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Cyclopropyl carbenoid insertion into alkenylzirconocenes—a convergent synthesis of alkenylcyclopropanes and alkylidenecyclopropanes

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Abstract—The insertion of cyclopropyl carbenoids into alkenylzirconocenes, derived by hydrozirconation of terminal alkynes, affords allylzirconium species which react with protons and isonitriles to afford alkenylcyclopropanes, and with aldehydes to afford alkylidene cyclopropanes. The addition of lithium carbenoid to zirconium occurs with the inversion of the organolithium centre.

Synthetic methods which form several carbon–carbon bonds in sequence are valuable for the efficient synthesis of complex molecules. The insertion of lithium carbenoids into metal–carbon bonds via a 1,2-metallate rearrangement[1] is a little investigated reaction which holds particular synthetic promise since the product retains the organometallic functionality of the starting material—the process is inherently iterative. We previously reported the convergent formation of allylzirconium compounds **1** by the insertion of heteroatom-substituted alkyl carbenoids into an alkenylzirconocene.[2] A problem with allylmetallics as intermediates is that 1,3-migration of the metal is facile, indeed the η^3-allyl form may be the most stable for transition metals. Unless one of the η^1-allyl forms is strongly favoured, or there is strong asymmetry in the bonding of metal to the two ends in the η^3-allyl form, mixtures of products may result on reaction with electrophiles. For the heteroatom-substituted examples **1** the zirconium is localised on the carbon indicated so that protonation occurs α- to the heteroatom, whereas with carbonyl compounds the γ-addition product is formed. Herein we report the convergent formation of cyclopropyl-containing allylzirconocenes **2** by the insertion of cyclopropyl carbenoids (1-lithio-1-halo-cyclopropanes)[3] into alkenylzirconocene chlorides in which the alkenylcyclopropane form of allylmetallic **2a** is far more stable than alkylidenecyclopropane isomer **2b** (Fig. 1).

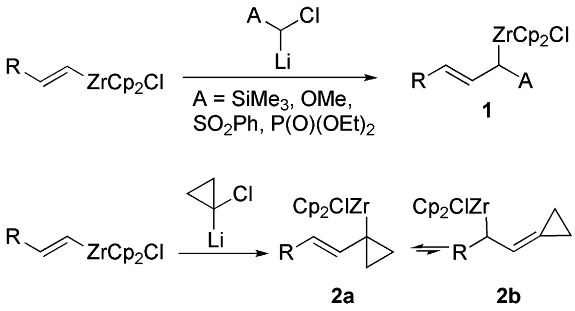

Figure 1. Convergent formation of allylzirconocene species.

Cyclopropane-containing compounds are of great interest to synthetic organic chemistry both as important building blocks,[4] and because they are key components of many compounds of biological interest.[5] Negishi et al. reported the addition of (1-bromo-2-methyl-2-phenylcyclopropyl)lithium to (*E*)-octenylzirconocene chloride in his pioneering studies on insertions into carbon–metal bonds via 1,2-metallate rearrangements.[1b] In related work, Harada and Oku reported the reaction of dialkylzincs with cyclopropyl lithium carbenoids to afford alkyl-cyclopropanes.[6] The reaction of trialkylmanganates with dibromocyclopropanes also probably occurs via a similar mechanism.[7]

Our studies started with cyclohexyl-fused cyclopropyl carbenoid **4**, which can be formed with a high selectivity for the thermodynamically more stable *endo*-lithium

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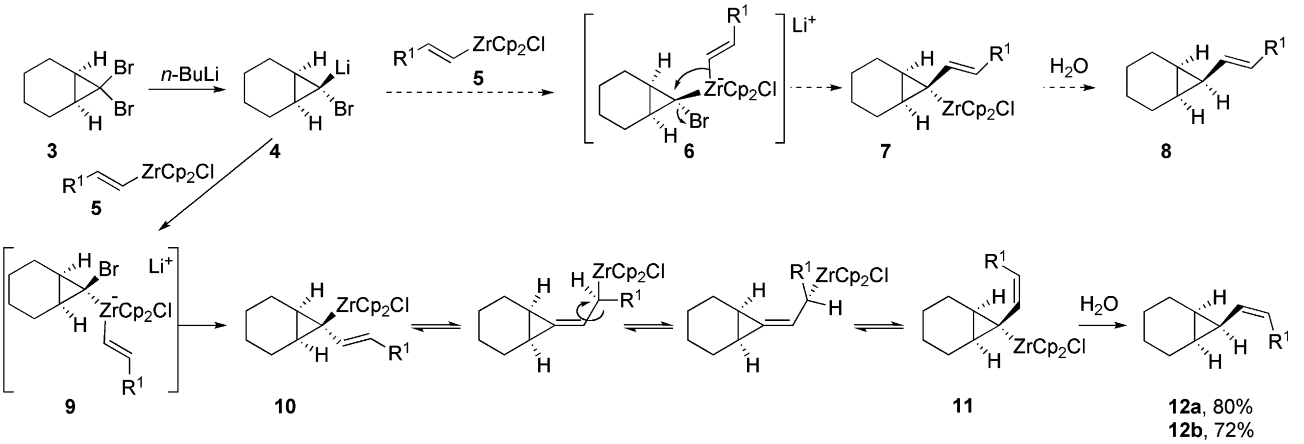
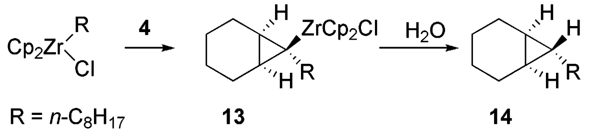
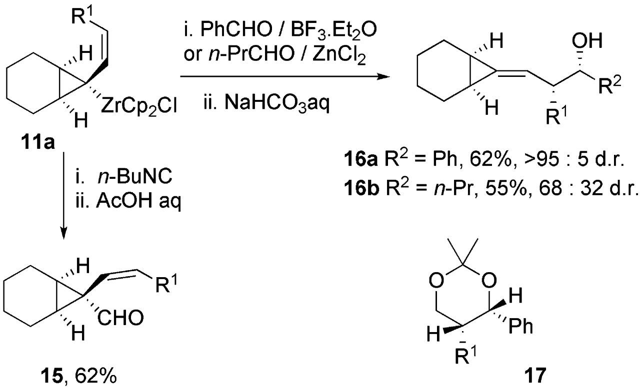


Scheme 1. Insertion of 7-bromo-7-lithionorcarane into alkenylzirconocenes. Series **a** $R^1 = n\text{-}C_6H_{13}$, series **b** $R^1 = \text{–}(CH_2)_3OSiMe_2t\text{-}Bu$.

isomer when a slight excess of dibromide **3** is used to promote isomerisation.[3b] Insertion into (*E*)-alkenylzirconocene chloride **5**, derived by hydrozirconation of 1-octyne or *tert*-butyldimethyl(pent-4-ynyloxy)silane, was expected to form the (*E*)-allylzirconium species **7**, with the zirconium lying on the *exo*-face, via 1,2-metallate rearrangement with inversion of the intermediate 'ate' complex **6**. Protonation would be expected to occur with retention of stereochemistry and position of the carbon–zirconium bond to give the (*E*)-*endo*-alkenyl-substituted norcarane **8** (Scheme 1). Much to our surprise, although the alkenyl group was indeed *endo*, it was clearly (*Z*)-isomer **12** (J_{HH} between alkene protons = 10.7 Hz) which had been formed in a good yield.[8] We would expect **12** to be derived by the protonation of organozirconium **11**, which could be formed from (*E*)-alkenyl-*endo*-zirconocene **10** via 1,3-metal shift to give the alkylidene cyclopropane isomer, rotation and a second 1,3-shift. The inversion of stereochemistry of the carbon carrying the zirconium is accompanied by geometric isomerisation of the alkene moiety. The isomerisation is in accord with DFT calculations, which indicate that **11** is 9 kJ/mol more stable than **10**.[9] The dicyclopentadienylzirconium chloride moiety is a larger group than 1-alkenyl so prefers to be on the less sterically crowded *exo*-face. The insertion of carbenoid **4** into *n*-octylzirconocene chloride gave the *exo*-octyl substituted norcarane **14** on protonation, presumably from the *endo*-organozirconium species **13**, which cannot undergo the same type of isomerisation as **10**. The reduction of **12a** with di-imide gave the *endo*-octyl epimer of **14**. One explanation for the initial formation of **10** rather than **7** is that attack of organolithium **4** on the zirconium to give the 'ate' complex **9** occurs with inversion of stereochemistry of the carbenoid centre. Although rare, there are examples of organolithium species reacting with inversion rather than retention of stereochemistry, for example, in certain transmetallations to tin.[10] An alternative, which cannot be ruled out on the basis of the experiments described above is that the carbenoid is undergoing rapid epimerisation, and that the small concentration of the *exo*-lithium species is trapped preferentially as it is much less sterically hindered thus leading directly to **9**.[11]



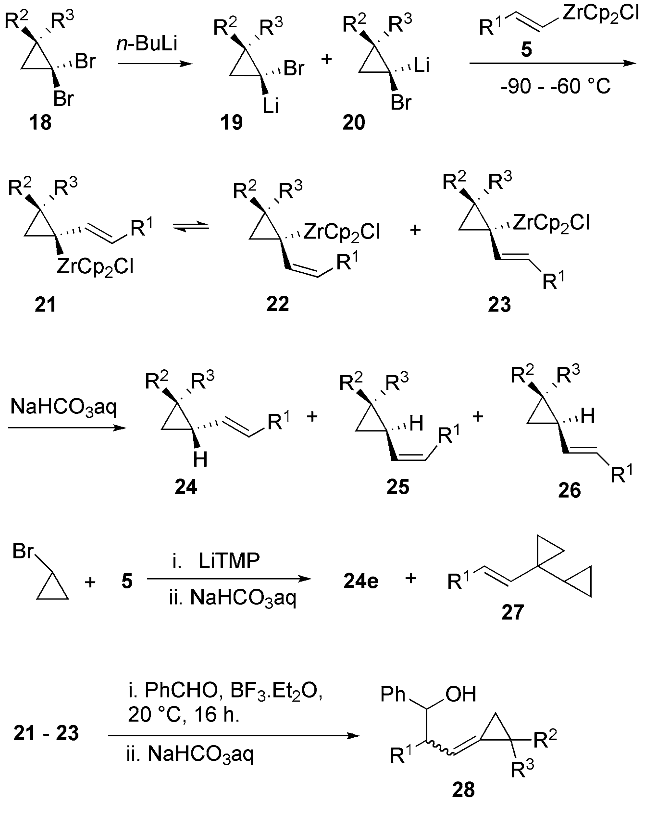
We briefly examined the reaction of **11a** with other electrophiles. Insertion of *n*-butylisocyanide into **11a** occurred with the same stereo- and regiochemistry as protonation to afford aldehyde **15** on mild acidic hydrolysis (Scheme 2). The addition of benzaldehyde to **11a** required $BF_3{\cdot}Et_2O$ for reaction (room temperature, 16 h), and occurred selectively at the position γ- to zirconium to afford the alkylidene cyclopropane **16a** in a reasonable overall yield (Scheme 2). The reaction was highly stereoselective to afford the *syn*-adduct, the stereochemistry of which was established by the conversion of **16a** to acetonide **17**.[12] Oxidative cleavage of alkylidenecyclopropane **16a** proved very difficult,[13] but use of 0.5 equiv of OsO_4 and 50 equiv $NaIO_4$ gave the required diol precursor of **17** in a 11% yield. The reaction of allylzirconium species with aldehydes has previously been observed to occur with a high *anti*-selectivity.[2,14] Presumably the difference in this case is due to the (*Z*)-stereochemistry of allylzirconium **11a** and, despite the presence of $BF_3{\cdot}Et_2O$, implies a cyclic transition



Scheme 2. Functionalisation of norcarane-allyl-zirconocene. $R^1 = n\text{-}C_6H_{13}$.

state. The use of $ZnCl_2$ (room temperature, 16 h) to activate the reaction gave a 55% yield of **16a** as a 4:1 *syn*:*anti* mixture. The addition of butanal only worked adequately with $ZnCl_2$ to give **16b** as a 2:1 *syn*:*anti* mixture.

To further probe the mechanism of insertion of the cyclopropyl carbenoids, and to extend the synthetic utility of the reaction, we next examined the insertion of the un-, mono- and 2,2-bis-substituted cyclopropyl carbenoids **19**/**20** (Scheme 3, Table 1). The phenyl- and butyl-substituted cyclopropyl carbenoids were formed from dibromides **18a** and **b**, predominantly as isomers **19** with the lithium *syn* to the substituent, as confirmed by protonation, and in accord with literature precedent.[3b,6b] Reaction with (*E*)-octenylzirconocene chloride, followed by protonation, gave mixtures of the three isomeric alkenylcyclopropanes **24**–**26**.[15] The isomer ratios are consistent with the major isomer **19** of the carbenoid reacting with organozirconocene **5** with overall retention (i.e., double inversion) to afford allylzirconium species **21**, which is in equilibrium with species **22** via the 1,3-metal shift—rotation—1,3-shift, as described for the conversion of **10** to **11**. The conversion of the (*E*)- to (*Z*)-alkene is energetically balanced by the migration of the zirconocene fragment to less hindered face. The minor isomer **20** of the cyclopropyl carbenoid gives only **23**, which has no tendancy to isomerise as the zirconium is on the less hindered face. In the cases of insertion of the 2,2-bis-substituted carbenoids **19c** and **19d**, the zirconium cannot avoid being *syn* to a substituent on the cyclopropyl ring, so there is little driving force for the (*E*)- to (*Z*)-alkene isomerisation, and only the former is observed. The good correlation between the ratio of carbenoid isomers present, and stereochemistry of the products formed in series **a**–**c** provides support for the proposed transmetallation from lithium to zirconium in the formation of the intermediate 'ate' complexes occurring with inversion of the organolithium centre. In the alternative explanation for the observed stereochemistry, trapping of the carbenoid from a rapidly equilibrating mixture, such a correlation would only be coincidental.



Scheme 3. Insertion of un-, mono- and 2,2-bis-substituted cyclopropyl carbenoids. $R^1 = n\text{-}C_6H_{13}$.

The unsubstituted cyclopropyl carbenoid **19e** was generated by in situ deprotonation of bromocyclopropane with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) and afforded only (*E*)-alkene **24e** on protonation, as expected, but in this case an additional product **27** resulting from the double insertion of the carbenoid was observed, even when only 1 equiv of the carbenoid was used. The use of 4 equiv of the carbenoid made **27** the major product and it was isolated in a 46% yield.

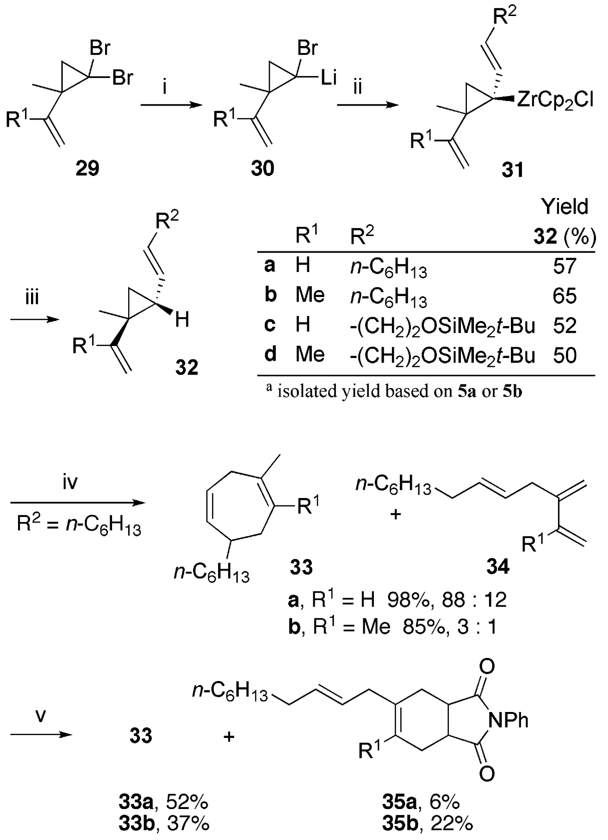
We next examined the reaction of the allylzirconium species **21**–**23** with benzaldehyde and obtained the alkylidene cyclopropane adducts **28** in a reasonable to poor yield (Scheme 3, Table 1).[16] In the cases of **28a**–**c** there are eight possible isomeric products—three stereocentres and *E*/*Z* alkene stereochemistry—so the reactions are highly stereoselective. We have not yet been able to determine unambiguously which isomers are formed.

Finally we examined the alkenyl-substituted cyclopropyl carbenoids **30** generated from dibromides **29** (Scheme 4). Reaction with alkenylzirconocenes **5** and protonation gave the *trans*-1,2-dialkenylcyclopropanes **32a**–**d** with excellent stereoselectivity. Heating the *trans*-dialkenylcyclopropanes **32a** and **b** at 180 °C for 1 h (microwave) gave reasonable yields of the required cycloheptadienes **33**;[17] however, there was substantial contamination with

Table 1. Alkenyl- and alkenylidine-cyclopropanes from insertion of cyclopropyl carbenoids into alkenylzirconocenes

	R^2	R^3	**19**:**20**	Yield **24**–**26** (%)	Ratio **24**:**25**:**26**	Yield **28** (%)	DR of **28**[a]
a	Ph	H	80:20	66	42:42:16	59	76:21:3
b	Bu	H	70:30	80	44:27:29	69	71:29
c	Ph	Me	80:20	77	81:0:19	58	61:33:6
d	Me	Me	NA	60	100:0:NA	8	85:15
e	H	H	NA	46	100:0:NA	18	>95:<5

[a] Diastereoisomer composition of **28** determined by NMR studies on crude and/or purified products.



	R^1	R^2	Yield **32** (%)
a	H	$n\text{-}C_6H_{13}$	57
b	Me	$n\text{-}C_6H_{13}$	65
c	H	$-(CH_2)_2OSiMe_2t\text{-}Bu$	52
d	Me	$-(CH_2)_2OSiMe_2t\text{-}Bu$	50

[a] isolated yield based on **5a** or **5b**

Scheme 4. Reagents and conditions: (i) ^{n}BuLi, −90 °C, 15 min; (ii) 0.5 equiv (*E*)-$Cp_2ZrCl(CH{=}CHR^2)$ **5**, R^1 = H, −90 to −40 °C over 5 h or R^1 = Me, −90 to 20 °C over 5 h; (iii) MeOH, $NaHCO_3$aq, 20 °C, 16 h; (iv) 180 °C, 1 h, μW, DMF; (v) 0.12 equiv or 0.5 equiv *N*-phenylmaleimide, toluene, 115 °C, 4 h.

the inseparable dienes **34** arising from a homodienyl-1,5-hydrogen shift (retro-ene reaction).[18] Reaction of the mixture with *N*-phenylmaleimide and chromatography allowed the isolation of pure **33**, together with the Diels–Alder adduct **35** of **34**.

Overall we have shown that the reaction of readily generated cyclopropyl carbenoids with alkenylzirconocenes provides a facile convergent route to alkenylcyclopropanes and alkylidenecyclopropanes, important intermediates in organic synthesis.[19,20] In each case the stereochemistry of the products is consistent with transmetallation from lithium to zirconium in the formation of an 'ate' complex occurring with the inversion of the organolithium centre.

Acknowledgements

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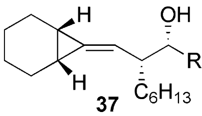
12. We have not proved the relative stereochemistry between the CH(hexyl)CH(OH)Ph fragment and the cyclohexyl–cyclopropane ring fusion, which can also be viewed as the alkene stereochemistry, but diastereoisomer **37** would only be accessible by the attack of the electrophile *anti*- to the zirconium, which is unlikely both because the cyclohexyl ring provides an effective steric block, and because it would then be very difficult to account for the *syn* stereochemistry observed.



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