α-Acetoxysulfones as "Chiral Aldehyde" Equivalents

Barry M. Trost, Matthew L. Crawley, and Chul Bom Lee

Department of Chemistry, Stanford University
Stanford, California 94305-5080

Received February 22, 2000
Revised Manuscript Received May 12, 2000

Stereocontrolled additions to double bonds represent an important method for asymmetric synthesis. The flexibility of the functionality of an α,β-unsaturated aldehyde has led to the search for effecting asymmetric additions to the double bond. Recently practiced strategies involve converting aldehydes into acetals with chiral diols.[1,2] A more efficient strategy would employ a chiral aldehyde derivative in which the chirality was created catalytically. We were attracted to an α-acetoxysulfone, **2**, since it places the stereogenic center adjacent to the double bond. Further, the aldehyde should be capable of being liberated under very mild conditions in which it could be reacted further. The two questions that must be addressed are (1) can such compounds be easily accessed with high enantiopurity and (2) will such derivatives exercise differential reactivity of the diastereotopic faces of the adjacent double bond?

Our strategy for the catalytic asymmetric synthesis of α-acetoxysulfones, **2**, derives from two observations: (1) the ability of sulfinates to function as nucleophiles in the asymmetric allylic alkylation (AAA) reaction[3] and (2) the ability to desymmetrize allylic gem diesters **1**.[4] The geminal esters **1** are readily accessed by the acid-catalyzed (0.1−1.0 mol % of either sulfuric acid or ferric chloride) addition of acetic anhydride and an aldehyde[5] or by the palladium-catalyzed redox addition of acetic acid to propargyl acetates.[6] Exposing a mixture of the geminal acetate **1** and sodium benzenesulfinate to a catalyst formed by mixing 2 mol % π-allylpalladium chloride dimer (**4**) and 6 mol % ligand **3** (or *ent*-**3**)[7] in a two-phase aqueous methylene chloride mixture employing tetrahexylammonium bromide (THAB) as a phase-transfer catalyst led to smooth reaction at room temperature to produce the acetoxysulfones. Further reactions of the α-acetoxysulfones did not occur under the conditions of the reaction. The results are summarized in Table 1.[8]

In all cases, except for that of *o*-nitrocinnamaldehyde (entry 3), the ee was ≥94%. In the case of trisubstituted alkenes as substrates (entries 2, 6, 7, and 11), the reactions were slower and did not go to completion within 24 h. The presence of a strong-electron-withdrawing group on the double bond (entry 11) did not adversely affect the reaction. In all cases, only one regioisomeric product was observed. Simply changing the chirality of the ligand inverts the chirality of the product (entries 6 and 7, 9 and 10). The absolute configuration is based upon the mnemonic[7] and the fact that the sulfinate nucleophile follows the mnemonic in other asymmetric alkylations involving different types of enantiodiscrimination.[3] The acetoxysulfones are quite stable and easily handled and chromatographed without special precautions. Most are white crystalline solids.

Having this new class of novel enantiomerically enriched acetal derivatives, their ability to provide for discrimination of diastereotopic faces of the adjacent double bond was probed. The value of diols and the lack of reports of asymmetric dihydroxylation of α,β-unsaturated aldehydes[9] led us to explore the dihydroxylation catalyzed simply by osmium tetroxide. Simply stirring a methylene chloride solution of the acetoxysulfone with 5 mol % osmium tetroxide (used as an aqueous solution), with NMO as

Table 1. Typical Examples of the AAA Reaction to Form α-Acetoxysulfones[a]

entry	R	R^1	ligand	time (h)	yield[b]	er	(ee)[d]
1	C_6H_5	H	*ent*-3	5	89% ***ent*-2a**	98:2	(96%)
2	C_6H_5	CH_3	3	24	85%[c] **2b**	97.5:2.5	(95%)
3	*o*-$O_2N-C_6H_4$	H	3	2	93% **2c**	92.5:7.5	(85%)
4	*n*-C_3H_7	H	3	4	94% **2d**	99:1	(98%)
5	*n*-C_6H_{13}	H	3	6	73% **2e**	97.5:2.5	(95%)
6	$(CH_2)_4$		3	24	80%[c] **2f**	>99:<1	(>99%)
7	$(CH_2)_4$		*ent*-3	24	85% ***ent*-2f**	>99:<1	(>99%)
8	*i*-C_3H_7	H	*ent*-3	10	85% ***ent*-2g**	>99:<1	(>99%)
9	$TBDMSOCH_2$	H	3	1	92% **2h**	97:3	(94%)
10	$TBDMSOCH_2$	H	*ent*-3	1	92% ***ent*-2h**	97:3	(94%)
11	$C_2H_5O_2C$	CH_3	3	12	85%[c] **2i**	99:1	(98%)

[a] All reactions were run using 2 mol % **4**, 6 mol % **3** (or ***ent*-3**), 20 mol % THAB with 1.0−1.5 equiv of sodium benzenesulfinate, 1.0 equiv Gem-diacetate in 1:1 water/methylene chloride at 0.4−0.5 M at room temperature unless noted otherwise. [b] Yields are for isolated pure product. [c] Yield based upon reacted starting material. [d] Determined by chiral HPLC using chiralcel OD and typically eluting with 9:1 heptane/2-propanol.

Table 2. Diastereoselective Dihydroxylation Acetoxysulfones[a]

entry	R	R^1	time (h)	product[b]	yield[c]	dr[d]
1	C_6H_5	H	24	*ent*-5a	77%	>98:2
2	C_6H_5	CH_3	24	5b	57%	>98:2
3	*o*-$O_2N-C_6H_4$	H	12	5c	83%	>98:2
4	*n*-C_3H_7	H	5	5d	80%	>98:2
5	*n*-C_6H_{13}	H	12	5e	84%	>98:2
6	*i*-C_3H_7		4	*ent*-5f	86%	>98:2
7	$TBDPSOCH_2$		12	5g	82%	95:5
8	$TBDPSOCH_2$	H	12	*ent*-5g	81%	95:5
9	$C_2H_5O_2C$	CH_3	12	6	94%	93:7

[a] All reactions were performed using 5% osmium tetroxide (4% aqueous solution) and 3 equiv of NMO at 0.1−0.2 M of substrate in methylene chloride at 0−5 °C. [b] All new compounds have been fully characterized spectrally and elemental composition established by high-resolution mass spectrometry and/or combustion analysis. [c] Isolated yields of pure compounds. [d] Determined by ^{1}H NMR spectroscopy.

(1) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004; Fukatani, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5911; Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3083; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447; Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.* **1990**, *55*, 2045; Mash, E. A.; Arterburn, J. B. *J. Org. Chem.* **1991**, *56*, 885.

(2) For reviews, see: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477; Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(3) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

(4) Trost, B. M.; Lee, C. B.; Weiss, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 7247.

(5) For some recent references, see: Pinnick, H. W.; Kochhar, K. S.; Bal, B. S.; Rajadhyaksha, S. N.; Deshpande, R. P. *J. Org. Chem.* **1983**, *48*, 1765; Fry, A. J.; Rho, A. K.; Sherman, L. R.; Sherwin, C. S. *J. Org. Chem.* **1991**, *56*, 3283; Deka, N.; Kalita, D. J.; Borah, R.; Sarma, J. C. *J. Org. Chem.* **1997**, *62*, 1563; Sydnes, L. K.; Soderberg, B. C. *Tetrahedron* **1997**, *53*, 12679. Chandra, K. L.; Saravanan, P.; Singh, V. K. *Synlett* **2000**, 359.

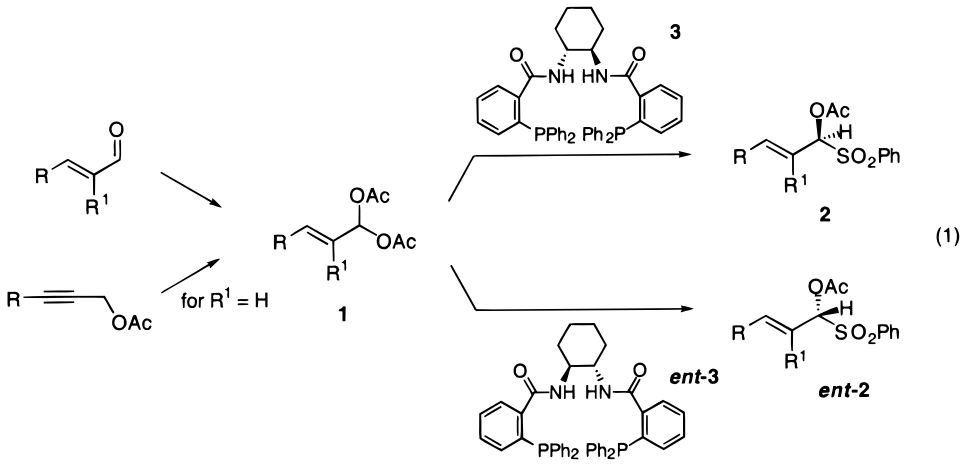
(6) Trost, B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335.

(7) Trost, B. M.; Van Vranken, D. L. Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. For a review, see: Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

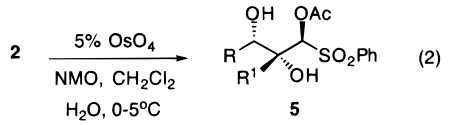
(8) All new compounds have been fully characterized spectroscopically and elemental composition established by high-resolution mass spectrometry and/or combustion analysis.

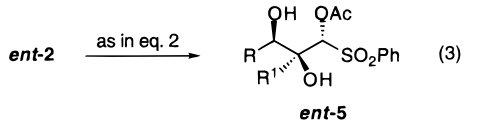
(9) Sharpless, K. B.; Kolb, H. C.; Van Nieuwenhze, M. S. *Chem. Rev.* **1994**, *94*, 2482; Sharpless, K. B.; Li, G.; Chang, H. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *29*, 355.

10.1021/ja000627h CCC: $19.00
Published on Web 06/10/2000

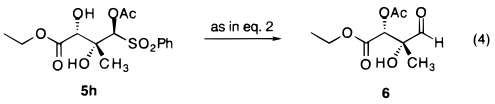


the stoichiometric reoxidant, at 0−5 °C produced the corresponding diols as shown in eqs 2 and 3 and Table 2. Running the

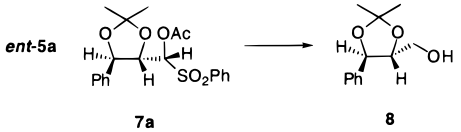


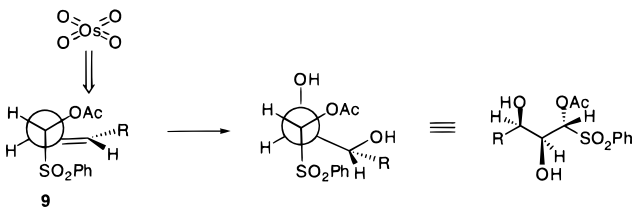


reaction at room temperature saw a significant drop in dr. For example, in the case of entry 7, the dr at room temperature was 5:1 instead of 19:1 at 0−5 °C. In the case of entry 9, the initial product, **5h**, was not stable and underwent acetyl migration with liberation of the free aldehyde **6** under the reaction conditions (eq 4). The stereochemistry of *ent*-**5a** (Table 2, entry 1) was



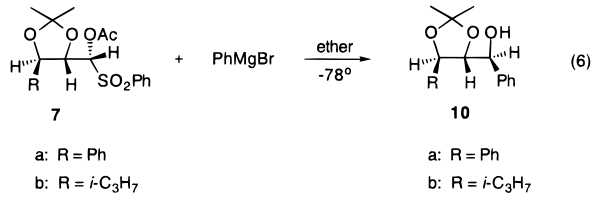
established by conversion to its acetonide **7** followed by DIBAL-H reduction, which led directly to the known primary alcohol **8** (eq 5) whose spectral data and sign of rotation establish the relative





and absolute stereochemistry.[10] The stereochemistries for the remaining examples are assigned by analogy. This stereochemistry is best in accord with the Stork-Houk-Jäger "inside alkoxy" model[11a] as in **9** which places the bulky electronegative phenylsulfonyl moiety anti as well as the Vedejs model.[11b]

One of the advantages of the acetoxysulfone is the ease of its unmasking under conditions suitable for the subsequent reactions of the aldehyde, thereby avoiding the need to work with sensitive aldehydes. For example, treatment of the acetonides **7a** or **7b** with excess phenylmagnesium bromide led to alcohols **10a**,**b** (eq 6), directly, with excellent dr (>98:2).



The acetoxysulfones serve as a novel class of chiral aldehyde equivalents that are acid-stable but base-labile. The two functionalities impart good diastereoselectivity in an electrophilic addition to the double bond. Thus, the availability of the acetoxysulfones in high enantiopurity translates to an asymmetric addition to one of the two enantiotopic faces of an α,β-unsaturated aldehyde. The utility of this strategy is exemplified by diol ***ent*-5f** obtained enantiomerically pure here compared with a 70% ee in the asymmetric dihydroxylation of methyl *E*-4-methyl-2-pentenoate to produce an intermediate toward lactacystin β-lactone.[12] The differences between the two functionalities suggests many other ways that the stereochemistry of the acetoxysulfone may translate into asymmetric bond-forming reactions involving their allylic nature. These studies will be reported in due course.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of Californina-San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Characterization data for **2a**−**2i**, **5a**−**5g**, **6**, **7a**, **7b**, **8a**, **8b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

JA000627H

(10) Zhou, W. S.; Yang, Z. C. *Tetrahedron Lett.* **1993**, *34*, 7075; Kazmaier, U.; Schneider, C. *Synthesis* **1998**, 1314.

(11) (a) Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031; (b) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094; (c) Also see: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1994**, *40*, 2247.

(12) Soucy, F.; Grenier, L.; Behnke, M. L.; Destree, A. T.; McCormack, T. A.; Adams, J.; Plamondon, L. *J. Am. Chem. Soc.* **1999**, *121*, 9967.