Equimolar amounts of thymidine, uridine, and thymine are bound to the host monolayer at 0.01 M.

The present results establish that thymidine, uridine, and thymine (substrates bearing the imide moiety) are bound to monolayer **1**, in preference to adenosine and adenine. Complementary hydrogen bonds between the diaminotriazine unit and the imide moiety (Figure 2) apparently caused the selective binding. The association constants of thymidine and thymine with monolayer **1** are estimated to be $(2 \pm 1) \times 10^2\ M^{-1}$, by assuming the Langmuir adsorption. This value is comparable to the association constant reported for 1-butylthymidine with diamide pyridine receptors in $CDCl_3$,[19] in spite of very different microenvironments between the two systems. The hydrogen bonding with solvent molecules, albeit weak, produces a serious detrimental effect in this type of host–guest interaction.[20] Therefore, it is surprising to observe efficient hydrogen-bonding interactions at the air–water interface. This effectiveness may be attributed to unique macroscopic properties of the air–water interface and/or cooperative action of organized diaminotriazine units. We have found that other water-soluble substrates (monosaccharides and amino acids) were efficiently bound to host monolayers at the air–water interface.[7,10,11] These molecular recognitions should have important bearing on the related processes occurring at surfaces of the biological molecular system.

(19) The association constants are 90 M^{-1} and 290 M^{-1}, depending on the receptor: Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561.

(20) Schneider, H.-J.; Juneja, R. K.; Simova, S. *Chem. Ber.* **1989**, *122*, 1211.

Stereoselective Formation of Carbon–Carbon Bonds through Metal Catalysis. The Zirconium-Catalyzed Ethylmagnesation Reaction

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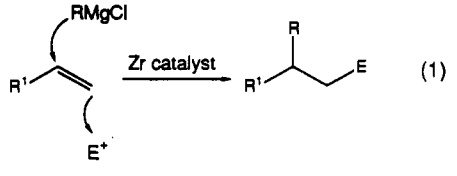
The design and development of stereoselective, catalytic reactions, especially those that effect formation of carbon–carbon bonds, is an important objective in chemical synthesis. In 1983, Dzhemilev reported that Cp_2ZrCl_2 catalyzes the addition of ethylmagnesium halides to simple alkenes (3–40%).[1] This transformation accomplishes a useful and unprecedented task: formation of a carbon–carbon bond by addition of an alkyl Grignard reagent to an unactivated olefin;[2] the initial product may then be employed in further bond-forming processes (eq 1). As part of a program aimed at the development of stereoselective metal-catalyzed reactions, we have examined the utility of the zirconium-catalyzed ethylmagnesation reaction.

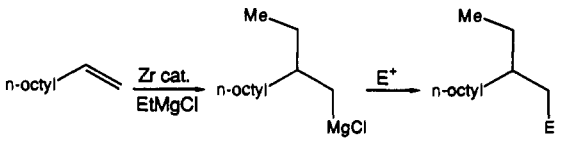


(1)

(1) (a) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 218–220. (b) Dzhemilev, U. M.; Vostrikova, O. S.; Sulmanov, R. M.; Kukovinets, A. G.; Khalilov, A. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 2053–2060. (c) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43–51 and references cited therein. These workers report that ethylmagnesation of 1-octene (acid quench) proceeds in 30% yield at 25 °C (ref 1b), and in 52% yield, but with diminished regioselectivity (7:1), only when the reaction is heated not lower than 60 °C (ref 1a).

(2) For a nickel-catalyzed double alkylation where α,β-unsaturated acetals may serve as substrates, see: Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 366–368.

Scheme I

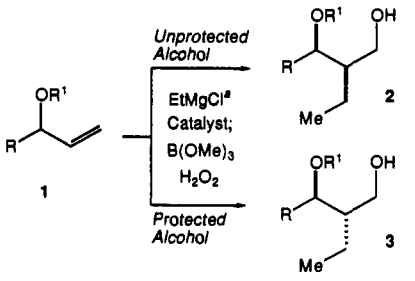


Electrophile	E	Yield
CH_3CHO	$CH(OH)CH_3$	55%
$B(OCH_3)_3$; H_2O_2	OH	60%
NBS	Br	60%
I_2	I	65%

Zr catalyst = Cp_2ZrCl_2, Cp_2ZrBu_2, or Cp_2ZrEt_2

Regioselectivity > 99:1

Table I. Diastereochemical Control in the Ethylmagnesation of Allylic Alcohols and Their Derivatives



substrate	R	R^1	catalyst (mol %)	2:3[b]	% yield[c]
1a	*n*-nonyl	H	Cp_2ZrCl_2 (5)	95:5	70
1b	cyclohexyl	H	Cp_2ZrCl_2 (5)	84:16	20[d]
	cyclohexyl	H	Cp_2ZrBu_2 (25)[e]	67:33	70
1c	*n*-nonyl	Me	Cp_2ZrCl_2 (5)	11:89	80
1d	*n*-nonyl	MEM	Cp_2ZrCl_2 (5)	10:90	53
1e	cyclohexyl	Me	Cp_2ZrBu_2 (5)	4:96	92
	cyclohexyl	Me	Cp_2ZrCl_2 (5)	4:96	60

[a] In all experiments, 3–4 equiv of freshly prepared EtMgCl was used. [b] Ratios were determined through GLC analysis of the corresponding acetonides or formals. [c] Isolated yields of purified products. [d] Sixty percent of the starting material was recovered. [e] Prepared at −78 °C in THF.

Carbometalations of simple monosubstituted alkenes by ethylmagnesium chloride can proceed more effectively than was reported previously.[1] Treatment of 1-decene with 3 equiv of Grignard reagent and 5 mol % Cp_2ZrCl_2 (12 h, 25 °C, Et_2O), followed by addition of 3–5 equiv of either acetaldehyde, B-$(OMe)_3/H_2O_2$ (−78 °C), NBS, or iodine, results in the formation of the addition products in 55–65% yield after silica gel chromatography (Scheme I).[3] *Thus, by a simple one-pot procedure, double alkylation or hydroxyalkylation of an alkene is accomplished in good yield.* In addition, the carbometalation reaction proceeds with excellent levels of regiocontrol (>99:1).[4]

In contrast to earlier reports that electron-withdrawing substituents significantly retard the rate of carbomagnesation,[1b,c] we find a variety of allylic alcohols and ethers to be suitable substrates. As is illustrated in Table I, ethylmagnesation of allylic alcohol **1a** affords the syn diol **2a** with 95:5 diastereoselectivity (70% isolated yield). Reaction of cyclohexyl derivative **1b** is stereoselective but sluggish under these conditions. However, we find that 20 mol % Cp_2ZrCl_2 or Cp_2ZrBu_2 in 50% THF/Et_2O serves well in this case; the desired products are obtained in 70% yield, albeit with diminished diastereoselectivity (67:33, syn:anti). We subsequently discovered that in reactions of allylic alcohols use

(3) The stereochemical identities of all compounds were determined through comparison with authentic materials. All compounds reported herein gave ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), IR, and combustion analysis data consistent with the structures given. See the supplementary material for details.

(4) GLC analysis indicates that the zirconium-catalyzed carbomagnesation of 1-heptene ($EtMgCl$, $B(OMe)_3/H_2O_2$) proceeds with 556:1 regioselectivity. This is contrary to the previous reports that ethylmagnesation of 1-octene occurs with 10:1 regioselectivity (ref 1a).

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Table II. Diastereochemical Control as a Function of Solvent[a]

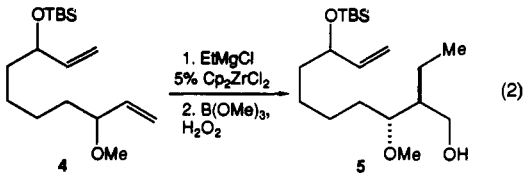
substrate	solvent	2:3	% yield
1a	Et_2O	95:5	70
1a	50% Et_2O/THF	73:27	70
1c	Et_2O	11:89	80
1c	50% Et_2O/THF	11:89	75

[a] Three equivalents of EtMgCl and 5 mol % Cp_2ZrCl_2 were used at 25 °C.

of THF as solvent results in higher yields but with diminution in stereocontrol (vide infra).

Ethylmagnesation of the allylic methyl ether **1c** and the methoxyethoxy ether **1d** affords the monoprotected diols **3c** and **3d** in 80% and 53% yields, respectively; however, it is the anti diastereomer that is formed predominantly with 89:11 and 90:10 selectivity.[5] In further contrast to the carbometalation of allylic alcohols, when the size of the β-alkyl substituent is increased from *n*-nonyl (**1c**) to cyclohexyl (**1e**), with 5 mol % Cp_2ZrCl_2 or Cp_2ZrBu_2 as catalyst, ethylmagnesation proceeds readily and the level of stereocontrol is enhanced to 96:4. Thus, *either syn or anti carbometalation products can be prepared with high stereochemical control, depending on the nature of the neighboring oxygen substituent.* The paucity of highly stereoselective functionalization of terminal alkenes renders such levels of asymmetric induction particularly noteworthy.

The carbomagnesation reaction shows sensitivity to steric encumbrance near the alkene center. Protection of the hydroxyl unit of **1a** as the *tert*-butyldimethylsilyl group completely inhibits the alkene from carbomagnesation; accordingly, carbometalation of diene **4** proceeds with >99% site selectivity and 90:10 stereoselectivity to afford the primary alcohol **5** in 70% isolated yield (eq 2).



(2)

70% yield; 90:10 diastereoselectivity; >99% site-selectivity

The reversal of diastereoselectivity observed with hydroxide (magnesium alkoxide) versus ether substrates is significant and might be attributed to the initial association of the metal alkoxide with the zirconium reagent. A set of observations that support this hypothesis are summarized in Table II. Stereoselectivity in ethylmagnesation of **1a** suffers severely when THF is employed as cosolvent; presumably, since THF is an effective ligand, it adversely affects the chelation of the magnesium alkoxide with the metal.[6] Stereochemical control in the carbometalation of allylic ethers (e.g., **1c**)[7] is not influenced by the presence of THF, and therefore, we project that reactions of these compounds probably do not involve two-point association of the substrate with the transition-metal complex.

A plausible mechanism for the carbometalation process may involve zirconocene ("Cp_2Zr") as the active catalyst. It has been established that decomposition of a dialkylzirconocene (prepared at −78 °C), which occurs upon warming to 25 °C, results in the formation of zirconocene.[8] An alkylmetallocene that has served as a reliable source of "Cp_2Zr" is the corresponding dibutyl derivative; that Cp_2ZrBu_2 is capable of serving as a potent initiator in the ethylmagnesation process indicates that zirconocene is involved in zirconium-catalyzed ethylmagnesations.[9] Formation of the zirconocene–alkene complex and its subsequent alkylation by the Grignard reagent may then lead to the final product.[10] Studies in connection with the further utility of transition-metal-catalyzed carbometalation of alkenes are in progress and will be reported in due course.

Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products (9 pages). Ordering information is given on any current masthead page.

(5) Et_2Mg reacts with **1c** to afford **3c** with similar levels of stereocontrol but at a faster rate (3 h). The higher reactivity of Et_2Mg has been demonstrated by Dzhemilev (see ref 1).

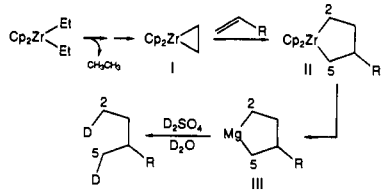
(6) The stereochemical outcome of the carbometalation of alcohols is not influenced by the nature of the metal alkoxide, as the sodium and potassium salts of **1a** afford similarly high levels of stereochemical control (92:8 and 94:6, syn:anti).

(7) With 100% THF, **1a** affords a 67:33 syn:anti ratio of isomers (85%), whereas stereoselectivity remains unaffected in the carbometalation of **1c** (70%).

(8) (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544–2546. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346 and references cited therein.

(9) MeMgCl, unlike EtMgCl, under otherwise identical conditions, affords no desired product. This observation is consistent with the contention that "Cp_2Zr" is the active catalyst, since in the absence of a β-hydride required for elimination, "zirconocene" (the zirconocene source or the alkene–zirconocene complex) cannot form and reaction does not take place. Moreover, Cp_2ZrEt_2 and Cp_2ZrBu_2 (5–10 mol %) fail to catalyze the addition of MeMgCl; rapid ligand exchange leads to the immediate formation of Cp_2ZrMe_2.

(10) In analogy to the zirconium-catalyzed carboalumination of alkenes (Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, A. R.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 207–208), a possible pathway may involve insertion of the alkene into i leading to the formation of ii, followed by ligand exchange to form iii. Where the reaction is quenched with H_3O^+, iii would yield the expected product. However, since the major product arises from trapping of 1 equiv of *other* electrophiles (see Tables I and II), and because <5% deuterium incorporation occurs at C2 (with 1-decene, **1a** and **1c** in Et_2O and Et_2O/THF, ^{13}C NMR analysis), such a mechanism is unlikely. Details of our mechanistic studies will be disclosed in a separate account.



Synthesis of the Core Trisaccharide of Esperamicin: Corroboration of the Proposed Structure for Its Rearrangement Product and Stabilization of the Core Trisaccharide Domain

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The discovery of esperamicin (**1**)[1] and calicheamicin[2] has stimulated interest at many levels.[3-6] The current perception is

(1) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461.

(2) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464.

(3) Synthesis: (a) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S.; Shulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 6890. (b) Schreiber, S. L.; Kiessling, L. L. *Tetrahedron Lett.* **1989**, *30*, 433. (c) Magnus, P.; Bennett, F. *Tetrahedron Lett.* **1989**, *30*, 3637. (d) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. (e) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (f) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626.

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