The Exo-Cyclic Effect: Strategy Employing *in Situ* Derivatization or Lewis Acid Complexation to Enhance Stereoselectivity in Hydrogen Transfer Reactions

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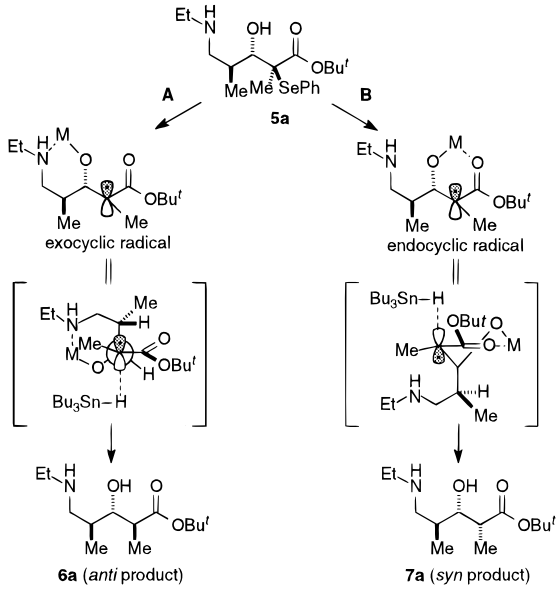
Asymmetric induction involving acyclic substrates in radical-based processes has attracted much attention in the last decade.[1] We have been particularly interested in the reactivity of radicals (**1**)[2] flanked by an ester and a stereogenic center in allylations, atom transfers, and hydrogen transfer reactions.[3] The facial discrimination of the radical can be significantly enhanced by the simple expedient of linking the R_1 and β-OMe groups (with the loss of two hydrogens). For example, the hydrogen transfer reaction of THF derivative **2** afforded a 12:1 ratio of *anti* and *syn* products, while that of its acyclic counterpart (**3**) displayed no stereoselectivity (1.1:1, *anti:syn*).[3] We have recently exploited this *exocyclic effect*[3] to synthetic advantage by developing a strategy employing bifunctional protecting groups to enhance the *anti*-selectivity of hydrogen transfer reactions of functionalized substrates, such as 1,2- and 1,3-diols,[4] -amino alcohols, and -diamines. However, a more elegant and practical strategy would involve generation of the exocyclic radical *in situ*, eliminating the need for additional protection and deprotection steps. To this end, we envisaged the use of *in situ* derivatization or Lewis acid bidentate complexation of the two targeted heteroatoms on the substrate (**4**). One complication of using Lewis acids for this strategy is the possibility of a competing alternate mode of complexation involving the ester carbonyl and β-OMe group to give an *endocyclic* radical (Scheme 1). We have found that the endocyclic radical arising from $MgBr_2 \cdot OEt_2$ complexation[5] of **1** affords excellent diastereoselectivity (20:1) under hydrogen transfer conditions but in favor of the *syn* product.[6]

Scheme 1



δ-Amino-β-hydroxyesters such as **5a** were chosen as substrates to study both modes of complexation or derivatization (Scheme 1).[7] To generate the desired exocyclic radicals through path A by *in situ* derivatization of the hydroxyl and amino groups, dichlorosilanes were used and afforded silyl *O,N*-acetals. This reaction path should afford predominantly the *anti* product from a transition state which is stabilized by both steric and electronic factors.[3] Reaction path B would be competitive when Lewis acids are used and would result in an erosion of *anti*-selectivity since the *syn* product is expected from reduction of the endocyclic radical.[6] In the absence of kinetic data, we had hoped to favor path A by using a sufficiently basic heteroatom X (in **4**), such as an amine, but whose basicity could be modified by an appropriate protecting group.

The hydrogen transfer reaction of **5a** proceeded with modest *anti*-selectivity (7:1) in the absence of additive (Table 1, entry 1). However, pretreatment of the substrate with Me_2SiCl_2 or Ph_2SiCl_2 produced *anti:syn* ratios of >100:1 and 85:1, respectively (entries 2 and 3). Interestingly, the use of Me_2BBr[8] or Bu_2BOTf also led to a significant enhancement (entries 4 and 5, 22:1 to 32:1) in diastereoselectivity, while 9-Br-9-BBN produced little effect (entry 6). In contrast, the use of $AlCl_3$ and $MgBr_2 \cdot OEt_2$ slightly favored the formation of *syn* product (entries 7 and 8) through the endocyclic radical. Similar trends were observed for the γ-dimethyl substrates (entries 9−23). In the absence of additives, the reduction of **5b** afforded a ratio of 13:1 in favor of the *anti* product (entry 9). This ratio can be increased 5−6-fold by the addition of Me_2SiCl_2, Me_2BBr, or Bu_2BOTf (entries 10−12), while a slight reversal of stereoselection resulted from the use of $MgBr_2 \cdot OEt_2$ (entry 13).

Interestingly, competition between the paths A and B can be tuned by modifying the electronic nature of the group on amine. Replacement of the R^1 ethyl group on the amine (in **5b**) by the more electron-withdrawing benzyl group (in **5c**) lowered *anti* selectivity (entries 15−17) presumably by decreasing the

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(1) (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296−304. (b) Smadja, W. *Synlett* **1994**, 1−26. (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions - Concepts, Guidelines and Synthetic Applications*; VCH: New York, 1996.

(2) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845−2848.

(3) (a) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166−1178. (b) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, E.; Jung, G. *J. Org. Chem.* **1995**, *60*, 288−289.

(4) Guindon, Y.; Faucher, A.-M.; Bourque, E.; Landry, S. R.; Caron, V. Manuscript submitted for publication.

(5) For recent examples of the effects of Lewis acid and hydrogen bonding in radical reactions, see: (a) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. *J. Am. Chem. Soc.* **1996**, *118*, 12528−12535. (b) Gerster, M.; Audergon, L; Moufid, N.; Renaud, P. *Tetrahedron Lett.* **1996**, *37*, 6335−6338. (c) Sibi, M. P.; Ji, J. G.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200−9201. (d) Chau, H.; Musa, O. S.; Martinez, F. N.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 2704−2710. (e) Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507−2508.

(6) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701−9702.

(7) Workup conditions were optimized to favor lactamization of the δ-amino-β-hydroxyester reduction products for ease of isolation and measurement of *anti:syn* ratios.

(8) Me_2BBr chemoselectivity is affected by neighboring groups, see: Guindon, Y.; Anderson, P. C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. E. *Pure Appl. Chem.* **1988**, *60*, 1705−1714.

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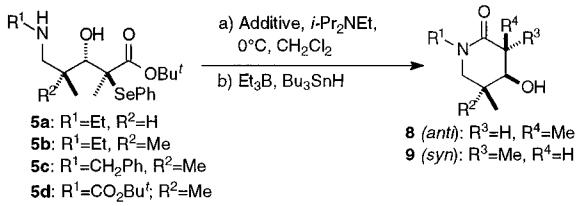
Table 1. Radical Reduction with *in Situ* Derivatization or Lewis Acid Chelation[a]



entry	substrate	additive	*anti:syn*[b]	yield (%)[c]
1	**5a**		7:1	80
2	**5a**	Me_2SiCl_2	>100:1	94
3	**5a**	Ph_2SiCl_2	85:1	89
4	**5a**	Me_2BBr	22:1	87
5	**5a**	Bu_2BOTf	32:1	79
6	**5a**	9-Br-9-BBN	11:1	95
7	**5a**	$AlCl_3$	1:2	97
8	**5a**	$MgBr_2{\cdot}OEt_2$	1:3	82
9	**5b**		13:1	87
10	**5b**	Me_2SiCl_2	85:1	85
11	**5b**	Me_2BBr	70:1	84
12	**5b**	Bu_2BOTf	70:1	67
13	**5b**	$MgBr_2{\cdot}OEt_2$	1:2	86
14	**5c**		5:1	89
15	**5c**	Me_2SiCl_2	40:1	84
16	**5c**	Me_2BBr	19:1	89
17	**5c**	Bu_2BOTf	11:1	85
18	**5c**	$MgBr_2{\cdot}OEt_2$	1:14	80
19	**5d**		1.4:1[d]	88[e]
20	**5d**	Me_2SiCl_2	2:1[d]	91[e]
21	**5d**	Me_2BBr	24:1[d]	90[e]
22	**5d**	Bu_2BOTf	10:1[d]	92[e]
23	**5d**	$MgBr_2{\cdot}OEt_2$	1:24[d]	57[e]

[a] Substrates (0.1 M) were pretreated with either Cl_2SiR_2 or Lewis acid for 30 min, followed by 1.1 (borane) or 2.2 equiv (silane or $AlCl_3$) of iPr$_2$NEt. When $MgBr_2OEt_2$ was used, no iPr$_2$NEt was added. Reactions were initiated by addition of Et_3B and Bu_3SnH (2.0 equiv). [b] Ratios determined for crude δ-lactams by 400 MHz ^{1}H NMR spectroscopy, GC or HPLC. [c] Yields based on isolated δ-lactams. [d] Ratios determined for crude β-hydroxyesters by 400 MHz ^{1}H NMR spectroscopy. [e] Yields based on isolated β-hydroxyesters.

preference for exocyclic radical formation (path A) and allowing endocyclic radical formation (path B) to be more competitive. Thus, enhanced *syn* selectivity was observed when $MgBr_2{\cdot}OEt_2$ was used (entry 18, 1:14). These trends are even more pronounced for the reactions of **5d**, which bears a *N*-Boc group (entries 19−23). In the absence of additive, the reduction proceeded with no diastereoselectivity (entry 19).[9] The nucleophilicity of the amine is so diminished by the electron-withdrawing Boc group that the addition of Me_2SiCl_2 (entry 20) generated little effect. Indeed no silyl *O*,*N*-acetal formation is detected by ^{1}H NMR after pretreatment of **5d** with Me_2SiCl_2. Furthermore, the β-hydroxyesters are isolated after the reduction of **5d**; in contrast, the reduction products arising from **5a**−**c** were isolated as δ-lactams. Interestingly, both Me_2BBr and Bu_2BOTf still prefer complexation to the nitrogen rather than ester carbonyl, affording good ratios of *anti* product (entries 21 and 22). Good *syn* selectivity was exhibited by the reduction of **5d** in the presence of $MgBr_2{\cdot}OEt_2$ (entry 23), as path B becomes more competitive with the reduced basicity of the amine.

Evidence for cyclic intermediates containing silicon was provided by the ^{1}H NMR spectrum of the silyl *O*,*N*-acetal derived from **5a**, which displayed a coupling constant (J = 8.8 Hz) consistent with a *trans* diaxial relationship between H_β and H_γ in a six-membered ring. The NMR spectrum of the reaction mixture resultant from the treatment of **5a** with Me_2BBr displayed a similar coupling constant (J = 9.3 Hz), which suggests the intermediacy of a complex involving the nitrogen.

We have suggested[3,4] that the enhanced diastereoselectivity of exocyclic radicals originates from the shielding provided by the γ-hydrogen (Scheme 1) to top-face attack of the exocyclic radical by the Bu_3SnH. In effect, the steric contribution of R_1 (see **1**) has been magnified in the cyclic series; by contrast, this top-face shielding is less efficient in acyclic substrates, which have more rotational freedom.[10] Since the nature of the ligands on the Lewis acid (or silane) have not yet been studied, there may be other factors contributing to the facial discrimination of the radicals described herein.

In conclusion, we have shown that *in situ* derivatization using dichlorosilanes or boron-based Lewis acid complexation is a viable strategy that can significantly enhance the *anti* selectivity of the hydrogen transfer reaction of functionalized acyclic substrates. Involving the intermediacy of exocyclic radicals, this mode of chelation (or derivatization) complements that of $MgBr_2{\cdot}OEt_2$ which leads to a reversal of diastereoselection, favoring the *syn* product. To better define the scope of this strategy, we have initiated studies on (a) the effect of the relative configuration of the substrates on the stereochemical outcome of the reaction, (b) controlling the nature of Lewis acid complexation in the hydrogen-transfer reaction, and (c) substrates bearing other heteroatom functionalities capable of *in situ* derivatization or complexation with Lewis acids.

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Supporting Information Available: Experimental procedures, characterization data for compounds, and structural proofs (33 pages). See any current masthead page for ordering and Internet access instructions.

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(9) The diastereoselectivity shown by the reduction of **5a** and **5b** in the absence of additive may be due to intramolecular hydrogen bonding between the amine and hydroxyl. In **5c** and **5d**, this interaction is diminished because of the electron-withdrawing group on the amine and the reduction proceeds with little if any selectivity.

(10) This model is consistent with observations of other substrates studied in our lab and with the *syn*-predictive transition state model proposed in refs 3 and 4.