

Catalytic Asymmetric Vinylation of Ketones

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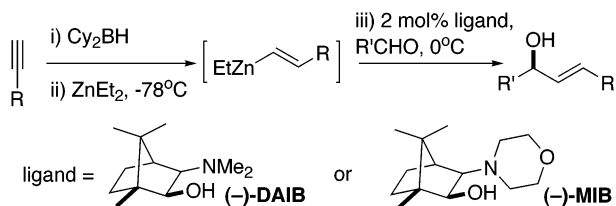
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Carbon–carbon bond-forming reactions lie at the very heart of organic synthesis. As such, the formation of these bonds using catalytic asymmetric methods has been the subject of intense research efforts. Despite the monumental success in the enantioselective addition of alkyl groups to aldehydes,^{1,2} resulting in the formation of secondary alcohols, few catalysts will promote the addition of organometallic reagents to ketones. Thus, a long-standing goal in asymmetric catalysis has been the synthesis of tertiary alcohols with high levels of enantioselectivity.^{3–5} The challenging nature of this class of transformations has attracted considerable attention, and the first breakthroughs have been reported recently.^{6–13} Our efforts have resulted in development of an efficient and highly enantioselective catalyst for the addition of allylzinc reagents to ketones.^{8,9} We are not aware, however, of any successful reports addressing the enantioselective vinylation of ketones. The products of this transformation are allylic alcohols, which are known for their utility in organic synthesis. In this communication, we report the results of an investigation into the enantioselective 1,2-addition of substituted and functionalized vinyl groups to ketones.

Our initial attempts to promote the vinylation of ketones employed methods developed by Oppolzer for reactions with aldehydes.^{14–16} The protocol is initiated by hydroboration of a terminal alkyne, transmetalation of the vinylborane to zinc, and addition to aldehydes in the presence of a catalyst derived from an amino alcohol, such as DAIB¹⁷ or MIB¹⁸ (Scheme 1). The reaction is very efficient and in most cases exhibits enantioselectivities over 90%.

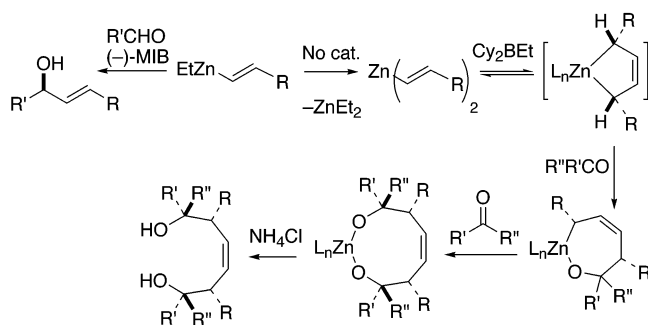
Scheme 1. Enantioselective Synthesis of Allylic Alcohols



When we employed this method with our catalyst for the addition of vinylzinc reagents to ketones using 1-hexyne or phenylacetylene, we were surprised to find that the allylic alcohol was not the major product.¹⁹ Instead, diols derived from coupling of alkynes, possibly through a metallocyclopentene intermediate, were isolated in yields as high as 86%. This reaction, and a proposed mechanism, are illustrated in Scheme 2.¹⁹ It is known that most divinylzinc compounds are stable to reductive dimerization processes, so we hypothesized that the byproduct, Cy₂BEt, was somehow involved in this reaction.

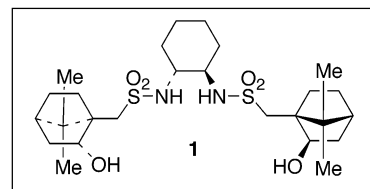
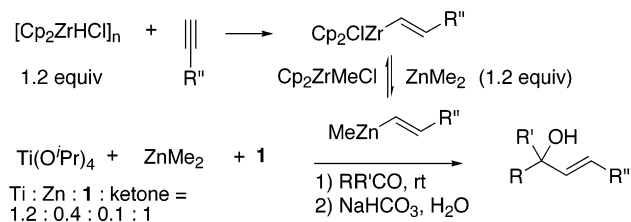
It was clear from these studies that the Oppolzer protocol would not provide access to the desired tertiary allylic alcohols and that an alternative method to generate vinylzinc reagents was required. We next turned our attention to the method developed by Wipf

Scheme 2. Proposed Reaction Mechanism



and co-workers^{20–22} consisting of hydrozirconation of terminal alkynes with Schwartz's reagent followed by transmetalation to zinc (Scheme 3).


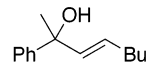

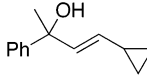

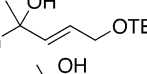

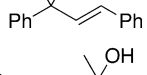
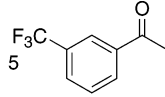
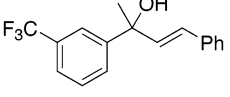
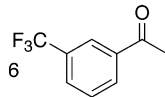
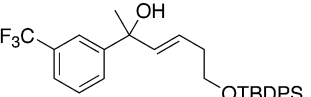
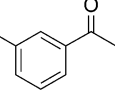
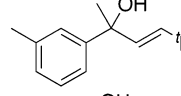
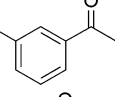
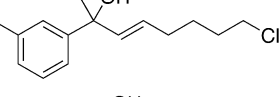

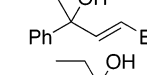
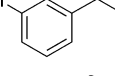
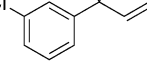

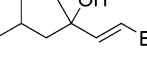
Scheme 3. Asymmetric Vinylation of Ketones



This protocol has been successfully used in the asymmetric vinylation of aldehydes.²⁰ To reduce the amount of alkyne and Schwartz's reagent to 1.2 equiv each, the catalyst was generated in a separate reaction vessel by combining ligand **1** (10 mol %), titanium tetraisopropoxide (1.2 equiv), and dimethylzinc (0.4 equiv). In this fashion, the dimethylzinc reacts with the 0.4 equiv of 2-propanol liberated on reaction of the ligand **1** with titanium tetraisopropoxide. Addition of dimethylzinc to the vinylzirconocene was followed by the catalyst and the substrate. Reactions were stirred at room temperature for 16–24 h, quenched with saturated NaHCO₃, and chromatographed on deactivated silica to afford the allylic alcohols in high yields and enantioselectivities (Scheme 3, Tables 1 and 2). Catalyst loadings of 10 and 5 mol % gave similar results, but reduction to 2 mol % resulted in a decrease in the enantioselectivity and yield. Care should be exercised in handling these allylic alcohols, as some are susceptible to racemization.

A variety of alkynes have been employed in the asymmetric vinylation reaction in Tables 1 and 2, indicating that the reaction

Table 1. Asymmetric Vinylation of Acyclic Ketones

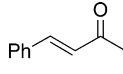
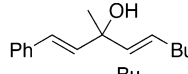
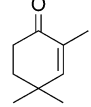
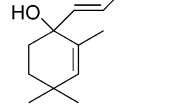
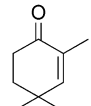
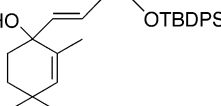
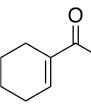
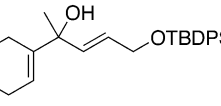
entry	substrate	product	ee (yield)
1			93 (85)
2			95 (90)
3			89 (92)
4			87 (92)
5			88 (84)
6			90 (94)
7			92 (93)
8			90 (98)
9			94 (90)
10			93 (93)
11			79 (85)

is compatible with functionalized substrates. Only small deviations in the enantioselectivities and yields are observed with 1-hexyne, cyclopropylacetylene, phenylacetylene, *tert*-butylacetylene, 1-chloro-5-hexyne, and protected propargyl and homopropargyl alcohols (compare entries 1–8, Table 1). High enantioselectivities (87–95%) were observed with acetophenone and derivatives bearing electron-withdrawing or -donating substituents (Table 1, entries 1–8). Propiophenone and 3-chloropropiophenone underwent addition with 93–94% enantioselectivity in high yields (Table 1, entries 9 and 10). The reaction of dialkyl ketone 4-methyl-2-pentanone proceeded with 79% enantioselectivity (Table 1, entry 11), suggesting that this class of substrates will give reasonable results.

Three distinct α,β -unsaturated ketones were examined in the asymmetric vinylation, and the resulting dienols were produced with excellent enantioselectivities (92–97%) and high yields (Table 2). It is noteworthy that only the 1,2-addition products were formed, and no conjugate addition product was isolated.

In summary, a protocol for the highly enantioselective addition of vinyl groups to aromatic, α,β -unsaturated, and dialkyl ketones is disclosed. This reaction couples Wipf's hydrozirconation/trans-

Table 2. Asymmetric Vinylation of Enones

entry	substrate	product	ee (yield)
1			92 (87)
2			97 (94)
3			94 (85)
4			92 (98)

metalation to zinc²² with our ketone addition catalyst to provide access to tertiary allylic alcohols of high ee. Future studies will involve use of highly functionalized alkynes and ketones to broaden the scope of this synthetically useful transformation.

Acknowledgment. We thank Dr. Celina García for preliminary experiments involving the Oppolzer hydroboration method. This work was supported by the NIH, National Institute of General Medical Sciences (GM58101).

Supporting Information Available: Procedures and full characterization of new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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