Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3209–3212

A catalytic and stoichiometric approach to the synthesis of the steroid B-ring en route to estratrienes

Pavel Herrmann and Martin Kotora*

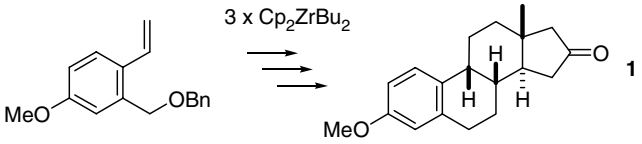
Department of Organic and Nuclear Chemistry, Faculty of Science, Charles University, Hlavova 8, 128 43 Praha 2, Czech Republic
Institute of Organic Chemistry and Biochemistry, Flemingovo nám. 2, 166 10 Praha 6, Czech Republic

Received 12 January 2007; revised 26 February 2007; accepted 7 March 2007
Available online 12 March 2007

Abstract—Zirconocene catalyzed cyclization of 2-(5-methoxy-3-penten-1-yl)styrene in the presence of organomagnesium reagents was studied. The cyclization proceeded in high isolated yields (up to 84%) with excellent trans-selectivity (>98%), which is unusual for the formation of cyclohexane derivatives. Catalytic cyclization in the presence of Cp_2ZrCl_2 proceeded as well with similar results. The reaction with (R,R)-$(EBTHI)_2ZrCl_2$ gave a cis/trans mixture of **5** in low yield and poor ee.

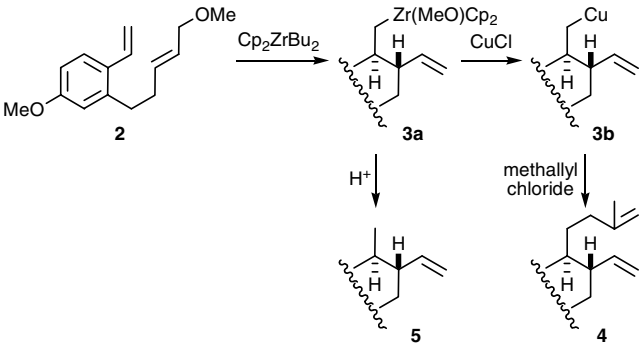
Transition-metal mediated or catalyzed processes are very important tools for the synthesis of carbo- and heterocyclic ring systems. Particularly interesting are those based on the coupling of unsaturated fragments at a transition metal center. In this regard, methods utilizing zirconium and titanium reagents play leading roles.[1] Although the majority of reported examples concern Zr- or Ti-mediated reactions, the catalytic variants of these processes have attracted considerable attention. Several groups have independently shown that non-conjugated α,ω-dienes can be cyclized into mono- or di(methylmagnesium) compounds in the presence of a catalytic amount of zirconocene (Cp_2ZrCl_2) and an organomagnesium reagent (usually BuMgX or Bu_2Mg). The rate, yields, stereoselectivity and selectivity for mono- or difunctionalized products are quite sensitive to the nature of the diene, the magnesium reagent and the reaction temperature, as well as the solvent used. Understanding the role of these factors and their influence on the course of the reaction is essential for the development of synthetically useful catalytic procedures.[2–4]

Recently, we reported a short synthesis of (±)-3-methoxyestra-1,3,5(10)-triene-16-one **1** from a substituted styrene by using several Cp_2ZrBu_2 based reactions (Scheme 1).[5] The synthesis of the steroid B-ring was accomplished by the zirconium-mediated cyclization of 2-(5-methoxy-3-penten-1-yl)styrene **2**, which afforded



Scheme 1. Zr-based synthesis of (±)-3-methoxyestra-1,3,5(10)-triene-16-one **1**.

organozirconium intermediate **3a** (Scheme 2). Subsequent addition of a catalytic amount of CuCl resulted in transmetallation of **3a** to organocopper intermediate **3b**. The formation of this species was essential for the reaction with methallyl chloride to afford diene **4**. It is noteworthy that the cyclization proceeded with excellent trans-stereoselectivity (>98%). Such high trans-selectivity was rather remarkable, because cyclizations of non-conjugated dienes containing a terminal allylic ether



Scheme 2. Synthesis of the steroid B-ring during the synthesis of **1**.

* Corresponding author. Tel.: +420 221 951 334; fax: +420 221 951 326; e-mail: kotora@natur.cuni.cz

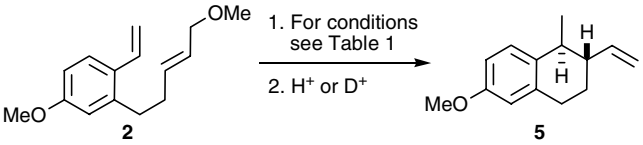
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.03.018

having a four-membered tether with a stoichiometric amount of zirconocene (or titanocene) usually gave products with preferential cis-substitution on the ring.[6–9] However, it was noticed that this trend was reversed with substrates having an aromatic ring as part of the tether connecting both double bonds. In addition, it was observed that the trans/cis ratio depended on the configuration of the allylic double bond.[10,11]

In addition, it was also shown that non-conjugated dienes containing a terminal allylic ether or an alcohol moiety could be cyclized under catalytic conditions to the corresponding vinyl(methyl)derivatives.[6,7,12,13] It was within this context that we set out to investigate the corresponding catalytic cyclization of **2** as an alternative synthesis of the steroid B-ring.

Initially, the cyclization of **2** was carried out under the classical stoichiometric conditions reported by Negishi (1.05 equiv Cp_2ZrCl_2, 2.1 equiv *n*-BuLi)[6,7,14] and Sato (1.1 equiv $(i\text{-PrO})_4Ti$, 2.2 equiv *i*-PrMgCl).[11b,c] The results are listed in Table 1 (Scheme 3). The former afforded the cyclized product **5** in 84% isolated yield with excellent 98% trans-stereoselectivity (entry 1).[15] This was in agreement with our previously observed results.[5] The titanium-mediated reaction gave **5** in a good 73% isolated yield and with the same stereoselectivity (entry 2).

Our study continued through examination of the Zr-catalyzed cyclization of **2** (Table 1). We soon established that cyclization of **2** in the presence of 10 mol % Cp_2ZrCl_2 and 4 equiv of BuMgCl (THF, 20 °C) led to the formation of the cyclized product **5** in 63% isolated yield with 98% trans-stereoselectivity. To assess the influence of the solvent on the course of the reaction, cyclizations were run under the same conditions in diethyl ether and toluene furnishing target compound **5** in 54% and 55% isolated yields, respectively. In these reactions the formation of higher molecular weight side-products was observed in small amounts (ca. 5%). Efficient cyclization of **2** was also observed in the presence of Bu_2Mg in toluene (66% isolated yield). Next our attention turned to investigate the possibility of catalytic enantioselective Zr-catalyzed cyclization. Racemic



Scheme 3. Cyclization of **2**–**5**.

(EBTHI)$ZrCl_2$ complex (10 mol %) was employed as the pre-catalyst in this study. Unfortunately, the cyclization did not proceed either in THF or Et_2O and the starting material was almost completely recovered (>90%) (entries 7 and 8). Analysis of the reaction mixture did not reveal even traces of the expected product **5**. This result indicated that even the stoichiometric reaction would not take place. A similar negative result was also obtained with (−)-(NMI)$ZrCl_2$ complex under the same reaction conditions (entry 9).

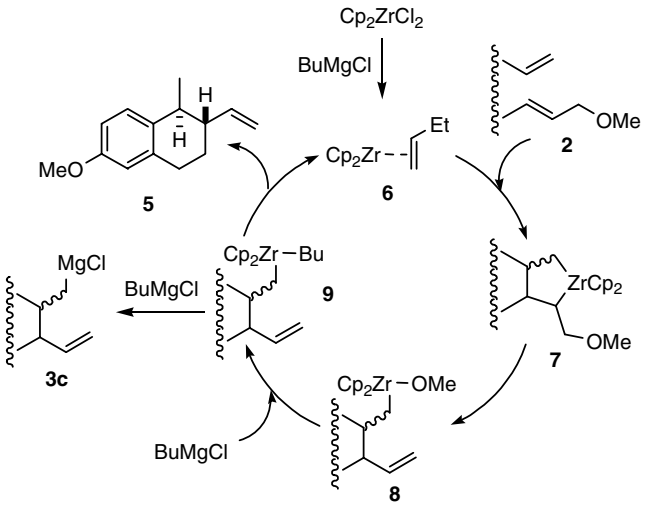
Partial cyclization of **2** with a catalytic amount of (*R*,*R*)-(EBTHI)$ZrCl_2$ to **5** (16% yield) was observed only after carrying out the reaction at 70 °C for 16 h (entry 10). Interestingly, the product was obtained as 1.1/1 mixture of trans and cis isomers.[16] The asymmetric induction in the trans isomer was 67% ee and 81% ee in the cis isomer. The reason for the observed low catalytic activity of chiral zirconocene complexes is unknown, especially since these complexes have been successfully used for the enantioselective cyclization of non-conjugated dienes containing a terminal or an internal allylic alcohol moiety.[3,13,17,18]

Next, we decided to study the reaction mechanism. In order to utilize the catalytic reaction for further synthetic purposes, it was necessary to obtain a new organometallic compound (an organomagnesium compound such as **3c**) at the end of the cyclization process. Quenching of the reaction mixture after the reaction in THF (conditions in entry 3) with DCl did not result in any incorporation of deuterium in product **5**. This result confirmed the previously proposed reaction mechanism (Scheme 4).[6,12] The mechanism of the catalytic cyclization reaction involves (i) replacement of butene in zirconocene-butene complex **6** by **2**, followed by cyclization to zirconacyclopentane **7**, (ii) elimination of the β-

Table 1. Stoichiometric and catalytic cyclization of **2**–**5**

Entry	Complex	Equiv	R–M	Equiv	Cond (°C, h)	Solvent	**5**, Yield[a] (%)
1	Cp_2ZrCl_2	1.05	*n*-BuLi	2.1	20, 16	THF	84
2	$(i\text{-PrO})_4Ti$	1.1	*i*-PrMgCl	2.2	20, 16	Et_2O	73
3	Cp_2ZrCl_2	0.1	BuMgCl	4	20, 16	THF	63
4	Cp_2ZrCl_2	0.1	BuMgCl	4	20, 16	Et_2O	54[b]
5	Cp_2ZrCl_2	0.1	BuMgCl	4	20, 16	Toluene	55[b]
6	Cp_2ZrCl_2	0.1	Bu_2Mg	4	20, 16	Toluene	66
7	*rac*-(EBTHI)$ZrCl_2$[c]	0.1	BuMgCl	4	20, 16	THF	0
8	*rac*-(EBTHI)$ZrCl_2$[c]	0.1	BuMgCl	4	20, 16	Et_2O	0
9	(−)-(NMI)$ZrCl_2$[d]	0.1	BuMgCl	4	20, 16	THF	0
10	(*R*,*R*)-(EBTHI)$ZrCl_2$[c]	0.1	BuMgCl	4	70, 16	THF	16[e] (67% ee)

[a] Isolated yields.
[b] Side-products (5%) were formed.
[c] Dichloro[*rac*-ethylenebis(4,5,6,7-tetrahydro-1-indenyl)]zirconium(IV).
[d] (−)-Dichlorobis(1-neomenthylindenyl)zirconium(IV).
[e] ^1H NMR yield.



Scheme 4. Reaction mechanism of the Zr-catalyzed cyclization.

methoxy group from **7** to form alkylzirconium compound **8**, (iii) substitution of MeO by BuMgCl to yield dialkylzirconocene **9**, and (iv) β-hydrogen elimination from the butyl group on zirconium to regenerate zirconocene-butene complex **6** and release cyclized product **5**. Although the result was not encouraging, we hoped that perhaps by changing the solvent used a second transmetallation of **9** instead of β-hydrogen elimination would promote formation of organomagnesium compound **3c**. It was previously reported that the transmetallation is promoted by using less polar solvents than THF and/or diorganomagnesium compounds.[4] However, quenching of the reaction carried out in Et_2O (entry 4), toluene (entry 5), or in the presence of Bu_2Mg (entry 6) with DCl did not yield any detectable amount of deuterated products.

We can conclude that 2-(5-methoxy-3-penten-1-yl)styrene **2** can be cyclized to the corresponding 2-methoxy-5-methyl-6-vinyl-tetrahydronaphthalene **5** with zirconium or titanium reagents under stoichiometric conditions with high trans-stereoselectivity. Catalytic cyclization proceeded as well, however, the use of a sterically more demanding zirconocene complex such as (EBTHI)$ZrCl_2$, which would allow an enantioselective reaction, did not occur in an acceptable yield. To the best of our knowledge this is the first example where the use of such a complex failed to promote the reaction. Perhaps, the observed results could be explained by steric factors, which may not allow the substrate to approach the reduced zirconcene and to form the crucial intermediate zirconacycle **7**. Moreover, unlike in the cyclization of α,ω-dienes, it was not possible to control the course of the reaction for the formation of (cycloalkylmethyl)magnesium compounds. Nonetheless, further research along these lines is under way.

Acknowledgement

We gratefully acknowledge the financial support from Project No. 322/2005/B-CH/PrF from the Grant Agency of Charles University and the Ministry of Education of the Czech Republic to the Center for Structural and Synthetic Application of Transition Metal Complexes (Project No. LC06070). The authors also thank Dr. I. Valterová for determination of ee and Dr. M. Buděšínský for discussions on NMR spectra (both from the Institute of Organic Chemistry and Biochemistry, Prague).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.018.

References and notes

1. (a) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, pp 1163–1184 (b) *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; (c) Negishi, E. *Dalton Trans.* **2005**, 827–848.
2. (a) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268–6270; (b) Wischmeyer, U.; Knight, K. S.; Waymouth, R. M. *Tetrahedron Lett.* **1992**, *33*, 7735–7738; (c) Knight, K. S.; Wang, D.; Waymouth, R. M.; Ziller, J. *J. Am. Chem. Soc.* **1994**, *116*, 1845–1854.
3. Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, Z.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614–6624.
4. Negishi, E.; Rousset, C. J.; Chouiery, D.; Maye, J. P.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1998**, *280*, 8–20.
5. Herrmann, P.; Kotora, M.; Buděšínský, M.; Šaman, D.; Císařová, I. *Org. Lett.* **2006**, *8*, 1315–1318.
6. Takahashi, T.; Kondakov, D. Y.; Suzuki, N. *Organometallics* **1994**, *13*, 3411–3412.
7. Takahashi, T.; Kotora, M.; Kasai, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2693–2694.
8. Bird, A. D.; Raynham, T. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3194–3204.
9. (a) Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synlett* **1998**, 451–453; (b) Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synthesis* **1998**, 557–568; (c) Kasatkin, A. N.; Checkfield, G.; Whitby, R. J. *J. Org. Chem.* **2000**, *65*, 3236–3238; (d) Hunter, R. A.; Macfarlane, D. S. P.; Whitby, R. J. *Synlett* **2006**, 3314–3318.
10. Campbell, A. J.; Taylor, R. J. K.; Wei, X. *Synlett* **1995**, 1237–1238.
11. (a) For selectivity in the formation of five-membered rings, see: Refs. 6 and 8; (b) Takayama, Y.; Gao, Y.; Sato, F. *Angew. Chem., Int. Ed.* **1997**, *36*, 851–853; (c) Takayama, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8351–8354.
12. Knight, K. S.; Waymouth, R. M. *Organometallics* **1994**, *13*, 2575–2577.
13. Degrado, S. J.; Adams, J. A.; Hoveyda, A. H. *Inorg. Chim. Acta* **2003**, *345*, 261–267.
14. (a) Negishi, E.; Cederbaum, F. R.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832; (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, R. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346.
15. *anti-1-Methyl-2-ethenyl-7-methoxy-(1,2,3,4-tetrahydronaphthalene)* (**5**). A mixture of **2** (1 mmol, 232 mg), Cp_2ZrCl_2

(0.1 mmol, 29 mg) and BuMgCl (2.0 M solution in THF, 4 mmol, 2 mL) in THF (5 mL) was stirred for 16 h at room temperature. The reaction mixture was quenched with 3 M HCl (aq), extracted with hexanes (3×10 mL), dried over anhydrous Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (98/2 hexanes/Et_2O) to afford 126 mg (63%) of the cyclized product **5** as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, $J = 6.9$ Hz, 3H), 1.60–1.68 (m, 1H), 1.90–1.96 (m, 1H), 2.09–2.16 (m, 1H), 2.60–2.70 (m, 1H), 2.73–2.82 (m, 2H), 3.78 (s, 3H), 5.03 (ddd, $J = 10.3$, 1.9, 0.9 Hz, 1H), 5.07 (ddd, $J = 17.2$, 1.9, 1.1 Hz, 1H), 5.82 (ddd, $J = 17.2$, 10.3, 8.0 Hz, 1H), 6.60 (d, $J = 2.8$ Hz, 1H), 6.72 (dd, $J = 8.5$, 2.8 Hz, 1H), 7.15 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (125.7 MHz $CDCl_3$) δ 21.40, 27.73, 28.73, 36.67, 46.37, 55.16, 112.16, 113.17, 114.23, 129.09, 133.21, 137.63, 142.92, 157.24; IR (CCl_4) ν 3079, 3009, 2839, 1640, 1609, 1577, 1501, 1466, 1454, 1377, 1299, 1277, 1257, 1161, 1040, 995, 917 cm^{-1}. MS-EI (m/z) 202.2 (M^+); HRMS-EI calcd 202.1357, found 202.1364. R_F (98/2 hexane/Et_2O) = 0.5.

16. *Characteristic ^{1}H NMR signals of the cis isomer*: δ 1.11 (d, $J = 7.2$ Hz, 3H) for the Me group, 5.00–5.10 (m, 2H), 5.90 (ddd, $J = 17.1$, 10.4, 7.1 Hz, 1H) for the vinyl group.
17. Yamaura, Y.; Mori, M. *J. Am. Chem. Soc.* **1999**, *40*, 3221–3224.
18. For the Zr-catalyzed enantioselective cyclization of α,ω-dienes, see: Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615–7616.