Tetrahedron Letters, Vol. 33, No. 50, pp. 7735-7738, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Stereoselective Cyclomagnesiation of 1,6-Heptadienes Catalyzed by Zirconocenes: Effects of Substituents, Solvent and Magnesium Reagents

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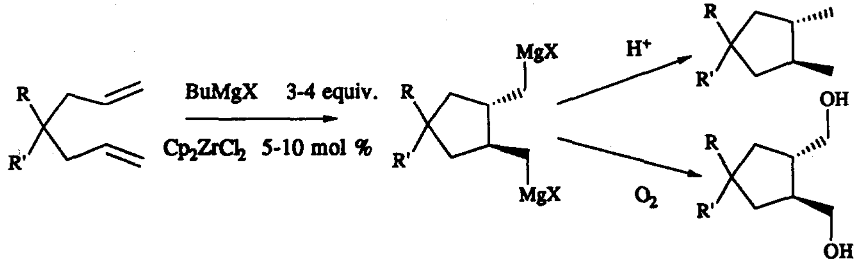
Abstract: Zirconocene dichloride acts as a catalyst precursor for the stereoselective cyclomagnesiation of an array of substituted 1,6-heptadienes in the presence of butylmagnesium chloride to form trans 1,2-(bis)methylmagnesium substituted carbocycles.

Carbocyclic ring systems possessing defined stereochemistry are present in a wide range of natural products. The development of stereoselective techniques for their efficient construction represents a significant synthetic goal. We have recently reported a novel catalytic process in which non-conjugated dienes react with organomagnesium reagents in the presence of a catalyst derived from zirconocene dichloride to yield 1,2-bis(methylmagnesium) substituted carbocyclic rings (eq. 1).[1,2] This reaction accomplishes a transformation similar to the stoichiometric, zirconium-mediated cyclization of non-conjugated dienes developed by Nugent and Negishi,[3] but is *catalytic in zirconium.* As we had previously noted significant differences in the stereoselectivity of the catalytic versus the stoichiometric cyclizations of 1,6-heptadiene, we initiated a series of investigations on the stereoselectivity of these reactions as a function of the reaction parameters. Herein we report studies of the effects of magnesium reagent, substrate, and solvent on the activity and stereoselectivity in the zirconium catalyzed cyclomagnesiation of 1,6-heptadienes.



(1)

The catalytic cyclomagnesiation reactions of heptadiene and octadiene derivatives[4] are sensitive to solvent.[1,2] The reaction proceeds smoothly in solvents such as diethyl ether, diisopropyl ether, or dibutyl ether;[5] more strongly coordinating solvents such as THF significantly inhibit the turnover rates. The cyclization of 9,9-diallylfluorine in diethyl ether at room temperature in the presence of 10 mol% Cp_2ZrCl_2 proceeds to 80% conversion after 9 hours; in contrast, only 30% conversion is observed in THF under these conditions.[6]

In contrast to the stoichiometric reactions, the catalytic cyclomagnesiation reaction will not tolerate unprotected hydroxyl groups. Unprotected 1,6-heptadiene-4-ol, 4,4-dimethyl-1,6-heptadiene-3-ol, diallylether, diallylsulfide and methyl diallylamine did not cyclize under standard conditions, even in the presence of excess Mg reagents.[7] In contrast, tertiary trimethylsilyl ethers, primary or secondary t-butyldimethylsilyl ethers, diallylaniline and acetonides cyclize smoothly to give good yields of cyclized products (Table 1).

Catalytic cyclization of substituted heptadienes are slower than 1,6-heptadiene. The bis($CH_2OTBDMS$) substituted diene requires six days using 10% catalyst to achieve complete conversion at room temperature in diethyl ether. However, cyclomagnesiation in refluxing isopropyl ether gives complete conversion in under three hours without diminished stereoselectivity. A similar enhancement in rate was observed for 4-*t*-butyldimethylsilyloxy-1,6-heptadiene, but in this case the trans selectivity decreased from 79 to 67%.

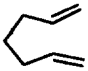
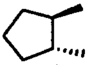
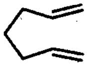
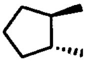
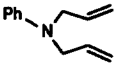
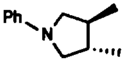
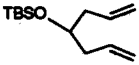
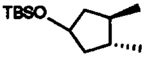
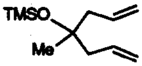
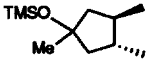
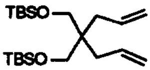
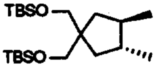
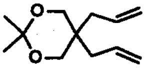
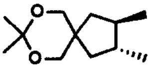
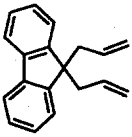
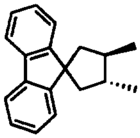
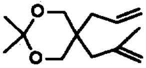
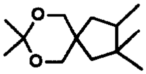
Geminal substitution at the 4-position of the heptadiene substrates increases the trans selectivity of the catalytic cyclization to 93-97% (Table 1). However, the trans selectivity for the catalytic cyclization of the parent 1,6-heptadiene with Bu_2Mg / Cp_2ZrCl_2 (64:36, t:c) in Et_2O is lower than the corresponding stoichiometric cyclization with BuLi or BuMgX / Cp_2ZrCl_2 (X=Br, Cl) in THF or Et_2O.[3,8] Higher trans selectivity (86:14 t:c) is observed with organomagnesium halides (BuMgCl or BuMgBr) than with dibutylmagnesium; nevertheless, the selectivity is still lower than that seen in the stoichiometric reaction with butylmagnesium halides, Bu_2Mg or with BuLi.[3]

Mechanistic studies to be reported elsewhere provide compelling evidence for zirconacyclopentane intermediates for these reactions.[1,2,6] One explanation for the lower selectivity of the catalytic cyclization is that the metallacycles isomerize under the catalytic conditions. Metallacycle formation is known to be reversible;[9] the lower selectivity of the catalytic reactions may reflect the thermodynamic stability of the zirconocene metallabicycles as well as the relative rates of isomerization and transmetallation. The relative thermodynamic stabilities for the heptadiene metallacycles are unknown, but the trans is favored for zirconacycles derived from octadiene.[9a] Catalytic cyclization of 1,7-octadiene at 25°C in ether, followed by hydrolysis affords an 82:18 cis:trans ratio of dimethylcyclohexanes, a ratio similar to that seen in stoichiometric reactions.[3,8] However, catalytic cyclization of 1,7-octadiene at 100°C in dibutyl ether results in a reversal of stereochemistry and yields a 31:69 cis:trans ratio of products. Thus, the stereochemistry of the cyclization will likely depend both on the the kinetic selectivity for the cyclization (which will vary as a function of the substrate and the catalyst) and the rate of metallacycle isomerization. Studies on the mechanism and stereochemistry of these reactions are continuing.

Acknowledgement

We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Table 1. Stereoselectivity in the Cyclization of 1,6-Heptadienes in Ether at Room Temperature

Entry	Substrate	Mg Reagent	time/days	Yld/%	Product	Stereoselectivity/t:c
1		Bu_2Mg	1	94[a]		64:36
2		BuMgCl	1	95[a]		86:14
3		BuMgCl	1	90[b]		33:67
4		BuMgCl	3	79[b]		79:21[c]
5		BuMgCl	3	45[b]		97:3[c]
6		BuMgCl	6	51[b]		93:7
7		BuMgCl	2	87[b]		95:5
8		BuMgCl	2	86[b]		95:5
9		BuMgCl	2	84[b]		

[a] By GC. [b] Isolated yield. [c] Mixtures of minor cis isomers were not separated and therefore the stereochemistry was not determined.

References and Notes.

1. Knight, K.S.; Waymouth, R.M. J. Am. Chem. Soc. **1991**, 113, 6268.
2. For related catalytic reactions involving the coupling of an ethylene moiety derived from ethylmagnesium reagents to terminal olefins see: Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C.J.; Negishi, E.-i. J. Am. Chem. Soc., **1991**, 113, 6266. (b) Hoveda, A.H.; Xu, Z. J. Am. Chem. Soc. **1991**, 113, 5079. (c) Hoveda, A.H.; Xu, Z. Morken, J.P.; Houri, A.F. J. Am. Chem. Soc. **1991**, 113, 8950-8952. (d) Lewis, D.L.; Muller, P.M.;Whitby, R.J.; Jones, R.V.H. Tetrahedron Lett. **1991**, 32,6797-6800. (e) Hoveda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. J. Am. Chem. Soc. **1992**, 114, 6692-6697.
3. Nugent,W. A.; Taber, D. F. J. Am. Chem. Soc. **1989**, 111, 6435-6437. Rousset, C.J.; Swanson, D.R.; Lamaty, F.; Negishi, E.-i. Tetrahedron Lett. **1989**, 30, 5105-5108.
4. Typical procedure: A 100 ml Schlenk flask was charged with 1.31g of 5,5-bis(1propenyl) 2,2-dimethyl 1,3-dioxolane, 200 mg of zirconocene dichloride, and 20 ml of diethyl ether. To this was added 10 ml of a 2.0M solution of BuMgCl in diethyl ether (Aldrich). The reaction was allowed to stir for 48 hours under nitrogen. The flask was cooled in an ice bath, and hydrolyzed via the slow addition of water. The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (15% EtOAc/Hex) yielded 1.17g (8.51mmol, 87 %) of a colorless oil.
5. Precipitation of magnesium halides is observed in diethyl, diisopropyl, or dibutyl ether as the reaction progresses; however, this does not appear to have adverse effects on reactivity.
6. Knight, K.S.; Wang, D.; Waymouth, R.M. manuscript in preparation.
7. In contrast, the related catalytic ethylmagnesiation of similar substrates with EtMgX reagents proceed in THF with good stereoselectivity (ref 2).
8. See also: (a) McDermott; J. X.; Wilson, M.E.; Whitesides, G. M. J. Am. Chem. Soc. **1976**, 98, 6529-6536. (b) Gell, K. I.; Schwartz, J. J. Chem. Soc., Chem. Commun. **1979**, 244. (c) Grubbs, R. H.; Miyashita, A. J. Chem. Soc., Chem. Commun. 1977, 964. (d) McLain, S. J.; Wood, C. D.; Schrock, R. R. J. Am. Chem. Soc. **1979**, 101, 4558-4570.
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(Received in USA 23 July 1992; accepted 15 September 1992)