# Tandem reactions on a zirconocene template

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Abstract: Co-cyclisation of alkenes with alkenes or alkynes and zirconocene gives zirconacycles which are further elaborated by the consecutive insertion of allyl, propargyl, or allenyl metal carbenoids and electrophiles. Insertion of other carbenoids give the first zirconacyclohexanes with the potential for further elaboration.

The intramolecular co-cyclisation of 1,n-dienes and -enynes with 'Cp$_2$Zr' (zirconocene) to give zirconacycles is a useful process for the synthesis of carbocyclic and heterocyclic systems[1]. It is most conveniently carried out using the 'zirconocene' equivalent zirconocene 1-butene (the Negishi reagent[2]) formed *in situ* from dibutylzirconocene (**Eq 1**). Efficient use of the metal relies on productive elaboration of the carbon-zirconium bonds in the intermediate zirconacycles[3] and this paper summarises some of our contributions.
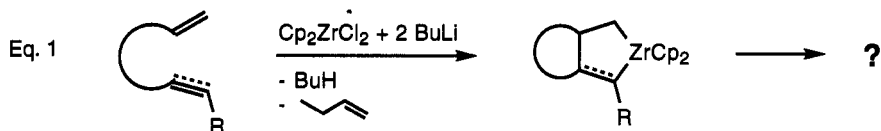
One useful elaboration method is carbonylation to give cyclopentanones or cyclopentenones, for example in our synthesis of the hypoglycaemic natural product tecomanine[4].
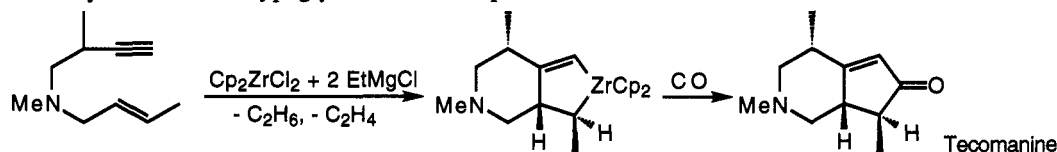

An intermediate in carbonylation is a zirconocene η^2-ketone complex, the nitrogen analogues of which (zirconocene η^2-imine complexes) have been shown to be useful carbometallating reagents[5]. We discovered that insertion of a variety of isocyanides into zirconacycles in the presence of suitable trapping

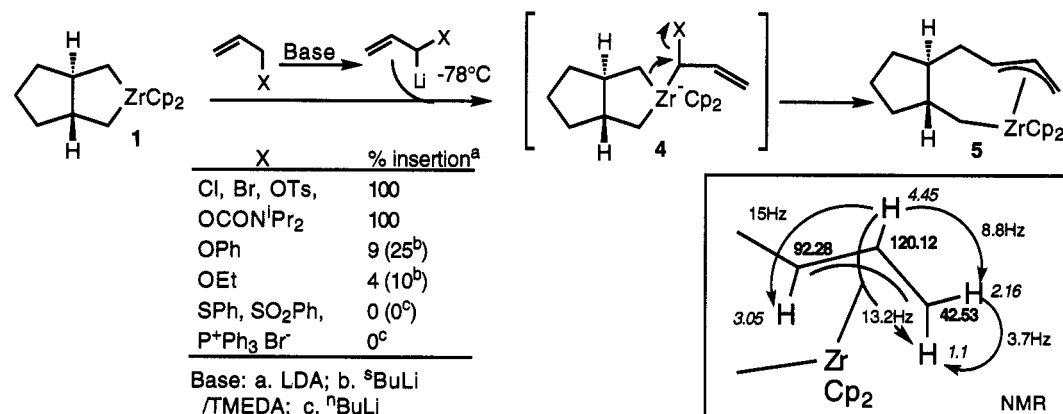RNC = PhNC, BuNC, CyNC, Me$_3$SiCN.
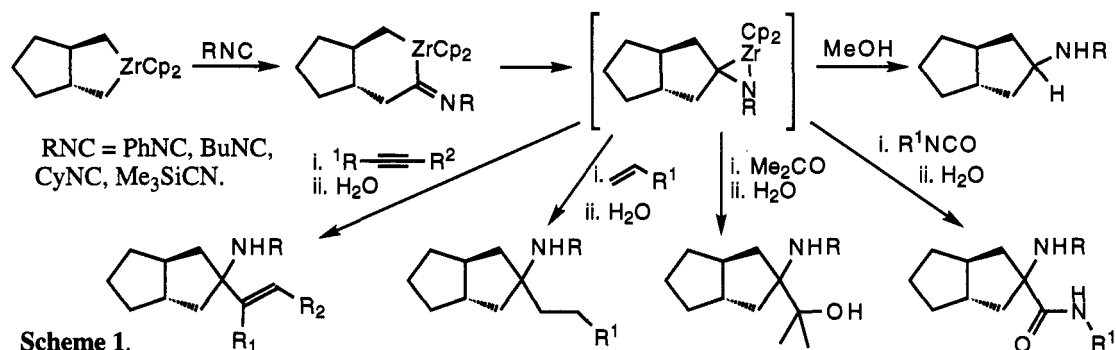
Scheme 1.

agents gave cyclopentylamines[6] (**Scheme 1**). The most useful is the insertion of trimethylsilyl cyanide (*via* its isocyanide isomer) to give primary amines. The transformations shown in **Scheme 1** are a good illustration of efficient use of the transition metal - four new carbon-carbon bonds are formed from four components in a one pot reaction.

The extremely fast (rapid at -130°C for CO) insertion of carbon monoxide[7] and isocyanides into carbon-zirconium bonds is due to their carbenic character. Reaction is initiated by donation of an electron pair to the 16 electron zirconium atom to form an unstable 18-electron complex and completed by rearrangement accompanied by return of the electrons. In an important paper Negishi described[8] the insertion of various metal carbenoids into the carbon-metal bond of acyclic zirconocene chlorides which is conceptually similar. We have extended this chemistry to zirconacycles, and to a wide range of metal carbenoids, particularly those which allow further elaboration by the addition of electrophiles.

Addition of lithium chloropropargylide to the zirconacycle **1** afforded the ring-expanded zirconium complex **3**, presumably *via* formation of the zirconate complex **2** (**Scheme 2**)[9]. NMR studies on **3** suggest that it is best viewed as the cycloalkyne form **3a** rather than the allene form **3b**. Quenching with methanol afforded an allene in good overall yield.
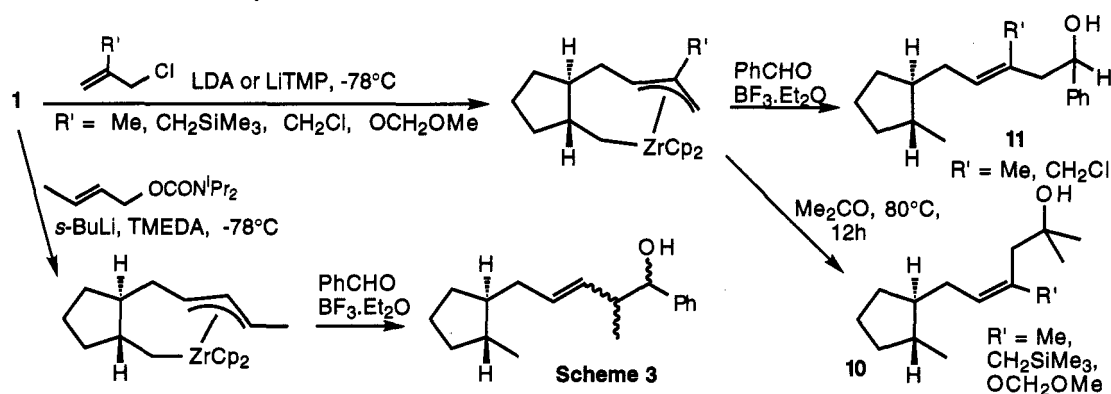

Scheme 2.
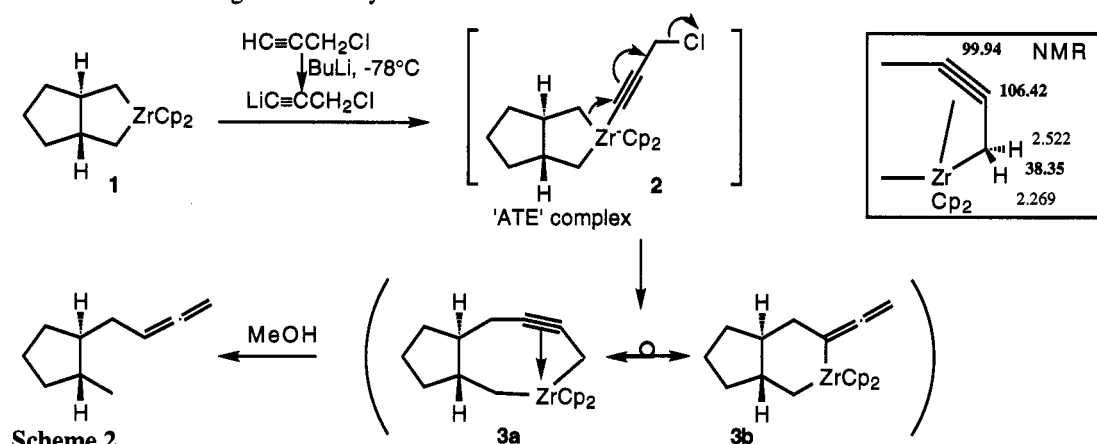
Allylzirconium reagents are known to undergo addition to a variety of carbonyl based electrophiles so a route to these offered potential for further elaboration. Reaction between the zirconacycle **1** and lithium chloroallylide, generated *in-situ* by deprotonation of allyl chloride, gave the allylzirconium complex **5**. Variation of the metal carbenoid was instructive. To form the 'ate' complex **4** the anion needs to be reactive, and for the 1,2-metallate rearrangement[10] which gives **5**, the leaving group X must be good. With the leaving groups bromide, chloride, and tosylate the insertion is quantitative despite the instability of the anions. N,N-diisopropylcarbamate is a worse leaving group, but the anion is more stable and again insertion is quantitative. Alkoxide and phenoxide leaving groups give poor conversions, and insertion fails with less nucleophilic anions.

X	% insertion[a]
Cl, Br, OTs,	100
OCON^{i}Pr$_2$	100
OPh	9 (25[b])
OEt	4 (10[b])
SPh, SO$_2$Ph,	0 (0[c])
P$^+$Ph$_3$ Br$^-$	0[c]

Base: a. LDA; b. ^{s}BuLi
/TMEDA; c. ^{n}BuLi

Heating **5** with various ketones followed by aqueous work-up gave the *cis*-alkene products **7**, presumably *via* a *cis*-decalin type transition state **6**. Insertion of aldehydes required $BF_3.Et_2O$ to avoid preferential attack on the cyclopentadienyl rings, but then occurred in excellent yields to give the *trans*-alkene products **9**, presumably *via* the open transition state **8**. In these transformations four components have been combined, and three new C-C bonds formed in a one-pot reaction with very high overall yields. To establish this as a generally useful synthetic method we need to demonstrate that each component can be varied widely.
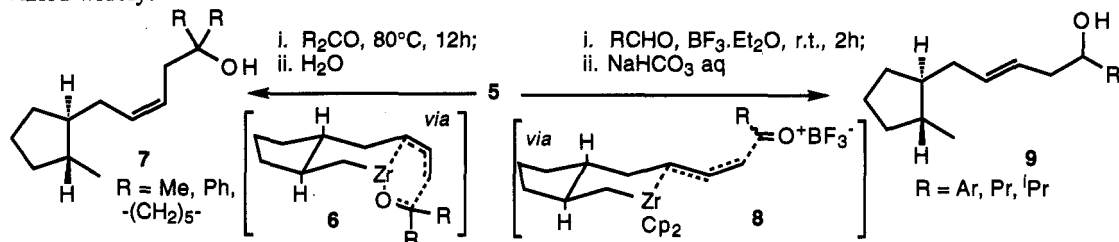
Variation of the allyl component.[9b] Insertion of lithiated methallyl chloride into **1**, followed by reaction with acetone, or benzaldehyde/$BF_3.Et_2O$ gave the complementary stereodefined trisubstituted alkenes **10** and **11**. The functionalised allyl components (2-trimethylsilylmethyl- and 2-chloromethyl- allyl chlorides) gave products containing nucleophilic (allyl silane) or electrophilic (allyl chloride) moieties. Insertion of lithiated 2-methoxymethoxy allyl chloride gave products containing a protected ketone (**Scheme 3**). Insertion of 3-substituted allyl carbamates into **1** was successful but further elaboration gave complex mixtures of E / Z and *erythro* : *threo* isomers.


Scheme 3

Variation of the electrophile.[9c] Aldehyde acetals in the presence of $BF_3.Et_2O$ added to **5** in high yield (**Scheme 4**). Aryl, vinyl, and alkyl substituents were successful, although several equivalents of the reagent were needed in the last case. At a higher oxidation level triethylorthoformate added slowly to give a protected aldehyde moiety. All attempts to insert ketals failed. Iminium salts, generated *in situ* from the
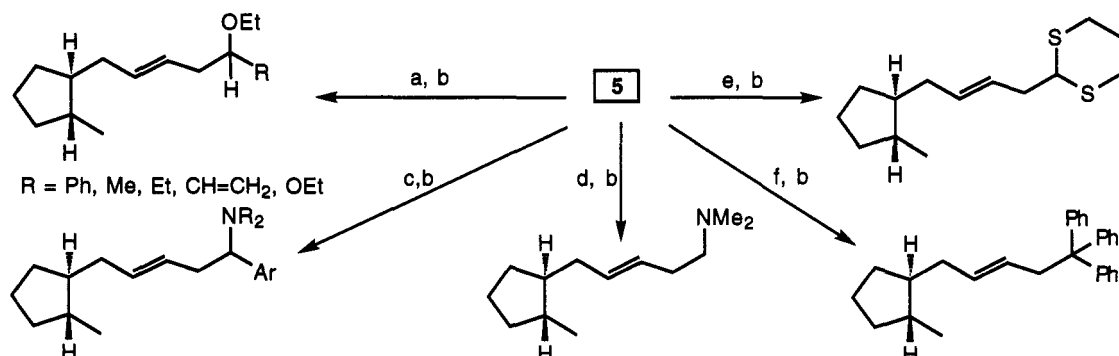
Scheme 4. a. $RCH(OEt)_2$ / $BF_3.Et_2O$, -78°C - r.t., 2h. b. i. MeOH; ii. $NaHCO_3$ aq, 12h, r.t. c. 1.5 eq $ArCH(NR_2)(OBu)$ / $BF_3.Et_2O$, -78°C - r.t., 2h.; d. 1.3 eq. $[CH_2=NMe_2]^+ I^-$, -78°C - r.t., 1.5h. e. 2 eq. 1,3-ditheniumtetrafluoroborate, -78°C - r.t., 1.5h. f. 1.3 eq. $Ph_3C^+BF_4^-$, -78°C - r.t., 1.5h.

1,1-aminoethers $(R_2N)(BuO)CHAr$ gave excellent yields of amines. Use of the pre-formed iminium salt, $[CH_2=NMe_2]^+$ I^- (Eschenmoser's salt) also worked well. Reaction of **5** with **1**, 3-dithenium tetrafluoroborate gave a 2-substituted-1,3-dithiane and even the stable carbocation, triphenylcarbenium tetrafluoroborate added. Electrophiles with less cationic character than the above failed to insert.

Variation in the zirconacycle[9d] Zirconacyclopentenes derived by co-cyclisation of enynes underwent the allyl carbenoid insertion specifically into the alkyl-zirconium bond. Addition of $RCHO/BF_3.Et_2O$ gave the elaborated products in excellent yields (**Scheme 5**). Formation of a monocyclic zirconium complex by reaction between *in situ* generated zirconocene ethylene and 2-butyne followed by addition of lithium chloromethallylide and 3-methyl-but-2-enal gave the stereodefined, non-natural sesquiterpene **12** in good overall yield illustrating the highly convergent nature of this methodology.
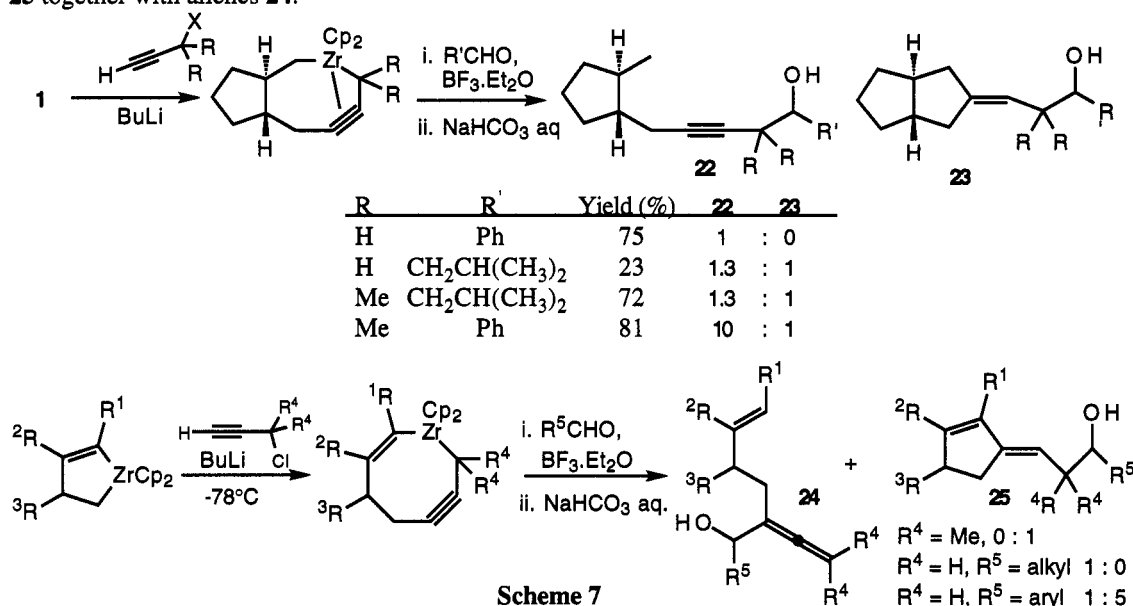
Scheme 5

$-A- = CH_2, CH_2CH_2, NCH_2Ph$

12 70% overall
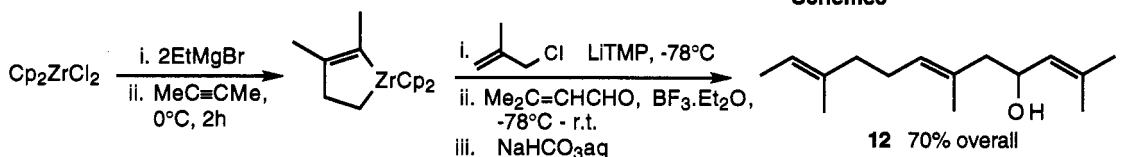
Efficient synthesis of the dolabellane bicyclo[9.3.0]tetradecane skeleton[9e] To illustrate the use of the tandem processes described above we have developed two routes to the bicyclo[9.3.0]tetradecane skeleton characteristic of the dolabellane diterpenes (e.g. acetoxyodontoschismenol) (**Scheme 6**). Zirconocene mediated co-cyclisation of **1**, 6-heptadiene followed by insertion of lithiated methallyl chloride gave the allyl zirconium species **13**. Reaction with triethylorthoformate followed by an iodinolytic work-up gave the iodide **14**. Reaction with lithio-1-(trimethylsilyl)-1-propyne, desilylation, deprotonation, and iodine quench gave the alkynyl iodide **15**. Careful hydrolysis of the acetal and an

Acetoxyodontoschismenol

Scheme 6
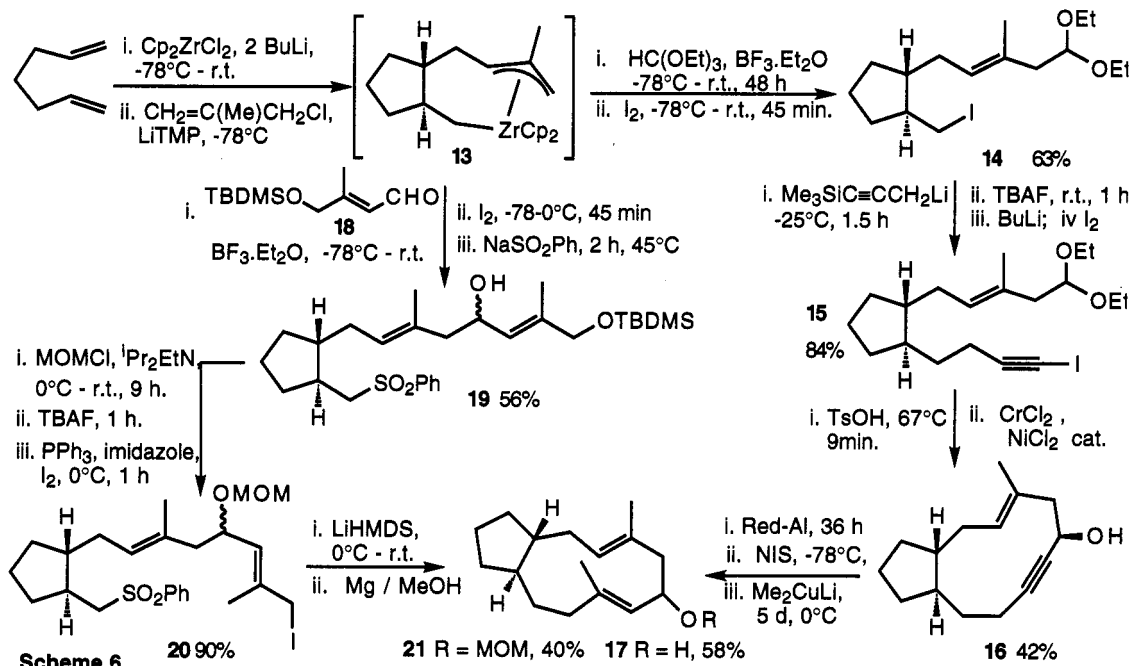
intramolecular Nozaki - Hiyama reaction afforded macrocycle **16** in good yield as a single diastereomer. Hydroalumination - iodination of the alkyne followed by reaction with lithium dimethylcupprate gave the desired dolabellane model **17**. Although successful the inclusion of two C-1 fragments in the synthesis is inelegant, and the acetal hydrolysis problematic so an alternative route was sought. Lewis acid catalysed reaction of methallyl zirconocene complex **13** with aldehyde **18** followed by iodinolytic work-up and reaction with sodium benzenesulphinate gave compound **16**, containing all the carbons required for **21**. A simple protection - deprotection sequence and conversion of the allylic alcohol to an allylic iodide gave the macrocyclisation precursor **20**. Slow addition of LiHMDS to a dilute solution of **18** followed by desulphonylation gave the required dolabellane model **21** in 5 steps, and 20% overall yield.

Consecutive insertion of allenyl or propargyl carbenoids and electrophiles.[9f] Further elaboration of zirconacycles resulting from insertion of 1-lithio-3-chloro-1-alkynes (allenyl carbenoid) (**Scheme 2**) proved complex. Whereas reaction of **3** with PhCHO/BF$_3$.Et$_2$O gave the expected acetylene **22** (**Scheme 7**), with alkyl aldehydes, or when 1,1-dimethylpropargyl chloride was used as the carbenoid precursor the cyclised product **23** was also formed. Unsaturated zirconacycles also gave the analogous cyclised product **25** together with allenes **24**.

| R	R'	Yield (%)	22		23
H	Ph	75	1	:	0
H	CH$_2$CH(CH$_3$)$_2$	23	1.3	:	1
Me	CH$_2$CH(CH$_3$)$_2$	72	1.3	:	1
Me	Ph	81	10	:	1

Scheme 7

Insertion of 1-lithio-1-chloro-2-alkynes (propargyl carbenoid) into various zirconacycles was efficient, and the resulting zirconacycles reacted cleanly with aldehydes to give alkyne products **26**[9g].

R = Ph, Bu, Me, SiMe$_3$
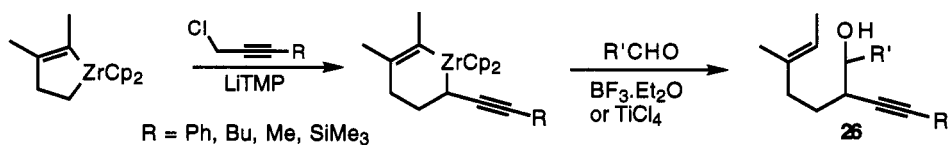
Ring expansion of zirconacyclopentanes to zirconacyclohexanes.[9h] With the methods we and others have developed to elaborate zirconacyclopentanes and pentenes it would be useful to be able to apply them also to zirconacyclohexanes. Treatment of **1** with a variety of metal carbenoids indeed provided the ring expanded products **27-29**, although the parent system (A = H) was not formed cleanly. Further elaboration of these remains to be investigated. The insertion of a variety of benzyl chlorides (aromatic and heteroaromatic) gave initially a mixture of diastereomers, but heating gave a single isomer **30**. Addition of a different benzyl carbenoid to **30** gave the specific product of double insertion **32** suggesting that the second insertion occurs only into the hydride

27 A = H, OMe, SPh, SiMe$_2$Ph, Br.
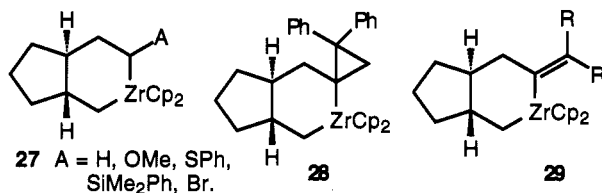
species **31** we suspect as mediating the epimerisation.
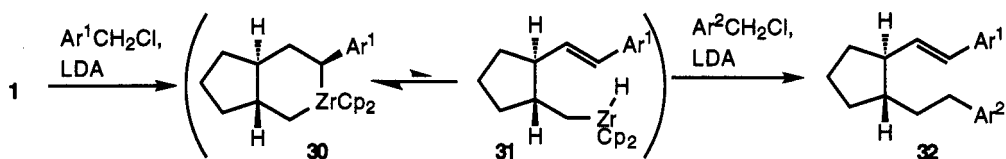
Conclusion.

We have discovered a variety of efficient tandem processes for elaborating organic fragments on a zirconocene template. Routes to zirconacyclohexanes which can be further elaborated by these, and other methods have also been developed.

Acknowledgements.

References.

1.   Negishi, E. I. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I. Eds.; Pergamon: Oxford, U.K., **1991**; Vol. 5; p 1163; Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124; Uesaka, N.; Mori, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4542; Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synlett* **1994**, 451.

2.   Rousset, C.J.; Swanson, D.R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105

3.   Carbonylation: Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521; Aldehyde insertion: Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695. Halogenation: Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435. Metathesis with other elements: Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880. Cu cat. allylation: Kasai, K.; Kotora, M.; Suzuki, N.; Takahashi, T. *J. Chem. Soc.; Chem. Commun.* **1995**, 109.Cu cat. reaction with RCOCl: Takahashi, T.; Kotora, M.; Xi, Z. F. *J. Chem. Soc., Chem. Commun.*, **1995**, 1503.

4.   Kemp, M. I.; Whitby, R. J.; Coote, S. J. Electronic Conference on Trends in Organic Chemistry (ECTOC-1) ISBN 0 85404 899 5, Eds. Rzepa, H. S. and Goodman, J. M. (CD-ROM), Royal Society of Chemistry publications, 1995. See also http://www.ch.ic.ac.uk/ectoc/

5.   Coles, N.; Harris, M.C.J.; Whitby, R. J.; Blagg, J. *Organometallics* **1994**, *13*, 190; Grossman, R.B.; Davis, W. M.; Buchwald, S.L. *J. Am. Chem. Soc.* **1991**, *113*, 2321.

6.   Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Tetrahedron Lett.* **1992**, *33*, 5655; *idem, ibid*, **1994**, *35*, 1445; *idem, Synlett* **1994**, 111; Probert, G. D.; Whitby, R. J.; Coote, S. J.*Tetrahedron Lett.*, 1995, *36*, 4113.

7.   Erker, G. *Acc. Chem. Res.* **1984**, *17*, 103.

8.   Negishi, E.; Akiyoshi, K.; O'Conner, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089.

9.   a. Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1994**, *35*, 785; b. *idem, ibid* **1994**, *50*, 9465; c. *idem, ibid* **1995**, *51*, 4109; d. Gordon, G. J.; Whitby, R. J. *Synlett* **1995**, 77; e. Luker, T.; Whitby, R. J. submitted to*Tetrahedron Lett.;* f. Gordon, G. J.; Whitby, R. J., submitted to *J. Am. Chem. Soc.*; g. *idem*, submitted to *Synlett.*; h. Fillery, S. F.; Whitby, R. J.; Blagg, J. submitted to *J. Am. Chem. Soc.*

10.   Kocienski, P.; Barber, C. *Pure and Appl. Chem.* **1990**, *62*, 1933.