Zirconium Mediated or Catalysed Highly Stereoselective Cyclization of 1,4,7-Trienes

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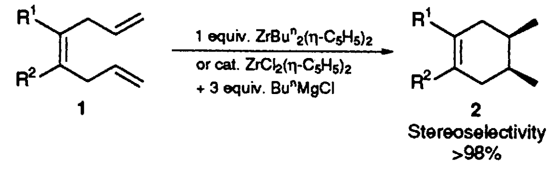
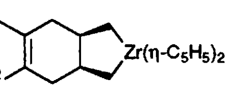
Cyclization of 1,4,7-trienes, which are easily prepared by double allylation reaction of alkynes, proceeded in the presence of a stoichiometric or catalytic amount of zirconocene compounds to give only *cis* isomers (>98% stereoselectivity).

Transition metal mediated or catalyzed intramolecular olefin–olefin coupling is very attractive and potentially useful. However, the major problem concerns the stereoselectivity of the cyclized products. When the cyclization provides a mixture of *cis* and *trans* stereoisomers, they are difficult to separate. Also when the ratio of *cis* to *trans* products is dependent on the substitutents, the reaction is not very synthetically useful. Zirconium mediated intramolecular coupling reactions of olefins have been reported[1] and amongst these, the stereochemistry of a cyclization reaction of hepta-1,6-diene was elegantly controlled using the $ZrCl_3(\eta\text{-}C_5Me_5)$ (99% *cis* isomer).[1e] However, use of the commercially available $ZrCl_2(\eta\text{-}C_5H_5)_2$ afforded a mixture of stereoisomers and the presence of minor isomers is a critical problem for further reactions. In this paper we report that the cyclization reactions of 1,4,7-trienes using $ZrCl_2(\eta\text{-}C_5H_5)_2$ gives only *cis* isomers (>98% stereoselectivity) in high yields.

Recently we have reported double allylation reactions of alkynes using zirconium and copper catalysts[2] and this provides a convenient preparative method for 1,4,7-trienes. When trienes such as **1a** were treated with Negishi reagent $[ZrCl_2(\eta\text{-}C_5H_5)_2 + 2LiBu^n]$, cyclization proceeded to give bicyclized zirconacyclopentanes **3**. After hydrolysis the product **2a** was obtained in 88% yield. The typical procedure used is as follows: to a solution of $ZrCl_2(\eta\text{-}C_5H_5)_2$ (1.25 mmol, 0.37 g) and THF (5 cm^3) was added 2 equiv. of $LiBu^n$ (1.7 mol dm^{-3}, 1.5 cm^3, 2.5 mmol) at −78 °C. The solution was stirred for 1 h at −78 °C and then **1a** (1.0 mmol) was added. The mixture was warmed to room temp. and stirred for 1 h. GC analysis of the aliquot of the mixture after hydrolysis showed that **2a**† was formed in 88% yield. The reaction mixture containing zirconacyclopentane **3** was quenched with 3 mol dm^{-3} aq. HCl and work-up gave an oily substance. Distillation or column chromatography afforded the desired compounds. The product **2a** was isolated in 81% yield. The reaction was carried out catalytically using $ZrCl_2(\eta\text{-}C_5H_5)_2$ (15 mg, 0.05 mmol), diethyl ether (5 cm^3), butylmagnesium chloride (2 mol dm^{-3} diethyl ether solution, 1.5 mmol)[1f–h] and triene **1a** (0.5 mmol). The mixture was stirred for 9 h at room temp. GC analysis of the reaction mixture after hydrolysis indicated that **2a** was formed in 93% yield based on triene **1a**. GC analysis and ^{1}H and ^{13}C NMR spectra of **2a** showed that only the *cis* isomer was formed and the *trans* isomer was not detected (>98% stereoselectivity).



Stereoselectivity >98%



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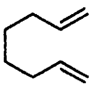

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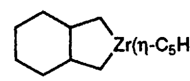

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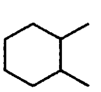

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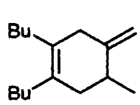

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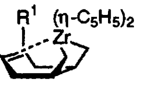
Results for a variety of trienes are shown in Table 1. In all cases only the one stereoisomer (*cis* >98% stereoselectivity) was observed and was independent of the substituents. Trienes with a substituent at the C-2 carbon such as **1e** and **f** also gave only one stereoisomer of cyclized compounds **2e–f**. It is known that the cyclization reaction of **4** using Negishi



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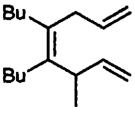

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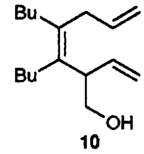

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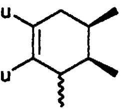

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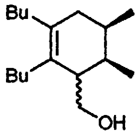

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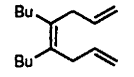
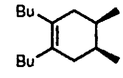
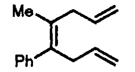
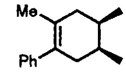
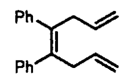
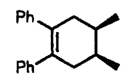
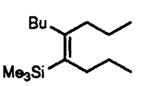
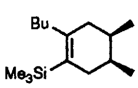
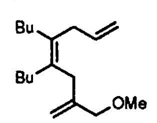
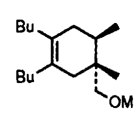
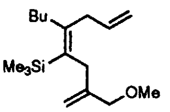
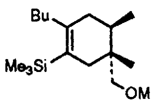
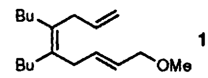
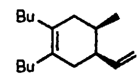
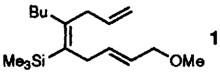
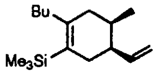
Table 1 Stereoselective cyclization of 1,4,7-trienes giving *cis* stereoisomers

1,4,7-Triene		Reaction condition^a	t/h	Product		Yield (%)^b
	**1a**	Stoichiometric Catalytic	1 6		**2a**	88 (81) 90
	**1b**	Stoichiometric Catalytic	1 3		**2b**	88 (70) 92
	**1c**	Stoichiometric Catalytic	1 9		**2c**	84 (80) 93
	**1d**	Stoichiometric Catalytic	1 9		**2d**	95 (60) 67
	**1e**	Stoichiometric Catalytic	1 6		**2e**	96 (75) 95
	**1f**	Stoichiometric Catalytic	1 6		**2f**	95 (85) 88
	**1g**	Stoichiometric Catalytic	1 6		**2g**	90 (79) 80^c
	**1h**	Stoichiometric Catalytic	1 6		**2h**	87 (80) 77^c

[a] In stoichiometric reaction 1.2 equiv. of $ZrBu_2(\eta\text{-}C_5H_5)_2$ was used (room temp). In catalytic reaction 1.5 equiv. of BuMgCl, 0.1 equiv. of $ZrCl_2(\eta\text{-}C_5H_5)$ was used, (room temp. 6–9 h). [b] GC yields. Isolated yields are given in parentheses. [c] After reaction the *cis* isomer gradually isomerized to the *trans* isomer.

reagent under the present conditions provides a 5:1 mixture of *cis/trans* isomers of **6**. Introduction of a double bond into the **4**, *i.e.* **1** thus markedly improves the stereoselectivity. The reaction product of cyclization prior to hydrolysis is the zirconacyclopentane **3** in the stoichiometric reactions. The *cis* isomer of **5** is known to gradually isomerize to the *trans* form at higher temperatures. Similarly, the *cis* isomer of **3** gave 15% of the *trans* isomer of **2a**‡ at 50 °C after 6 h along with the formation of decomposition product **7** (41%) after hydrolysis.

The four carbon atoms associated with the double bond in the six-membered ring system are fixed in a plane. This is responsible for the high stereoselectivity which is independent of substituents on the double bonds. The zirconium atom in **3** might interact with the double bond as shown in **8**.

Recently we have reported stoichiometric or catalytic intramolecular allylation reactions of compounds which have both a terminal double bond and an allylic ether moiety.[3] In this case the stereoselectivity was dependent on the substituent and the best ratio of *cis/trans* obtained was 92:8. However, as shown in Table 1, for 1,4,7-triene systems such as **1g** and **h**, highly stereoselective intramolecular allylation occurred to give **2g** and **2h**. In catalytic reactions of **1g** and **h**, we observed a gradual *cis* to *trans* isomerization although this did not occur during the cyclization reaction. Cyclized products **2g** or **2h** in a catalytic reaction isomerized in the presence of zirconium species, although the mechanism of the isomerization is not as yet clear. Under stoichiometric conditions the products did not isomerize.

When the 1,4,7-triene has a substituent at the C-3 carbon such as in **9** and **10**, a mixture of diastereoisomers such as **11** (76%, 1:1) and **12** (63%, 1.2:1) was obtained. The stereochemistry of the substituent at the C-3 carbon thus could not be controlled in this cyclization reaction.

In order for the cyclized products to be of use in further reactions, their functionalization is important. Intermediate zirconacyclopentanes **3** can be converted into various functionalized compounds by carbonylation, iodination, oxidation, and other reactions which have been well documented.[1,4]

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Footnotes

† **2a**, *cis* isomer: ^{1}H NMR ($CDCl_3$, $SiMe_4$) δ 0.80 (d, J = 6.6 Hz, 6H), 0.90 (t, J = 6.9 Hz, 6H), 1.2–1.4 (m, 8H), 1.6–1.8 (m, 4H), 1.9–2.1 (m, 6H); ^{13}C NMR ($CDCl_3$, $SiMe_4$) δ 14.16, 15.74, 22.93, 30.89, 31.93, 32.69, 35.99, 128.35.

‡ **2a**, *trans* isomer: ^{13}C NMR ($CDCl_3$, $SiMe_4$) δ 14.18, 19.48, 22.97, 30.93, 32.72, 35.40, 38.99, 129.72.

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1 For zirconium mediated intramolecular coupling reactions of olefins, see (*a*) I. Gell and J. Schwartz, *J. Chem. Soc., Chem. Commun.*, 1979, 244; (*b*) I. Gell and J. Schwartz, *J. Am. Chem. Soc.*, 1981, **103**, 2687; (*c*) H. Yasuda, K. Nagasuna, M. Akita, K. Lee and A. Nakamura, *Organometallics*, 1984, **3**, 1470; (*d*) C. J. Rousset, D. R. Swanson, F. Lamaty and E. Negishi, *Tetrahedron Lett.*, 1989, **30**, 5105; (*e*) W. A. Nugent and D. F. Taber, *J. Am. Chem. Soc.*, 1989, **111**, 6435; (*f*) K. S. Knight and R. M. Waymouth *J. Am. Chem. Soc.*, 1991, **113**, 6268; (*g*) U. Wischmeyer, K. S. Knight and R. M. Waymouth, *Tetrahedron Lett.*, 1992, **33**, 7735; (*h*) K. S. Knight, D. Wang, R. M. Waymouth and J. Ziller, *J. Am. Chem. Soc.*, 1994, **116**, 1845.

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