# α-(Arylsulfonamido)borneols as Auxiliaries in Asymmetric Synthesis: An Efficient and Highly Stereoselective Method for the Reduction of α-Keto Esters

Yi Bin Xiang,* Ken Snow, and Michel Belley

*Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, Quebec, Canada H9R 4P8*

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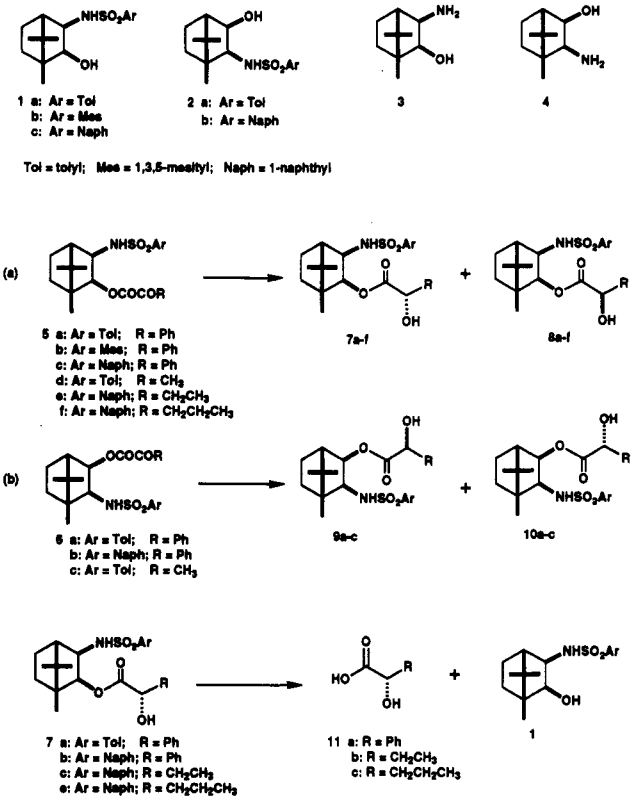
*Summary:* A method for preparation of enantiomerically pure α-hydroxy esters by stereoselective reduction of chiral α-keto esters under convenient conditions ($LiAlH(OCEt_3)_3$, THF, 0 °C) has been developed. The compounds *exo,exo*-3-(arylsulfonamido)-2-borneol and *exo,exo*-2-(arylsulfonamido)-3-borneol have been used as novel auxiliaries to achieve highly diastereoselective reductions. The auxiliaries can be removed by mild saponification (LiOH, THF–$H_2O$, rt) without racemization of the reduced products.

Optically pure α-hydroxy acid derivatives are important synthetic intermediates for the construction of natural products.[1] Among the many methods for the preparation of these compounds,[2] the simple and practical diastereoselective reduction of chiral α-keto derivatives has attracted much attention.[3] In the course of our studies on α-sulfonamido alcohols in asymmetric synthesis,[4] we discovered that chiral α-keto esters **5** and **6** can be highly stereoselectively reduced to α-hydroxy esters **7** and **10** with $LiAlH(OR)_3$ under standard conditions (THF, 0 °C, 1 h) in excellent yields. The level of stereoselection in these reactions has been found to surpass the highest level of stereoselection reported in the literature for the analogous reductions.[3g,f] The experimental procedures on the reduction are simple, straightforward, and operable for large scales. The auxiliaries can be easily removed under mild saponification conditions and recovered.

The compounds *exo,exo*-3-amino-2-borneol (**3**) and *exo,exo*-2-amino-3-borneol (**4**) were prepared from (+)-camphor according to literature procedures.[5,6] Treatment of amino alcohol **3** or **4** with 1.05 equiv of arylsulfonyl chloride in $CH_2Cl_2$ in the presence of triethylamine and a catalytic amount of (*N,N*-dimethylamino)pyridine (DMAP) at room temperature afforded high yields of crystalline sulfonamido alcohols **1** and **2**, respectively. Reaction of **1** or **2** with α-keto acid chloride in 1,2-dichloroethane at reflux or, in better yield, in dichloromethane at room temperature in the presence of pyridine gave corresponding α-keto esters **5** or **6**.

**Scheme I**




We began our study with ester **5a**.[7] Reduction of **5a** with 1 equiv $BH_3$ at 0 °C gave **7a** and **8a** in good yield, but with low stereoselectivity (Table I, entry 1). It is interesting to note that no hydrogen formation was observed under the reactions conditions.[8] Many hydride complexes were tested as reducing agents for the experiments as illustrated in Table I. While the reduction with sodium borohydride and its derivatives gave low diastereoselectivities (Table I, entries 2, 3), high stereoselectivities were observed with L- or K-Selectride (Aldrich) (Table I, entries 4–6). Under carefully controlled conditions (toluene–ether, −90 °C, 5 min) with 1 equiv of either L- or K-Selectride, the ester **5a** was highly stereoselectively reduced to the α-hydroxy ester **7a**. However, the lack of convenience of the reaction conditions limited these reductions to small scales only. More convenient and practical conditions (THF, 0 °C, 1 h) were possible when $LiAlH(OR)_3$[9] was used for the reduction. These condi-

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(5) For preparation of amino alcohol **3**, see: Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299.

(6) For preparation of amino alcohol **4**, see: Kouklovesky, C.; Pouilhes, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672.

(7) All the reactions in the text were performed under inert atmosphere (Ar or $N_2$) and with dried solvents.

(8) It is not very surprising that the reaction between $BH_3$·THF and the acidic proton on the sulfonamido group is a slow process. The slow reactions between $BH_3$·THF and phenol have been previously reported in the literature. (a) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637. (b) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510.

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Table I. Reduction of 3-(Arylsulfonamido)-2-borneol α-Keto Ester 5

| | ester | [H⁻] | equiv | solvent | temp (°C) | time (min) | yield[a] (%) | ratio[b] 7/8 |
|---|---|---|---|---|---|---|---|---|
| 1 | 5a | $BH_3$ | 1.0 | THF | 0 | 60 | 90 | 62/38 |
| 2 | 5a | $NaBH_4$ | 1.1 | tBuOH/THF | 0 | 360 | 73 | 61/39 |
| 3 | 5a | $NaBH(OAc)_3$ | 1.1 | THF | rt | 960 | 93 | 64/36 |
| 4 | 5a | L-Selectride | 1.0 | THF | −78 | 10 | 95 | 84/16 |
| 5 | 5a | L-Selectride | 1.0 | ether/Tol | −90 | 5 | 94 | 97/3 |
| 6 | 5a | K-Selectride | 1.0 | ether/Tol | −90 | 5 | 57 | 96/4 |
| 7 | 5a | $LiAlH(OCCH_3)_3$ | 1.1 | THF | 0 | 60 | 96 | 96/4 |
| 8 | 5a | $LiAlH(OCEt_3)_3$ | 1.1 | THF | 0 | 60 | 97 (88) | 98/2 |
| 9 | 5b | $LiAlH(OCEt_3)_3$ | 1.1 | THF | 0 | 60 | 90 (73) | 96/4 |
| 10 | 5c | $LiAlH(OCEt_3)_3$ | 1.1 | THF | 0 | 60 | 96 (91) | 99/1 |
| 11 | 5d | $LiAlH(OCEt_3)_3$ | 1.1 | THF | 0 | 60 | (90) | 99/1 |
| 12 | 5e | $LiAlH(OCEt_3)_3$ | 1.1 | THF | 0 | 60 | (84) | 99/1 |
| 13 | 5f | $LiAlH(OCEt_3)_3$ | 1.2 | THF | 0 | 60 | (97) | 99/1 |

[a] Crude yield according to HPLC analysis; isolated yield indicated in parentheses. [b] Ratio determined from HPLC or by 300-MHz $^1$H-NMR analysis of crude reaction mixture.

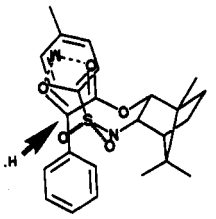

Figure 1.

Table II. Reduction of 2-(Arylsulfonamido)-3-borneol α-Keto Ester 6 with $LiAlH(OCEt_3)_3$[a]

| | ester | solvent | temp (°C) | time (min) | yield[b] (%) | ratio[c] 9/10 |
|---|---|---|---|---|---|---|
| 1 | 6a | THF | 0 | 60 | 96 (88) | 4/96 |
| 2 | 6b | THF | 0 | 60 | 91 (89) | 1/99 |
| 3 | 6c | THF | 0 | 60 | (65) | 5/95 |

[a] 1.1 equiv of reducing reagents was used. [b] Crude yield according to HPLC analysis; isolated yield indicated in parentheses. [c] Ratio determined from HPLC or by 300-MHz $^1$H-NMR analysis of crude reaction mixture.

tions gave not only even higher stereoselectivities, but also excellent chemical yields (Table I, entries 7, 8).

The preferential formation of (*S*)-α-hydroxy ester **7a** may be rationalized as follows[3b,g] (see Figure 1): the α-keto ester **5a** may exist in a s-cis conformation during the reduction through coordination of the oxygen atoms of the two carbonyl groups with a metal ion; the cis vicinal toluenesulfonamide group on the rigid bornane frame effectively blocks the *si*-face of the ketone; therefore the hydride could selectively attack the *re*-face of the ketone to form the ester **7a**. On the basis of such a rationalization, we expected that the reduction should proceed at an even higher level of stereoselection if the borneol auxiliary had a more sterically demanding arylsulfonamide group. This expectation was realized when the reduction of α-keto esters **5c** or **6b**, which have a naphthalenesulfonamide group, gave practically the single products (*S*)-α-hydroxy ester **7c** and (*R*)-α-hydroxy ester **10b**, respectively (Table I, entry 10, and Table II, entry 2).

To examine the efficiency of α-(sulfonamido)borneols as chiral auxiliaries in the reduction of α-keto esters, aliphatic α-keto esters **5d–f** and **6c** were prepared and

Table III. Hydrolysis of Chiral α-Hydroxy Ester 7 to Acid 11[a]

| | ester | R | acid | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | 7a | Ph | 11a | 93 | 93[b] |
| 2 | 7c | Ph | 11a | 94 | 97[b] |
| 3 | 7e | Et | 11b | 89 | 98[c] |
| 4 | 7f | Pr | 11c | 89 | 98[c] |

[a] All the reactions were performed in THF–$H_2O$/LiOH (4–6 equiv) at rt for 1 h. [b] Enantiomeric excess (% ee) was determined by the comparison of $[\alpha]_D$ value with literature.[11] [c] Enantiomeric excess (% ee) was determined by $^1$H-NMR spectroscopy of Mosher esters of corresponding methyl esters.[10]

subjected to reduction. Under the same conditions described above, all these α-keto esters gave nearly pure diastereoisomers **7d–f** and **10c** (Table I, entries 11–13 and Table II, entry 3).

The auxiliaries can be easily removed by treatment of the reduction product with LiOH (1 M) in THF–$H_2O$ at room temperature for 1 h and recovered by the usual workup. No racemization of the reduced products was observed after hydrolysis. The absolute stereochemistry and the enantiomeric excess (% ee) presented in Table III were determined by comparison of the optical rotations of the products with the literature values[11] or by $^1$H-NMR spectroscopy of Mosher esters of corresponding methyl esters.[10]

In conclusion, α-(arylsulfonamido)borneols have been successfully used as new types of chiral auxiliaries for the reduction of α-keto esters to achieve a very high stereoselection. The efficiency and convenience of the reduction and the mild conditions for the removal of the auxiliaries without racemization suggest that this method will be generally useful in the synthesis of chiral α-hydroxy esters.

**Supplementary Material Available:** Experimental procedures and spectral data for all new compounds (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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