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Acyclic Diastereoselection in the Hydroboration Process. Documented Cases of 1,3-Asymmetric Induction

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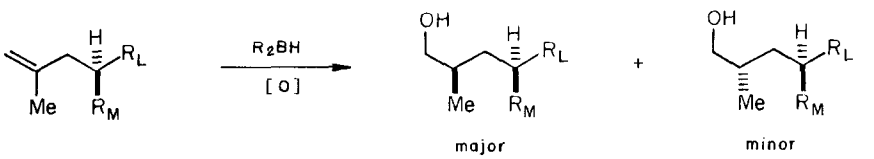
Summary: Good levels of 1,3-asymmetric induction have been observed in the hydroboration of terminal olefins (eq. 1). A considerable level of generality has been noted in this reaction and a transition state model has been proposed to account for the observations.

The acyclic diastereoselection noted for a variety of chemical reactions constitutes a topic of great current interest,[1] and the documentation of general trends noted in this area has important implications in both macrolide and polyether antibiotics synthesis. Within this context, acyclic stereocontrol in the hydroboration process involving impressive levels of 1,2-asymmetric induction has recently been established by Kishi and co-workers.[2]

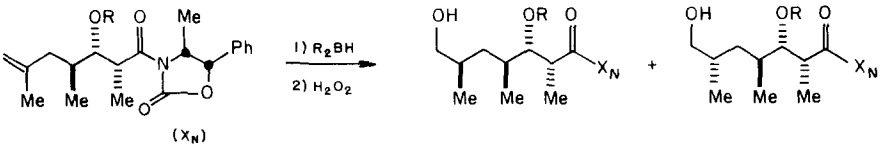
The purpose of this communication is to disclose our observations on the generality of the acyclic stereocontrol noted in the general hydroboration reaction illustrated below where R_L and R_M are sterically dominant and subordinate ligands respectively (eq. 1). In conjunction with our studies in the area of



(1)

macrolide synthesis,[3] we made the unanticipated observation that the hydroboration of **1**, either as the unprotected alcohol or as the silyl ether, with $BH_3 \cdot SMe_2$ (2-3 equiv, CH_2Cl_2, 3 h) followed by peroxide-bicarbonate oxidative workup afforded predominantly the **2R** alcohol diastereomer (**2R:2S** = 78:22, Scheme I, entry A). Likewise, both disiamylborane (entry B) and thexylborane (entry C) (2 equiv, CH_2Cl_2, 0°C, 5-7 h) afforded similar results, but with slightly improved diastereoselection (**2R:2S** = 85:15).[4] *Optimal conditions involving the use of thexylborane, prepared from $BH_3 \cdot SMe_2$, (2 equiv, CH_2Cl_2 or THF, 0°C, 5 h) and silyl ether **1b** afforded a 79% isolated yield of the diastereomerically pure alcohol **2R**,*[5] readily separated from the minor **2S** diastereomer by flash chromatography. In view of the documented olefin diastereofacial bias imposed by the architectural features of the molecule, it was surprising that

Scheme I



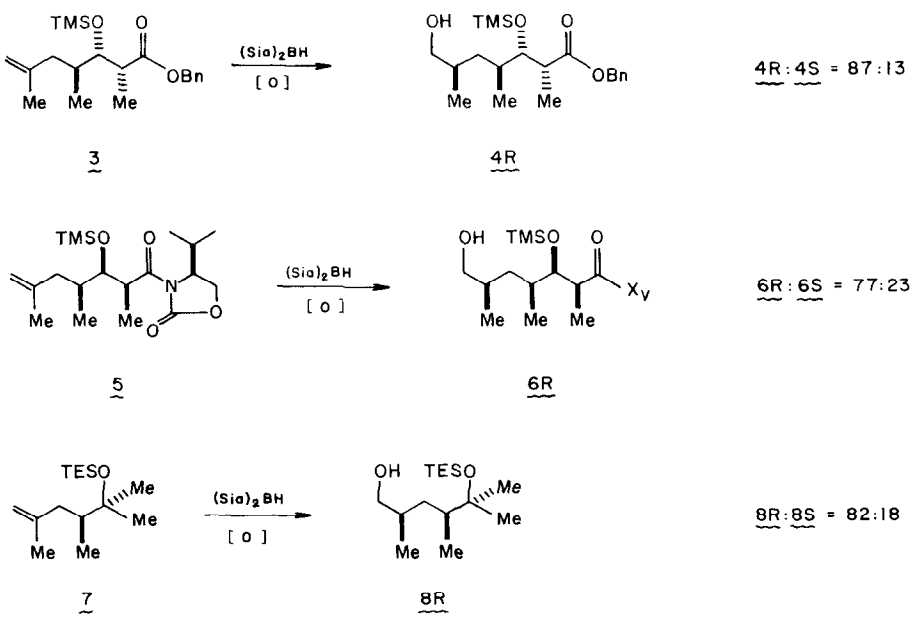
1a, R = H
b, R = SiMe3

2R 2S

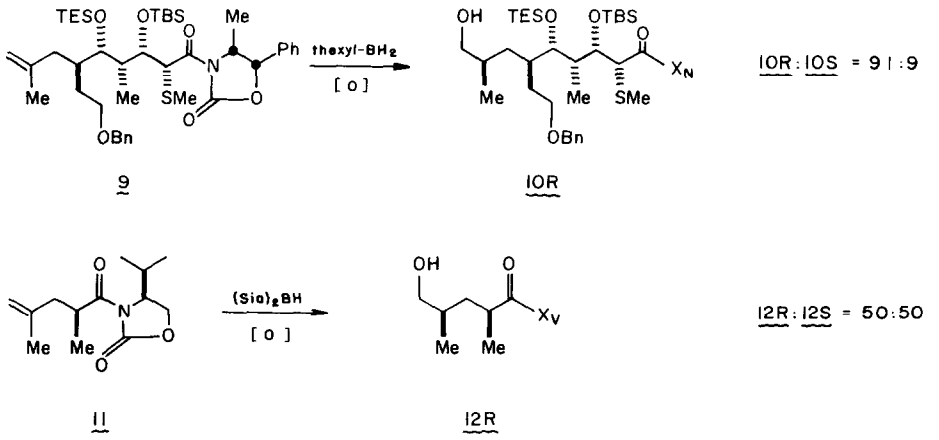
Entry	Substrate	R_2BH (0°C)	Ratio (2R:2S)
A	1b	BH_3	78:22
B	1b	$(Sia)_2BH$	85:15
C	1b	Thexyl-BH_2	85:15
D	1a	$(Sia)_2BH$	87:13
E	1b	(-)-IPC-BH_2	83:17
F	1b	(+)-IPC-BH_2	79:21

hydroboration diastereoselection could not be further enhanced via the use of the chiral monoalkylboranes derived from (+) and (-)-α-pinene (entry E, F).[6] The corresponding (+)- and (-)-pinene-derived dialkylboranes behaved in a similar fashion. In view of the unanticipated results noted above we have further explored the potential generality of these observations. A general survey of a number of olefinic substrates (Scheme II) with regard to diastereoselective hydroboration under the previously defined conditions (0°C) reveals

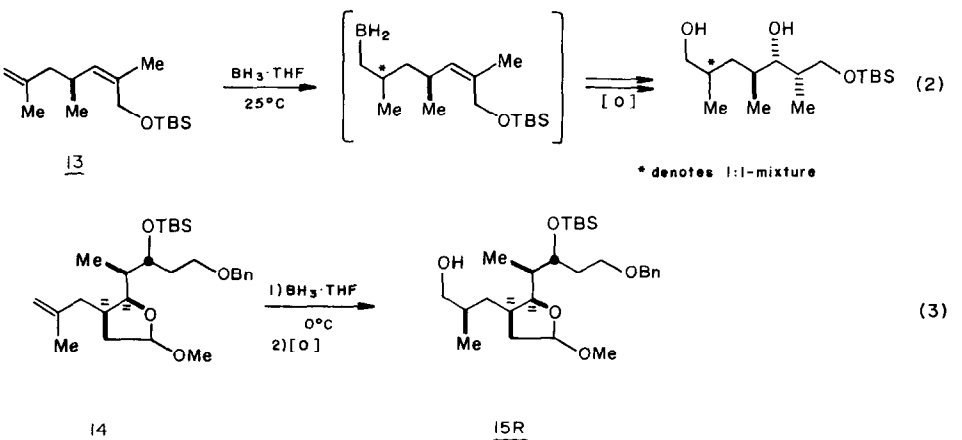
Scheme II



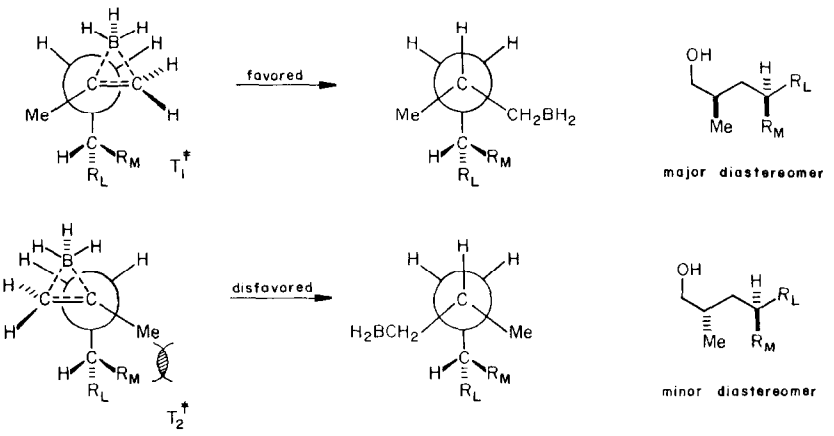
Scheme II (continued)



several important points. A comparison between olefins **1** or **3** and the diastereomeric substrate **5** reveals that preferential si-facial olefin hydroboration appears to be directed primarily by the proximal center of asymmetry in each of the three substrates. This conclusion is substantiated by the analogous result obtained from the hydroboration of olefin **7** containing the one putative methyl-bearing asymmetric center. Hydroboration of the related olefin **9** (c.f. **9** vs **1**) where the methyl substituent of C_4 has been replaced by a slightly larger ligand, CH_2CH_2OBn, exhibits the same sense of induction with comparable selectivity. These results, taken in conjunction with the complete lack of asymmetric induction noted in the hydroboration of **11** suggest that there is a definite "size requirement" for the ligands on the asymmetric center. The lower steric volume of the carbonyl substituent in **11**, and the attendant lack of asymmetric induction, is fully consistent with the lack of stereoselectivity noted in the first step of the hydroboration of diene **13** (eq. 2).[7] In both of these cases, the respective trigonal substituents, appended to the resident asymmetric center, do not possess a sufficient steric bias to create even a weak diastereofacial preference during hydroboration. Finally, based upon the data presented in Scheme II, it is not surprising that the hydroboration of olefin **14**, recently reported by Nicolaou, proceeds stereoselectively in the illustrated fashion (eq. 3).[8]



Although the $\Delta\Delta G^{\dagger}_{273°}$ values for the examples cited in Scheme II fall in the range of 0 → 1.0 kcal/mol, the predictable transfer of chirality, even with modest levels of asymmetric induction, is crucial to synthesis design. The working model that we have established for the observed π-facial selectivity is illustrated below. In both transition states, $T_1^{\dagger}$ and $T_2^{\dagger}$, the allylic substituent ($-CHR_MR_L$) is ordered antiperiplanar to the partially formed B-C bond in full accord with the recent theoretical studies of Houk[9] on olefin addition reactions. The related transition state conformational preferences for carbonyl addition are now well accepted.[10] The subtle, but useful, olefin diastereofacial bias may be created when the sterically dominant ligand, R_L, adopts the illustrated anti-conformation. In this orientation, we propose that the destabilizing feature which disfavors transition state $T_2^{\dagger}$ is the developing methyl ↔ R_M non-bonding interaction. Related arguments might also apply to analogous ketone reductions, and experiments designed to test this point are in progress.



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References and Notes

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(4) Diastereomer ratios were determined by capillary gas chromatography employing 30M x 0.32 mm WCOT columns (Carbowax 20M; Methyl Silicone SE-54).
(5) All compounds prepared during the course of this study afforded consistent elemental analyses and spectral data.
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