Zirconium-Catalyzed Asymmetric Carbomagnesation[1]

James P. Morken, Mary T. Didiuk,[2a] and
Amir H. Hoveyda*,[2b]

Department of Chemistry, Merkert Chemistry Center
Boston College, Chestnut Hill, Massachusetts 02167

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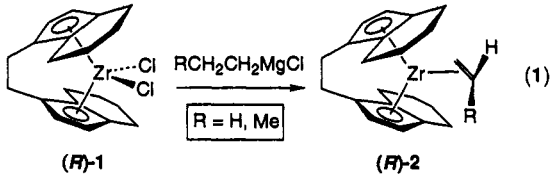
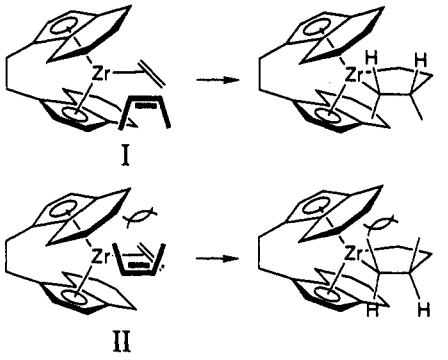
Development of catalytic asymmetric reactions stands as one of the most important objectives in modern chemical synthesis. The ubiquitous nature of carbon–carbon bonds renders catalytic carbon–carbon bond formation of particular value. Regio- and stereoselective zirconocene-catalyzed addition of alkylmagnesium halides to alkenes,[3] a process that has been under extensive study in our laboratories,[4] falls into the latter category of transformations.[5] From the outset, we realized that if the union of an unactivated alkene and a Grignard reagent were to be effected in an enantioselective fashion, a useful catalytic asymmetric carbon–carbon bond-forming reaction would be at hand. Herein, we report the results of our preliminary investigations in the area of asymmetric catalytic carbomagnesation.

To initiate our studies, we selected ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride ([(EBTHI)$ZrCl_2$])[6] (**1**) as the chiral catalyst. Treatment of **1** with alkylmagnesium halides leads to the formation of the derived zirconocene–alkene complex (e.g., **2**),[7] which is efficient in inducing carbomagnesations (eq 1).



With the structurally simplest complex ((*R*)-**2** with R = H), examination of molecular models indicates that reaction with a *cis*-disubstituted olefin should afford high enantiofacial selectivity. As shown below, one mode of addition (I) would lead to the intermediate zirconacyclopentane without unfavorable steric interactions, whereas reaction through the alternative enantioface is hindered by the cyclohexyl unit of the tetrahydroindenyl ligand **II**.



Our mechanistic investigations[4c] illustrate that disubstituted olefins are not sufficiently reactive in catalytic carbomagnesations, unless either ring strain is incorporated into the substrate or a neighboring heteroatom is able to facilitate carbometalation. In the latter case, reaction appears to proceed via a substrate–zirconate complex (a biszirconocene intermediate). Moreover, due to the inductive effect of an adjacent heteroatom, *direct* metallacyclopropane addition to the alkene can be facilitated, presumably since the developing electron density at the incipient C–Zr bond is stabilized by the electron-withdrawing substituent. Within this context, stoichiometric addition of $Cp_2Zr(H_2C{=}CH_2)$ to allylic ethers occurs with >95:5 regioselectivity in favor of the head-to-head metallacyclopentane (C–Zr bond adjacent to the C–O bond).[8] Initial studies, with (*R*)-**1** as catalyst, showed that reactions of disubstituted olefins that contain a homoallylic heteroatom are unfavorably sluggish, probably because formation of the corresponding bimetallic intermediate is sterically too demanding.[7] Therefore, to study asymmetric carbomagnesation, we opted for *cis*-disubstituted allylic ethers where the inductive effect would be able to enhance reactivity.

Treatment of cyclic olefins with 5 equiv of EtMgCl or *n*-PrMgCl in the presence of 10 mol % (*R*)-**1** at 25 °C for 12 h affords the carbomagnesation products in good yield and excellent enantioselectivity (Table I).[9] The purity of the chiral catalyst was determined by the ^{1}H NMR analysis of the derived bis(*O*-acetyl (*R*)-mandelate) derivative.[10] Accordingly, we employed catalyst batches where the minor diastereomer was not within the limits of detection (calibrated <2.5%, 300-MHz ^{1}H NMR). Similar to cyclic ether **3**, where homoallylic alcohol **4** is formed enantioselectively, cyclic amine **7** provides dialkylamine **8** with similar levels of enantiocontrol (>95%, entry 3).[11] Ethylmagnesation of dihydropyran **9** (entry 4) occurs efficiently and regioselectively,[8] whereas the corresponding propylmagnesation

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(2) (a) Clare Boothe Luce Graduate Fellow. (b) NSF National Young Investigator, 1992–1997; Eli-Lilly Grantee, 1992–1994; American Cancer Society Junior Faculty Research Awardee, 1993–1995.

(3) (a) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR Ser. Khim.* **1983**, *32*, 218–220. (b) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M.; Kukovinets, A. G.; Khalilov, A. M. *Iz. Akad. Nauk SSSR Ser. Khim.* **1983**, *32*, 2053–2060. (c) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43–51, and references cited therein. (d) Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Mulukhov, R. R.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1989**, *38*, 207–208. (e) Dzhemilev, U. M.; Sultanov, R. M.; Gaimaldinov, R. G.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1991**, *40*, 1388–1393.

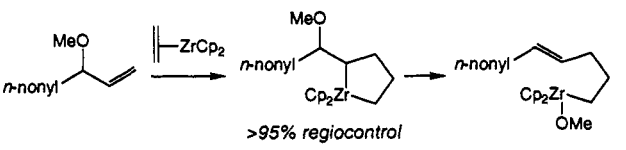
(4) (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079–5080. (b) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950–8952. (c) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z.-M. *J. Am. Chem. Soc.* **1992**, *114*, 6692–6697.

(5) For related studies, see: (a) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268. (b) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268–6270. (c) Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797–6800. (d) Wischmeyer, U.; Knight, K. S.; Waymouth, R. M. *Tetrahedron Lett.* **1992**, *33*, 7735–7738.

(6) Wild, F. R. W. P.; Wasiucionek, H.; Huttner, G.; Brintzinger, H. *J. Organomet. Chem.* **1985**, *288*, 63–67.

(7) Hoveyda, A. H.; Morken, J. P. *J. Org. Chem.*, in press. We assume that the complex derived from *n*-PrMgCl is as shown (unfavorable steric interactions are minimized). For a geometrically related zirconocene–imine complex, see: Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321–2322.

(8) In contrast, carbomagnesation with homoallylic alkoxides and ethers, where the inductive effect is greatly diminished, does not result in any addition product. Houri, A. F.; Didiuk, M. T.; Xu, Z.-M.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.*, in press.



(9) Catalytic carbomagnesation of substrates shown in Table I is faster than that of the alkene product. For example, with **3**, after 6 h, <5% double alkylation is observed. However, after 12 h, significant amounts of the saturated product are detected.

(10) Schafer, A.; Karl, E.; Zsolnai, L.; Huttner, G.; Brintzinger, H.-H. *J. Organomet. Chem.* **1987**, *328*, 87–99.

(11) The corresponding benzylamine (cf. **7**) affords only 15% carbomagnesation product (>95% ee). Carbomagnesations of six-membered amines are significantly slower.

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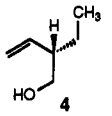
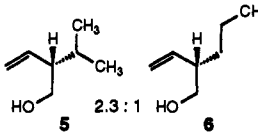
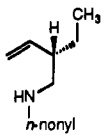
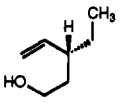
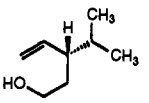
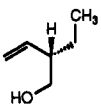
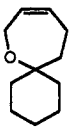
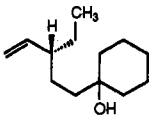
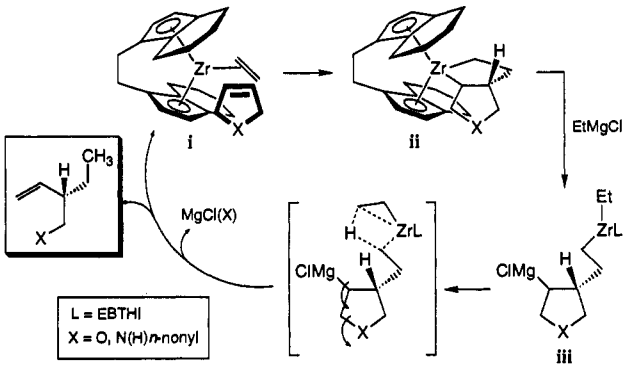
Table I. Enantioselective Carbomagnesation of Cyclic Alkenes[a]

entry	substrate	Grignard reagent	product	ee (%)[b]	yield (%)[c]
1	 3	EtMgCl	 4	>97	65
2	 3	*n*-PrMgCl	 5 2.3 : 1 6	>95	40
3	 7	EtMgCl[d]	 8	>95	75
4	 9	EtMgCl	 10	95	73[e]
5	 9	*n*-PrMgCl	 11	98	40[f]
6	 12	EtMgCl	 4	90	65[e]
7	 13	EtMgCl	 14	92	75[e]

[a] Reaction conditions: 10 mol % (*R*)-**1**, 5.0 equiv of alkylMgCl, THF, 25 °C, 6–12 h. [b] Enantiomeric excess determined by GLC (BETA-DEX 120 chiral column by Supelco, entries 1, 4–6) or analysis of the 300-MHz ^{1}H NMR spectrum of the derived (*S*)-MPTA esters in comparison with authentic enantiomers and authentic racemic material (see supplementary material). [c] Isolated yields of purified products. [d] Reaction run at 4 °C for 12 h. [e] In addition, 10–15% of starting material was recovered. [f] Reaction proceeds to ~50% conversion (60% yield based on recovered starting material).

proceeds to ~50% conversion. However, in the latter case (entry 5), the 2-propyl adduct[4c] **11** is formed with excellent regio- and enantiofacial control. The outcome of carbomagnesation of **9** with *n*-PrMgCl is in contrast to the reaction of **3** with the same Grignard reagent, where a 2.3:1 mixture of 2-propyl (**5**)[4c] and *n*-propyl (**6**) adducts are formed in >95% enantioselectivity. It is plausible that in the reaction of the more reactive **3**, addition of alkene to the more substituted C–Zr bond of **2** (R = Me) is less favored on the basis of steric grounds; therefore, insertion into the usually less reactive primary C–Zr bond is observed.[12] Entries 6 and 7 of Table I indicate that seven-membered acetals

Scheme I



and ethers[13] are appropriate substrates for enantioselective carbomagnesation as well.

A plausible mechanism for asymmetric carbomagnesation may be proposed on the basis of previous investigations reported from these[4,7,8] and other laboratories (Scheme I).[3,5] Enantioselective insertion of alkene into **2** leads to the formation of **ii**; regiocontrolled cleavage of the zirconacyclopentane by alkylmagnesium halide affords the sterically less hindered primary bis((tetrahydroindenyl)alkyl)zirconium chloride **iii**. Regeneration of **2** and elimination of the magnesium halide salt results in the observed product. Formation of the 2-propyl adduct from *n*-PrMgCl is congruent with extant reports,[4c] and the regioselective insertion of zirconacyclopropane in six- and seven-membered ring ethers (where the C–Zr bond is formed proximal to the oxygen atom) can be explained according to the aforementioned influence of the electron-withdrawing group on the formation of the metallacyclopentane.

In summary, a highly enantioselective coupling of EtMgCl and *n*-PrMgCl with readily available cyclic alkenes is reported. Since the resulting products contain the easily functionalizable alkene and alcohol moieties, they can be employed in the preparation of other useful chiral synthons. Further examination of the catalytic, asymmetric carbomagnesation and studies in connection to issues of kinetic resolution are in progress and will be reported shortly.

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Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products (11 pages). Ordering information is given on any current masthead page.

(12) With unsymmetrical zirconocene–alkene complexes, insertion preferably occurs at the more substituted C–Zr bond, see: (a) Reference 3c. (b) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521–3523. It is noteworthy that addition of *n*-PrMgCl to **3**, catalyzed by Cp_2ZrCl_2, affords racemic **5** exclusively.

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