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Stereocontrol in Radical Processes through the Exocyclic Effect: Dual Role of Triethylboron as Radical Initiator and in Situ Derivatization Agent

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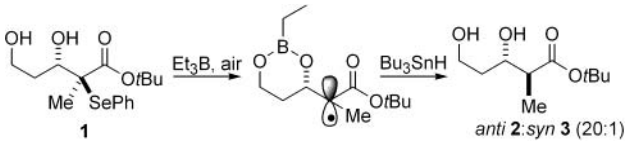
ABSTRACT

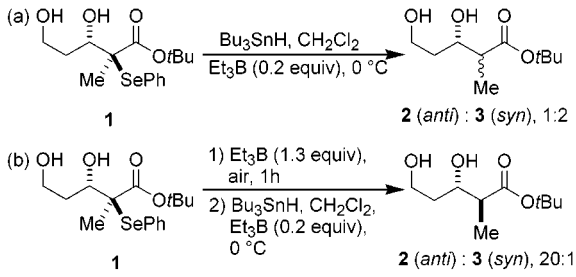


The diastereoselectivity of radical processes involving 1,3-diols is increased significantly with a simple and efficient strategy using the exocyclic effect. Boronate derivatives are successfully formed in situ by treatment of an equimolar amount of Et_3B in the presence of oxygen. This step is followed by the mediation of a carbon-centered radical α to the cyclic boronate to give the *anti* reduced product with high stereocontrol. The sequence is also extended to *β*-amino alcohols.

Asymmetric induction of acyclic substrates has always been a major challenge in synthetic organic chemistry. However, strategies[1] employing chiral auxiliaries, Lewis acids, and more recently chiral tin hydride and chiral Lewis acids have been applied successfully in hydrogen transfer, allylation, addition, and atom transfer reactions. In light of the degree of stereocontrol exhibited by radical-mediated reactions, these methodologies may well have the potential to be complementary to ionic processes.

We have been particularly interested in the reactivity of radicals flanked by an ester and a stereogenic center bearing a heteroatom. Hydrogen transfer and allylation reactions involving such radicals have been shown to proceed with excellent diastereoselectivity for substrates bearing a sterically demanding alkyl or aromatic group at C-3.[2] However, these reactions proceed with low selectivity for substrates bearing a small substituent at C-3, such as the hydroxyalkyl chain in **1** (Scheme 1, eq a). We have discovered a simple

Scheme 1



solution to this problem wherein pretreatment of the substrate **1** with air and a *stoichiometric* amount of Et_3B confers excellent facial discrimination of the radical during hydrogen

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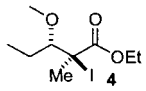
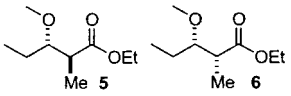
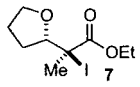
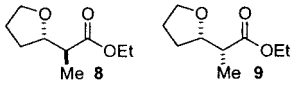
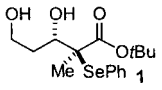
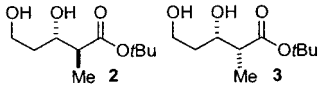
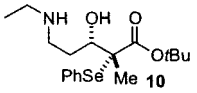
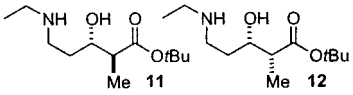
transfer to afford preferentially the *anti* product (Scheme 1, eq b). Reported herein are the results leading to this remarkable finding and a rationale for the dramatic enhancement in diastereoselectivity.

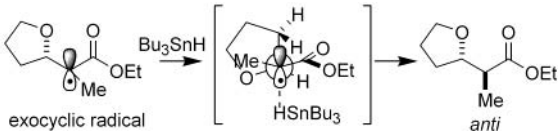
Initial insight into a strategy for overcoming the problem of poor stereoselectivity came from our studies of **4**. Little selectivity resulted from the hydrogen transfer to this substrate (Table 1, entry 1), but an 8-fold enhancement in *anti* preference was realized from the simple expedient of linking the ethyl and methoxy groups at C-3 to afford **7** (entry 2).[2d] The presence of a ring adjacent to the radical center—the *exocyclic* radical—presumably imposed steric constraints that permitted superior facial discrimination during the Bu_3SnH attack (Scheme 2).

Table 1. Radical Reduction with in Situ Derivatization or Lewis Acid Chelation[a]

entry	substrate	additive(s)	ratio[b] *anti*:*syn*	yield[c] (%)
				
1[d]	**4**	none[d]	1.5:1[e]	89
				
2[d]	**7**	none[e]	12:1[f]	90
				
3	**1**	Me_2SiCl_2, iPr_2NEt[h]	11:1	73
4[g]	**1**	none	1:2	79
5	**1**	Et_3B, N_2[i]	1:1	--
6	**1**	Et_3B, air[i]	20:1	90
7	**1**	Bu_2BOTf, iPr_2NEt, air[j]	20:1	70
8	**1**	Bu_2BOTf, iPr_2NEt, N_2[j]	14:1	79
				
9	**10**	None	1.5:1	87[k]
10	**10**	Me_2SiCl_2, iPr_2NEt[h]	6:1	86[l]
11	**10**	Et_3B, N_2[i]	5:1	50[k]
12	**10**	Et_3B, air[i]	5:1	81[l]
13	**10**	Et_3B, air[i,m]	17:1	78[l]
14	**10**	TMB	8:1	--
15	**10**	TMB[m]	17:1	77[k]

[a] All reactions performed in CH_2Cl_2 at 0 °C with 0.1 M substrate concentration, 2.0 equiv of Bu_3SnH, and 0.2 equiv of Et_3B. [b] Ratios determined for crude products by 400 MHz ^1H NMR spectroscopy, GC, or HPLC. [c] Isolated yields. [d] See ref 2d for preparation of substrate and characterization of products. [e] Reaction temperature was −78 °C. [f] Reaction conducted at −30 °C in toluene. [g] Relative configuration of substrate and products determined by NOE experiments using lactone derivatives. [h] 2.2 equiv of iPr_2NEt was used. [i] 1.3 equiv of Et_3B was used. [j] 1.1 equiv of iPr_2NEt was used. [k] Yields for isolated δ-lactam products, for which the relative configuration was determined by NOE experiments. [l] Yields for isolated N-Boc derivatives. [m] Reaction conducted at −78 °C in toluene.

Scheme 2



From these results, a strategy was developed using bifunctional protecting groups to enhance the *anti* selectivity of hydrogen transfer reactions involving *acyclic* 1,2- and 1,3-diol substrates.[2f] While offering excellent *anti* selectivity, this approach required steps of protection and deprotection of the diols prior to and following the reaction, respectively.

In situ derivatization studies were initiated to circumvent this problem.[3] An extension of the strategy therein was applied to diol **1** for the present study. Pretreatment of **1** with Me_2SiCl_2 in the presence of iPr_2NEt followed by reaction with Bu_3SnH led to good diastereoselectivity (11:1) through the intermediacy of a carbon centered radical α to a silyl ketal (entry 3). This result contrasted that of the reduction conducted in the absence of additives, where poor diastereoselectivity was noted (entry 4, 1:2).[4] Trace amounts of a (single) cyclic ethylboronate byproduct were found in the latter reaction. Given that only the initiator could have provided the boron source necessary for the boronate formation, we were intrigued by the possibility that Et_3B could be used to form the desired six-membered ring required for the establishment of the exocyclic effect, thus replacing the need for other additives. The prospect that Et_3B was playing a dual role (protection of the diol and initiation of the radical chain) became apparent.

To explore this, substrate **1** was pretreated with a stoichiometric amount of Et_3B prior to reduction. Surprisingly,

(1) See for example: (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Liotta, D. C.; Durkin, K. A.; Soria, J. J. *Chemtracts* **1992**, *5*, 197. (c) Smadja, W. *Synlett* **1994**, 1. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions—Concepts, Guidelines and Synthetic Applications*; VCH: New York, 1996. (e) Guindon, Y.; Jung, G.; Guérin, B.; Ogilvie, W. W. *Synlett* **1998**, *3*, 213. (f) Guindon, Y.; Guérin, B.; Rancourt, J.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Pure Appl. Chem.* **1996**, *68*, 89. (g) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (h) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562; *Angew. Chem.* **1998**, *110*, 2704. (i) Nanni, D.; Curran, D. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2417.

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(3) Guindon, Y.; Liu, Z.; Jung, G. *J. Am. Chem. Soc.* **1997**, *119*, 9289.

(4) The slight preference for *syn* product is attributed to the intermediacy of an endocyclic radical wherein the 3-OH is linked to the carbonyl via a hydrogen bond.

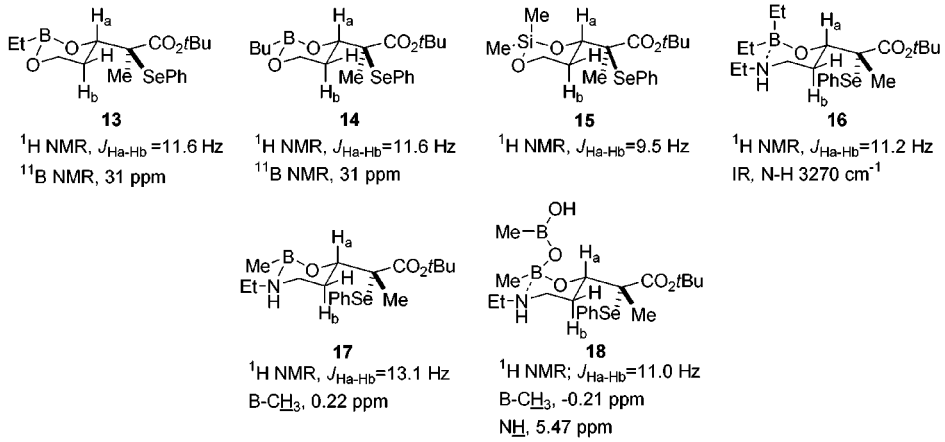


Figure 1.

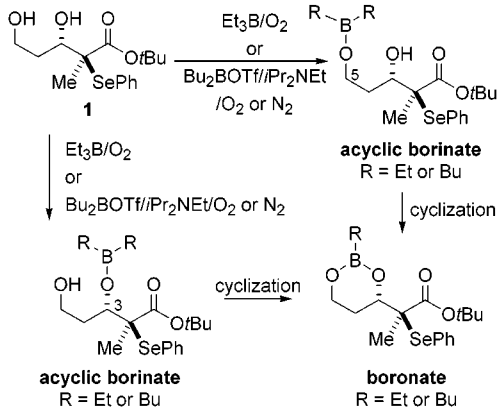
only traces of cyclic boronate were produced and no diastereoselectivity was observed (entry 5, 1:1). However, when dry air was introduced during pretreatment of **1**, the reduction proceeded with a dramatic enhancement in diastereoselectivity (20:1) in favor of the *anti* product (entry 6). Oxygen was evidently essential to the formation of the cyclic boronate (**13**, Figure 1) from diol **1**.[5,6] Et_3B thus proved to be not only an effective initiator but also an essential player in controlling diastereoselectivity through the exocyclic effect. Curiously, the diastereoselectivity noted for the hydrogen transfer reaction of the carbon-centered radical α to the cyclic boronate (entry 6, 20:1) by Bu_3SnH was superior to that of the silyl ketal radical (entry 3, 11:1). Furthermore, the stability of the boronate substrate and products allowed for easy isolation and characterization. The free diol compounds were recovered easily by coevaporating the reaction mixture with MeOH and/or prolonged contact with silica gel.

The analogous butylboronate **14** (Figure 1) was obtained by treatment of diol **1** with Bu_2BOTf and *i*Pr_2NEt under an air atmosphere. Remote from the reactive radical center, the alkyl group on the boron had little effect on the facial selectivity of the reduction (entries 6 and 7, 20:1). Under a N_2 atmosphere, the addition of Bu_2BOTf and *i*Pr_2NEt (cf. entries 7 and 8) to diol **1** led to the rapid formation of cyclic boronate **14**.[7] This suggested that, in the formation of the cyclic boronate with Et_3B, oxygen had contributed to accelerating the first step of the reaction wherein the acyclic borinate (at C-3 or C-5) was formed (Scheme 3). The addition of 0.5 equiv of dinitrobenzene (DNB) to the reaction mixture did not prevent the formation of cyclic boronate **13** with substrate **1**; however, the hydrogen transfer step was inhibited, suggesting that free radicals were not involved in the oxygen-dependent boronate formation.

In situ derivatization using Et_3B and air, followed by hydrogen transfer, was then extended to amino alcohol substrate **10** in order to explore the generality of this sequence in conferring stereocontrol. Again, an enrichment of the *anti* product was observed when the reduction was preceded by substrate treatment with Et_3B, although the increases in diastereoselectivity were less pronounced than for diol **1** (cf. entries 4−6 and entries 9, 11, 12). For this series, exposing the reaction mixture to air during Et_3B-pretreatment had no impact on the stereochemical outcome (cf. entries 11 and 12). When the reaction was performed with Me_2SiCl_2, selectivity similar to that achieved with Et_3B was observed (entries 10−12). To understand the puzzling differences in reactivity between the diol and the amino alcohol, we looked at the reactive intermediate following derivatization for structural information.

Figure 1 shows that the vicinal coupling constant values (J_{Ha-Hb}) of **13** and **14** were similar to that of silyl derivative **15**. The large values of J_{Ha-Hb} indicated an *anti* relative stereochemistry between Ha and Hb, thus supporting the formation of the cycle from diol **1**. It was clear from NMR and IR spectroscopic data that amino alcohol **10** did not react with Et_3B in a manner analogous to diol **1**. Two ethyl groups and a N−H bond consistent with the structure of borinate

Scheme 3



(5) Incomplete flush of the reaction vessel with nitrogen may have left sufficient O_2 to permit formation of traces of cyclic boronate even without deliberate exposure of the reaction mixture to air.

(6) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.

(7) The formation of boronate **14** was monitored by ^{1}H NMR.

16 (Figure 1) were evident with or without pretreatment exposure to air, a finding that accounts for the identical levels of selectivity seen for these two experiments (entries 11 and 12). A large vicinal coupling constant ($J_{Ha-Hb} = 11.2$ Hz) supported a cyclic intermediate (**16**, Figure 1), which would be expected to exhibit enhanced *anti* selectivity relative to the underivatized substrate (cf. entry 9 and entries 11 and 12). More importantly, from a preparative standpoint, it was possible to achieve good *anti*:*syn* ratios (17:1, entry 13) for **10** by conducting the reaction in toluene and lowering the reaction temperature to −78 °C.

Despite the more vigorous conditions (i.e., refluxing toluene) needed for the reaction of **10** with trimethylboroxine (TMB) to give a mixture of **17**, **18** and boric acid (Figure 1), the levels of diastereoselectivity exhibited by the reduction (8:1 and 17:1, entries 14 and 15) were similar to those obtained following Et_3B pretreatment (5:1 and 17:1, entries 12 and 13).[8]

The role of activating agents (e.g., pivalic acid,[9] diethylborylpivalate[10]) and full mechanistic details have yet to be delineated for reactions of alcohols with Et_3B. Studies directed at better understanding the essential role of air in the diol series are presently underway.[11]

In conclusion, these studies have uncovered a new role for Et_3B in radical reduction besides chain initiation. Enhanced *anti* selectivity is attributed to the mediation of a carbon-centered free radical α to a cyclic boronate brought on by the Et_3B-pretreatment of the substrate prior to the reduction. This novel use of Et_3B as an in situ derivatization agent thus offers expedience and excellent stereocontrol in hydrogen transfer reactions of bifunctionalized substrates such as 1,3-diols and β-amino alcohols.

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Supporting Information Available: Experimental procedures and characterization data for **1**, **10**−**12**, **13**, and **14**, boronates **2′** and **3′** (derivatives of **2** and **3**, respectively), and lactone **1′** (derivatized from **1**); determination of relative configuration for compounds **1**−**3**, **11**, and **12**; and NMR spectra for compounds **2**, **3**, **11**, **12**, **2′**, **3′**, and lactone **1′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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