Pergamon

Tetrahedron Letters 41 (2000) 6201–6205

TETRAHEDRON
LETTERS

Insertion of metallated epoxynitriles into organozirconocene chlorides. A convergent synthesis of 2-cyano-1,3-dienes

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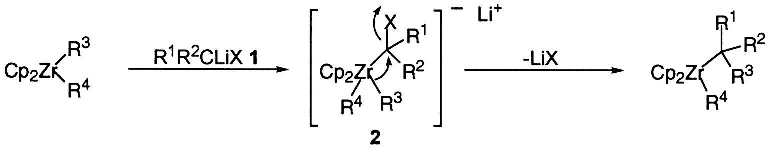
Received 16 May 2000; accepted 14 June 2000

Abstract

Lithiated epoxynitriles insert efficiently into alkenylzirconocene chlorides via a 1,2-metallate rearrangement to form intermediates which eliminate $Cp_2Zr(Cl)O^-$ to afford substituted 2-cyano-1,3-dienes. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: zirconium; carbenoid; metallated epoxides; epoxynitrile; cyanodiene.

Recently, we have shown that insertion of a wide range of metal carbenoids (R^1R^2CLiX, **1**) into carbon–zirconium bonds is a fast and efficient process,[1] possibly occurring via 1,2-rearrangement of a 'zirconate' intermediate **2** (Eq. (1)).[2] Here we describe the use of α-lithiated α,β-epoxynitriles as carbenoid components in the reaction with organozirconocene chlorides. Metallated epoxides play an important role in organic synthesis either as nucleophiles or (more usually) as implied intermediates in the formation of carbenes.[3] Generally a stabilising group is needed to allow formation by deprotonation,[4] although unstabilised systems may be generated by tin/lithium exchange.[5] The reaction of lithiated α-silylepoxides with organoaluminiums via a mechanism including intramolecular nucleophilic ring opening followed by β-elimination of R_2AlO^- to afford vinylsilanes has been reported (Eq. (2)).[6,7] It is likely that other reactions of oxiranyl carbanions with organometallics, which have been described as occurring via insertion of carbenes into carbon–metal bonds, actually occur via such 1,2-metallate rearrangements.



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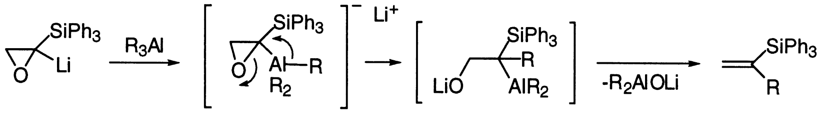
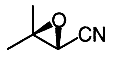
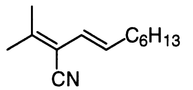
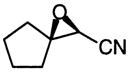
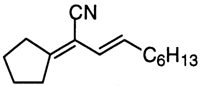
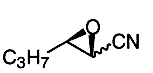
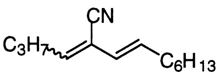
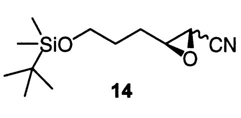
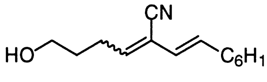
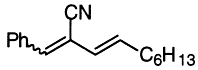


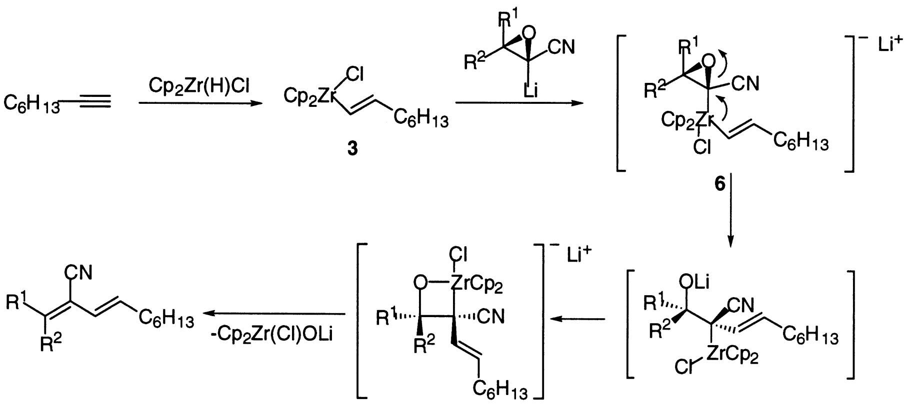
(2)

α,β-Epoxynitriles[8] are readily deprotonated with LDA[4c] but in the absence of an electrophile they underwent extremely rapid self-condensation even at –90°C.[9] Slow addition of LDA to a mixture of (*E*)-1-octenylzirconocene chloride (**3**) (readily available by hydrozirconation of 1-octyne with the Schwartz reagent[10]) and 2,3-epoxy-3-methylbutyronitrile (**4**) in THF at –90°C followed by warming to –60°C and acidic hydrolysis afforded (*E*)-2-cyano-1,3-diene **5** in good yield (Table 1, entry 1). A reasonable mechanism for the transformation includes epoxide opening by 1,2-migration of the alkenyl fragment in the 'ate'-complex **6** followed by *syn*-β-elimination of the zirconium alkoxide (Scheme 1). In contrast to **3**, octylzirconocene chloride reacted with the epoxide **4** in the presence of LDA to give 3-cyano-2-methylundec-2-ene in low yield. The reaction of **3** with the cyclic β,β-disubstituted epoxynitrile **8** led to the expected 1,3-diene **9** together with a small amount of the 1,4-diene **10** (entry 2). The formation of **10** is presumably due to γ-deprotonation of the α,β-unsaturated nitrile **9** with LDA to give the pentadienyllithium species **11**

Table 1
Insertion of lithiated epoxynitriles into (*E*)-1-octenylzirconocene chloride (**3**)[a]

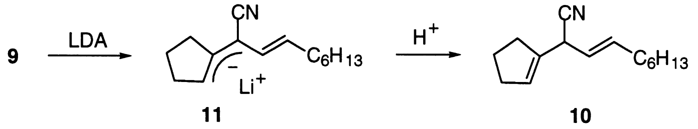
Entry	Epoxide	*Z* : *E*[b]	Product	*Z* : *E*[b]	Yield, %[c]
1	 **4**		 **5**		64
2	 **8**		 **9**[d]		42
3	 **12**	100:0	 **13**	90:10	57
4		0:100		53:47	64
5[e]	 **14**	100:0	 **15**	88:12[f]	55
6[e]		0:100		51:49[f]	67
7	 **16**	100:0	 **17**	95:5	70
8		0:100		87:13	74

[a] Addition of LDA (1.3 equiv.) to a mixture of **3** (1.0 equiv.) and an epoxide (1.3 equiv.) in THF at –90 °C, then warming to –60 °C over 1 h before quenching with 2 M HCl aq. [b] According to GC unless stated otherwise. [c] Isolated yields based on 1-octyne. [d] The product contained 8% of the 1,4-diene **10** according to NMR data. [e] After addition of 2 M HCl aq. the reaction mixture was stirred overnight at 20 °C. [f] According to NMR data.



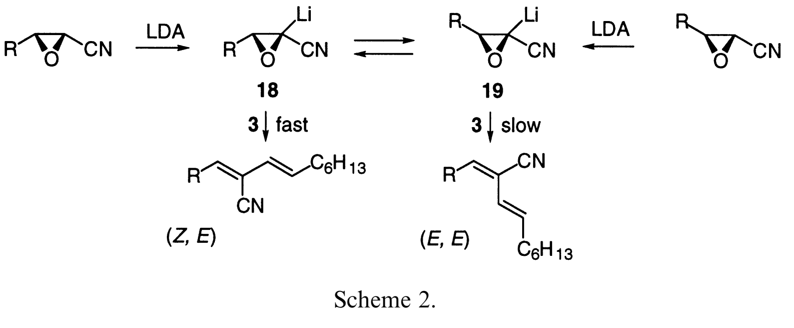
Scheme 1.

which underwent α-protonation on hydrolysis (Eq. (3)). Indeed, treatment of **9** with 1 equiv. of LDA (THF, –78°C, 30 min) followed by quenching with 2 M HCl aq. afforded the β,γ-unsaturated nitrile **10** in 78% yield (Eq. (3)). The (*Z*)- and (*E*)-β-monoalkylsubstituted epoxynitriles **12** reacted with **3** giving the expected cyanodiene **13**[11] as 90:10 and 53:47 mixtures of (*Z, E*)- and (*E, E*)-isomers, respectively (entries 3 and 4). The presence of a protected hydroxyl in the starting material (the epoxides **14**) did not significantly affect either the yield or stereoselectivity (entries 5 and 6). In a similar way, the (*Z*)- and (*E*)-β-phenylsubstituted epoxides **16** furnished the cyanodiene **17**[11] as mixtures of Δ^3-double-bond isomers with the (*Z*,*E*)-isomer predominating in both cases (entries 7 and 8). However, the yields and stereoselectivities were considerably higher than in the reactions of β-alkylsubstituted epoxides.



(3)

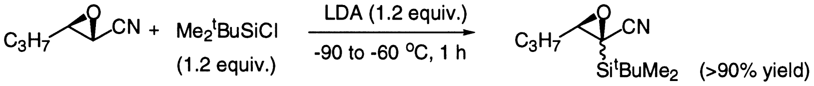
The lack of stereoselectivity in the reaction of (*E*)-1-octenylzirconocene chloride (**3**) with β-monosubstituted epoxynitriles cannot be explained within the mechanism shown in Scheme 1 where both 1,2-migration and β-elimination stages are stereospecific. A plausible explanation is that the initially formed α-lithiated epoxides **18** and **19** are not configurationally stable and interconvert rapidly under the reaction conditions (Scheme 2).[12] The reaction of **3** with the



Scheme 2.

(*Z*)-isomer **18** to afford (*Z, E*)-cyanodienes is faster than with the (*E*)-isomer **19** probably due to the steric repulsion between a *trans*-β-substituent in **19** and the Cp-ligands. The fact that the (*Z*)-epoxynitriles **12**, **14**, **16** which give the more reactive **18** as the initial lithiation product showed higher stereoselectivity in the reaction with **3** than the corresponding (*E*)-epoxides (entries 3 versus 4, 5 versus 6, and 7 versus 8) is in good agreement with the explanation.

To confirm the mechanism of loss of stereochemical integrity we examined generation/trapping of the carbenoid formed from the epoxynitrile (*E*)-**12** (Eq. (4)). Treatment of (*E*)-**12** with LDA in the presence of $Me_2(t\text{-Bu})SiCl$ gave a significant decrease in stereochemical purity of the silylation product **20** compared with the starting epoxide. Addition of LDA to a 1:1:1 mixture of (*E*)-**12**, **3** and $Me_2(t\text{-Bu})SiCl$ gave only **20** in more than 90% yield, suggesting that silylation of the carbenoid is much faster than its trapping with the alkenylzirconocene compound.



(*E*)-**12**, *E* : *Z* > 96:4

20, *Z* : *E* = 88:12

(4)

Overall we have shown that the insertion of lithiated α,β-epoxynitriles into alkenylzirconocene chlorides represents a convergent and efficient route to a range of 2-cyano-1,3-dienes.[13,14]

Acknowledgements

We thank the Engineering and Physical Sciences Research Council (EPSRC) for a postdoctoral award (GR/N00647). R.J.W. thanks Pfizer for generous uncommitted support.

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7. Recently we have found that the reaction of lithiated α-silylepoxides with zirconacycles proceeds in a similar way, see: Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 5275.
8. The starting α,β-epoxynitriles were prepared by Darzan's reaction of $ClCH_2CN$ with the corresponding aldehydes in MeCN—50% NaOH aq.—cetyltrimethylammonium chloride (cat.) system. The initially formed ~1:1 mixtures of (*E*)- and (*Z*)-epoxides proved to be easily separable by column chromatography.
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11. The stereochemistry of the (*Z, E*)- and (*E, E*)-2-cyano-1,3-dienes **13**, **15**, **17** was determined by comparison of chemical shifts of the CN- and olefinic C-3-carbons in their ^{13}C NMR spectra. For all the compounds δ_{CN} was a

2.2–3.1 ppm lower field and $\delta_{C\text{-}3}$ was a 4.9–5.4 ppm higher field for (*Z*,*E*)-isomers compared to (*E*,*E*)-isomers due to the γ-gauche effect.

12. For a similar isomerisation of lithiated benzothiazolyl-substituted epoxides, see Ref. 4e.
13. For other synthetic routes to 2-cyano-1,3-dienes, see: (a) Arthur Jr., P.; Miegel, J. K.; Mochel, W. E.; Pratt, B. C.; Werntz, J. H. *J. Org. Chem.* **1958**, *23*, 803. (b) Nakano, M.; Okamoto, Y. *Synthesis* **1983**, 917. (c) Masuyama, Y.; Yamazaki, H.; Toyoda, Y.; Kurusu, Y. *Synthesis* **1985**, 964. (d) Bestmann, H. J.; Schmidt, M. *Angew. Chem.* **1987**, *99*, 64; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 79. (e) Janecki, T. *Synthesis* **1991**, 167.
14. Typical experimental procedure: To a stirred suspension of $Cp_2Zr(H)Cl$ (0.284 g, 1.10 mmol) in THF (10 mL) was added 1-octyne (0.110 g, 1.00 mmol). The mixture was stirred at 20°C for 1 h to give a clear yellow solution of **3**. After cooling to –90°C 2,3-epoxy-3-methylbutyronitrile (**4**) (0.126 g, 1.30 mmol) was added followed by a solution of LDA [1.30 mmol, freshly prepared from diisopropylamine (0.131 g, 1.30 mmol) and BuLi (1.30 mmol, 2.5 M in hexanes) in 2 mL of THF]. The mixture was stirred at –90 to –60°C over 1 h and quenched by addition of 2 M HCl aq. After stirring at 20°C for 30 min and extraction with ether the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (40–60 petroleum ether:EtOAc, 8:1) to give (*E*)-2-methyl-3-cyano-2,4-undecadiene (**5**) (0.122 g, 64% yield).