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Achieving High Selectivity and Facile Displacement with a New Thiol Auxiliary for Boron-Mediated Aldol Reactions

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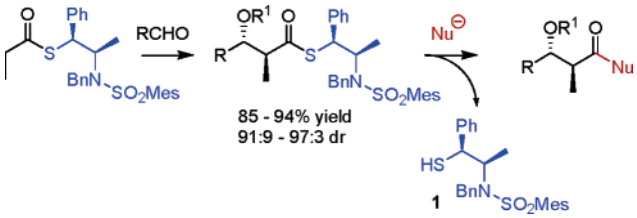
ABSTRACT



Synthesis of a new thiol auxiliary (1) is readily achieved (in five or six steps, >74% overall yield from norephedrine) and is shown to give high diastereoselectivity in boron-mediated *anti*-aldol reactions with a range of aldehydes. This new thiol auxiliary may be directly displaced by a range of nucleophiles under very mild conditions, to give the corresponding phosphonate esters, alcohols, acids, SNAC thiolesters, and methyl esters.

Despite recent advances in the catalytic aldol and organocatalytic aldol reactions,[1] auxiliary-controlled aldol reactions have maintained their place as one of the principle means through which the aldol reaction finds application in synthesis.[2] This is primarily due to the high yields and high diastereoselectivities which may be attained in auxiliary-controlled reactions and the facile separation of diastereomeric aldol adducts which allows the subsequent isolation of enantiopure species. Two auxiliaries currently have predominance in the field:[2] the Evans' oxazolidinone[3a−c] and its oxazolidinethione and thiazolidinethione counterparts for *syn*-aldol reactions and the Abiko−Masamune norephedrine-derived auxiliary for a range of *anti*-aldol reactions.[3d,e] However, for an auxiliary-based strategy to be truly useful, the auxiliary must be removable under a range of conditions.[4] Although this has clearly been demonstrated for the Evans' oxazolidinone, and to a lesser extent for the Abiko−Masamune auxiliary, there are still some nucleophilic displacement reactions which (though highly desirable synthetically) are unachieveable, or very low yielding, with either of these auxiliaries because of competitive retro-aldol or elimination reactions. In the course of synthetic studies directed toward the synthesis of the marine natural product octalactin A,[5] we have encountered these problems first hand.[6] Direct displacement by a phosphonate anion of the norephedrine-derived auxiliary in an *anti*-aldol adduct resulted in extensive decomposition of the aldol adduct through a retro-aldol mechanism, such that the acylated auxiliary was

(1) For recent reviews, see: (a) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941−956. (b) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682−4698. (c) Kazmaier, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2186−2188. (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (e) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570−579. (f) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858−860.

(2) (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65−75. (b) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947.

(3) (a) Evans, D. A.; Bartroli, J. A.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77−91. (c) Evans, D. A.; Shaw, J. T. *Actual. Chim.* **2003**, 35−38. (d) Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586−2587. (e) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387−395.

(4) For a recent review of auxiliary-mediated reactions, see: Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899−1930.

(5) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682−4683.

(6) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245−8248.

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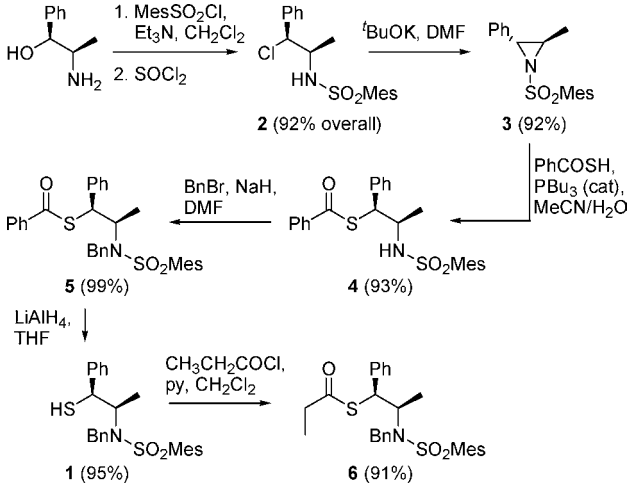
the major recovered product at the end of the reaction.[7] Following our earlier success in the achiral manifold with the use of thiolesters to address this displacement problem,[8] we therefore set out to develop a high-yielding route to a thiol alternative of the Abiko−Masamune auxiliary (Scheme 1).

Scheme 1. Synthesis of the Thiol Analogue of the Abiko−Masamune Auxiliary



(1*S*,2*R*)-(+)-Norephedrine was converted into its mesitylene sulfonamide,[3d,e] and subsequent treatment with thionyl chloride gave alkyl chloride **2** with net retention of stereochemistry.[9] The chloride was converted into aziridine **3**,[10] which was opened regio- and stereoselectively (>95:5) with thiolbenzoic acid in the presence of catalytic PBu_3.[11] Treatment of thiolbenzoate **4** with benzyl bromide and sodium hydride gave benzyl sulfonamide **5** exclusively.[12] Reduction of the benzoate using $LiAlH_4$ gave the thiol auxiliary **1** in excellent yield. Thiol **1** could also be accessed through saponification with NaOMe, thus avoiding the need for tedious purification from aluminum salts (five or six steps from norephedrine, >74% overall yield). The thiol was converted into its propionate derivative **6**, to allow the determination of the levels of diastereoselectivity that it could confer in a range of aldol reactions. The X-ray crystal structure of **6** has confirmed the overall net retention of stereochemistry of this synthetic sequence (Figure 1).

It has been reported by Abiko and Masamune that selective enolization may be achieved in the boron-mediated aldol

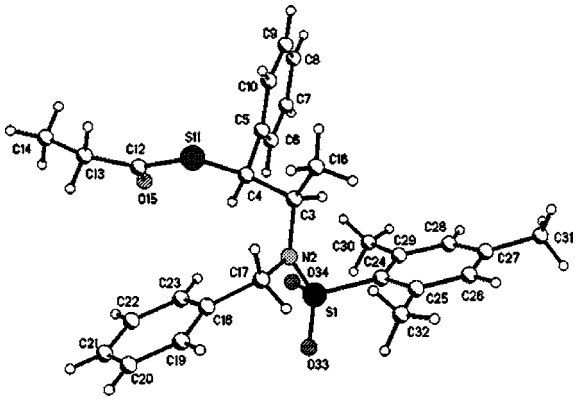
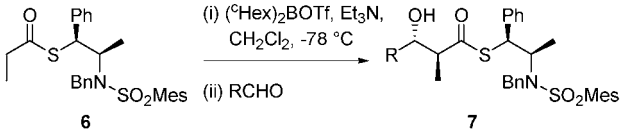
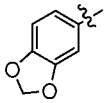


Figure 1. Crystal structure of thiopropionate **6**.

reaction of the norephedrine-derived auxiliary through the appropriate choice of reagents, thus leading to either *anti*- or *syn*-aldol adducts.[3d,e] With the classical oxygenated auxiliary, the formation of *anti*-aldol adducts is controlled by the presence of bulky ligands on the boron [(^{c}Hex)$_2$BOTf] and the addition of Et_3N at low temperatures to form the kinetic *E*(*O*)-enolate. We therefore set out by using these

Table 1. *anti*-Aldol Reaction of Thiopropionate **6**



R	product	yield (%)[a] dr[b]	cf. Abiko-Masamune
	**7a**	92 (93:7)	79 (98:2)
	**7b**	90 (92:8)	97 (96:4)[13]
	**7c**	94 (92:8)	95 (98:2)[13]
	**7d**	94 (94:6)	--
	**7e**	85 (91:9)	93 (95:5)[13]
	**7f**	91 (97:3)	--

[a] Isolated yield of the major diastereomer. [b] Diastereomeric ratio determined by ^{1}H NMR integration.

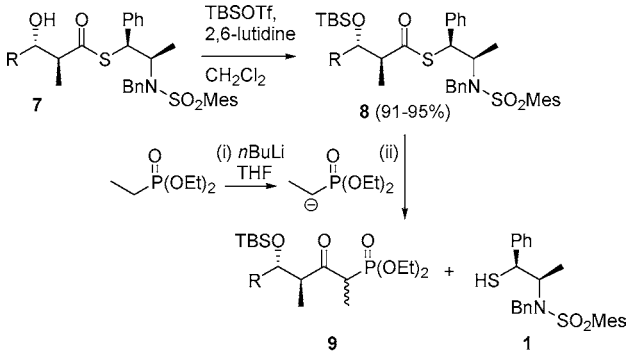
(7) Howells, G. E.; Hulme, A. N.; White, J. W. Unpublished results.
(8) Hulme, A. N.; Howells, G. E.; Walker, R. E. *Synlett* **1998**, 828−830.
(9) Flores-Parra, A.; Suarez-Moreno, P.; Sanchez-Ruiz, S. A.; Tlahuextl, M.; Jaen-Gaspar, J.; Tlahuext, H.; Salas-Coronado, R.; Cruz, A.; Noth, H.; Contreras, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1661−1672.
(10) On a small scale, direct conversion of the sulfonamido alcohol to aziridine **3** was achieved through in situ generation of the mesylate (MsCl, Et_3N, 87%).
(11) Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 726−730.
(12) Significant levels of benzoate migration and concomitant thiol benzylation were observed when benzylation was attempted in the presence of other bases.

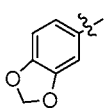
optimized conditions with thiol auxiliary **1**. Gratifyingly, we found that we could obtain *anti*-aldol adducts with a range of aldehydes (vinyl, alkyl, and aromatic) in high yield and with high selectivity using the thiol auxiliary **1** (Table 1).[13] In all cases, our yields were comparable to that of the established Abiko−Masamune auxiliary, and only a minor erosion of diastereoselectivity was observed. As with the classic auxiliary, the minor diastereomer is thought to be the other anti diastereomer, rather than the syn diastereomer.[3d,e] This confirms the high selectivity of enolate formation in these reactions but suggests a minor erosion of facial selectivity of the resultant enolate in switching from the ester to the thiolester.

The main focus for the synthesis of the thiol auxiliary **1** was its potentially facile displacement with a range of nucleophiles. Of most immediate synthetic relevance to us was the displacement of the auxiliary by phosphonate nucleophiles (Table 2), which might then allow direct extension of the aldol adduct using a Horner−Wadsworth−Emmons (HWE) reaction.[14] Treatment of protected aldol adducts **8** with the lithium anion of diethyl ethane phosphonate was shown to give the desired phosphonate esters **9** in high yield (78−91%) and with varying diastereoselectivity adjacent to the phosphonate (3:2 to 4:1 ratio of diastereomers). However, the diastereomeric phosphonate esters were not separated, as previous studies have shown that both give equal selectivity in the HWE reaction.[6] In all cases, the auxiliary **1** was also recovered in excellent yield (79−91%).

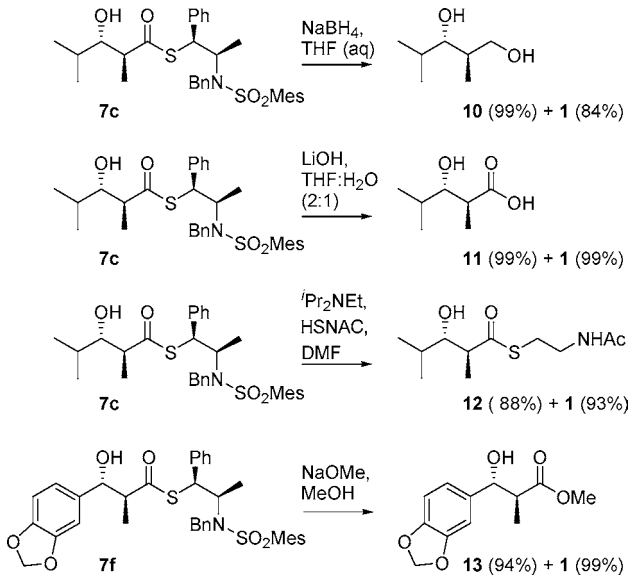
After the successful displacement of auxiliary **1** was achieved with a phosphonate anion, we decided to investigate the displacement reaction with other mild nucleophiles (Scheme 2). Initially, we examined reduction of the aldol adducts to give the diol, a reaction which is typically achieved with rather harsh conditions ($LiAlH_4$, DIBALH) with the classic Abiko−Masamune auxiliary.[15] In contrast, we found that upon treatment of **7c** with $NaBH_4$ diol **10** was obtained in high yield in only 1 h (99%). We then decided to investigate the hydrolysis reactions of aldol adducts **7**, the counterparts of which have been shown to be quite sluggish with the classic auxiliary. LiOH-mediated hydrolysis of the thiolester **7c** was complete in only 30 min (as opposed to the typical 24−48 h reaction times required for hydrolysis of the Abiko−Masamune auxiliary)[16] and gave an excellent yield of the corresponding acid **11** (99%, Scheme 2).[17]

Table 2. Phosphonate Displacement of Auxiliary **1**



R	phosphonate	yield **9** (%)	yield **1** (%)
	**9a**	90	91
	**9b**	81	85
	**9c**	89	85
	**9d**	91	79
	**9f**	78	80

Scheme 2. Nucleophilic Displacement Reactions of *anti*-Aldol Adducts **7**



(13) Optimum conditions for aldol coupling with thiol auxiliary **1** were found to be: 3.0 equiv of Et_3N [cf. 2.4 equiv reported in ref 3e] and 2.0 equiv of $(^cHex)_2BOTf$ [cf. 2.0 equiv reported in ref 3e]. When conducting milligram scale reactions, an excess of aldehyde (3.0+ equiv) was used.

(14) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(15) For recent synthetic examples, see: (a) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223−226. (b) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215−4234. (c) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III. *Org. Lett.* **2002**, *4*, 2841−2844. (d) Amarasinghe, K. K. D.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 9366−9367.

(16) For recent synthetic examples, see: (a) Kiho, T.; Nakayama, M.; Kogen, H. *Tetrahedron* **2003**, *59*, 1685−1697. (b) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Sekhar, B. B. V. S.; Hicken, E. J. *Org. Lett.* **2002**, *4*, 3549−3552.

Similarly, transthiolesterification of **7c** was achieved under the extremely mild conditions reported by Raines et al. (*N*-acetylcysteamine, $^{i}Pr_2NEt$)[18] in only 1 h, to give an excellent yield of the SNAC thiolester **12** (88%). This latter procedure is notable because it avoids the need for a two-step hydrolysis/thiolesterification process which is typically used in the case of polyketide starter units derived from the Evans oxazolidinone.[19] [The use of trimethylaluminum in these transthiolesterification reactions as reported by Willis et al. (*N*-acetylcysteamine, Me_3Al, THF, 0 °C)[20] was not viable.[21]] Finally, transesterification of aldol adduct **7f** was very readily achieved by treatment with sodium methoxide, giving methyl ester **13** in 94% yield in only 30 min. In all of the successful displacement reactions, auxiliary **1** was recovered in high yield (84−99%).

In conclusion, we have developed an auxiliary which promotes highly selective *anti*-aldol adduct formation, while also offering facile displacement with a range of nucleophiles. The high yields associated with these reactions, relative ease of synthesis of the thiol auxiliary **1**, and its excellent bench stability make it an attractive alternative for use in synthesis.

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Supporting Information Available: Experimental procedures for the synthesis of thiol auxiliary **1**, for the synthesis of thiopropionate **6** and an *anti*-aldol reaction to give **7c**, and for the displacement reactions to give compounds **9c** and **10**−**13**. Spectroscopic data for compounds **7b** and **7e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) If the hydrolysis reactions were left for extended time periods, partial degradation of the thiol auxiliary **1** was observed.

(18) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939−1941.

(19) For recent examples of the two-step synthesis of SNAC thiolesters, see: (a) Wu, J.; Zaleski, T. J.; Valenzano, C.; Khosla, C.; Cane, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 17393−17404. (b) Aldrich, C. C.; Venkatraman, L.; Sherman, D. H.; Fecik, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 8910−8911. (c) Hartung, I. V.; Rude, M. A.; Schnarr, N. A.; Hunziker, D.; Khosla, C. *J. Am. Chem. Soc.* **2005**, *127*, 11202−11203.

(20) Le Sann, C.; Muñoz, D. M.; Saunders, N.; Simpson, T. J.; Smith, D. I.; Soulas, F.; Watts, P.; Willis, C. L. *Org. Biomol. Chem.* **2005**, *3*, 1719−1728.

(21) Complex mixtures were obtained under these conditions including the products of elimination and retroaldol reactions.