Diastereoselectivity in the Borane Methyl Sulfide Promoted Hydroboration of α-Alkoxy-β,γ-unsaturated Esters. Documentation of an Alkoxy-Directed Hydroboration Reaction†

James S. Panek* and Feng Xu

Department of Chemistry, Metcalf Center for Science and Engineering, Boston University, Boston, Massachusetts 02215

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Summary: α-Alkoxy-β,γ-unsaturated methyl esters of structural type 1 undergo an alkoxy-directed hydroboration with the mild hydroborating reagent borane–methyl sulfide complex (BH_3·SMe_2) in THF from 0 °C to room temperature, and after standard alkaline hydrogen peroxide oxidation the 1,3-diol product 2 is produced with useful levels of selectivity favoring the anti diastereomer.

Diastereoselective addition reactions to olefins and carbonyl groups in which the reagent is directed through a temporary complexation with a Lewis basic site within the molecule have found widespread use in organic chemistry. Notable examples of directed reactions which serve to illustrate their utility in synthesis include the hydroxyl-directed cyclopropanation,[1] hydrogenations,[2] carbonyl reductions,[3] epoxidations,[4] osmylation,[5] formylation,[6] and most recently directed rhodium(I) and iridium(I)-catalyzed hydroboration reactions.[7] The directing group provides the basis for an organized transition state that often results in predictable and useful levels of regio- and stereochemical control. Although many stereoselective reactions have been shown to be "directed reactions", no general procedure has been reported for an uncatalyzed alkoxy-directed olefin hydroboration with BH_3, alkylboranes (RBH_2), or dialkoxyboranes (RO_2BH).[8,9]

In connection with our studies directed at the development of stereoselective reactions that may be used in the total synthesis of the ansamycin natural products, herbimycin A[10] and (+)-macbecin-I,[11] we have had the opportunity to explore reaction conditions that may effect a stereoselective hydroxylation of the *E* double bond of the α-alkoxy-β,γ-unsaturated methyl ester 1 (Scheme I) derived from our developing chiral allylsilane bond construction methodology.[12]

We were presented with the possibility of conducting an intramolecular hydroboration on the β,γ-unsaturated ester 1 wherein the directing alkoxy group is produced from a selective borohydride reduction of the methyl ester.[13] The effective hydroborating agent would be generated in the form of a dialkoxyborane.[14] An intramolecular addition to the proximal olefin would then produce a 1,3-diol, after alkaline hydrogen peroxide oxidation. In this paper we wish to report a convenient method for the stereoselective hydroxylation based on an alkoxy-directed hydroboration reaction of α-alkoxy-β,γ-unsaturated methyl esters under mild reaction conditions with BH_3·SMe_2 (0 °C → rt) in THF. A standard alkaline hydrogen peroxide oxidation is used to give the 1,3-diol in good yield favoring the anti diastereomer (Scheme I).

1,3-Diol Formation. Our experiments indicate that the alkoxy group next to the ester plays a pivotal role in this hydroboration process. Apparently, the inductive effect of the oxygen activates the ester toward hydride reduction by BH_3·SMe_2 so that the rate of ester reduction competes favorably with the intermolecular olefin hydroboration pathway. Presumably, the reduction step results in the generation of an intermediate dialkoxy borane which undergoes an intramolecular hydroboration producing the

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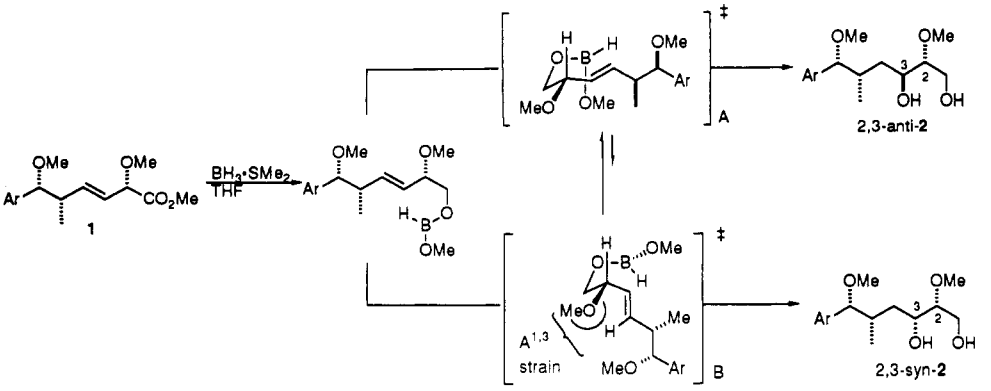
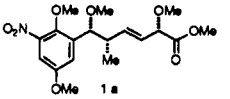
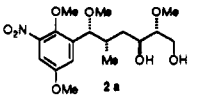
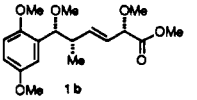
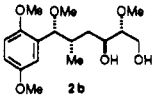
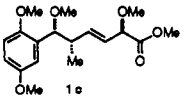
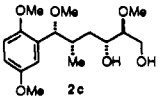
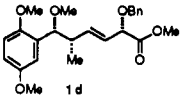
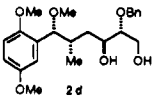
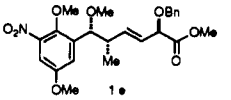
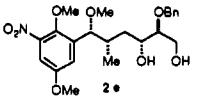
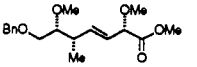
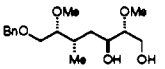
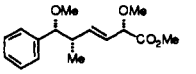
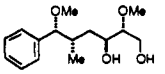
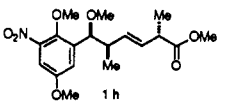
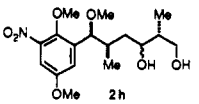
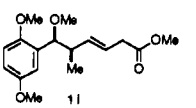
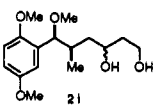
Scheme I



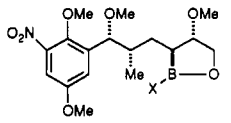
1,3-diol, after oxidation of the cyclic boronate ester.[15] In the initial finding of the directed hydroboration reaction a 0.1 M THF solution of the α-alkoxy-β,γ-unsaturated ester **1a** (Table I, entry 1) was treated with BH_3·SMe_2 (1.05 equiv) at 0 °C. The reaction was warmed to room temperature after 2 h. Stirring was continued for 12 h before standard oxidation [H_2O_2 (7.0 equiv) and NaOH (7.0 equiv), 12 h] afforded the 1,3-diol **2a** as a 8:1 mixture of 2,3-anti/2,3-syn diastereomers.[16] Once the authenticity of the hydroboration as a directed process was established, a series of related α-substituted-β,γ-unsaturated esters were surveyed to determine its generality. The results of those experiments are summarized in Table I. The presumption that ester reduction precedes the olefin hydroboration was supported by the observation that when the reaction temperature was maintained between −10 and 0 °C only ester reduction was observed.[17] For example, in the hydroboration reactions of **1a** and **1b** only the primary homoallylic alcohols were produced in 88 and 92% yield, respectively. That finding is consistent with the notion that 0.66 molar equiv (2.0 hydride equiv) of the BH_3·SMe_2 complex is consumed in the ester reduction step with the formation of the dialkoxyborane. The third hydride equiv is consumed in the subsequent hydroboration step of one

Table I. Diastereoselective Alkoxy-Directed Hydroborations of α-Substituted-β,γ-unsaturated Esters

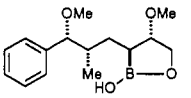
entry	substrate	1,3-diol product[a]	% yield[b]	ratio[c]
1.	 1a	 2a	85	8:1
2.	 1b	 2b	81	7:1
3.	 1c	 2c	75	4:1
4.	 1d	 2d	78	7.3:1
5.	 1e	 2e	79	6:1
6.	 1f	 2f	61	5:1
7.	 1g	 2g	82	7:1
8.	 1h	 2h	79	1:1[d]
9.	 1i	 2i	81	1:1[d]

[a] The hydroboration reactions were carried out in dry THF (0.1–0.2 M) in substrate with 1.05 equiv of BH_3·SMe_2 from 0 °C to rt. [b] Ratios of diastereomers were determined by ^1H NMR spectroscopic analysis of the crude product. [c] Yields refer to diastereomerically pure 1,3-diols after chromatography on SiO_2. [d] Plus Σ of other isomers.

(15) For two cases, **1a** and **1g**, we have characterized the intermediate cyclic boronates produced from an intramolecular hydroboration with a dialkoxy borane; see supplementary material for details.



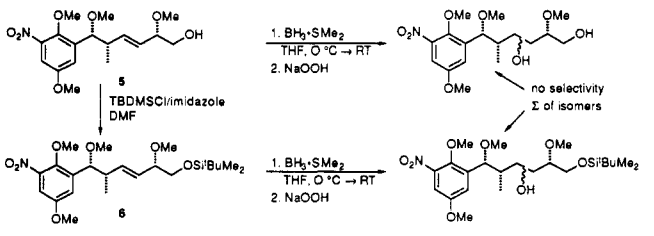
cyclic boronate ester **3 a**: X = OMe; boronic acid **3 b**: X = OH, both are derived from **1 a**



cyclic boronic acid **4 a** derived from the hydroboration of **1 g** after SiO_2 chromatography

(16) The stereochemistry of the major reaction products was assigned as the anti-1,3-diol and is based on the analysis of ^1H-NMR coupling constants ($^3J_{H2,H3}$) of the derived acetonides (2,2-dimethoxypropane, cat. *p*-TsOH), see supplementary material for details.

(17) Additional evidence for an intramolecular reaction was obtained from the attempted hydroboration reaction of the homoallylic alcohol **5** and the homoallylic *tert*-butyldimethylsilyl ether **6**, a substrate not capable of forming an alkoxy borane. Both **5** and **6** were derived from the ester **1a** by a selective reduction of the methyl ester. Consistant with a heteroatom-directed hydroboration is the fact that both substrates exhibited a complete loss of regio- and stereoselectivity producing essentially a statistical mixture of reaction products under the prescribed conditions for the hydroboration.



of the diastereotopic olefin faces.

Diastereoselection. In general, good levels of diastereoselection were achieved in the hydroboration of α-alkoxy-β,γ-unsaturated methyl esters with preference for the formation of the 2,3-anti product (entries 1–7). In contrast, the α-methyl-β,γ-unsaturated ester **1h** (entry 8) afforded a statistical mixture of all possible isomers. Without activation of the ester moiety by the alkoxy group, the intermolecular olefin hydroboration pathway competes with ester reduction resulting in a complete loss of selectivity (entries 8, 9). The predominant formation of the 2,3-anti-diastereomer is consistent with that expected for an intramolecular hydroboration of chiral homoallylic alcohols and is opposite to the model proposed by Kishi for intermolecular hydroboration of chiral allylic ethers.[18] The data obtained from these experiments indicate that the relative stereochemistry of the alkoxy substituent between the ester group and the double bond does not affect the sense of diastereoselection. For the cases shown in Table I, the hydroboration reactions of α-alkoxy esters proceded in a stereochemically consistant manner. The production of the 2,3-anti diastereomer is independent of the existing relative stereochemical relationships. The all syn-substrates showed slightly higher selectivity than the anti diastereomers. For instance, the syn and anti diastereomers **1b** and **1c** are converted to the 2,3-anti diols with 1.05 equiv of BH_3·SMe_2 with ratios of 7:1–4:1, respectively. The difference in the stereoselectivity observed in the hydroboration reactions maybe a function of the degree of $A^{1,3}$ strain associated with the respective double-bond rotamers in the transition states, $\Delta G^{\ddagger}$ TS_B > $\Delta G^{\ddagger}$ TS_A (Scheme I). It is interesting to note that the size of the alkoxy substituent does not effect the selectivity as shown with α-methoxy and benzyloxy groups; compare entries 1 and 2 with 4.

In summary, we have shown that borane methyl sulfide is an effective reagent for the sequential reduction–hydroboration of α-alkoxy-β,γ-unsaturated methyl esters affording 1,3-diols with useful levels of selectivity. With the data obtained from these initial experiments four lines of evidence have emerged supporting the notion of a heteroatom-directed hydroboration: (i) prior ester reduction, (ii) opposite sense of diastereoselection is obtained from that which is expected from an intermolecular hydroboration of an allylic ether,[18,19] (iii) the isolation and characterization of cyclic boronates **3a,b** and **4a**, and (iv) nonselective hydroboration of the homoallylic TBDMS ether derivative **6**. The observations cited above support the assertion that the hydroboration is alkoxy directed however, the implication of a dialkoxy borane as the effective hydroborating agent is in opposition to conventional wisdom that alkoxy boranes are too unreactive to hydroborate olefins. Further studies and applications concerning the alkoxy-directed hydroboration are in progress and will reported in due course.

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Supplementary Material Available: Experimental procedures and spectral data for all reaction products as well as relative stereochemical proof of the major and minor 1,3-diols (7 pages). This material is contained in many 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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Catalytic Chromium(0)-Promoted Higher-Order Cycloaddition Reactions

James H. Rigby,* Kevin M. Short, Humy S. Ateeq, and James A. Henshilwood

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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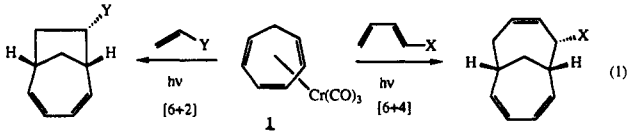
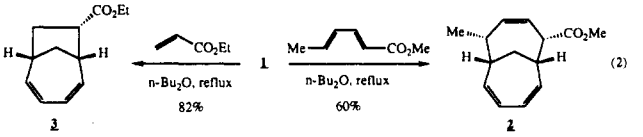
Summary: Transition-metal-promoted [6π + 4π] and [6π + 2π] higher-order cycloaddition reactions can be effected thermally or by employing a chromium metal catalyst. The resultant products are identical in all respects to those generated photochemically.

Recently, we[1] and others[2] have reported that a variety of transition-metal π complexes can be induced to undergo smooth and efficient higher-order cycloaddition via photochemical activation (eq 1). The resultant adducts are particularly rich in stereochemical information and may serve as useful building blocks for natural product synthesis.



(1)

We now wish to disclose that thermal activation of (η^6-cycloheptatriene)tricarbonylchromium(0) (**1**) and related complexes in the presence of appropriate 4π and 2π partners also provides [6 + 4] and [6 + 2] cycloadducts, respectively, which are identical in all respects to those derived from the photoinduced process (eq 2). Furthermore, we have demonstrated that these same transformations can also be effected employing only a catalytic quantity of the transition metal.



(2)

The stoichiometric, thermal versions of these reactions can be achieved by simply heating a mixture of complex

(1) (a) Rigby, J. H.; Henshilwood, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5122. (b) Rigby, J. H.; Ateeq, H. S. *Ibid.* **1990**, *112*, 6442 and references cited therein.

(2) For other recent advances in this area, see: (a) Van Houwelingen, T.; Stufkens, D. J.; Oskam, A. *Organometallics* **1992**, *11*, 1146. (b) Chaffee, K.; Sheridan, J. B.; Aistars, A. *Ibid.* **1992**, *11*, 18. (c) Fischler, I.; Grevels, F.-W.; Leitich, J.; Özkar, S. *Chem. Ber.* **1991**, *124*, 2857. (d) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Sheldrick, W. S.; Exner, R. *Ibid.* **1991**, *124*, 3. (e) Kreiter, C. G. *Adv. Organomet. Chem.* **1986**, *26*, 297. (f) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678.

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