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Insertion of metallated epoxides into zirconacycles

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Abstract

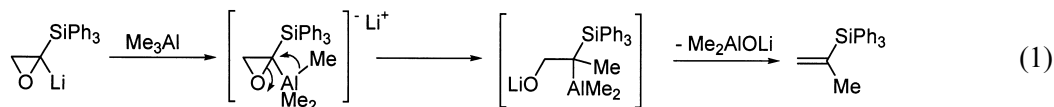
Metallated epoxides (epoxysilanes, epoxynitriles, epoxystyrene) insert efficiently into zirconacycles via a 1,2-metallate rearrangement to form intermediates which eliminate $\text{Cp}_2\text{Zr}(\text{R})\text{O}^-$ to afford substituted alkenes. © 2000 Elsevier Science Ltd. All rights reserved.

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The early transition metal induced intramolecular co-cyclisation of 1,*n*-dienes, -enynes, and -diynes to give metallacyclopent-anes, -enes, and -dienes is a useful method for carbon–carbon bond formation.¹ To fully realise their potential as intermediates in organic synthesis methods for elaboration of these metallacycles incorporating further organic fragments are needed. A variety of methods have been developed including carbonylation,² isocyanide insertion,³ and various copper catalysed processes.⁴ A characteristic of organozirconocene complexes is that the metal usually has a 16 electron configuration. Donation of an electron pair to the metal forms a much more nucleophilic 18 electron species. Based on this idea we have been investigating the insertion of lithium carbenoids into zirconacycles.^{5,6} Best developed is the insertion of lithium chloroallylide to form an allylzirconocene complex which may be further elaborated with a variety of electrophiles.^{5a,b} We now report the insertion of lithiated epoxides into zirconacycles. Metallated epoxides have an important place in organic chemistry as indicated by two recent reviews.⁷ They may be used as nucleophiles, but more usually are implied intermediates in the formation of carbenes. Generally a stabilising group is needed to allow formation by deprotonation,⁸ although unstabilised systems may be generated by tin/lithium exchange.⁹ Reaction of lithiated α -silylepoxides with organoaluminiums to afford alkenylsilanes via a mechanism including intramolecular nucleophilic ring opening followed by β -elimination has been reported (Eq. (1)).¹⁰ It is likely that other reactions of metallated epoxides with organometallics which have been described as occurring via insertion of carbenes into the carbon–metal bonds, actually occur via such 1,2-metallate

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rearrangements. It should be noted that α -metallation of epoxides greatly increases the electrophilicity of the adjacent C–O bond so direct nucleophilic ring opening is also possible.¹¹

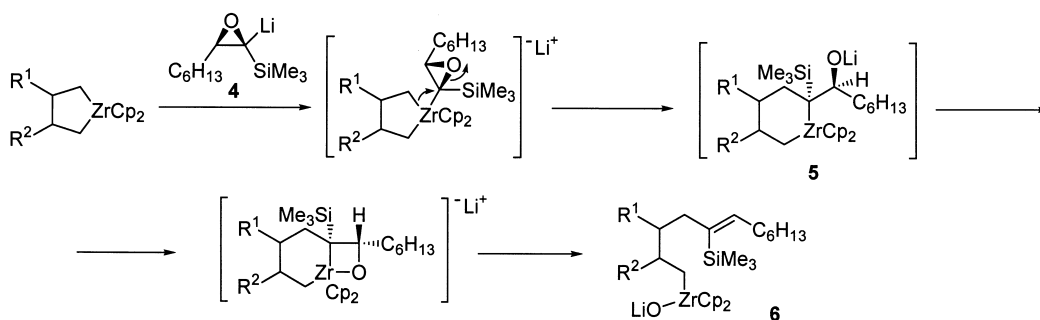


Deprotonation of *cis*-1-trimethylsilyl-1,2-epoxyoctane with ^sBuLi/TMEDA in ether at -100°C ^{8b} followed by addition of the zirconacycle **1** (formed from 4,4-dimethoxymethylhepta-1,6-diene and dibutylzirconocene)^{2a,12} in THF afforded after quenching with 2 M HCl aq. the (*Z*)-alkenylsilane containing product **2**¹³ together with some of the double inserted product **3** (Table 1, entry 1). The total yield was increased by using 1.8 equiv. of the metallated epoxide **4** but surprisingly with no effect on the ratio of mono- to di-inserted products (entry 2). A reasonable mechanism for the transformation is given in Scheme 1. The lack of effect of lithium carbenoid excess on the ratio of **2** to **3** suggests that the second insertion must take place with the zirconacyclohexane **5**, and that the acyclic alkylzirconium compound **6** is inert. We have previously found that $\text{Cp}_2\text{Zr}(\text{OR}^1)(\text{R}^2)$ species are inert towards carbenoid insertions.¹⁴

Table 1
Insertion of lithiated *cis*-trimethylsilyl-1,2-epoxyoctane (**4**) into zirconacycles^a ($\text{R} = \text{C}_6\text{H}_{13}$)

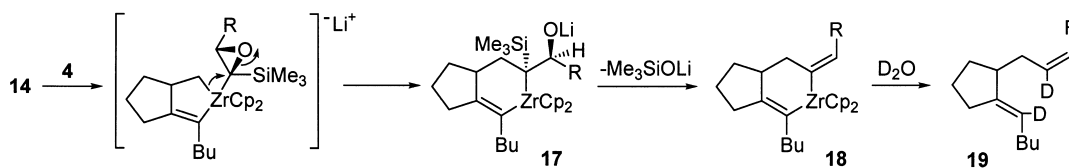
Entry	Zirconacycle	Products	Yield ^b
1			68%, 2 : 3 = 78 : 22
2	1		81% ^c , 2 : 3 = 77 : 23
3			80%, 8 : 9 = 93 : 7
4	7		60% ^d
5			72%, 12 : 13 = 84 : 16
6	11		71%, 12 : 13 = <5 : >95
9			72%, 15 : 16 = 79 : 21
7			
7			43%, 21 : 22 = 74 : 26
8	20		60% ^c , 21 : 22 = 78 : 22

^a Addition of a zirconacycle in THF to 1.3 equiv. of **4** in Et₂O at -100°C , then warming to -30°C over 2 h before quenching with 2M HCl aq. ^b Isolated yields based on diene, enyne or alkyne precursors of the zirconacycles, except entries 3 and 4 which were based on Cp_2ZrCl_2 . ^c 1.8 equiv. of **4** was used. ^d The reaction mixture was worked up with I_2 , 3 equiv., -60 to -30°C over 1h.

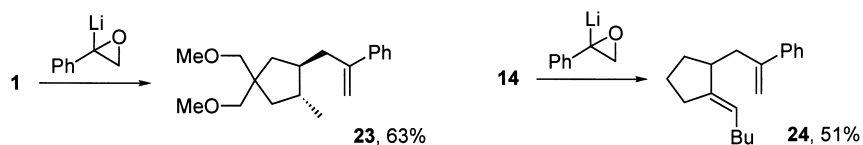


Scheme 1. Mechanism of formation of vinyl silanes

Warming dibutylzirconocene to room temperature under an ethylene atmosphere forms the parent zirconacyclopentane **7**.¹⁵ Addition of **7** to the lithiated epoxide **4** followed by aqueous work-up gave the expected alkenylsilane **8** with a small amount of the di-inserted product **9** (entry 3). Work-up with iodine gave a good yield of the iodide **10** (entry 4) confirming the presence of a carbon–zirconium bond in the final product **6** (Scheme 1). Co-cyclisation of 1,7-octadiene with dibutylzirconocene (-78 to 20°C , then 20°C , 2 h) leads to predominantly the *cis*-fused zirconacycle **11**. Subsequent heating for 2 h at 57°C isomerises the mixture to predominantly the *trans*-fused zirconacycle.¹⁶ Both *cis*-**11** and *trans*-**11** insert the lithiated epoxide **4** to form the alkenylsilanes **12** and **13** after hydrolysis with no corresponding double insertion products (entries 5 and 6). The bicyclic zirconacyclopentene **14** readily prepared from undec-1-en-6-yne and dibutylzirconocene^{2b} reacted with **4** to afford the alkenylsilane **15**¹³ together with the (*Z*)-alkene product **16** (entry 7). The formation of **16** is presumably due to eliminating Me_3SiO^- (together with $\text{Cp}_2\text{Zr}(\text{R})\text{O}^-$ as shown in Scheme 1) from the intermediate **17** giving the zirconacyclohexene **18** (Scheme 2). The generation of **18** was confirmed by deuteration to give **19**. We have previously found that carbenoid insertion into (α -substituted-alkenyl)-zirconium bonds does not occur,¹⁴ so the lack of the double insertion product was expected. Reaction of **4** with the zirconacyclopentene **20** prepared from the parent zirconacyclopentane **7** and 4-octyne¹⁵ occurred as with **14** to afford a mixture of the alkenylsilane **21** and the (*Z*)-alkene product **22** (entries 7 and 8). It was interesting that attempted insertion of **4** into the zirconacycle **20** formed in the more usual way from zirconocene dichloride, 2 equivalents of ethylmagnesium chloride, and 4-octyne¹⁷ failed. A reasonable explanation is that the lithiated epoxide underwent rapid transmetalation with magnesium chloride present in the reaction mixture to afford an unreactive magnesium species.

Scheme 2. Mechanism of formation of *cis*-alkene products ($\text{R} = \text{C}_6\text{H}_{13}$)

Styrene oxide was readily deprotonated with $t\text{BuLi}$ /TMEDA at -90°C ^{8a,c} and reacted with the saturated and unsaturated zirconacycles **1** and **14** to give the styrenes **23** and **24**, respectively, in reasonable yield provided that two equivalents of the rather unstable carbenoid was used (Scheme 3).



Finally we examined the insertion of epoxides carrying the electron withdrawing cyano-group at the α -position. These are readily deprotonated with LDA by using an in situ generation technique.^{8c} However, in the absence of an electrophile the epoxynitriles underwent extremely rapid self-condensation even at -90°C (Eq. (2)). Addition of LDA to a mixture of the zirconacycles **1**, **25** and the epoxynitriles **26**, **27** in THF at -90°C followed by warming to -60°C and acidic work-up gave the expected α,β -unsaturated nitriles **28**, **29**, **30** and **31** as shown in Table 2. The yield could be increased by changing to a reverse addition method where the epoxide was added to a mixture of the zirconacycle and LDA (entries 3 and 6). The reaction of the β -monosubstituted epoxynitrile **32** with the zirconacycle **1** gave the expected α,β -unsaturated nitrile **33** in excellent yield with good selectivity for the (*Z*)-isomer (entry 7). The observed stereochemistry is not expected from the mechanism shown in Scheme 1.¹⁸ To make use of the carbon–zirconium bond present in the

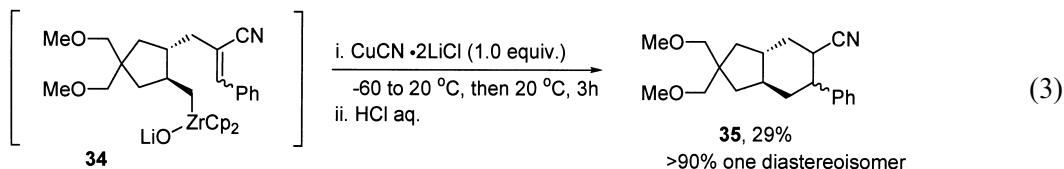
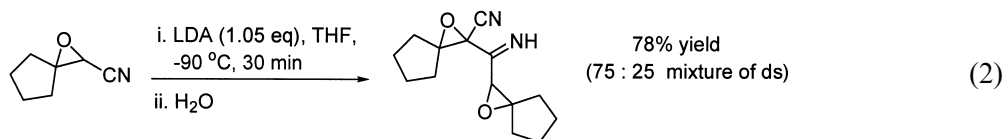
Table 2
Insertion of lithiated α,β -epoxynitriles into zirconacycles^a

Entry	Epoxide	Zirconacycle	Product	Yield, % ^b
1				70
2	26			65
3	26	25	29	70 ^c
4		1		66
5	27	25		50
6	27	25	31	64 ^c
7		1		88

^a Addition of 1.3 equiv. of LDA to a mixture of a zirconacycle and an epoxide (1.3 equiv.) in THF at -90°C , then warming to -60°C over 1 h before quenching with 2M HCl aq. ^b Isolated yields based on diene or enyne precursors of the zirconacycles.

^c Addition of an epoxide to a mixture of a zirconacycle and LDA.

presumed intermediate organozirconium species **34** we treated the reaction mixture with copper cyanide to afford the cyclohexane product **35** as >90% one diastereoisomer via intramolecular conjugate addition of an organocopper species generated by Zr/Cu exchange (Eq. (3)).¹⁹



Acknowledgements

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References

- Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p. 1163. Broene, R. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, p. 323.
- (a) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, F. E.; Cedrebaum, D. R.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
- Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Synlett* **1994**, 110. Probert, G. D.; Whitby, R. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 4113 and references cited therein.
- Kasai, K.; Kitora, M.; Suzuki, N.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 109. Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407. Takahashi, T.; Nishihara, Y.; Hara, R.; Huo, S. Q.; Kitora, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1599. Liu, Y. H.; Shen, B. J.; Kitora, M.; Takahashi, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 949. Takahashi, T.; Xi, Z. F.; Kitora, M.; Xi, C. J.; Nakajima, K. *Tetrahedron Lett.* **1996**, *37*, 7521. Takahashi, T.; Kitora, M.; Xi, Z. F. *J. Chem. Soc., Chem. Commun.* **1995**, 1503.
- (a) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1994**, *35*, 785. (b) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1994**, *35*, 9465. (c) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1995**, *36*, 4109. (d) Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1996**, *37*, 7661. (e) Gordon, G. J.; Whitby, R. J. *Synlett* **1995**, 77. (f) Tuckett, M. W.; Watkins, W. J.; Whitby, R. J. *Tetrahedron Lett.* **1998**, *39*, 123. (g) Fillery, S. M.; Gordon, G. J.; Luker, T.; Whitby, R. J. *Pure Appl. Chem.* **1997**, *69*, 633. (h) Gordon, G. J.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1997**, 1045 and 1321.
- This type of 1,2-metallate rearrangement was first noted with acyclic organozirconocene chlorides by Negishi: Negishi, E.; Akiyoshi, K.; O'Connor, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089.
- Satoh, T. *Chem. Rev.* **1996**, *96*, 3303. Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337.
- (a) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1976**, *121*, C-10. (b) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042. (c) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835. (d) Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 897. (e) Florio, S.; Ingrassio, G.; Troisi, L.; Lucchini, V. *Tetrahedron Lett.* **1993**, *34*, 1363.

9. Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, 32, 615.
10. Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, 32, 2783.
11. Boche, G.; Bosold, F.; Lohrenz, J. C. W.; Opel, A.; Zulauf, P. *Chem. Ber.* **1993**, 126, 1873.
12. Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, 111, 6435.
13. The (*Z*)-configuration of the silyl-substituted double bonds in **2**, **15** was confirmed by comparison of their ¹H and ¹³C NMR data with those of the corresponding (*E*)-isomers (see: Dishington, A. P.; Douthwaite, R. E.; Mortlock, A.; Muccioli, A. B.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 323 for (*Z*)- and (*E*)-3-trimethylsilyl-3-hexenes). The compounds (*E*)-**2** and (*E*)-**15** were prepared in 12 and 17% yields, respectively, by treatment of lithiated *trans*-1-trimethylsilyl-1,2-epoxyoctane with the zirconacycles **1** and **14**.
14. Kasatkin, A. N.; Whitby, R. J., unpublished results.
15. Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, 60, 4444.
16. Akita, M.; Yasuda, H.; Yamamoto, H.; Nakamura, A. *Polyhedron* **1991**, 10, 1. Taber, D. F.; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, 116, 9457.
17. Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, 34, 687.
18. In contrast with the reported configurational stability of many lithiated α -silyloxyepoxides,^{8b} conjugation with the cyano-group might facilitate the interconversion of the stereoisomeric oxiranyllithiums under the reaction conditions (see Ref. 8e). The (*Z*)-isomer giving the (*Z*)- α,β -unsaturated nitrile **33** by the reaction with **1** (Scheme 1) is probably more reactive toward carbenoid insertions for steric reasons.
19. For copper catalysed conjugate addition reactions of alkylzirconocene chlorides, see: Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, 56, 6494. Wipf, P.; Xu, W. J.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, 50, 1935.