

A One-Pot Diastereoselective Synthesis of *cis*-3-Hexene-1,6-diols via an Unusually Reactive Organozinc Intermediate

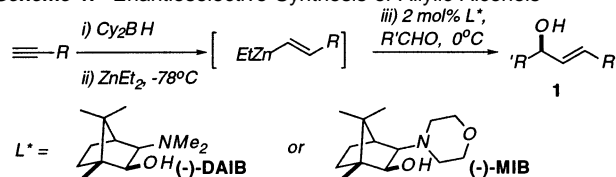
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Use of readily available reagents to create densely functionalized structures in a highly diastereoselective fashion is important to enhance synthetic efficiency. As part of our program to develop carbon-carbon bond forming reactions to prepare allylic,¹ homoallylic,² and tertiary alcohols³ with high enantioselectivities, we set out to design a method for the asymmetric vinylation of ketones. Our approach was akin to the vinylation of aldehydes developed by Oppolzer^{4,5} involving hydroboration of a terminal alkyne, transmetalation to zinc, and carbonyl addition to form the C-C bond (Scheme 1). This process gives excellent enantioselectivities

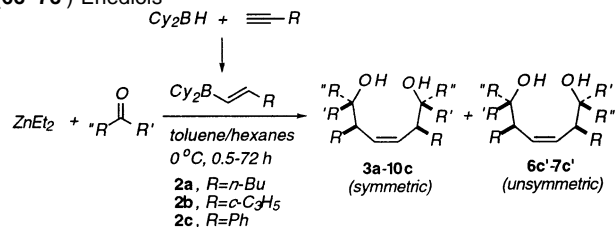
Scheme 1. Enantioselective Synthesis of Allylic Alcohols



with aldehydes^{1,5,6} using Noyori's DAIB⁷ or Nugent's MIB ligand,⁸ but is currently unknown for ketones.

In the process of studying the vinylation of ketones (in the absence of MIB), we trapped an unusually reactive organozinc species. This transient intermediate arises via reductive coupling of vinyl groups. It is trapped by insertion of 2 equiv of ketone or aldehyde, resulting in generation of two new C-C single bonds and a C-C double bond (Scheme 2). In most cases, this multistep

Scheme 2. Synthesis Symmetric (3a-10c) and Unsymmetric (6c'-7c') Enediols



process proceeds with excellent diastereoselectivity in the establishment of the *cis*-double bond geometry and relative stereochemistries at up to four centers.

Diethylzinc reacts very slowly with benzaldehyde at 0 °C (1% conversion in 8 h)⁹ and shows virtually no reaction with ketones at this temperature. Combination of diethylzinc and cyclohexanone at 0 °C followed by addition of the alkenylborane **2a**, derived from hydroboration of 1-hexyne, led to formation of a single diastereomer (**3a**) in 77% yield (Scheme 2, Table 1, entry 1). The *cis*-olefin geometry and the relationship between the stereogenic centers were established by NMR spectroscopy and X-ray crystallography, as outlined below. Analogous products were generated from cyclohexanone using cyclopropylacetylene and phenylacetylene (entries

Table 1. Vinyl Coupling/Carbonyl Insertion Products from Scheme 2

entry	ketone	R-C≡C-R =	t (h)	products (dr)	yield
1		<i>n</i> -Bu	20	3a (>20:1)	77
2		<i>o</i> -C ₃ H ₅	18	3b (>20:1)	75
3		Ph	12	3c (>20:1)	86
4	Ar = 4-C ₆ H ₄ -Me	<i>o</i> -C ₃ H ₅	18	4b (>20:1)	81
5	Ar = 4-C ₆ H ₄ -Me	Ph	72	4c (>20:1)	52
6	Ar = 4-C ₆ H ₄ -Cl	<i>n</i> -Bu	24	5a (>20:1)	76
7	Ar = 4-C ₆ H ₄ -Cl	<i>o</i> -C ₃ H ₅	24	5b (>20:1)	78
8	Ar = 4-C ₆ H ₄ -Cl	Ph	14	5c (>20:1)	56
9	Ar = Ph	Ph	24	6c:6c' (5.5:1)	80
10	Ar = 3-C ₆ H ₄ -Me	<i>n</i> -Bu	5	7a:7a' (1:1)	72
11	Ar = 3-C ₆ H ₄ -Me	<i>o</i> -C ₃ H ₅	5	7b:7b' (1:1)	70
12	Ar = 3-C ₆ H ₄ -Me	Ph	5	7c:7c' (2:1)	80
13	R = Ph	Ph	0.5	8c:8c' (>20:1)	47
14	R = 4-C ₆ H ₄ -OMe	Ph	1	9c:9c' (>20:1)	76
15	R = <i>o</i> -Hex	Ph	0.5	10c:10c' (>20:1)	80

2 and 3). To evaluate the reactivity of the organozinc intermediate, less reactive benzophenone derivatives were employed as substrates. Use of 4,4'-dimethylbenzophenone or 4,4'-dichlorobenzophenone in Scheme 2 also gave the 1,6-diol products (entries 4-8). A single diastereomer of the product was detected in entries 1-8.

Use of unsymmetric ketones led to generation of two additional stereocenters with variable diastereoselectivity at the quaternary positions. Reaction of acetophenone with vinyl borane **2c** resulted in formation of the symmetric and unsymmetric diastereomers **6c** and **6c'** in a 5.5:1 ratio (Scheme 2). The syn disposition of the phenyl groups from the phenylacetylene in **6c** was established by an X-ray diffraction study of the major product (Figure 1). To minimize steric crowding during the ketone insertion step, the phenyl groups of acetophenone orient opposite those derived from the alkyne. The minor, unsymmetric product (**6c'**) also has a *cis*-double bond based on the olefinic coupling in the ¹H NMR spectrum (11.0 Hz) but differs in the stereochemistry of one of the quaternary centers. Use of 3-methylacetophenone with 1-hexyne, cyclopropylacetylene, and phenylacetylene resulted in generation of 1:1 to 2:1 mixtures of the symmetric and unsymmetric diastereomers (entries 10-12).

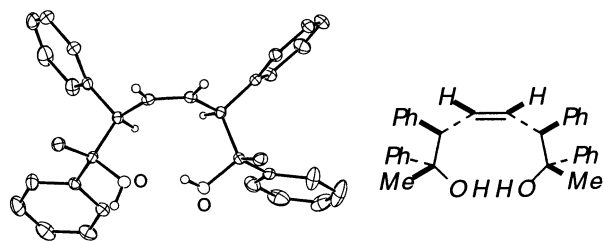
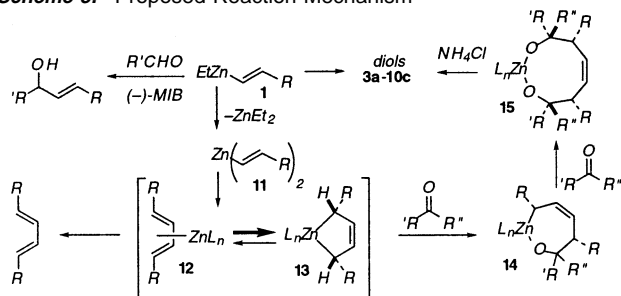


Figure 1. Structure of *cis*-enediol **6c**.

When the reaction of vinyl borane **2c**, diethylzinc, benzaldehyde, and (–)-MIB was conducted under the conditions in Scheme 2, the vinyl addition product was isolated in 67% yield with 91% ee. Less than 10% of the reductive coupling product **8c** was isolated. In the absence of MIB, however, the coupling product **8c** predominated and was isolated in 47% yield, while the vinylation product was isolated in 21% yield (based on aldehyde). The product distribution is determined by the relative rates of the vinyl addition vs reductive coupling (Scheme 3). The action of the catalyst derived

Scheme 3. Proposed Reaction Mechanism



from MIB accelerates the vinyl addition, steering the product composition toward the allylic alcohol. Less reactive aldehydes would, therefore, be expected to result in increased reductive coupling and subsequent diol formation. Consistent with this prediction, subjecting 4-methoxybenzaldehyde to the reaction conditions in Scheme 2 (no MIB) resulted in formation of **9c** in 76% yield with no allylic alcohol detected (Table 1, entry 14). Cyclohexanecarboxaldehyde also underwent coupling to give the diol **10c** (60% yield) with only a small amount of vinyl addition product (entry 15). Reactions with these aldehydes gave a single diastereomer of the product in each case. Such control of stereochemistry over six carbons is generally very difficult to achieve.

As shown in Scheme 3, we propose that the highly reactive organozinc intermediate is metalocyclopentene **13**. While divinylzinc compounds are stable with respect to reductive elimination,¹⁰ alkenylborates have been shown to couple to give dienes in the presence of copper^{11,12} or zinc halides.¹⁰ Molander and Zinke¹⁰ have demonstrated that dialkylborinates (*B*-methoxy-9-BBN) induce reductive coupling in related vinylzinc species. In the presence of aldehyde or ketone, the intermediate is trapped before dissociation of the diene can occur. As illustrated in Scheme 3, when no trap was added, diene was liberated and isolated in 70% yield (*R* = Ph). This is in contrast to group(IV) diene complexes which do not lose diene directly, but do insert carbonyl groups.^{13–15} Ad-

ditionally, use of 1-hexyne in Scheme 2 in the presence of 1,4-diphenyl-1,3-butadiene gave **3a** (no **3c** was detected). This indicates that the diene did not exchange with the proposed metalocyclopentene intermediate (**13**, Scheme 3). Additionally, mixing 1,4-diphenyl-1,3-butadiene, zinc powder, and cyclohexanone resulted in no reaction.

In summary, we have generated an unusually reactive organozinc species that smoothly adds to ketones and aldehydes. Using this procedure, simple, readily available materials can be converted into complex, densely functionalized *meso*-1,6-enediol products with excellent control over diastereoselectivity. Desymmetrization of *meso* compounds¹⁶ is proving to be a powerful tool in the synthesis of complex natural products, because it simplifies synthesis and provides a method for establishing stereochemistry at several centers simultaneously.^{17–22} Efficient desymmetrization of these diols can potentially lead to enantiopure material with two, four, or even more stereocenters.¹⁶ On the basis of the observed reactivity and selectivity, we propose that the intermediate in Scheme 3 is a metalocyclopentene complex.

Acknowledgment. This paper is dedicated to the memory of Professor Antonio González, a pioneer in natural product chemistry in the Canary Islands, Spain. We thank Dr. Ivan Keresztes and Prof. Don Berry for helpful discussions. This work was supported by the NIH (GM58101).

Supporting Information Available: Procedures, full characterization of 1,6-diols, and details of the structure of **6c** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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