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Pentadienylzirconium compounds: easily accessible new reagents for selective pentadienylation reactions

Philippe Bertus, Franck Cherouvrier and Jan Szymoniak*

Réactions Sélectives et Applications, CNRS and Université de Reims, 51687 Reims Cedex 2, France

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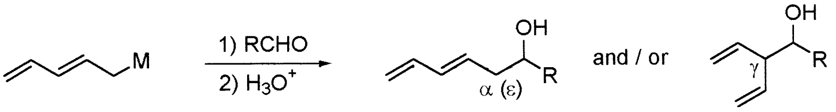
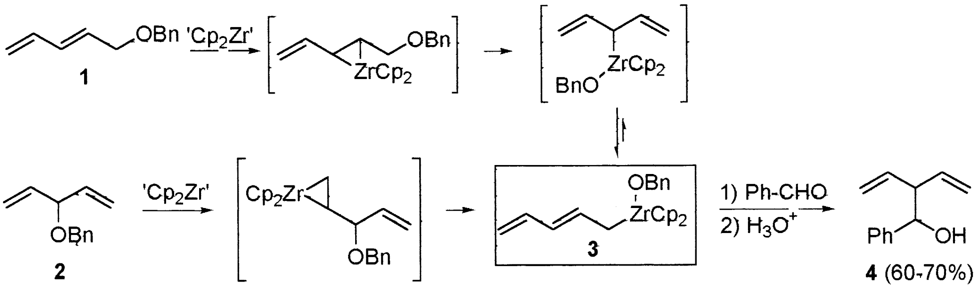
Abstract—2,4-Pentadienylzirconium complexes are generated from 2,4- or 2,2′-pentadienyl ethers in turn. These compounds react in situ with aldehydes and ketones in a totally γ-regioselective manner and with predominant *anti* stereoselectivity to produce bis(homoallylic) alcohols in good yields. Iodocyclization of one of these alcohols represents regio- and stereocontrolled short entry to functionalized tetrahydrofurans. © 2001 Elsevier Science Ltd. All rights reserved.

Whereas the addition of allylmetals to carbonyl compounds is a well-known reaction,[1] the analogous reaction involving pentadienylmetals has been much less developed. The use of lithium-, magnesium-, zinc-, tin-, silicon- and indium-based reagents have been reported.[2] These reagents, which are usually generated from 5-bromo-1,3-pentadienyl derivatives or by metalation of dienes, add to aldehydes with varying degrees of α (ε) versus γ regioselectivity (Scheme 1). Moreover, almost nothing is known about the stereoselectivity of these pentadienylation reactions.[3]

An efficient procedure for preparing allylzirconium species involves the oxidative addition of zirconocene ('Cp_2Zr')[4] to allylic ethers.[5] We anticipated that new pentadienylzirconium compounds could be generated in an analogous fashion from dienyl ethers. Since the Cp_2Zr residue in organozirconocenes tends to migrate to the least hindered terminal position,[4,6] we reasoned that isomeric pentadienyl ethers **1** or **2** could be employed to produce regioselectively the unique 2,4-pentadienylzirconium species **3** (Scheme 2). In this manner, one synthetic advantage of the method would be the possible use of different substrates. To test the aforementioned hypothesis, compounds **1** and **2** were easily prepared by reaction of acroleine with vinylmagnesium bromide (followed by acidic isomerization to form the dienol precursor of **1**) and etherification



Scheme 1.



Scheme 2.

Keywords: zirconium; γ-pentadienylation reaction; homoallylic alcohols; regiocontrol; tetrahydrofurans.

* Corresponding author.

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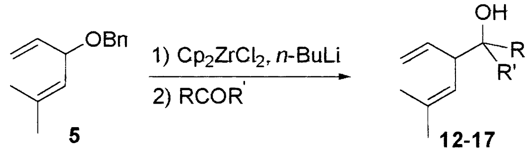
(NaH, BnBr).[7] Thereafter, the oxidative addition reaction was investigated. In an initial experiment, the Taguchi protocol for the generation of allylzirconiums from allylic ethers was applied.[5c] Compound **1** or **2** (1 equiv.) was added to the mixture of Cp_2ZrCl_2 (1.3 equiv.) and 2.6 equiv. of *n*-BuLi at −78°C, the temperature was raised to 20°C (3 h), benzaldehyde (1.5 equiv.) was added at 0°C and the reaction carried out at rt for 2 h. Alternatively, the following simplified procedure has been developed.[8] To a solution of **1** (or **2**) (1 mmol) and Cp_2ZrCl_2 (1.1 mmol) in THF (4 mL) *n*-BuLi (2.2 mmol, 2.5 M in hexane) was added slowly via syringe at 0°C. The reaction mixture was then refluxed for 0.5 h. Benzaldehyde (1.2 equiv.) was added and the reaction carried out at rt for 1 h. After a conventional hydrolytic workup (1 M HCl) followed by flash chromatography, the dienol **4** was obtained as a sole product, in 60–70% yields, by using each of the two procedures (Scheme 2). Also, noteworthy was the unique formation of **4** starting from the isomeric pentadienyl ethers **1** or **2**. Clearly, irrespective of the substrate structure, the coupling with benzaldehyde occurred regioselectively at the γ-position of the same zirconium species **3**. In this manner, *the overall transformation appeared as doubly regioselective*, both in the formation of the organozirconium reagent and in its successive addition to aldehyde.

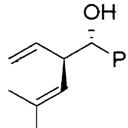
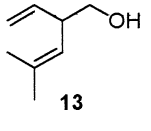
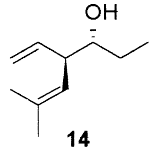
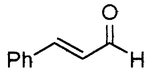
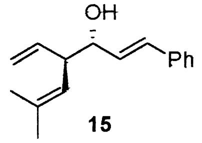
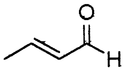
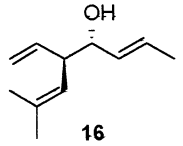
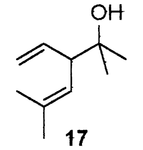
To further investigate the regio- and stereochemical outcome of the reaction we next used pentadienyl ether **5** as a substrate.[9] Several carbonyl compounds were employed and the reactions carried out according to the simplified procedure, as above. As shown in Table 1, in all cases the reaction occurred in a γ-regioselective manner to afford solely the branched alcohols **12**–**17**. Benzaldehyde, aliphatic and unsaturated aldehydes gave good yields (entries 1–5). The α,β-unsaturated aldehydes **9** and **10** afforded the unique 1,2-addition products **15** and **16** (entries 4 and 5). The reaction employing acetone also proceeded smoothly to give the terpene **17** (santolina alcohol) (entry 6). Starting from the aldehydes **6**, **8** and **9** similar good diastereoselectivities were obtained. Particularly, the reaction of benzaldehyde afforded **12**, as an 86:14 mixture of diastereomers (**12a** and **12b**).[10] Attempts to separate these isomers and to determine the *anti*/*syn* configuration failed.

To establish the stereochemistry, we therefore turned to the use of a cyclization method. The iodocyclization of homoallylic alcohols was reported to proceed generally via a 5-*endo*-trig pathway, leading to substituted tetrahydrofurans.[11] Using $I_2/NaHCO_3$ in acetonitrile as solvent, high stereoselectivities were obtained.[12] However, there have been no reports on the analogous reactions employing bis(homoallylic) alcohols such as **12**. Particularly, in this case, the level of regioselection with regard to different C=C double bonds remained uncertain. We were pleased to find that the iodocyclization reaction of **12** (using the I_2–$NaHCO_3$–MeCN method) occurred with a total regioselectivity, in a 5-*endo*-trig manner and *exclusively on the more substituted C=C*

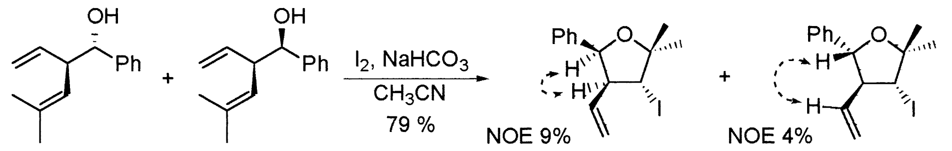
Table 1. Reaction of **5** (1 mmol) and Cp_2ZrCl_2 (1.1 mmol) with *n*-BuLi (2.2 mmol) in THF, followed by the addition of a carbonyl compound (1.2 mmol)



5 → **12-17**

Entry	Carbonyl compound	Product[a]	Yield (%)[b] (*anti*/*syn*)[c]
1	Ph-CHO **6**	 **12**	96 (86 : 14)
2	$(CH_2O)_n$[d] **7**	 **13**	81 (-)
3	Et-CHO **8**	 **14**	84 (93 : 7)
4	 **9**	 **15**	81 (86 : 14)
5	 **10**	 **16**	70 (90 : 10)
6	Me_2CO **11**	 **17**	72 (-)

[a] Only the configuration of the major isomer (*anti*) is shown. – [b] Isolated yields. – [c] Determined by ^1H-NMR. – [d] Paraformaldehyde, 10 eq.



12a **12b** **18a** **18b**

12a/**12b** = 86:14

18a/**18b** = 85:15

Scheme 3.

double bond. Furthermore, the reaction appeared as totally stereoselective. Only two diastereomeric tetrahydrofurans **18a** and **18b** were formed in 85:15 ratio, i.e. the same as the initial ratio of **12a** and **12b**.[10] The regio- and stereochemical outcome of the iodocyclization reaction made the configurational assignment possible, directly on **18**. The 2,3-*cis*-and 2,3-*trans* relationship (Ph, vinyl) was assigned to **18a** and **18b**, respectively, on the basis of NOE experiments, as indicated in Scheme 3. These attributions were confirmed by the marked difference in the ^{1}H NMR chemical shifts of the vinyl α-hydrogen (-CH=CH$_2$), upfield-shifted for **18a** (δ 4.84) in comparison with **18b** (δ 5.65). Consequently, the *anti* configuration was assigned to the major diastereomer **12a** while the *syn* configuration was assigned to the minor diastereomer **12b**. The predominant *anti* diastereoselection can be rationalized by assuming a conventional chair-like six-membered transition state for these γ-pentadienylation reactions.[13] The overall reaction sequence leading to **18** exemplifies a short and stereoselective synthesis of a tetrahydrofuran derivative with functionalized end groups at C3 and C4.[14]

In summary, 2,4-pentadienylzirconium compounds have been generated in a regioconvergent manner from the easily available 2,4- or 2,2′-pentadienyl ethers. These new reagents have been demonstrated to react with aldehydes and ketones with complete γ-regioselectivity and predominant *anti* stereoselectivity. Because a wide variety of 2,4-pentadienylzirconiums may be easily prepared, the method should be convenient for the synthesis of various bis(homoallylic) alcohols.

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4. For reviews of 'Cp$_2$Zr' chemistry, see: (a) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755. (b) Negishi, E.; Kondakov, D. Y. *Chem. Soc. Rev.* **1996**, *26*, 417. (c) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124.
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7. The pentadienyl ethers are quite stable compounds, in contrast to the more sensitive pentadienyl bromides.
8. We have proved that this new procedure is also useful for the preparation of allylzirconiums from allylic ethers.
9. Compound **5** was easily prepared in two steps by reaction of 3-methyl-2-butenal with vinylmagnesium bromide followed by etherification with BnBr.
10. Spectral data for **12** and **18**. Major isomer **12a** (*anti*): ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.33 (s, 3H), 1.61 (s, 3H), 2.25 (s, 1H), 3.24 (q, $J=8.3$ Hz, 1H), 4.49 (d, $J=7.6$ Hz, 1H), 5.02 (d, $J=9.4$ Hz, 1H), 5.16 (d, $J=16.0$ Hz, 1H), 5.17 (d, $J=11.3$ Hz, 1H), 5.78 (ddd, $J=16.0$, 11.3, 8.0 Hz, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 17.9 (CH$_3$), 26.8 (CH$_3$), 51.6 (CH), 76.4 (CH), 117.0 (CH$_2$), 122.0 (CH), 126.7 (CH), 127.3 (CH), 127.8 (CH), 134.5 (C), 138.0 (CH), 142.1 (C); MS (EI): *m/z* (%) = 184 (4, M–H$_2$O), 169 (10), 106 (48), 105 (52), 94 (39), 77 (100). Minor isomer **12b** (*syn*): ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.61 (s, 3H), 1.78 (s, 3H), 2.25 (s, 1H), 3.27 (masked, 1H), 4.48 (masked, 1H), 4.93 (d, $J=17.2$ Hz, 1H), 4.96 (d, $J=10.4$ Hz, 1H), 5.15 (masked, 1H), 5.60 (ddd, $J=17.2$, 10.4, 6.9 Hz, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR (125 MHz) δ 18.3 (CH$_3$), 26.1 (CH$_3$), 51.0 (CH), 77.0 (CH), 116.1 (CH$_2$), 122.3 (CH), 127.0 (CH), 127.5 (CH), 128.0 (CH), 136.6 (C), 137.4 (CH), 141.9 (C). Major isomer **18a**: ^{1}H NMR (500 MHz, CDCl$_3$) $\delta = 1.55$ (s, 3H), 1.56 (s, 3H), 3.43 (dt, $J=11.3$, 9.6 Hz, 1H), 3.82 (d, $J=11.3$ Hz, 1H), 4.84 (ddd, $J=16.7$, 9.8, 9.8 Hz, 1H), 4.97 (dd, $J=10.0$, 1.7 Hz, 1H), 5.08 (dd, $J=16.7$, 1.3 Hz, 1H), 5.16 (d, $J=9.4$ Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 24.8 (CH$_3$), 25.8 (CH$_3$), 38.1 (CH), 57.9 (CH), 80.7 (CH), 82.7 (C), 118.8 (CH$_2$), 126.8 (CH), 127.4 (CH), 128.0 (CH), 135.0 (CH), 139.5 (C). Minor isomer **18b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.47 (s, 3H), 1.61 (s, 3H), 2.96 (dt, $J=11.3$, 9.2 Hz, 1H), 4.02 (d, $J=10.9$ Hz, 1H), 4.67 (d, $J=9.4$ Hz, 1H), 5.06 (d,

$J = 17.0$ Hz, 1H), 5.24 (dd, $J = 10.2$, 0.9 Hz, 1H), 5.65 (ddd, $J = 17.0$, 10.2, 8.7 Hz, 1H), 7.22–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7 (CH_3), 29.5 (CH_3), 39.0 (CH), 61.5 (CH), 82.5 (C), 83.6 (CH), 120.2 (CH_2), 125.9 (CH), 127.7 (CH), 128.2 (CH), 134.2 (CH), 140.5 (C).

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