Catalytic Asymmetric Vinylation and Dienylation of Ketones

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · JULY 2005

Impact Factor: 12.11 · DOI: 10.1021/ja0425740 · Source: PubMed

2 AUTHORS, INCLUDING:

Hongmei Li
Merck
26 PUBLICATIONS **805** CITATIONS

SEE PROFILE

J|A|C|S
ARTICLES
Published on Web 05/21/2005

Catalytic Asymmetric Vinylation and Dienylation of Ketones

Hongmei Li and Patrick J. Walsh*

Contribution from the P. Roy and Diana T. Vagelos Laboratories, University of Pennsylvania, Department of Chemistry, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

Received December 10, 2004; E-mail: pwalsh@sas.upenn.edu

Abstract: A solution to the long-standing problem of catalytic asymmetric vinylation of ketones is reported. Vinylzinc reagents are generated via hydrozirconation of terminal alkynes followed by transmetalation to zinc. In the presence of our catalyst, which is formed in situ from a bis(sulfonamide) diol ligand (**1**) and titanium tetraisopropoxide, the vinylzinc reagent undergoes 1,2-addition to a variety of ketones and enones with enantioselectivities (typically >90%) and high yields. This method is tolerant of functional groups, including alkyl, aryl and vinyl halides, esters, silyl protected alcohols, sulfides, and alkenes. Thus, enantioenriched tertiary allylic alcohols bearing a variety of functional groups can be prepared. It has also been found that 2,2-disubstituted vinylzinc reagents, substitution patterns not accessible through hydrozirconation, can be added to ketones with high enantioselectivities to generate trisubstituted allylic alcohols. Furthermore, we have developed an asymmetric addition of dienyl groups to ketones in the presence of our catalyst. This method enables the synthesis of dienols in high yields with enantioselectivities as high as 94%.

Introduction

Carbon−carbon bond-forming reactions are of fundamental importance in the construction of natural and unnatural products. As such, the formation of these bonds using catalytic asymmetric methods has been the focus of many research groups. One of the most powerful methods for the catalytic asymmetric generation of carbon−carbon bonds is the enantioselective addition of organometallic reagents to aldehydes and ketones. The products of these addition reactions are enantioenriched secondary and tertiary alcohols, which are valuable synthetic intermediates. Early efforts to develop enantioselective additions of alkyl groups to aldehydes and ketones date back over 50 years and involved use of Grignard reagents and chiral solvents.[1] This, and related investigations involving organolithiums, were thwarted by the inherent reactivity of these reagents.[2−5] Use of temperatures below −100 °C proved successful in the asymmetric additions of alkyl groups to ketones, but were impractical due to the low temperature, stoichiometric chiral ligand, functional group incompatibility, and limited substrate scope.[6,7] To circumvent the rapid, uncatalyzed carbonyl additions of reactive organolithium and magnesium reagents, Oguni and Omi[8] focused on the use of organozinc reagents, which react very slowly with aldehydes in the absence of a catalyst. In the presence of catalysts derived from chiral amino alcohols, however, dialkylzinc reagents add to aldehydes efficiently and with high enantioselectivities.[9,10]

Since this seminal work, many catalysts have been developed that promote the addition of dialkylzinc reagents to aldehydes.[9−12] In sharp contrast, few catalysts exhibit levels of reactivity and enantioselectivity similar to those of ketones.[13] As a result, the catalytic enantioselective synthesis of tertiary alcohols has remained a long-standing goal in asymmetric catalysis.[11,13−15] The synthetic potential of these challenging reactions has attracted considerable effort. Several breakthroughs have been reported recently and include development of efficient and highly enantioselective catalysts for the asymmetric addition of alkyl,[15−18] allyl,[19−25] aryl,[26−29] and alkynyl[30,31] groups to ketones and alkyl[32−34] and alkynyl[35] groups to α-keto esters.

(1) Cohen, H. L.; Wright, G. F. *J. Org. Chem.* **1952**, *17*, 432−446.
(2) Seebach, D.; Dorr, H.; Bastani, B.; Ehrig, V. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 982−983.
(3) Inch, T. D.; Lewis, G. J.; Sainsbury, G. L.; Sellers, D. J. *Tetrahedron Lett.* **1969**, *41*, 3657−3660.
(4) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905−913.
(5) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597−1606.
(6) Weber, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 84−86.
(7) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117−6128.
(8) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823−2824.
(9) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.
(10) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.
(11) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886.
(12) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2794.
(13) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284−287.
(14) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.
(15) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749−760.
(16) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971.
(17) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544−9545.
(18) Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448−455.
(19) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061−1063.
(20) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697−3699.
(21) Kim, J. G.; García, I. F.; Kwiatkowski, D.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 12580−12585.
(22) Cunningham, A.; Woodward, S. *Synlett* **2002**, 43−44.
(23) Cunningham, A.; Mokal-Parekh, V.; Wilson, C.; Woodward, S. *Org. Biomol. Chem.* **2004**, *2*, 741−748.
(24) Hanawa, H.; Kii, S.; Maruoka, K. *Adv. Synth. Catal.* **2001**, *1*, 57−60.
(25) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910−8911.
(26) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446.
(27) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641−3644.

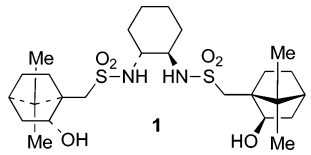
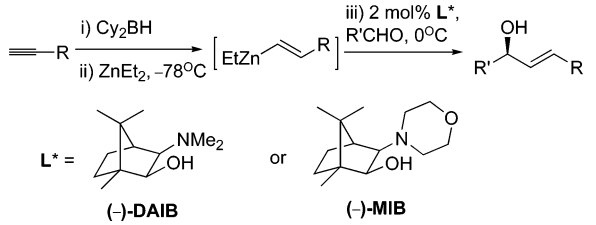


Figure 1. Structure of ligand **1**.

Scheme 1. Enantioselective Vinylation of Aldehydes by Oppolzer's Method

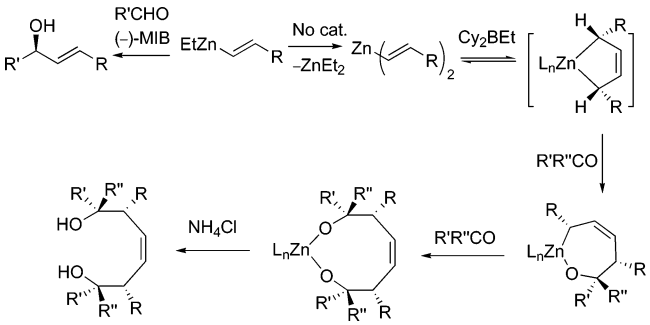


Our efforts have resulted in development of an efficient and highly enantioselective catalyst for the addition of dialkylzinc[16−18] and diphenylzinc[27,28] reagents to ketones.

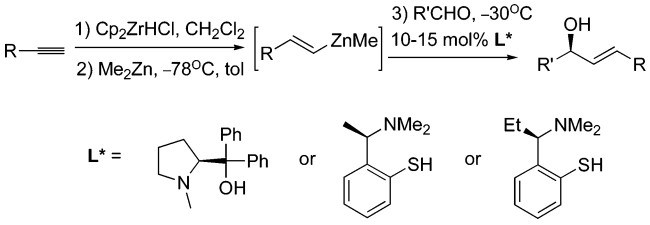
The asymmetric vinylation of aldehydes and ketones has also attracted significant attention.[36−38] The products of these reactions, chiral secondary and tertiary allylic alcohols, are useful intermediates in organic synthesis and are pervasive in natural products. Highly enantioselective catalysts for the vinylation of aldehydes have been developed by Oppolzer,[36] Wipf,[37−39] and others.[40−42] Oppolzer's method consists of hydroboration of terminal alkynes, transmetalation to zinc, and addition to aldehydes in the presence of Noyori's DAIB-based catalyst[43] with high enantioselectivities (Scheme 1). We have reported enantioselective routes to α-amino acids and γ-unsaturated-β-amino acids employing Oppolzer's method with Nugent's ligand MIB.[44−46] Efforts to develop catalysts for the vinylation of ketones that exhibit high levels of enantioselectivity, however, remained challenging.

Our initial attempts to promote the vinylation of ketones employed Oppolzer's method to generate the vinylzinc reagent in combination with our titanium-based catalyst formed from ligand **1**[15,16] (Figure 1). We were surprised to find that the anticipated allylic alcohols were not the major products.[47] Instead, diols derived from coupling of alkynes, possibly through

Scheme 2. Proposed Reaction Mechanism for the Formation of Allylic Alcohols, through Ligand Accelerated Catalysis, and *cis*-Enediols in the Absence of a Catalyst



Scheme 3. Enantioselective Vinylation of Aldehydes by Wipf's Method



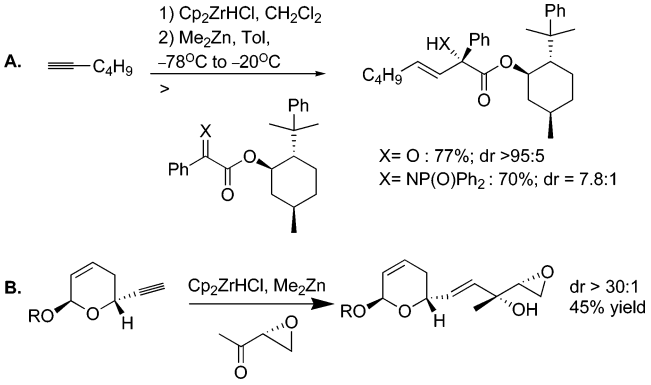
a metallocyclopentene intermediate, were isolated in good yields. This reaction and a proposed mechanism are illustrated in Scheme 2.[47] Interestingly, divinylzinc compounds are normally stable to reductive dimerization. We hypothesized that the byproduct, Cy_2BEt, was somehow involved in this unexpected coupling reaction. Whatever the mechanism of this interesting reaction, it was clear from these studies that the Oppolzer protocol would not provide access to the desired tertiary allylic alcohols with our catalyst and that an alternative method to generate vinylzinc reagents was required.

We then turned our attention to the generation of vinylzinc reagents by the method of Wipf and co-workers.[37,48,49] This protocol involves hydrozirconation of terminal alkynes with Schwartz's reagent,[50] transmetalation to zinc, and addition to aldehydes with good to excellent enantioselectivities (Scheme 3).[48,49] Wipf and co-workers have also reported the vinylation of chiral α-keto ester with excellent diastereoselectivities (>95:5) using their protocol (Scheme 4A).[51] Jacobsen and co-workers also employed this method in the vinylation of a chiral epoxy ketone with excellent diastereoselectivity (>30:1) in the total synthesis of fostriecin (Scheme 4B).[52] We are not aware, however, of any successful reports addressing the catalytic asymmetric vinylation of unactivated ketones.

We report herein the full details of our development of a highly enantioselective method for the vinylation of ketones and enones. In this procedure, we have employed Wipf's protocol to generate vinylzinc intermediates, which are subsequently added to ketones and enones in the presence of our titanium-based catalyst. An improved procedure is outlined that gives increased yields and enantioselectivities with lower catalyst

(28) Li, H.; García, C.; Walsh, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5425−5427.
(29) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955−1957.
(30) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895−2898.
(31) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057−5058.
(32) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668−12669.
(33) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781−3784.
(34) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5489−5492.
(35) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451−3453.
(36) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170−173.
(37) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269−1279.
(38) Wipf, P.; Kendall, C. *Chem.-Eur. J.* **2002**, *8*, 1778−1784.
(39) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639−644.
(40) Dahmen, S. D.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119−4122.
(41) Ji, J.-X.; Qiu, L.-Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589−1590.
(42) Bräse, S.; Dahmen, S.; Höfener, S.; Lauterwasser, F.; Kreis, M.; Ziegert, R. E. *Synlett* **2004**, 2647−2669.
(43) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072.
(44) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225−12231.
(45) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677−10683.
(46) Chen, Y. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 3702−3703.
(47) García, C.; Libra, E. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 3210−3211.
(48) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454−6455.
(49) Wipf, P.; Jayasuriya, N.; Ribe, S. *Chirality* **2003**, *15*, 208−212.
(50) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115−8116.
(51) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449−2452.
(52) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667−3669.

Scheme 4. Diastereoselective Vinylation of Chiral Ketones and Related Derivatives



Scheme 5. Asymmetric Vinylation of Ketones

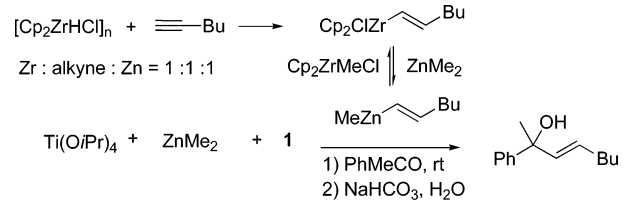


Table 1. Reaction Conditions for the Asymmetric Vinylation of Ketones

entry	Cp_2ZrHCl (equiv)	L* (mol %)	$Ti(O^iPr)_4$ (equiv)	Me_2Zn[a,b] (equiv)	solvent	yield (%)	ee (%)
1	1.0	10	1.2	0.4	tol	62	92
2	1.2	10	1.2	0.4	tol	85	93
3	1.0	10	1.2	0.4	tol/hex	61	92
4	1.2	10	1.2	0.4	Et_2O/tol	92	94
5	1.2	10	1.2	0.4	CH_2Cl_2	94	94
6	1.2	5	1.2	0.4	tol	90	95
7	1.2	2	1.2	0.4	tol	48	86
8	1.0	0	1.2	0.4	tol	<10	rac
9	1.2	10	0	0	tol		rac
10	1.2	10	0.6	0.4	tol	93	96
11	1.2	10	0.2	0.4	tol	83	95
12	1.2	10	0.1	0.4	tol	50	42
13	1.2	10	1.2	0	tol	98	95
14	1.2	5	0.6	0	tol	98	95

[a] The amount of Me_2Zn used in catalyst preparation. [b] 1.2 equiv of Me_2Zn was used in the transmetalation step in all cases.

loading as compared to our initial report.[53] Finally, the scope of the organozinc additions has been significantly expanded to include 2,2-disubstituted vinyl and dienyl groups.

Results and Discussion

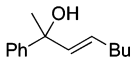
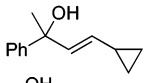
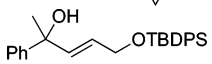
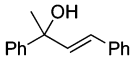
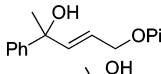
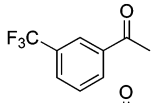
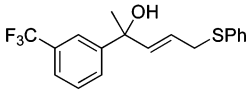
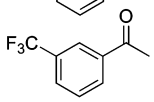
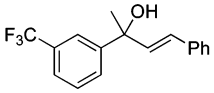
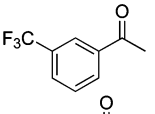
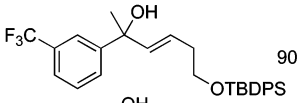
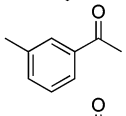
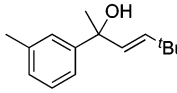
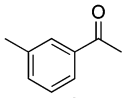
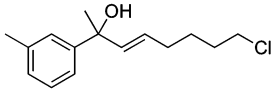
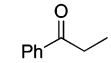
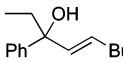
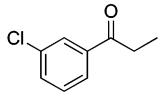
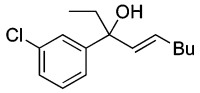
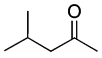
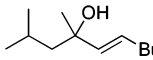
1. Reaction Optimization. We initiated our investigation into the vinylation of ketones using Wipf's method as shown in Scheme 5. We chose acetophenone and 1-hexyne for optimization of the reaction (Table 1). To minimize the amount of alkyne and Schwartz's reagent,[54,55] the catalyst was generated in a separate reaction vessel by combining ligand **1** (10 mol %), titanium tetraisopropoxide, and dimethylzinc (40 mol %). The purpose of the 40 mol % dimethylzinc was to react with the 4 equiv of 2-propanol liberated on reaction of the ligand **1** with titanium tetraisopropoxide. In initial experiments, we used conditions similar to those in our asymmetric alkylation of ketones.[16] Employing 1.0 equiv of Schwartz's reagent, 10 mol % ligand **1**, and 1.2 equiv of titanium tetraisopropoxide with toluene as solvent at room temperature resulted in formation of the product in 62% isolated yield and 92% enantioselectivity after 20 h (entry 1). Increasing Cp_2ZrHCl to 1.2 equiv resulted in an increase in the isolated yield to 85% (entry 2). Next, we focused our attention on variation of the reaction medium. Using toluene/hexanes (1:2) or toluene/diethyl ether (1:2) solvents resulted in an increase in reaction time to around 50 h with little change in the enantioselectivities (entries 3−4). Using dichloromethane as solvent gave similar results to toluene (entry 5). Based on these results, and the stability of toluene solutions of dialkylzinc reagents, we chose to use toluene in subsequent experiments. In the next phase of the reaction optimization, we explored the impact of the ratio of ligand **1** to $Ti(O^iPr)_4$. Catalyst loadings of 10 and 5 mol % gave similar results, but reduction to 2 mol % resulted in a decrease in the enantioselectivities and yields (entries 2, 6, and 7). Without ligand (entry 8) or $Ti(O^iPr)_4$ (entry 9), the reaction only gave very small amounts (<10% yield) of racemic product after 2 days. Employing 0.6 equiv of the titanium tetraisopropoxide led to an increase in enantioselectivity (entry 10), while further decreasing the titanium tetraisopropoxide resulted in a drop in yield and/or enantioselectivity (entries 11 and 12).

An important observation was made when the catalyst was generated without addition of the 0.4 equiv of dimethylzinc, which had been used to sequester the 2-propanol liberated during catalyst formation. Under these conditions, the reaction gave the highest yield and enantioselectivity, even at 5 mol % ligand loading (entries 13 and 14). This new procedure has the advantages of requiring less dimethylzinc and simplifying catalyst preparation. Furthermore, the improved procedure uses half the ligand loading (5 mol %) and results in higher enantioselectivities and yields. We compared enantioselectivities and yields using our original reaction conditions (entry 2, Table 1) and the improved protocol (entry 14, Table 1) with several substrates (Table 2). Although the factors responsible for the increase in enantioselectivity with the new protocol are not clear at this time, we speculate that the liberated 2-propanol generated on reaction of the ligand **1** with titanium tetraisopropoxide may react with the product of transmetalation, $Cp_2ZrMeCl$, generating methane and $Cp_2Zr(O^iPr)Cl$. It has been suggested that the coordinatively unsaturated $Cp_2ZrMeCl$ promotes the racemic vinylation of aldehydes, resulting in a slight decrease in product ee.[48] A similar background reaction promoted by $Cp_2ZrMeCl$ may be possible in our ketone vinylation reaction, albeit to a lesser extent. The alkoxide byproduct, $Cp_2Zr(O^iPr)Cl$, is less Lewis acidic than $Cp_2ZrMeCl$ and is unlikely to activate the ketone and promote the racemic addition.

2. Vinylation of Ketones. We have employed a variety of alkynes in the asymmetric vinylation of ketones, indicating that the reaction is compatible with functionalized substrates (Table 2). Only small deviations in the enantioselectivities and yields were observed employing 1-hexyne, cyclopropyl acetylene, phenylacetylene, *tert*-butyl acetylene, 1-chloro-5-hexyne, phenyl propargylic sulfide, and protected propargyl and homopropargyl alcohols with acetophenone derivatives. High enantioselectivities (86−95%) were observed with acetophenone derivatives bearing electron-withdrawing or -donating substituents (Table 2, entries

(53) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538−6539.
(54) Buchwald, S. L.; LaMaire, S. J.; Neilsen, R. B.; Watson, B.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895−3898.
(55) Buchwald, S. L.; LaMaire, S. J.; Neilsen, R. B.; Watson, B.; M, K. S. *Org. Synth.* **1993**, *71*, 77−82.

Table 2. Asymmetric Vinylation of Acyclic Ketones with (*R*,*R*)-**1**

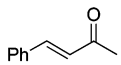
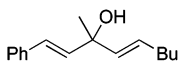
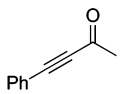
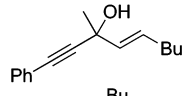
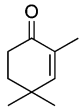
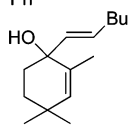
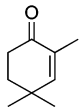
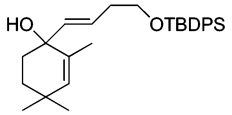
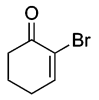
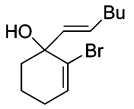
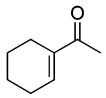
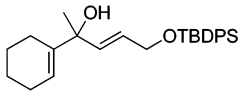
entry	substrate	product	ee[d] (yield[c]) [config]
1			93 (85)[a] [*S*]
2			95 (98)[b] [*S*]
3			95 (90)[a] [*S*]
4			89 (92)[a] [*S*]
5			91 (98)[b] [*S*]
6			87 (92)[a] [*S*]
7			90 (92)[b] [*S*]
8			86 (89)[a] [*S*]
9			89 (90)[b] [*S*]
10			88 (95)[b]
11			88 (84)[a]
12			90 (80)[b]
13			90 (94)[a]
14			92 (93)[a]
15			97 (99)[b]
16			90 (98)[a]
17			94 (90)[a] [*S*]
18			93 (93)[a]
19			79 (85)[a]
20			80 (88)[b]

[a] Reaction conditions: Cp_2ZrHCl:alkyne:Me_2Zn = 1:1:1 (1.2 equiv relative to the ketone), 10 mol % **1**, 1.2 equiv of Ti(O*i*Pr)$_4$, 0.4 equiv of Me_2Zn. [b] Improved reaction conditions: Cp_2ZrHCl:alkyne:Me_2Zn = 1:1:1 (1.2 equiv), 5 mol % **1**, 0.6 equiv of Ti(O*i*Pr)$_4$. [c] Isolated yields. [d] The ee was determined by GC or HPLC (see Supporting Information).

1−16). Propiophenone and 3′-chloropropiophenone underwent addition with 93−94% enantioselectivities and high yields (Table 2, entries 17 and 18). The reaction of the challenging dialkyl ketone 4-methyl-2-pentanone proceeded with 79−80% enantioselectivity (entries 19 and 20), suggesting that this class of substrates will give reasonable results.

Higher enantioselectivities were obtained using the new procedure. For example, with acetophenone the enantioselectivity increased from 93% to 95% and with 2,2-dimethylpropionic acid 2-propynyl ester from 86% to 89% (Table 2, entries 1, 2 and 8, 9, respectively). Yields were also observed to increase with the improved protocol. The absolute configurations of the tertiary allylic alcohols listed in Tables 2, 4, and 5 were determined by cleavage of the double bond with ozone followed by workup with LAH (see Supporting Information). Measurement of the optical rotation of the resultant diols indicated that reactions with the ligand (*R*,*R*)-**1** gave the (*S*)-

Table 3. Asymmetric Vinylation of Enones and Ynones with (*R*,*R*)-**1**

entry	substrate	product	ee[d] (yield[c])
1			92 (87)[a]
2			79 (81)[b]
3			97 (94)[a]
4			94 (85)[a]
5			92 (42)[b]
6			92 (98)[a]

[a] Reaction conditions: Cp_2ZrHCl:alkyne:Me_2Zn = 1:1:1 (1.2 equiv), 10 mol % **1**, 1.2 equiv of Ti(O*i*Pr)$_4$, 0.4 equiv of Me_2Zn. [b] Reaction conditions: Cp_2ZrHCl:alkyne:Me_2Zn = 1:1:1 (1.2 equiv), 5 mol % **1**, 0.6 equiv of Ti(O*i*Pr)$_4$. [c] Isolated yields. [d] Ee was determined by GC or HPLC (see Supporting Information).

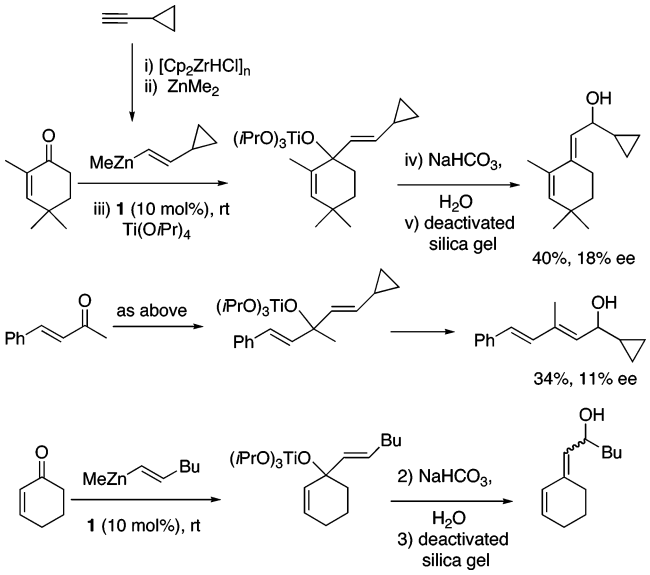
configuration of the tertiary alcohols. This is consistent with sense of stereoinduction previously observed with alkyl additions to ketones with (*R*,*R*)-**1**.[18]

It should be noted that, when handing tertiary allylic alcohols, care must be exercised during workup and purification to avoid erosion of the enantioselectivities through partial racemization. We found that performing workups under basic conditions with aqueous $NaHCO_3$ proved successful in most cases. The crude products were subject to chromatography on silica deactivated with triethylamine.

3. Vinylation of Enones and Ynones. We also examined the asymmetric vinylation of enones using our catalyst. The products of enone vinylation are densely functionalized alcohols bearing two allylic double bonds that can be selectively elaborated. Vinylation of the acyclic conjugated enone *trans*-4-phenyl-3-buten-2-one occurred with 92% enantioselectivity and 87% yield (Table 3, entry 1). Interestingly, 4-phenyl-3-butyn-2-one gave the product in 79% enantioselectivity, suggesting that the catalyst has difficulty differentiating between the carbonyl oxygen lone pairs syn to the methyl versus syn to an alkyne. The groups flanking the carbonyl in the ynone are more similar in size than those of the enone (entries 1 vs 2). Two cyclic conjugated enones were also examined, and the resulting dienols were produced with excellent enantioselectivities (92−97%, entries 3−5). Although addition to 2,4,4-trimethyl-2-cyclohexenone gave high yields (85−94%), that of 2-bromo-2-cyclohexenone was substantially reduced (42% yield). A similar reduction in yield was observed in the phenyl addition to this ketone.[28] The exocyclic enone cyclohexenyl methyl ketone also gave excellent yield and enantioselectivity (entry 6).[27]

In a few cases, TLC of the reaction mixtures indicated formation of several products. Upon quenching the reaction,

Scheme 6. Isolation of Rearrangement Products Illustrate the Sensitivity of the Tertiary Allylic Alcohols and Some Limitations of the Ketone Vinylation Method



no addition products were isolated, but low yields of rearranged products formed, as outlined in Scheme 6. This reaction was observed with in the addition of vinylcyclopropane to conjugated enones 2,4,4-trimethylcyclohexen-2-one and *trans*-4-phenyl-3-buten-2-one, but not in the addition to acetophenone (Table 2, entry 3). It is likely that the ability of the cyclopropyl group to stabilize adjacent carbocations is responsible for lowering the barrier to rearrangement. It is interesting to note that the rearrangement products were not racemic, but exhibited low ee's. We were surprised to find that a similar rearrangement product was obtained on addition of a 1-hexenyl group to cyclohexenone.

4. Addition of Dienyl Groups to Ketones. Given the success of our asymmetric vinylation of ketones and enones outlined above, we desired to explore the asymmetric addition of dienyl groups to ketones. The dienol products are valuable intermediates in organic synthesis and may find applications in diastereoselective Diels−Alder reactions, for example. The hydrozirconation of 1-ene-3-ynes has been reported to give the dienylzirconocenes with the zirconium at the dienyl terminus.[56,57] We investigated the hydrozirconation of 2-methyl-1-buten-3-yne by ^{1}H NMR spectroscopy in C_6D_6 to evaluate the chemoselectivity of this reaction. Indeed, the hydrozirconation proceeded cleanly to provide the dienyl product, as judged by the trans coupling constant of 18.7 Hz of the zirconium-bound dienyl group.

Employing the optimized conditions for the asymmetric vinylation reaction from Table 1 (entry 14), we examined three enyne substrates (Scheme 7). Initially, we studied the reaction of 1-ethynyl-1-cyclohexene, because hydrozirconation of the trisubstituted double bond was expected to be much slower and would not interfere with reaction at the triple bond. As indicated by the results outlined in Table 4, the hydrozirconation, transmetalation, and asymmetric addition to acetophenone and derivatives occurred smoothly to give the dienol products with high enantioselectivity and yield (entries 1−3). No isomerization of the double bond was observed in this reaction, as determined by NMR spectroscopy. Similar results were obtained with 4-methyl-3-decen-1-yne (entries 4 and 5). We next investigated the use of 2-methyl-1-butene-3-yne in the asymmetric addition reaction. We were initially concerned that the reaction might be complicated by hydrozirconation of the terminal double bond.

Scheme 7. Asymmetric Addition of Dienyl Groups to Ketones

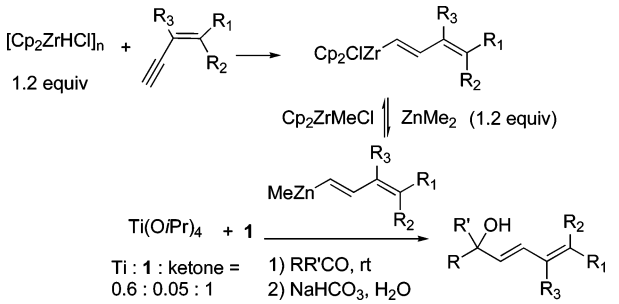
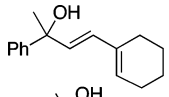
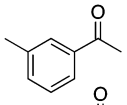
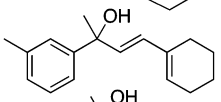
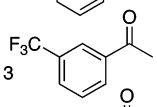
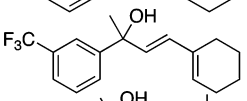
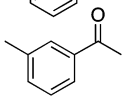
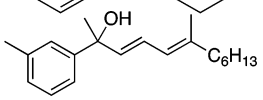
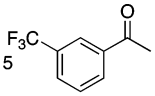
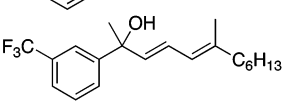
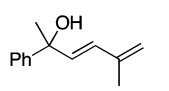
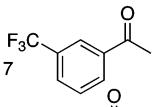
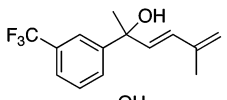
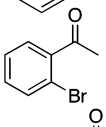
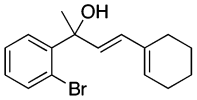
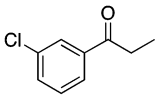
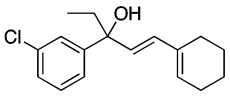
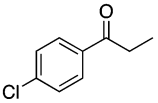
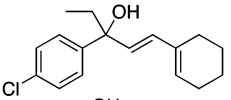
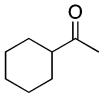
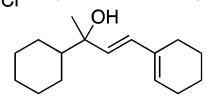
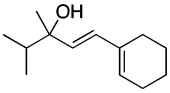


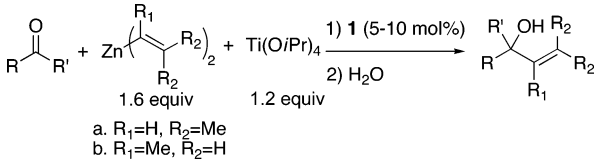
Table 4. Asymmetric Dienylation of Acyclic Ketones with (*R*,*R*)-**1**

entry	substrate	product	ee[b] (yield[a]) [config]
1			89 (89) [*S*]
2			92 (92)
3			87 (93)
4			89 (68)
5			94 (88)
6			93 (99) [*S*]
7			90 (84)
8			87 (42)
9			89 (85)
10			79 (80)
11			77 (87)
12			42 (68)

[a] Isolated yields. [b] Ee's were determined by GC or HPLC (see Supporting Information).

(56) Fryzuk, M. D.; Bates, G. S.; Stone, C. *J. Org. Chem.* **1991**, *56*, 7201−7211.
(57) Fryzuk, M. D.; Bates, G. S.; Stone, C. *Tetrahedron Lett.* **1986**, *27*.

Scheme 8. Vinylation of Ketones from Divinylzinc Reagents

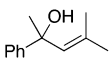
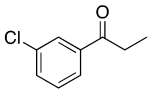
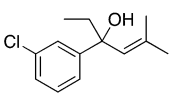
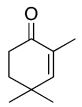
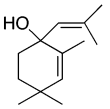
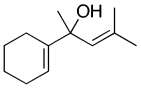


Fortunately, hydrozirconation of the alkene proved to be significantly slower than reaction of the alkyne, resulting in yields of the dienol product as high as 99% (entries 6 and 7).

The three enynes outlined above were used with acetophenone and propiophenone derivatives bearing electron-withdrawing and -donating groups, as illustrated in Table 4. Acetophenone and derivatives bearing electron-donating or -withdrawing substituents gave high enantioselectivities (87−94%, Table 4, entries 1−8). Although the yield of the addition product with 2′-bromoacetophenone was lower (42%), the enantioselectivity remained high (87%, entry 8). It is anticipated that the aryl bromide product in entry 8 could be further elaborated through cross-coupling reactions. A lower enantioselectivity was observed with 4′-chloropropiophenone than with the 3′-chloro derivative (entries 9 and 10). It is not clear at this time what factors are responsible for this difference in enantioselectivity. The dialkyl derivative, cyclohexyl methyl ketone, underwent addition in 77% enantioselectivity and 87% yield, while 3-methyl-2-butanone exhibited only 42% enantioselectivity (68% yield). Despite the high yields and enantioselectivities for most substrates outlined in Table 4, some limitations to the addition of dienyl groups to ketones were found. We were not able to isolate addition products derived from enone substrates. These reactions gave multiple products, likely due to rearrangement reactions similar to those outlined in Scheme 6. To our knowledge, the results in Table 4 constitute the first reported examples of catalytic asymmetric addition of dienyl groups to ketones.

5. Vinylation of Ketones with Preformed Divinylzinc Reagents. Hydrozirconation of terminal alkynes enables access to a wide range of (*E*)-disubstituted allylic alcohols. This method, however, does not permit the generation of trisubstituted allylic alcohols. To evaluate the prospect of asymmetric addition of vinyl groups with substitution patterns that are not accessible via hydrozirconation, we prepared two divinylzinc reagents, bis-(2-methyl-1-propenyl)zinc and bis(1-methylvinyl)zinc. These divinylzinc reagents were prepared from zinc bromide, lithium, and corresponding 1-bromo alkene.[58,59] The application of these divinylzinc reagents in the addition to ketones in the presence of our catalyst was undertaken as outlined in Scheme 8. Employing bis(2-methyl-1-propenyl)zinc with acetophenone, 2,4,4-trimethyl-2-cyclohexenone and 1-acetyl-1-cyclohexene gave excellent enantioselectivities and good yields (Table 5, entries 1, 2 and 5−7). In contrast, 3′-chloropropiophenone gave only 75% ee (97−99% yield). Unfortunately, when bis(1-methylvinyl)zinc was employed under the same reaction conditions, none of the desired addition products were isolated. We believe that the failure of this reagent to undergo addition is due to the increased steric hindrance of the methyl group alpha to the zinc. This result was quite unexpected, because the catalyst readily promotes addition of phenyl groups to ketones.[27,28]

Table 5. Asymmetric Vinylation of Ketones with (*R*,*R*)-**1**

entry	substrate	product	Ligand (mol%)	ee[b] (yield[a]) [config]
1			10	93 (95) [*S*]
2			5	89 (94) [*S*]
3			10	75 (99)
4			5	60 (97)
5			5	94 (86)
6			10	96 (70)
7			5	88 (67)

[a] Isolated yields. [b] The ee's were determined by GC or HPLC (see Supporting Information).

Conclusion

Despite the fact that the catalytic asymmetric vinylation of aldehydes had been introduced in 1992,[36] the analogous addition reaction with ketone substrates remained an unsolved challenge for over a decade. In this manuscript, we report the development and scope of the first catalytic system for the asymmetric addition of vinyl groups to ketones to prepare (*E*)-disubstituted tertiary allylic alcohols in high enantioselectivities and yields. Our procedure employs the hydrozirconation/transmetalation protocol developed in the Wipf laboratories. The resulting vinylzinc intermediates readily add to ketones in the presence of catalyst generated from the bis(sulfonamide) diol ligand **1** and titanium tetraisopropoxide. We have also presented a new procedure for the asymmetric vinylation that requires half the ligand loading, half the titanium tetraisopropoxide, and less dimethylzinc than employed in our initial disclosure.[53] This new protocol results in increased yields and enantioselectivities.

The results of this study also demonstrated that the hydrozirconation, transmetalation, and asymmetric addition to ketones can be conducted in the presence of a variety of functional groups including alkyl chlorides, sulfides, esters, and silyl protected alcohols.

The classes of vinyl groups that can now be added to ketones with our catalyst have been expanded. We have determined that enynes are good substrates for the hydrozirconation, transmetalation, and asymmetric addition protocol. The products of these reactions, enantioenriched tertiary dienols, can be formed with high enantioselectivities and yields. Such compounds were previously inaccessible via catalytic asymmetric methods. Finally, we have demonstrated that trisubstituted allylic alcohols can be prepared from isolated bis(2-methylpropenyl)zinc in high yields and enantioselectivities. With the methods outlined here, a variety of tertiary allylic alcohols are now easily prepared with enantioselectivities and yields suitable for use in asymmetric synthesis.

(58) Shibata, T.; Nakatsui, K.; Soai, K. *Inorg. Chim. Acta* **1999**, *296*, 33−36.
(59) Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608−13609.

Experimental Section

Only representative procedures and characterization of the products are described here. Full details can be found in the Supporting Information. Caution should be exercised when using dialkylzinc reagents.

General Protocol A. Preparation of 4-Cyclohex-1-enyl-2-phenyl-but-3-en-2-ol. To a suspension of Cp_2ZrHCl (155 mg, 0.60 mmol) in CH_2Cl_2 (2.0 mL) under N_2 was added 1-ethynyl-1-cyclohexene (71 μL, 0.60 mmol), and the reaction mixture was stirred for 10 min at room temperature, resulting in a homogeneous yellow solution. The solvent was removed in vacuo, and the residue was dissolved in dry toluene (2.0 mL), cooled to −78 °C, and treated with Me_2Zn (0.30 mL, 2.0 M in toluene, 0.60 mmol) for 10 min. In another Schlenk flask were mixed ligand **1** (13.7 mg, 0.025 mmol, 5 mol %) in 1.0 mL of toluene and $Ti(O^iPr)_4$ (0.22 mL, 1.4 M toluene solution, 0.30 mmol) at room temperature, and the mixture was stirred for 15 min. The resulting solution was added to the Schlenk flask containing the vinylzirconocene and dimethylzinc at −78 °C. After the addition, the solution was warmed to 0 °C, and acetophenone (59 μL, 0.50 mmol) was added. The reaction mixture was warmed to room temperature and stirred under N_2 until TLC showed complete consumption of the ketone. The reaction mixture was quenched with saturated $NaHCO_3$ (5 mL), diluted with EtOAc, filtered through Celite, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 40 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on deactivated silica gel (Et_3N/SiO_2 = 2.5% V/V, hexanes:EtOAc/96:4) to give the product as an oil: $[\alpha]^{20}_D = -1.8$ (*c* 1.37, $CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 1.41−1.52 (m, 4H), 1.54 (s, 3H), 1.95−1.97 (m, 4H), 5.64 (m, 1H), 5.82 (d, J = 15.9 Hz, 1H), 6.32 (d, J = 15.9 Hz, 1H), 7.07−7.10 (m, 1H), 7.18−7.21 (m, 2H), 7.50−7.52 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (C_6D_6, 125 MHz): δ 22.9, 23.0, 25.0, 26.2, 30.3, 74.6, 125.8, 126.9, 128.4, 129.7, 131.5, 133.3, 135.5, 148.2 ppm. IR (neat): 3424, 3026, 2929, 2860, 1714, 1669, 1492, 1445 cm^{-1}. HRMS *m*/*z* 228.1509 [M^+; calcd for $C_{16}H_{20}O$: 228.1514].

General Procedure B. Preparation of 4-Methyl-2-phenyl-pent-3-en-2-ol. Ligand **1** (27.3 mg, 10 mol %) was weighed into the well-dried Schlenk flask and loaded into the drybox. The bis(2-methyl-1-propenyl)zinc reagent (140 mg, 0.8 mmol) was weighed under N_2 and combined with 2 mL of toluene, followed by titanium(IV) isopropoxide (0.43 mL, 0.60 mmol, 1.4 M toluene solution). After the reaction mixture was stirred at room temperature for 10 min, acetophenone (59 μL, 0.50 mmol) was added neat. The flask was sealed and removed from the drybox. The reaction mixture was stirred at room temperature until TLC showed completion consumption of the ketone. The reaction was then quenched with H_2O, extracted into CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on deactivated silica gel (Et_3N/SiO_2 = 2.5% V/V, hexanes:EtOAc/95:5) to provide the product as an oil: $[\alpha]^{20}_D = -5.0$ (*c* 1.17, $CHCl_3$). ^{1}H NMR (C_6D_6, 500 MHz): δ 1.39 (s, 3H), 1.48 (s, 3H), 1.55 (s, 3H), 1.69 (br, 1H), 5.62 (s, 1H), 7.06 (t, J = 7.4 Hz, 1H), 7.19 (dd, J = 7.6, 7.5 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (C_6D_6, 125 MHz): δ 19.1, 26.7, 34.1, 73.8, 125.6, 126.4, 128.2, 133.2, 136.1, 149.8 ppm. IR (neat): 3434, 3025, 2971, 2923, 1663, 1491, 1446, 1374 cm^{-1}. HRMS *m*/*z* 158.1091 [$(M - H_2O)^+$; calcd for $C_{12}H_{14}$: 158.1095].

Acknowledgment. We thank Dr. Celina García for preliminary experiments involving the Oppolzer hydroboration method and Dr. Aaron Maestri for his help preparing divinylzinc reagents. This work was supported by the NIH (GM58101). We also thank Akzo Nobel for a gift of dialkylzinc reagents. This manuscript is dedicated to our colleague Prof. Amos B. Smith, III, on the occasion of his 60th birthday. His leadership in synthesis and his service to the organic community have been exemplary.

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

JA0425740