*, 5171. Further study of the reaction and application is under investigation