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# Olefins Turned Alkylating Agents: Diastereoselective Intramolecular Zr-Catalyzed Olefin Alkylations

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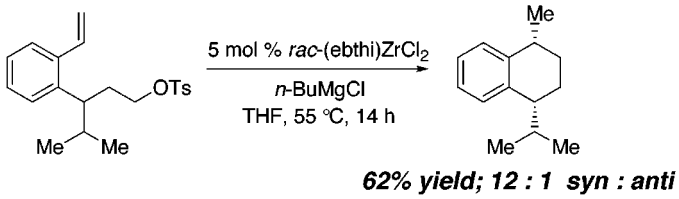
## ABSTRACT




***62% yield; 12 : 1 syn : anti***

**The first examples of intramolecular Zr-catalyzed electrophilic alkylation of aryl olefins are disclosed. Substituted carbo- and heterocycles are prepared efficiently and diastereoselectively.**

During the past several years, research in these laboratories has involved the design and development of various catalytic regio- and stereoselective protocols for alkylations of olefins.[1,2] Investigations in connection to reactions of activated alkenes, such as α,β-unsaturated enones,[3] allylic acetals,[4] or phosphates,[5] have benefited from precedence regarding fundamental reactivity. In contrast, studies on transformations of unactivated olefins[1] typically require identification of less appreciated reactivity profiles. We have thus been able to develop efficient and highly selective Zr-catalyzed intermolecular alkylations of allylic and homoallylic alcohols and ethers, where reactions proceed via metalacyclopentane intermediates. However, various limitations, such as the inability of Grignard reagents other than ethylmagnesium halides to undergo efficient addition,[6] have led us to seek alternative and more general strategies for catalytic alkylations of unactivated alkenes.[7] We have accordingly been involved in the development of Zr-catalyzed electrophilic olefin alkylations. These processes effect net coupling of an olefin and common electrophiles such as alkyl halides and tosylates (Scheme 1).[8,9] In these catalytic electrophilic

(1) For selected examples of diastereoselective Zr-catalyzed olefin alkylations, see: (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079−5080. (b) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692−6697. (c) Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614−6624. For selected examples of Zr-catalyzed enantioselective olefin alkylations, see: (d) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6697−6698. (e) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123−3124. (f) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291−4298. (g) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351. (h) Adams, J. A.; Heron, N. M.; Koss, A. M.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 854−860.

(2) For reviews on stereoselective alkylations of olefins, see: (a) Hoveyda, A. H.; Heron, N. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 431−454. (b) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535−544.

(3) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (b) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* In press.

(4) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650.

(5) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460.

(6) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097−7104.

(7) For efficient and enantioselective Zr-catalyzed additions of various alkylaluminum reagents to unactivated alkenes, see: (a) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771−10772. (b) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577−1578. (c) Kondakov, D. Y.; Wang, S.; Negishi, E. *Tetrahedron Lett.* **1996**, *37*, 3803−3806. (d) Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713−1716. (e) Wipf, P.; Ribe, S. *Org. Lett.* **2001**, *3*, 1503−1505.

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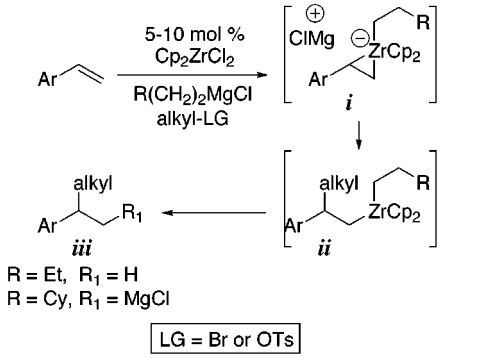
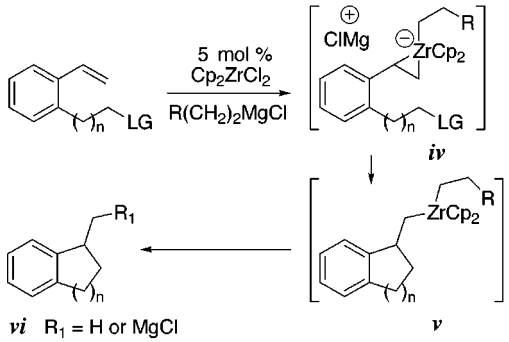
**Scheme 1**

■ ***Zr-Catalyzed Intermolecular Electrophilic Alkylation***




■ ***Zr-Catalyzed Intramolecular Electrophilic Alkylation***

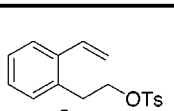
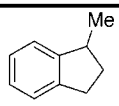
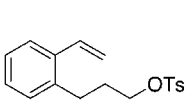
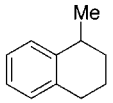
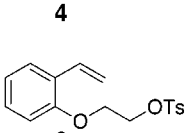
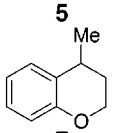
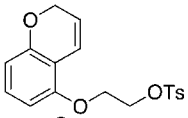
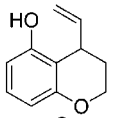



alkylations, the C−C $\pi$ system is rendered highly nucleophilic through association with the transition metal catalyst (cf. ***i***, Scheme 1). It is thus the alkyl group of the electrophile that becomes incorporated within the product structure (vs the alkyl group of the Grignard reagent); the role of the Grignard reagent is only to generate a potent nucleophile in the form of a reactive zirconate (cf. ***i***, Scheme 1). To enhance the synthetic utility of the catalytic electrophilic alkylations, we recently introduced protocols that afford the more versatile alkylmagnesium products ($R_1$ = MgCl in ***iii***, Scheme 1) instead of the corresponding branched alkanes ($R_1$ = H in ***iii***, Scheme 1);[8b] these studies were guided by various key mechanistic data.

A potential advantage of the Zr-catalyzed electrophilic alkylation is that it may be carried out in an intramolecular manner (formation of ***v*** via ***iv***, Scheme 1). This strategy would provide a unique catalytic pathway for the synthesis of carbo- and heterocyclic structures. Moreover, the enhanced structural organization inherent in intramolecular reactions may allow for effective relay of asymmetry. We now report the first examples of Zr-catalyzed intramolecular electrophilic alkylations of aryl olefins; the first diastereoselective examples of this new catalytic alkylation process are also disclosed. These catalytic C−C bond-forming reactions are efficient and provide a new route for the stereoselective synthesis of a range of polycyclic structures.

As illustrated in entry 1 of Table 1, treatment of unsaturated tosylate **2** with 5 mol % of $Cp_2ZrCl_2$ (**1**) and 5 equiv of EtMgCl (55 °C, THF) leads to the formation of carbocycle **3** in 70% isolated yield. The catalytic C−C bond formation can be used to synthesize six-membered carbo- and heterocycles as well. Zr-catalyzed conversion of unsaturated tosylates **4** and **6** (entries 2−3, Table 1) under identical conditions affords bicycle **5** and chromane **7** in 87% and 60% isolated yields, respectively. Unsaturated chromene **8** is readily converted to **9** by the Zr-catalyzed process, a transformation that may be viewed as an intramolecular electrophilic allylic substitution.[10]

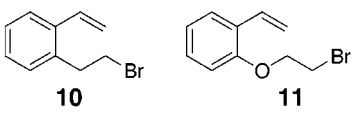
**Table 1.** Zr-Catalyzed Intramolecular Electrophilic Alkylation of Aromatic Olefins[a]

| entry | substrate | product | yield (%)[b] |
|---|---|---|---|
| 1 |  **2** |  **3** | 70 |
| 2 |  **4** |  **5** | 87 |
| 3 |  **6** |  **7** | 60 |
| 4 |  **8** |  **9** | 77 |

[a] Conditions: 5 mol % of $Cp_2ZrCl_2$ (**1**), 5 equiv of EtMgCl, THF, 55 °C, 3.5 h (entries 1−3); 5 mol % of **1**, 2 equiv of *n*-BuMgCl, THF, 55 °C, 14 h (entry 4). [b] ≥95% conv in all cases, determined by analysis of $^1$H NMR spectra of unpurified product mixtures. Isolated yields after silica gel chromatography.

Several issues regarding the data shown in Table 1 merit mention: (1) In the absence of catalyst, none of the tosylates undergo any form of alkylation (<2% by $^1$H NMR analysis).

(2) Reactions with the corresponding bromides can lead to the formation of uncatalyzed alkylation products. Thus, subjection of **10**, the corresponding bromide of **2**, to the above conditions but in the absence of **1**, leads to the formation of **3** (60% conversion); with bromide **11** (cf. **6**, entry 3, Table 1), only ∼15% conversion to **7** is observed.[11]



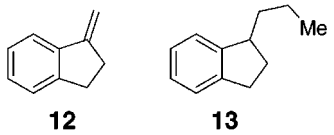

(3) Although alkyl bromides undergo uncatalyzed ring closures, these reactions are noticeably faster in the presence

(8) (a) de Armas, J.; Kolis, S. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 5977−5983. (b) de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2001**, *3*, 2097−2100. For a related report, see: (c) Terao, J.; Watanabe, T.; Saito, K.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, *39*, 9201−9204.

(9) For a recent report on Rh-catalyzed allylation of styrenes, see: Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun.* **2001**, 237−238.

of 5 mol % of **1**. For example, whereas reaction of bromide **11** proceeds to 50% conversion within 3.5 h without catalyst, with 5 mol % of **1**, >95% conversion is observed within the same period of time.

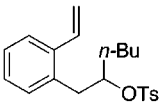
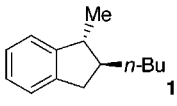
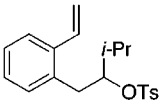
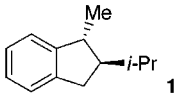
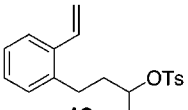
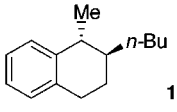
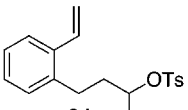
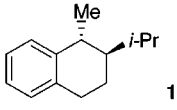
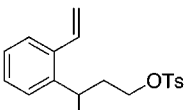
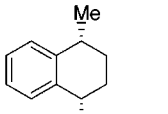
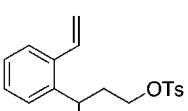
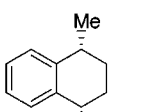
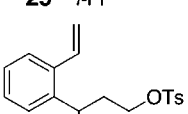
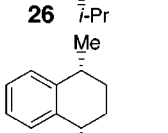
(4) Depending on the substrate, varying amounts of minor byproducts are generated (400 MHz $^1$H NMR analysis). These byproducts are represented by **12**[12] and **13**[13] for the catalytic reaction of **2** (entry 1, Table 1). Thus, 20% of **12** and 10% of **13** are also formed in the catalytic alkylation of **2**. In the intramolecular alkylation of **6**, <2% of the derived exocyclic olefin is observed, but the unpurified reaction mixture contains 8% of the product corresponding to **13** (entry 3, Table 1). No detectable levels of byproducts are formed in reactions of **4** and **8** (entries 2 and 4, Table 1).



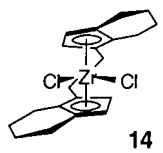

**12** **13**

Next, we began our examination of diastereoselective Zr-catalyzed intramolecular alkylations. As illustrated in entry 1 of Table 2, *treatment of secondary tosylate **15** with 5 mol % of **1** in the presence of 5 equiv of n-BuMgCl leads to the formation of **16** in 68% isolated yield with excellent diastereoselectivity* (>25:1).[14] Although catalytic closure of **17** (entry 3) is facile, indane **18** is obtained with lower stereocontrol (7:1). To improve stereochemical induction, we utilized the sterically more demanding *rac*-(ebthi)$ZrCl_2$ (**14**) as the catalyst.[15,16] As depicted in entry 4, this modification led to the formation of **18** in 68% yield and >25:1 diastereoselectivity. Although the use of **14** as the catalyst leads to high yield and stereoselectivity with **15** as well (entry 2), this strategy does not provide a solution to the lack of stereoselection observed in the otherwise efficient formation of tetrahydronaphthalene **20** (entries 5−6). As illustrated in entries 7−8, similar results are obtained with tosylate **21**, regardless of the catalyst used. It should however be noted that reaction of tosylate **21** (entry 7) can be carried out in the presence of EtMgCl (vs *n*-BuMgCl) without generating any detectable amount of the intermolecular ethylmagnesation product (<2%).[1a]

**Table 2.** Diastereoselective Intramolecular Electrophilic Alkylation of Aromatic Olefins[a]

| entry | substrate | major product | catalyst (mol %) | anti : syn [b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 |  **15** |  **16** | **1** (5) | >25 : 1 | 68 |
| 2 | | | **14** (10) | >25 : 1 | 72 |
| 3 |  **17** |  **18** | **1** (5) | 7 : 1 | 68 |
| 4 | | | **14** (10) | >25 : 1 | 68 |
| 5 |  **19** |  **20** | **1** (5) | 1 : 1 | 87 |
| 6 | | | **14** (10) | 1 : 1 | 73 |
| 7 |  **21** |  **22** | **1** (5) | 1 : 1.3 | 94[d] |
| 8 | | | **14** (10) | 1 : 1.3 | 75 |
| 9 |  **23** |  **24** | **1** (5) | 1 : 6.5 | 85 |
| 10 | | | **14** (5) | 1 : 13 | 62 |
| 11 |  **25** |  **26** | **1** (5) | 1 : 5.5 | 86 |
| 12 | | | **14** (5) | 1 : 11.5 | 66 |
| 13 |  **27** |  **28** | **1** (5) | 1 : 5 | 76 |
| 14 | | | **14** (5) | 1 : 9 | 58 |

[a] Conditions: indicated mol % of $Cp_2ZrCl_2$ (**1**) or *rac*-(ebthi)$ZrCl_2$ (**14**), 5 equiv of *n*-BuMgCl, THF, 55 °C, 3.5 h for **1**, 14 h for **14**. [b] Determined by GLC (CD-GTA column) and $^1$H NMR analysis. [c] Isolated yields after silica gel chromatography. For entries 1−4, the yield also includes 20−25% of the corresponding olefinic product (cf. **12**); <10% of related products observed in entries 5−14. [d] Reaction performed with EtMgCl.




**14**

The Zr-catalyzed alkylations shown in entries 9−14 of Table 2 are synthetically significant, as they allow for effective control of 1,4 relative stereochemistry. Reactions proceed to completion in all cases, and levels of diastereo-

(10) Reaction of **8** is carried out in the presence of *n*-BuMgCl, since use of EtMgCl leads to the formation of substantial amounts of unidentified products. In other cases, either of the two Grignard reagents may be used with similar efficiency.

(11) The major product (~50%) is phenol **i**, formed presumably by generation of the magnesium halide of **11** followed by a $\beta$-alkoxide elimination.


**i**

(12) Exocyclic alkenes such as **12** are formed through $\beta$-hydride abstraction involving the benzylic H through the dialkylzirconocene intermediate. See refs 8a,b for details.

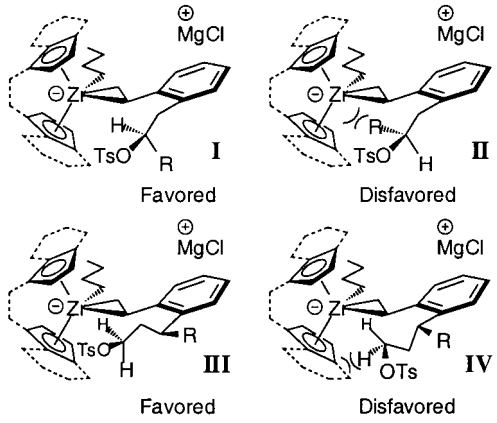
(13) The mechanism for the formation of compounds represented by **13** is not clear at the present time. This may involve catalytic ethylmagnesation of the styrene olefin followed by intramolecular reaction of the resulting benzylic magnesium halide with the neighboring tosylate or bromide.

(14) The stereochemical identity of **16** and **18** was established through comparison with previously reported data. See: Troutman, M. V.; Apella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916−4917.

(15) Reactions are less efficient with lower catalyst loadings. As an example, when **15** is treated with 5 mol % of **14** (THF, 55 °C, 14 h), **16** is isolated in 52% yield.

(16) For a review of the utility of chiral metallocenes in stereoselective synthesis, see: Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1263−1284.

**Scheme 2**[a]




[a] For clarity and ease of depiction, models corresponding to different enantiomers are shown.

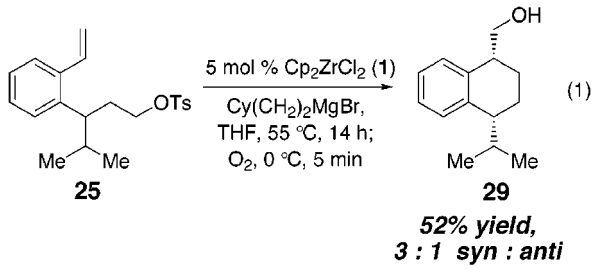
selectivity are improved when (ebthi)$ZrCl_2$ (**14**) is utilized.[17] The stereochemical identity of the major isomer (*syn*) has been established through determination of the X-ray structure of **28** (see Supporting Information).

Although detailed mechanistic studies regarding the intramolecular Zr-catalyzed alkylations have not yet been performed, models illustrated in Scheme 2 offer a plausible rationale for the stereochemical outcomes in Table 2. It may be suggested that, for the formation of five-membered ring products shown in entries 1−4 of Table 2, mode of addition **I** should be favored on steric grounds (vs **II**). A similar argument can be made for the preference of **III** (vs **IV**) in connection to transformations depicted in entries 9−14 of Table 2. These models offer an explanation for the higher degree of stereoselectivity in transformations promoted by **14**; steric interactions with the chiral ligand are more severe in **II** and **IV**. It is however difficult to explain why the formation of six-membered rings in entries 5−8 of Table 2 is nonselective. It should also be noted that these models assume that the intermediate zirconate is alkylated with retention of stereochemistry. Although alkylmetals are typically shown to react with retention,[18] there is as yet no definitive experimental evidence to support this hypothesis in regard to Zr-catalyzed electrophilic alkylations.

(17) Related studies with enantiomerically pure **14** are in progress.

(18) For examples of alkylation of alkylmetals with retention of stereochemistry, see: (a) Jensen, F. R.; Nakamaye, K. L. *J. Am. Chem. Soc.* **1966**, *88*, 3437−3438. (b) Hoffman, R. W.; Holzer, B. *Chem. Commun.* **2001**, 491−492.

In conclusion, we have developed a unique method for efficient formation of a range of aromatic carbo- and heterocycles by stereoselective Zr-catalyzed electrophilic alkylation of olefins. Reactions proceed effectively with $Cp_2ZrCl_2$ and (ebthi)$ZrCl_2$ and provide excellent levels of diastereoselectivity. Many of the products obtained by the present method would be otherwise significantly more difficult to access—particularly in a diastereoselective fashion. Moreover, it is important to note that, as illustrated by the example shown in eq 1, selection of an appropriate




Grignard reagent (to favor Zr−Mg exchange vs $\beta$-hydride abstraction)[8b] can lead to the formation of carbomagnesation products in intramolecular alkylations, thus extending the synthetic potential of these catalytic processes.[19,20] The utility of this class of C−C bond-forming reactions has not yet been extended beyond non-aryl olefins. However, in terms of application to the synthesis of biologically significant molecules, it appears that it is the efficient and selective alkylation of aryl alkenes that will be of notable significance.[21] Applications to total synthesis of medicinally important agents and development of additional catalytic olefin alkylations are in progress.

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**Supporting Information Available:** Complete experimental procedures and spectral and analytical data for all reaction substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For examples where carbomagnesation products are reacted with various electrophiles (other than oxygen), see ref 8b.

(20) Under conditions shown in eq 1, formation of carbomagnesation products is less efficient with (ebthi)$ZrCl_2$ (vs $Cp_2ZrCl_2$). Related studies are in progress.

(21) For two representative examples, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074−9075. (b) Sato, K.; Yoshimura, T.; Shindo, M.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 309−314.