Graphical Abstract

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Diastereoselective Ni-catalyzed 1,4-hydroboration of chiral dienols[#]

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[#]This article is submitted in memory of Professor Harry Wasserman, an inspirational figure in organic chemistry.

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ABSTRACT

The Ni-catalyzed hydroboration of dienols occurs in a 1,4 fashion and delivers a *syn*-propionate motif in high diastereoselectivity and with a stereodefined trisubstituted crotylboronic ester. The boronic ester can be further manipulated to provide carbon-carbon or carbon-oxygen bonds.

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Polyketides are an important class of natural products that often exhibit potent biological activity.¹ Accordingly, significant efforts have been directed towards their efficient construction.² The most common methods for laboratory assembly of polyketides involve aldol³ and allylation⁴ reactions. Strategies that employ stereoselective hydroboration of allylic alcohols and ethers have also been developed (Scheme 1).^{5,6} While the above-described strategies are effective, they generally target fully hydrated ketide subunits with installation of dehydration sites accomplished by separate olefination reactions. Even though many strategies for stereocontrolled olefination reactions have been developed, it is still the case that construction of some motifs remains a challenging task. Recently, we developed a Ni-catalyzed hydroboration of dienes that provides (*Z*)-crotylboronic esters and, upon oxidative work-up, delivers the derived alcohols.⁷ The capacity for this reaction to install both hydroxyl functionality and stereodefined unsaturation sites suggested that it might offer a useful tool for stereocontrolled construction of a dehydrated diketide unit and thereby facilitate rapid construction of complex polyketide fragments. An important consideration in developing this strategy is whether neighboring hydroxylic functional groups can be used to control the product configuration (Scheme 1). Indeed, this transformation feature enabled a key route for our recent strategy for the synthesis of the natural product discodermolide.⁸ In this manuscript, we provide additional details about this reaction and demonstrate that, in addition to oxidation, the product boronate may be engaged in other bond constructions and enable strategic cascade reaction sequences.

Scheme 1

Diastereoselective Hydroboration of Allylic Alcohols

Prior studies of the Ni-catalyzed hydroboration^{7a} revealed that the reaction of 2,4-dimethyl-1,3-pentadiene occurred efficiently and with high olefin *Z/E* selectivity. To initiate studies on the stereoselective hydroboration of dienes, we examined chiral dienol **1** (Table 1) under related reaction conditions. Reaction of **1** at 0 °C for 3 h with pinacolborane and 2.5% each of Ni(cod)₂ and PCy₃, followed by oxidative workup furnished the hydroboration product in good yield, moderate diastereoselection and excellent olefin *Z* stereoselectivity. While the substrate reacted well, a significant improvement in both yield and stereoselection was observed upon incorporation of appropriate protecting groups. As depicted in Table 1, use of a TES protecting group (entry 2) furnished the reaction product in not only excellent yield, but also in enhanced selectivity relative to the unprotected substrate (12:1 vs. 6:1 dr). Use of larger protecting groups served to enhance selectivity such that with the TBDPS-protected substrate in entry 4, the product was obtained as a single stereoisomer according to ¹H NMR analysis. It should be noted that, in all cases the indicated 1,4-hydroboration product

was the only detectable compound; regioisomeric products or those arising from 1,2-hydroboration were not observed.

Table 1. Catalytic Hydroboration of Chiral Dienol Derivatives.

entry	R	% yield ^a	dr ^b
1 ^c	H	56	6:1
2	TES	93	12:1
3	TBS	89	14:1
4	TBDPS	80	>20:1
5 ^d	Bn	72	7:1

(a) Yield is of isolated purified material and is an average of two experiments. Product consists of >20:1 *Z:E* alkene in all cases. (b) Determined by ¹H NMR analysis. (c) Reaction employed 2 equiv of HBpin. (d) reaction for 12 h.

Examination of other substrates in the diastereoselective diene hydroboration reaction was undertaken with the set of substrates depicted in Table 2. Relative to substrate **1**, an alkyl substituent at the carbinol carbon reacted with an enhanced level of stereoselection (cf. entries 1-3, Table 2 vs. entry 3, Table 1). Dienes with branching adjacent to the chiral center required longer reaction times but still provided good yields of reaction products and very good levels of stereoselection (entries 2 and 3). While a Weinreb⁹ amide-derived substrate proved unreactive (entry 6), it is significant that dienes with alternate protected oxygen functionality and esters participated in the reaction and provided products with excellent diastereomeric purity (entry 4 and 5). A *Z*-diene, when subjected to the reaction conditions (entry 7), required extended reaction time and higher temperature; however, a high level of stereoselection was obtained. Importantly, the *Z*-diene delivered the same product stereoisomer as obtained from the *E* substrate. This observation suggests that high levels of stereocontrol can be obtained even if mixtures of olefin isomers are employed in the reaction. Suspecting that only dienes able to adopt the *S*-cis conformation would react, the substrate in entry 8 was examined and its lack of reactivity confirmed this notion. However, the substituent required to facilitate the formation of the *S*-cis conformer is not limited to CH₃ as occurs in entries 1-7; indeed both phenyl- and silyl-substituted dienes underwent hydroboration in excellent yield and good diastereoselectivity (entries 9-10). Of note, the PhMe₂Si-substituent should offer a convenient handle for additional alkene transformations.¹⁰

Table 2. Scope of the Diastereoselective Ni-Catalyzed Hydroboration of Dienols.^a

entry	substrate	product	% yield ^b	dr
1			90	>20:1
2 ^c			98	10:1
3 ^{c,d}			86	7:1
4 ^c			88	>20:1
5 ^e			80	>20:1
6 ^{c,f}		-	NR	-
7 ^{c,d}			40	17:1
8 ^{c,f}		-	NR	-
9 ^{c,d}			91	9:1
10 ^{c,f,g}			84	>10:1

(a) Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H₂O₂ and 3 M NaOH. (b) Isolated yield of purified material. Values are an average of two experiments. (c) Reaction for 12 h. (d) Reaction at rt. (e) Oxidation with NaBO₃. (f) Reaction at 40 °C. (g) Product consists of 3:1 *Z:E* mixture.

An attractive feature of diene hydroboration is that the intermediate crotylboronic ester may be further manipulated in useful ways. As depicted in Scheme 2, the unpurified reaction mixture was directly subjected to single-flask bond-forming reactions, in addition to oxidation. For example, as depicted in equation 1, homologation using the Matteson protocol delivered the homoallylic alcohol, after oxidation, in excellent yield.¹¹ Employing Aggarwal's conditions for protodeboronation, the crotylboron underwent allylic protonation to selectively provide the terminal alkene.¹² Lastly, when the intermediate was treated with *m*-CPBA, the boronate was oxidized to the alcohol and, concomitantly, the alkene was epoxidized with good diastereoselectivity.¹³

Scheme 2. Hydroboration/Functionalization Tandem Sequences.

A significant feature of the hydroboration products represented in Table 2 is that the trisubstituted alkene maps well onto polyketide frameworks. Thus it was anticipated that stereoselective hydrogenation might be employed to readily furnish skipped methyl fragments that are often found in macrolide structures.¹⁴ To examine this possibility, hydroboration product **2** was converted to homoallylic alcohol **3** as depicted in Scheme 3. Subjection of **3** to catalytic directed hydrogenation indeed furnished the saturated hydrocarbon in excellent overall yield and high diastereoselection.

Scheme 3. Stereoselective Hydrogenation of Hydroboration Derivative.

A rationale for the stereochemical outcome of the Ni-catalyzed diene hydroboration is depicted in Scheme 4. Consonant with a hypothesis by Burgess,¹⁵ we suspect that the Ni complex associates with the diene in a manner that positions the metal complex antiperiplanar with respect to the adjacent oxygen atom. This orientation allows the π system of the diene to mix

with the C-O σ^* and enhance backbonding between the metal and the alkene. A conformation wherein the carbinol hydrogen atom is directed towards the metal complex (A, Scheme 3) and the carbinol substituent directed away would serve to minimize steric interactions with the catalyst thereby leading to a stereocontrolled reaction. This hypothesis provides a clear rationale for the observation that larger oxygen protecting groups serve to enhance selectivity and that the *Z*-alkene in entry 7 is not only less reactive, but also delivers the same product as the *E* alkene in Table 1.

Scheme 4. Model for *Syn*-Selectivity in Ni-Catalyzed Hydroboration of Dienes.

In conclusion, we have described a diastereoselective Ni-catalyzed 1,4-hydroboration of dienes. This reaction provides a *syn*-propionate unit with high diastereoselectivity and concomitantly yields a trisubstituted (*Z*)-crotylboronic ester positioned for further polyketide construction. Further studies of the use of this reaction in complex molecule synthesis are underway.

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