VIP Organocatalysis

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Highly Enantioselective α Alkylation of Aldehydes with 1,3-Benzodithiolylium Tetrafluoroborate: A Formal Organocatalytic α Alkylation of Aldehydes by the Carbenium Ion**

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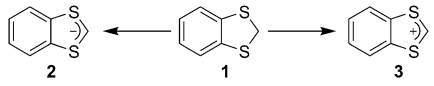
The benzodithiol heterocycle **1** (Scheme 1) is an interesting and readily available synthon for organic synthesis.[1] The application of the easily formed carbanion **2** and carbocation



Scheme 1. Benzodithiol as precursor of anionic **2** and cationic **3**.

3 can give considerable advantages when designing complex syntheses. The anion **2**, which is a practical acyl anion equivalent, can be easily generated by simple deprotonation with strong bases such as *n*BuLi.[2] The carbenium ion **3** is also a useful electrophile,[3] and can be easily prepared by hydride exchange with triphenyl carbenium salts.[4] The stability of **3** is between that of the tropylium and tritylium carbenium ions.[5] The stable benzodithiolylium tetrafluoborate **3a** is commercially available and can be easily handled without any precautions.

Several significant results in the field of α alkylation of aldehydes were recently reported, in which attempts were made to solve what is considered the "Holy Grail" of organocatalysis.[6,7] We have recently contributed to this field, and have focused our attention on the development of new methodologies for the α alkylation of aldehydes[8] by S_N1-type reactions[9] with alcohols.[10,11] We have also found that stable and isolable carbenium ions can be used in organocatalytic enantioselective α alkylation of aldehydes[12] by using secondary amines (MacMillan catalyst).[7c] The stability and reactivity of the versatile 1,3-benzodithiolylium cation attracted our attention. Not only can the organocatalytic α alkylation of **3** constitute the addition of a formyl equivalent, but the introduction of the 1,3-benzodithiol group in a stereoselective fashion can also allow the generation of an anionic (**2**) or cationic (**3**) equivalent. Furthermore, deprotection of 1,3-benzothiole with Raney Ni can give direct access to a methyl group.[13] Herein we report the first practical and highly organocatalytic stereoselective addition of the commercially available cation **3a** to various functionalized aldehydes and the easy functionalization of the isolated adducts.

Formylation of aldehydes is of major importance in synthesis,[14] and the cationic formylation of enolates has also been studied.[15,16] Scolastico, Hopper, and their respective co-workers used ephedrine in the synthesis and use of chiral formyl cations.[17] Furthermore, the diastereoselective addition of an enamine to a chiral formyl cation was reported.[18]

We have investigated the model reaction (Table 1) with different bases and organocatalysts. In general, the reaction was poorly promoted by proline derivatives. The presence of the base was necessary to capture the HBF_4 liberated by the reaction of the carbenium ion. The nature of the base was crucial for the reaction; organic bases such as 1,6-dimethylpyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), or Et_3N resulted in poor yields because of side reactions of the 1,3-benzodithiol unit.[19] Inorganic bases were more suitable for the transformations; in terms of yield, NaH_2PO_4 was found to be most suitable. Enantiomeric excesses and yields were further optimized by screening different organocatalysts **5a–f** in different solvents and reaction conditions. The desired product was produced with excellent enantioselectivity and high yields in a 1:1 mixture of CH_3CN and H_2O after reduction to the corresponding alcohol by $NaBH_4$ in MeOH. The use of the easily prepared and commercially available catalysts **5a** in the presence of water[20] gave excellent enantiocontrol in the reaction with propanal. The stability of the 1,3-benzodithiolylium carbenium is high in the presence of water and no decomposition of the carbenium ion occurs. The scope and limitations of this new formylation reaction have been extensively investigated (Scheme 2). Aldehydes bearing a variety of functional groups were investigated by using the optimized protocol. Notably, a wide array of aldehydes are applicable to this formylation reaction. The reaction was quite tolerant of a large variety of functional groups such as chloro and cyano groups, and amides and acetals. The enantiomeric excesses obtained were in the range 92–97% with different batches of MacMillan catalyst and carbenium ions.[21] Remarkably, the formylation provides straightforward access to a variety of valuable

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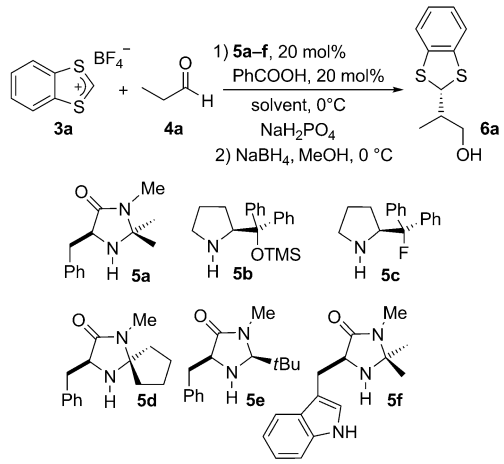
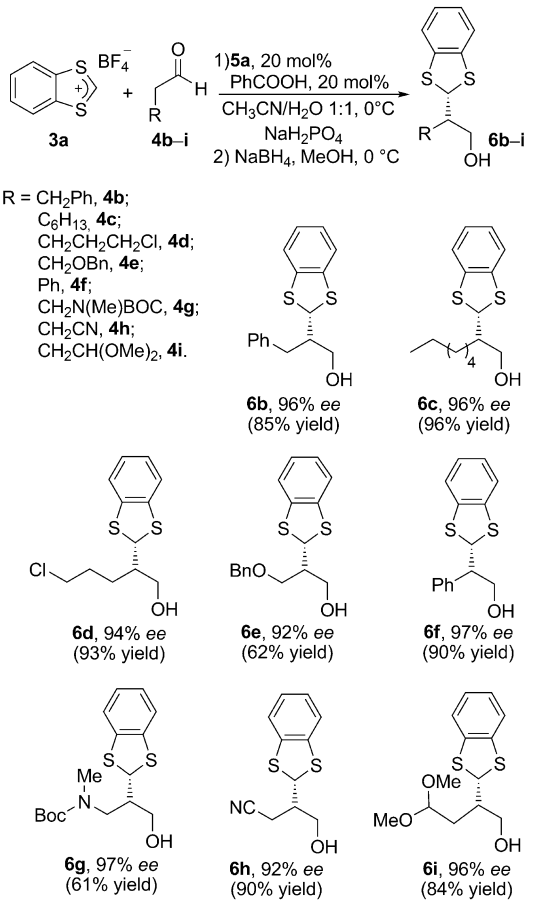
Table 1: Organocatalyst-promoted addition of propanal to the benzodithiolylium cation.

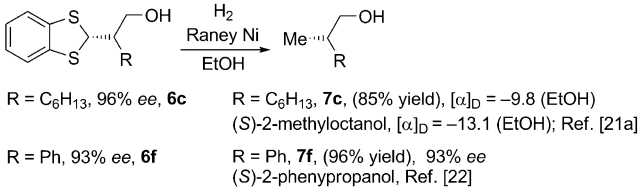


Entry[a]	Cat.	Solvent	Yield [%][b]	*ee* [%][c]
1	**5a**	CH_2Cl_2	90	50
2	**5b**	CH_2Cl_2	26	25
3	**5c**	CH_2Cl_2	50	40
4	**5d**	CH_2Cl_2	30	30
5	**5e**	CH_2Cl_2	87	6
6	**5a**	H_2O	54	87
7	**5d**	H_2O	42	80
8	**5e**	H_2O	51	36
9	**5f**	H_2O	73	72
10	**5a**	CH_3CN	76	80
11	**5a**	H_2O/CH_3CN 9:1	82	91
12	**5a**	H_2O/CH_3CN 1:1	96	96
13	**5a**	H_2O/THF 1:1	44	63

[a] The reactions were performed at 0 °C with 1 equiv of **3a**, 3 equiv of aldehyde **4a** in the presence of 20 mol% of catalysts **5a–f**, and with 1 equiv of NaH_2PO_4. 20 mol% of PhCOOH was used as a co-catalyst and the reactions were run until completion, as determined by TLC (16–24 h). [b] Yield after chromatographic purification. [c] Determined by analysis of the isolated products by HPLC on a chiral stationary phase. See the Supporting Information for details.



Scheme 2. Organocatalytic alkylation of functionalized aldehydes **4b–i** with the cation **3a**.



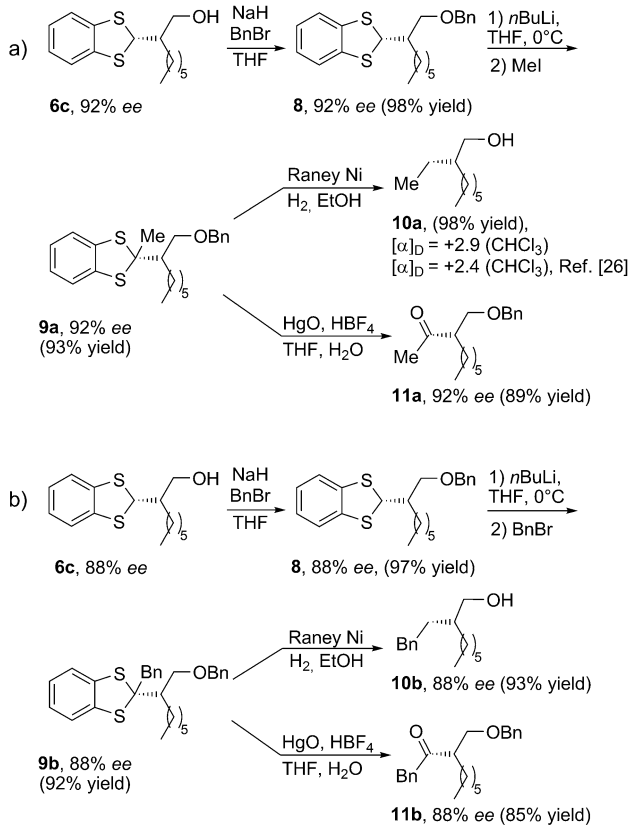
Scheme 3. Determination of absolute configuration of the products **7c** and **7f**.

precursors. Also, as the 1,3-benzodithiol group can be easily removed by Raney Ni in the presence of hydrogen,[22] this organocatalytic formylation provides a convenient procedure for the challenging organocatalytic α methylation of aldehydes.

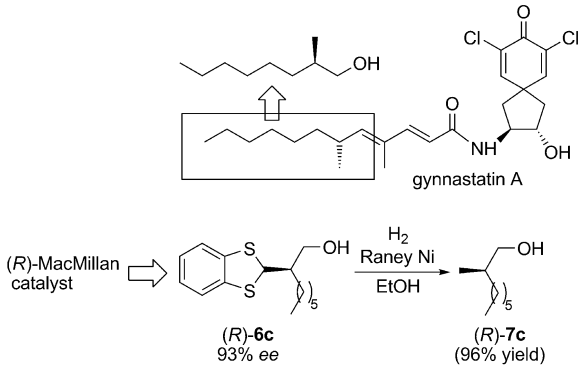
The absolute configurations of the products were determined through the transformation of adducts **6c** and **6f** to the corresponding products **7c**[23] and **7f** (Scheme 3).[24] In the case of **7f**, HPLC analysis was compared to the reported elution time, while the absolute configuration of **7c** was assigned by comparison with the reported optical rotation value. In both cases, the (*S*)-MacMillan catalyst gave the (*S*)-configured product. The reaction with Raney Ni occurs without racemization, as was verified in the case of the substrate **6f**.[25] It is worth noting that the elimination of the benzodithiol group in **7f** allows rapid access to anti-inflammatory drugs such as profens.[26]

To prove the versatile and easy transformation of the adduct **6c** obtained by the organocatalytic formylation, we have performed some preliminary investigations (Scheme 4). The product **6c** was transformed in a quantitative manner to the corresponding benzyl ether **8**, which was lithiated with *n*BuLi at 0 °C in THF and treated with MeI and BnBr at 0 °C. The alkylation reaction was fast and quantitative. In the case of the product **10b**, after treatment with Raney Ni, no racemization was observed. On the other hand, adducts **9a**,**b** are easily transformed into the corresponding ketones **11a**,**b** by treatment of the 1,3-benzodithiol adducts with HgO in the presence of HBF_4.[27] The reactions occurred in high yields, and in both cases we observed no racemization in the final products.

In the preliminary application of our methodology we have focused our attention on the preparation of a key intermediate in the synthesis of gymnastatin A (Scheme 5) and we have accomplished a straightforward total synthesis of



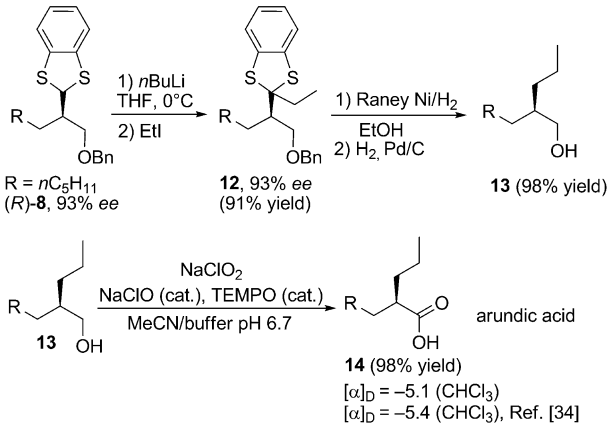
Scheme 4. Alkylation of the benzothiol derivative with MeI and BnBr and successive elimination with Raney Ni and HgO. Bn = benzyl.



Scheme 5. Synthesis of (*R*)-2-methyloctanol, a key intermediate in the synthesis of gymnastatin A.

arundic acid (Scheme 6). Gymnastatins have been reported to exhibit antibacterial activity and cytotoxicity towards cultured P388 cancer cells. The total synthesis of gymnastatins A–C has previously been reported.[29] In most cases, the lateral acid chain was prepared from (*R*)-2-methyloctanol by oxidation to the corresponding aldehyde followed by iterative Wittig reactions. The (*R*)-2-methyloctanol was obtained in a straightforward and direct manner by using our method.

Alkylation of octanal with 1,3-benzodithiolylium was catalyzed by the (*R*)-MacMillan catalyst **5a** to afford **6c** in high yield and stereoselectivity. The product was then treated



Scheme 6. The enantioselective synthesis of arundic acid, with organocatalytic formylation as the key step.

with Raney Ni, without protection of the alcohol, to afford the (*R*)-2-methyloctanol **7c** in high yield.

Arundic acid **14** is currently undergoing phase II development for the treatment of acute ischemic stroke as well as clinical development for other neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.[30,31] Arundic acid can be prepared in a simple manner by using our methodology. The benzylation of derivative (*R*)-**6c** occurred in a quantitative manner when the alcohol was treated with NaH and BnBr. Derivative **8** was metalated with *n*BuLi at 0 °C and then alkylated in high yield with EtI. After successive treatment with Raney Ni/H_2 and Pd/C/H_2,[32] we obtained the alcohol **13** in quantitative yield. Oxidation of **13** with $NaClO_2$ in the presence of catalytic amount of NaClO and 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO)[33] gave excellent results in terms of yields and selectivity in affording the desired arundic acid.

In conclusion, we have described the first organocatalytic stereoselective α addition of a formyl group to aldehydes. The reaction tolerates a large range of functional groups and was performed in the presence of water. The benzodithiol group can be easily metalated with *n*BuLi and can be further reacted with other electrophiles. The possibility to reduce the benzodithiol with Raney Ni allows easy access to a methyl group. This procedure is therefore a useful methodology in the synthesis of natural products and makes our organocatalytic methodology a surrogate for the quite challenging organocatalytic enantioselective α methylation of aldehydes. Further studies into the application of 1,3-benzodithiol cation in organocatalytic reactions are currently under investigation.[35]

Experimental Section

General procedure: Carbenium ion **3a** (0.1 mmol, 1 equiv) and aldehyde (0.3 mmol, 3 equiv) were added at 0 °C to a vial containing MacMillan catalyst **5a** (0.02 mmol, 20 mol %). PhCOOH (0.02 mmol, 20 mol %) in CH_3CN/H_2O 1:1 (0.5 mL), and NaH_2PO_4 (0.1 mmol, 1 equiv) were added at 0 °C. The mixture was stirred for 24 h at same temperature. The solvent was evaporated under reduced pressure and the crude reaction mixture was diluted with MeOH. $NaBH_4$ (2 equiv) was added at 0 °C and the reaction was stirred for a further 30 min.

The reaction was quenched with water and MeOH was evaporated under reduced pressure. The aqueous phase was extracted with Et_2O (2×5 mL). The collected organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 9:1).

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