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Highly Diastereoselective Addition of Cinnamylzinc Derivatives to α-Chiral Carbonyl Compounds

Guillaume Dunet, Peter Mayer, and Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-Universität, Butenandtstrasse 5-13, 81377 München, Germany

paul.knochel@cup.uni-muenchen.de

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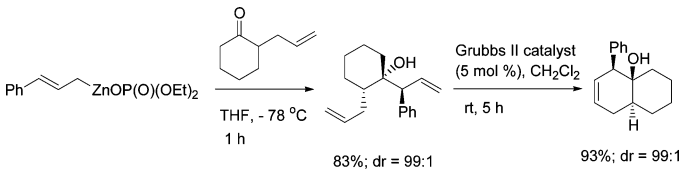
ABSTRACT



Cinnamylzinc reagents react with cyclic and acyclic α-chiral ketones under very mild conditions (–78 °C, 1 h), yielding the corresponding homoallylic alcohols bearing three adjacent stereocenters with high diastereoselectivity. An extension of this reaction to enantioenriched α-chiral ketones is also described.

The stereoselective formation of a carbon−carbon bond is of greatest importance in asymmetric synthesis. Especially challenging is the stereoselective generation of quaternary centers.[1] This can nonetheless be achieved by the addition of allyl metals to carbonyl derivatives.[2] Although allylic lithium and magnesium reagents display a high reactivity, they are unstable and their synthesis can be difficult.[3] Recently, we have shown that allylic zinc reagents offered a good alternative.[4] They can be readily prepared from the corresponding allylic chlorides or phosphates via a LiCl-mediated direct zinc insertion in high yields, and they react diastereoselectively with carbonyl derivatives under very mild conditions (−78 °C, 1 h). Herein, we wish to report that allylic zinc reagents add also to α-chiral ketones, leading to the corresponding homoallylic alcohols bearing three adjacent stereocenters in a highly diastereoselective manner (Table 1 and Scheme 1). Thus, when cinnamylzinc phosphate (**1a**) was reacted with 2-methylcyclohexanone (**2a**) at −78 °C, the reaction was complete after 1 h and the homoallylic alcohol **3a** was isolated in 90% yield as a single diastereoisomer (dr = 99:1; Scheme 1).[5]

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(2) For allylmetal additions, see: (a) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 11. (c) *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, E21 ed.; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3. (d) Yasuda, M.; Hirata, K.; Nishino, M.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13442. (e) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827. (f) Li, S. W.; Batey, R. A. *Chem. Commun.* **2004**, 1382. (g) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1865. (h) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

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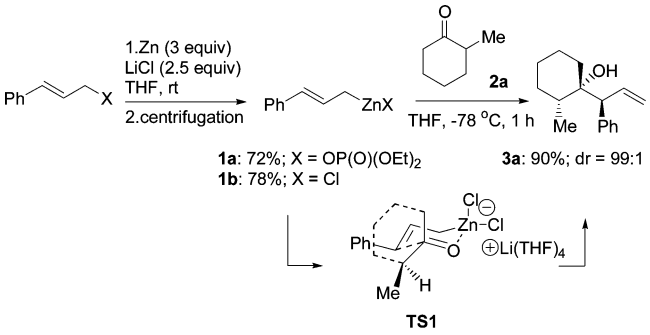
Table 1. Reaction of Cinnamylzinc Reagents[a] with Cyclic α-Chiral Ketones

entry	allylzinc reagent	ketone of type **2**	product of type **3**[b]	yield (%)[c]
1	**1a**	**2b**	**3b**: dr = 99:1	87
2	**1a**	**2c**	**3c**: dr = 99:1	83[d]
3	**1a**	**2d**	**3d**: dr = 98:2	90
4	**1a**	**2e**	**3e**: dr = 99:1	73
5	**1b**	**2f**	**3f**: dr = 99:1	87
6	**1a**	**2g**	**3g**: dr = 98:2	92[d]
7	**1a**	**2h**	**3h**: dr = 99:1	26
8	**1a**	**2i**	**3i**: dr = 99: 1	75
9	**1c**: X = OP(O)(OEt)$_2$	**2b**	**3j**: dr = 86:14	90

[a] Unless stated otherwise, all reactions were carried out with 1 mmol of ketone and 1.2 mmol of allylic zinc reagent at −78 °C for 1 h. [b] The dr was determined by NMR. [c] Isolated yield of analytically pure product. [d] Structure determined by X-ray analysis.

This reaction could then be extended to various α-chiral cyclohexanones, regardless of the substitution pattern in the α-position of the keto function. Thus, α-methoxycyclohexanone (**2b**) reacted smoothly with **1a**, leading to the corresponding homoallylic alcohol (**3b**) in 87% yield and dr = 99:1 (entry 1 of Table 1) within 1 h at −78 °C. Likewise, larger substituents such as an α-acetoxy or an α-benzyloxy group led to the corresponding homoallylic alcohols **3c** and **3d** in 83−90% yield and high diastereoselectivities (entries 2 and 3). Similarly, other heteroatom-substituted cyclohexanones reacted smoothly with reagents **1a** and **1b**. Thus, the chloro- and thiophenyl-substituted homoallylic alcohols (**3e** and **3f**) were both isolated with dr > 98:2 (entries 4 and 5). Under the same conditions, 3-(2-oxocyclohexyl)propionitrile (**2g**) reacted with allylzinc reagent **1a**, affording within 1 h at −78 °C compound **3g**, whose structure was confirmed by X-ray analysis (92%; dr = 99:1; entry 6).[6] Interestingly, when 2-phenylcyclohexanone (**2h**) was reacted with cinnamylzinc phosphate (**1a**) under the same conditions, the corresponding homoallylic alcohol (**3h**) was isolated in 26% yield (dr = 98:2; entry 7). This may be explained by the competitive deprotonation of the benzylic proton α to the keto function.[7] Similarly, 2-methylcyclopentanone (**2i**) led to the alcohol **3i** in 75% as a single diastereoisomer when reacted with **1a** (dr = 99:1; entry 8). The substitution pattern on the allylic system is important, and a decreased diastereoselectivity was observed when the substituted allylic reagent **1c** was reacted with 2-methoxycyclohexanone (**2b**), leading to the alcohol **3j** in 90% yield with dr = 86:14 (entry 9).

Scheme 1. Diastereoselective Addition of Cinnamylzinc Reagents to α-Chiral Ketones



The selectivity observed in this reaction can be rationalized by considering a cyclic chair-like transition state (**TS1**), where the allylic zinc reagent approaches from the sterically less crowded side (opposite side of the methyl group, as depicted in Scheme 1).

This addition proved to be a valuable tool to build polycyclic systems. Thus, when 2-allylcyclohexanone was added to cinnamylzinc phosphate (**1a**), the alcohol **3k** was obtained in 83% yield as a single diastereoisomer (dr = 99:1). Subsequent metathesis[8] with Grubbs II catalyst[9] (5 mol %) led to the bicyclic alcohol **4** in 93% yield, whose structure was confirmed by X-ray analysis (Scheme 2).

Likewise, we have prepared spiro-tetrahydrofurans in a two-step procedure starting from the homoallylic alcohols **3b** and **3d** (Scheme 3). After a hydroboration−oxidation

(5) When cinnamylzinc chloride (**1b**) was reacted with **2a**, the alcohol **3a** was isolated in 97% yield and dr = 99:1.

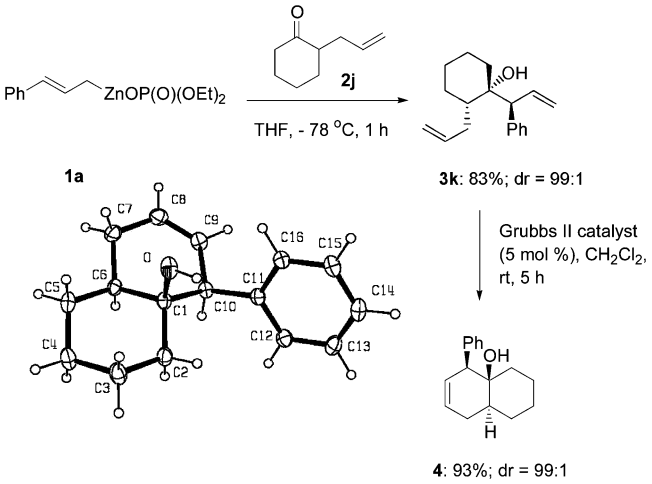
(6) Crystallographic data for compounds **3c** (CCDC 664517), **3g** (CCDC 664518), **4** (CCDC 664519), **6b** (CCDC 664520), and **8** (CCDC 664521) are available free of charge via www.ccdc.cam.ac.uk/data-request/cif.

(7) Most of the ketone remained unreacted (GC analysis).

(8) For a review on ring-closing metathesis, see: Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(9) (a) Trnka, T. M; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

Scheme 2. Synthesis of Bicyclic Alcohol **4**



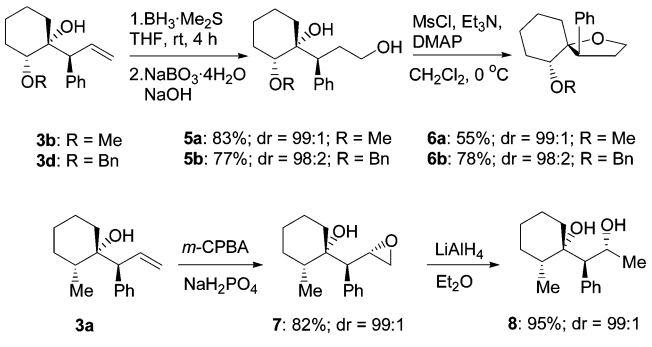
sequence, the corresponding diols **5a** and **5b** were cyclized by the action of MsCl in the presence of Et_3N, leading to the spiro-compounds **6a** and **6b** in 55−78% yield.

Finally, the prepared alcohols were found to undergo a selective epoxidation directed by the free OH group.[10] Thus, the homoallylic alcohol **2a** was treated with *m*-CPBA to yield the corresponding epoxide **7** in 82% yield as a single diastereoisomer. Subsequent $LiAlH_4$-mediated opening of the epoxide led to the diol **8**, bearing four contiguous stereocenters with a defined configuration (the structure of **8** was confirmed by X-ray analysis).

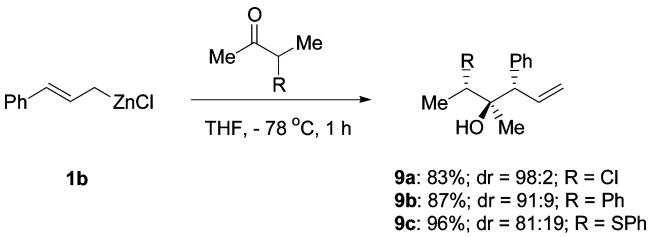
The reaction of allylic zinc reagents with acyclic α-substituted ketones was also studied. Thus, cinnamylzinc chloride (**1b**) was treated with 3-chlorobutan-2-one in THF at −78 °C. After 1 h, the homoallylic alcohol **9a** was isolated in 83% yield as a single diastereoisomer (dr ≥ 98:2; Scheme 4).

When others groups, such as Ph or SPh, were used as substituents, the addition reaction afforded the corresponding homoallylic alcohols with lower selectivity. Thus, the alcohol **9b** was isolated in 87% yield (dr = 91:9). Under the same conditions, the thiophenyl alcohol **9c** was obtained in almost quantitative yield as a mixture of two diastereoisomers (96%; dr = 81:19).

Scheme 3. Synthesis of Spiro-Compounds **6a**,**b** and Diol **8**

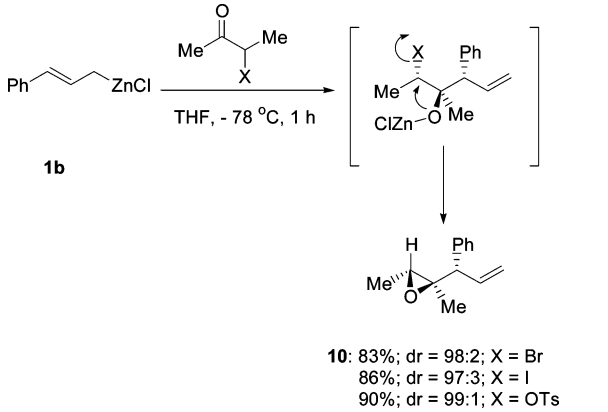


Scheme 4. Reaction of Cinnamylzinc Reagents with Acyclic α-Chiral Ketones



Interestingly, when other 3-halobutan-2-ones were reacted with cinnamylzinc chloride (**1b**) under the same reaction conditions, the corresponding homoallylic alcohols were not isolated; instead, epoxide **10** was obtained diastereoselectively. Likewise, 3-tosyloxybutan-2-one led to epoxide **10** when reacted with cinnamylzinc chloride (**1b**; Scheme 5).

Scheme 5. Synthesis of Epoxide **10**



In this case, the observed selectivity can be explained by considering the Cornforth model.[11]

This diastereoselective addition could then be applied to enantioenriched α-chiral ketones, affording the corresponding homoallylic alcohols without loss of stereochemistry. Thus, when (2*S*)-2-methoxycyclohexanone[12] ((2*S*)-**2b**; 94% ee) was treated with cinnamylzinc chloride (**1b**) at −78 °C for 1 h, the corresponding alcohol (2*S*,1*R*,1′*S*)-**3b** was obtained in 81% yield (dr = 99:1; 94% ee, Scheme 6).

Likewise, the reaction of (3*R*)-3-tosyloxybutanone[13] with **1b** led to the enantioenriched epoxide **10**, which, upon treatment with $LiAlH_4$, afforded the homoallylic alcohol **11** in good yield (87%; dr = 99:1; 99% ee; Scheme 7). This

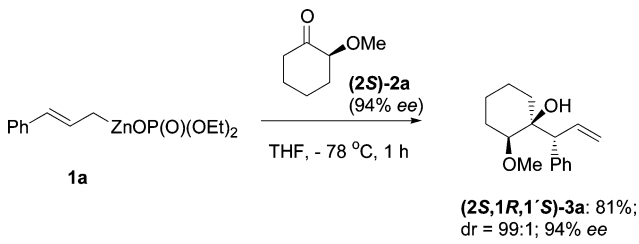
(10) See: Houk, K. N.; Liu, J.; DeMello, N. C; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147.

(11) (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (b) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761. (c) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920.

(12) Prepared by the PDC oxidation of the commercially available (2*S*)-methoxycyclohexan-(1*S*)-ol.

(13) Prepared from the commercially available (2*R*,3*R*)-butan-2,3-diol in a two-step sequence: monotosylation and PDC oxidation.

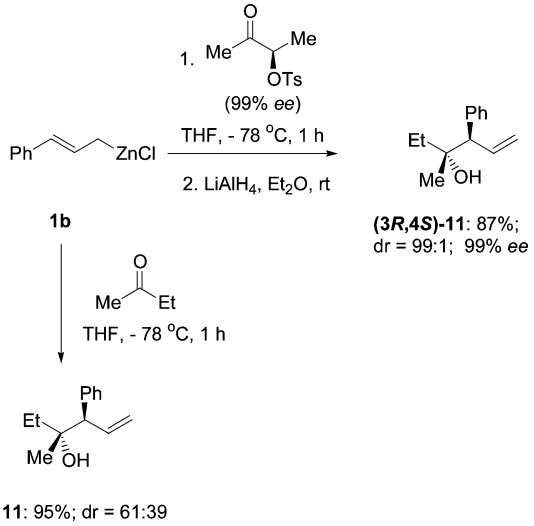
Scheme 6. Synthesis of Enantioenriched Homoallylic Alcohol **3a**



result contrasts with the direct reaction of butanone with cinnamylzinc chloride (**1b**) that displays a poor diastereoselectivity (dr = 61:39), showing the advantage of our approach.

In summary, we have shown that cinnamylzinc derivatives add to various cyclic and acyclic α-chiral ketones, affording the corresponding homoallylic alcohols bearing three contiguous stereocenters with high diastereoselectivity.[14,15] These alcohols proved to be a valuable tool to achieve the synthesis of complex polycyclic compounds in a stereocontrolled manner. This allyl metal addition was then applied to enantioenriched ketones, leading to the corresponding homoallylic alcohols with retention of stereochemistry. Extensions of this method are currently underway in our laboratories.

Scheme 7. Synthesis of Enantioenriched Homoallylic Alcohol **11**



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Note Added after ASAP Publication. Products **3b**−**k** in Table 1 and Scheme 2 contained an extra carbon in the version published ASAP December 8, 2007; the corrected version was published ASAP December 12, 2007.

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

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(14) Preparation of cinnamylzinc chloride (**1a**): LiCl (1 g, 25 mmol) was placed in a nitrogen-flushed Schlenk flask and dried 3 min at 450 °C under high vacuum (0.1 mbar). The operation was repeated before zinc dust (2 g, 30 mmol) was added. The mixture was heated to 450 °C for another 3 min under high vacuum. THF (5 mL) was subsequently added, and the zinc was activated with DBE (0.1 mL) and TMSCl (0.05 mL). A solution of cinnamyl chloride in THF (15 mL) was subsequently added at 25 °C, and the suspension was further stirred at this temperature for 1 h. After centrifugation, the zinc species was titrated via iodolysis.

(15) **Typical Procedure**: Preparation of 2-methyl-1-(1-phenylallyl)-cyclohexanol (**3a**): A solution of the 2-methylcyclohexanone (450 mg, 4 mmol) in THF (4 mL) was added dropwise to a solution of cinnamylzinc phosphate (**1a**, 4.8 mmol, 1.2 equiv) at −78 °C. The resulting solution was further stirred at this temperature for 1 h. The reaction was subsequently quenched with water (1 mL) and extracted several times with diethyl ether. The organic phases were combined, dried over $MgSO_4$, and concentrated to afford a crude product. Purification by flash chromatography (eluent: pentane/ether = 8:2 + 1% Et_3N) provided the pure compound **3a** (824 mg, 90%) as a colorless oil (dr = 99:1).