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The Tandem Insertion of Allyl Carbenoids and Aldehydes or Ketones into Zirconacyclopentanes: Variation of the Allyl Moiety and Functionalisation of the Final Carbon-Zirconium Bond.

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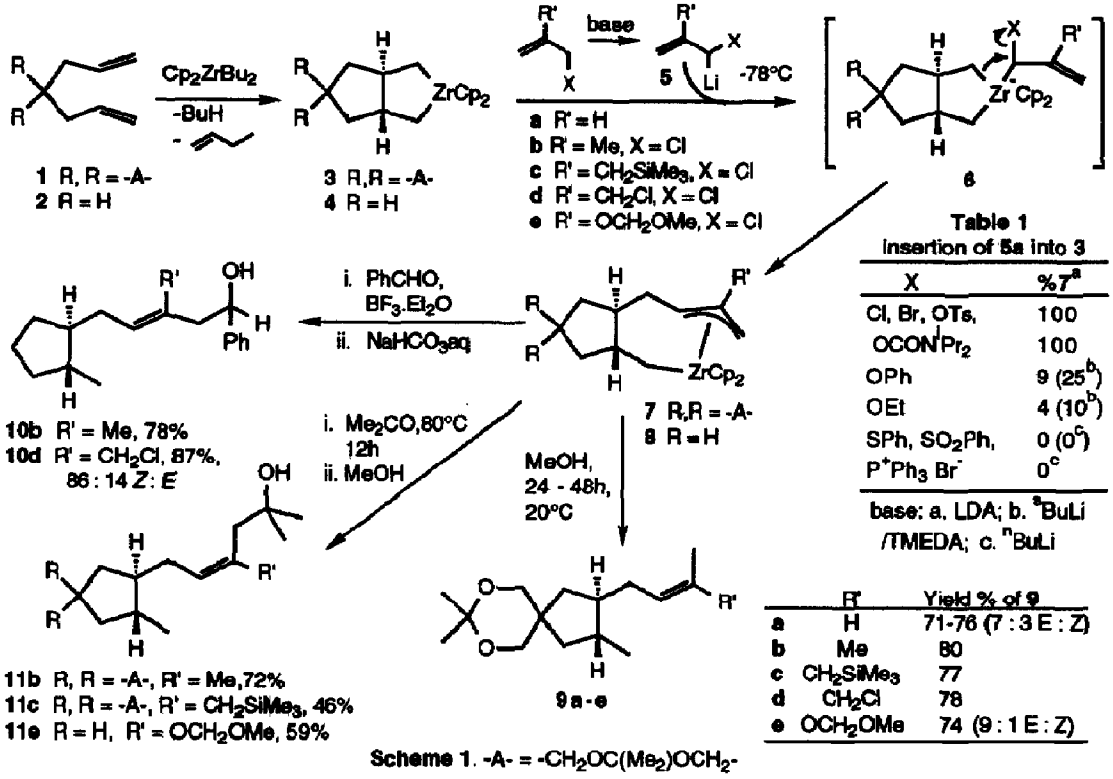
Abstract. *In situ* deprotonation of 2-methyl, 2-chloromethyl-, 2-trimethylsilylmethyl-, and 2-methoxymethoxy-substituted allyl chlorides generates allyl carbenoids which insert into zirconacyclopentanes to afford allyl zirconocenes. Allyl bromides, *p*-toluenesulphonates, or *N,N*-diisopropylcarbamates may also be used. The allyl zirconocenes undergo further reaction with aldehydes / $BF_3.Et_2O$ or ketones to give oxazirconacycles which may be protonated, halogenated, or oxygenated to afford organic products.

A wide variety of zirconacycles are available by convergent routes from simple organic precursors[1], and have great potential as intermediates in organic synthesis. The development of methods for productively elaborating the carbon-zirconium bonds in these zirconacycles is crucial[2]. We recently reported[3] the tandem insertion of lithium chloroallylide and aldehydes or ketones into saturated bicyclic zirconacycles e.g. **3** and **4**, (readily obtained by co-cyclisation of 1,6-dienes using the 'Negishi reagent' dibutylzirconocene[4]) to give elaborated cyclopentanes such as **10** and **11** (R'=H) on aqueous work up. The overall process comprises a four component coupling (as the alkenes need not be linked) in which the metal is used as a template upon which the organic fragments are assembled. To establish this as a generally useful synthetic method we need to demonstrate that each component can be varied widely. In this communication we report our attempts to vary the key component - the allyl carbenoid. We also demonstrate that the final carbon-zirconium bond may be successfully functionalised by halogenation and oxygenation.

Variation in the leaving group. For successful insertion two properties are required of the allyl carbenoid **5**. The anion must be nucleophilic enough to form the 'ate' complex **6**, and X must be a good leaving group for the rearrangement **6** - **7** to occur. This combination of properties make **5** very unstable, a problem which is somewhat alleviated by its generation *in situ*. The insertion of simple allyl carbenoids **5**[5] carrying a variety of groups X was attempted in order to establish the limits of these criteria (**Table 1**). When deprotonated *in situ* with lithium diisopropylamide (LDA) allyl bromide was as efficient as allyl chloride in the insertion reaction. Pleasingly metallated allyl *p*-toluenesulphonate and allyl *N,N*-diisopropylcarbamate[6] also gave quantitative conversion to the allyl complex **7a** and 71-76% yields of the isolated protonated products[7] **9a**. The easy formation of *p*-toluenesulphonates and *N,N*-diisopropylcarbamates from allylic alcohols make them attractive reagents. Allyl phenyl ether and allyl ethyl ether gave signs of success (**Table 1**) but allyl phenyl sulphide, allyl phenyl sulphone, and allyl triphenylphosphonium bromide failed to insert when deprotonated *in situ* with LDA, *n*-BuLi or *s*-BuLi / *N,N,N',N'*-tetramethylethylenediamine (TMEDA).



Scheme 1. -A- = $-CH_2OC(Me_2)OCH_2-$

2-Substituted allyl component. The successful insertion of lithiated methallyl chloride **5b** into **3** and **4** to afford **7b** and **8b**[8] (Scheme 1) demonstrates that simple 2-substituents are tolerated. Subsequent benzaldehyde / $BF_3.Et_2O$ insertion into **8b** and acetone insertion into **7b** afforded **10b** and **11b** respectively on aqueous work-up. It is remarkable that the stereochemistry of the trisubstituted alkene is reversed in the formation of these two products, in particular the Z stereochemistry of **11b** is unprecedented[9,10,11]. Protonation of **7b** afforded the alkene **9b**. Work-up with MeOD gave >90% deuteration of the '*cis*' methyl (δ_C 17.90 p.p.m.) rather than the '*trans*' (δ_C 25.93 p.p.m.).

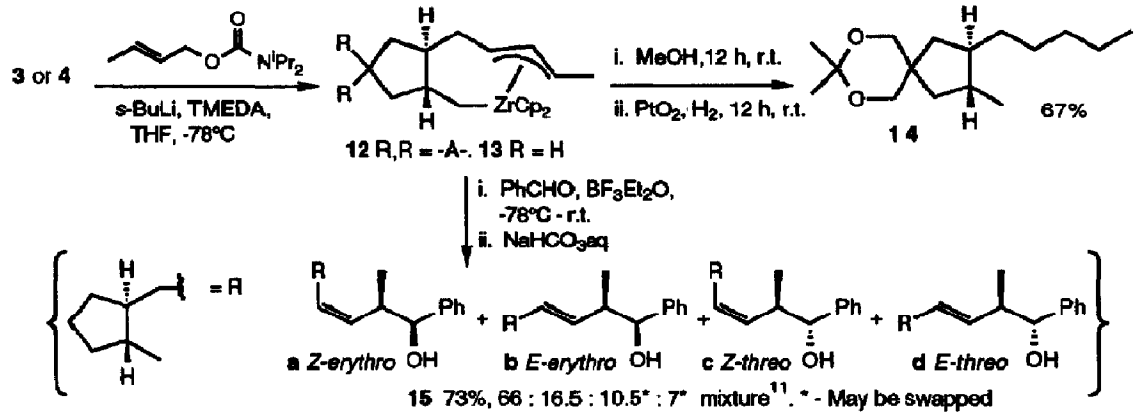
For the synthesis of polycyclic targets the incorporation of allyl components which may be later elaborated is important. This was accomplished by the insertion of lithiated 2-trimethylsilylmethyl-[12] and 2-chloromethyl- allyl chlorides **5c** and **d** to give **7c,d** and **8d**, and hence the organic products **9c,d**, **10d**, and **11c** (Scheme 1). These contain potentially nucleophilic (allyl silane) or electrophilic (allyl chloride) moieties for further elaboration.

2-Heteroatom substituted systems were examined next. Lithiated 2-methoxymethoxy allyl chloride[13] gave the expected allyl complexes **7e** and **8e** and hence the final organic compounds **9e** and **11e** containing a protected ketone moiety.

3-Substituted allyl component Attempts to insert 3-substituted allyl systems into **3** proved difficult. Under *in situ* lithiation conditions (LDA) crotyl chloride (4 : 1 *E* : *Z*) gave only 20% insertion, a situation which was not improved by using 5 equivalents of the reagent. Pure (*Z*)-1-chloro-2-pentene gave a similar result indicating that the geometry of the double bond was not critical. 1-Chloro-3-methyl-2-butene gave no insertion product suggesting that one problem may be 1,4-elimination of hydrogen chloride in these systems. With 1.2-equivalents of cinnamyl bromide / LDA all the starting zirconacycle **3** reacted, but the resulting allyl zirconocene was much less clean than usual (estimated 50% yield from NMR). For the rearrangement **6** - **7** to occur the allyl system must bind to the zirconium through the same carbon as the leaving group (as in **6**). With 1,3-

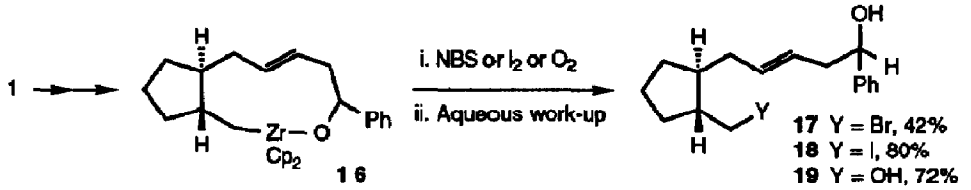
dichloropropene as the substrate this requirement is always met, but still only 25% insertion was obtained.

Allyl carbamates are efficiently lithiated at the α-position through 'proximity induced' deprotonation, and the anions are relatively stable[6]. We were delighted to find that addition of *s*-BuLi (1.3 eq.) and TMEDA (1.2 eq) to a mixture of the zirconacycles **3** or **4** and crotyl *N,N*-diisopropylcarbamate[6] (1.3 eq) in THF at -78°C gave quantitative conversion to the allyl complexes **12** and **13** (each single isomers). Protonation of **12** gave a mixture of double bond isomers (both *E/Z* and positional), *in situ* hydrogenation affording **14** in 67% yield. Insertion of benzaldehyde into **13** occurred with complete regiocontrol, but gave a mixture of geometric- and diastereo-isomers **15a-d**. The 1,2-stereoselectivity was 4.8 : 1 *erythro* : *threo*, and the *erythro* isomer consisted of a 4 : 1 mixture of *Z*- to *E*- geometric isomers[14]. The predominant formation of the *Z*-alkene **15a** is the opposite selectivity to that obtained with unsubstituted[3] or 2-substituted allyl systems.



Scheme 2. -A- = $-CH_2OCMe_2OCH_2-$.

Functionalisation of the final carbon-zirconium bond. The final key to exploiting the tandem insertion protocol described above is the successful functionalisation of the carbon-zirconium bond in the presumed oxazirconacycle products of the carbonyl insertion reactions e.g. **16**. Whereas N-bromosuccinimide gave a moderate yield of the corresponding bromide **17**, the iodinolytic and oxygenolytic work-ups gave excellent overall yields of the funtionalised derivatives **18** and **19**.



Conclusion

The tandem allyl carbenoid insertion / carbonyl addition protocol for elaborating zirconacycles has been extended in three important ways: allyl *p*-toluenesulphonates and *N,N*-diisopropylcarbamates may be used as sources of the metal carbenoid; 2-substituted allyl fragments, including some usefully functionalised for further elaboration, insert to give stereodefined trisubstituted alkenes; and the final carbon-zirconium bond from the metallacycles may be functionalised by oxygenation or halogenation.

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4. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
5. The allyl carbenoids **5** were generated *in situ* by addition of 1.2eq. of $^{i}Pr_2NLi$ or lithium 2,2,6,6-tetramethylpiperidide (for subsequent aldehyde/$BF_3.Et_2O$ reactions) to a mixture of the metallacycle (**3** or **4**), and the allyl precursor (1.2 eq).
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7. All organic compounds were characterised by high field ^{1}H and ^{13}C NMR, IR, MS and either HRMS or elemental analysis. All yields are for isolated compounds based on the starting dienes **1** or **2**. **10b** and **d** were formed as 2 : 1 mixtures of diastereomers between the side chain and ring stereocentres.
8. The (*E*)-stereochemsitry of **7a** and **8a** is certain (ref 3), that of the trisubstituted alkene analogues **b** - **e** is not, but is in accord with that assigned for lower homologues (formed by diene - alkene or diene - alkyne coupling on the metal), one of which has been proven by X-ray crystallography: Kai, Y.; Kanehisa, N.; Miki, K.; Kasai, N.; Mashima, K.; Nagasuna, K.; Yasuda, H.; Nakamura, A. *Chem. Lett.* **1982**, 1979.
9. The ketone insertion products of **7a** were erroneously assigned as the (*E*)-alkene adducts in our previous communication (ref 3). This must be corrected to (*Z*) on the basis of the carbon-13 shifts of the allylic carbons, and an 11Hz *cis*-coupling revealed by high field NMR studies on the benzophenone adduct.
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11. The *E*-geometry of **10b** and *Z*-geometry of **11b** follow from the carbon-13 shifts of the vinylic methyl groups (δ_C 16.3 and 21.6 p.p.m. respectively), the former shifted upfield by the γ-gauche effect c.f. the vinylic methyl resonances in (*E*)- and (*Z*)-3-methyl-oct-3-en-1-ol come at δ_C 16.0 and 21.6 p.p.m. respectively : Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. The $\underline{C}H_2Cl$ carbons of **9d** and **10d** come at δ_C 52.71 and 45.90 p.p.m. respectively confirming the shown geometries c.f. Coll, J.C.; Wright, A. D. *Aust. J. Chem.* **1987**, *40*, 1893. The $\underline{C}H_2SiMe_3$ carbons of **9c** and **11c** come at δ_C 30.15 and 29.44 p.p.m. respectively c.f. (*Z*)-2-methyl-2-butenyl-trimethylsilane where the analogous carbon comes at δ_C 22.84 p.p.m.: Alberts, V.; Cuthbertson, M. J.; Hawker, D. W.; Wells, P. R. *Org. Magn. Res.* **1984**, 22, 556. The vinylic proton of the major and minor isomers of **9e** come at δ_H 4.66 and 4.49 p.p.m. confirming that the former is the *Z*-geometry. The stereochemistry of **11e** has not been proven.
12. Lee, T. V.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F.S.; Yeoh, H. T. L. *Tetrahedron* **1989**, *45*, 5877.
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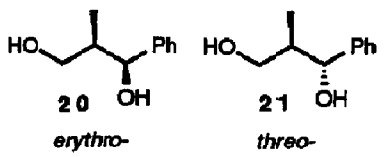
14. Note that this neglects the existence of diastereomers due to the relative configurations of the side chain and ring which cause splitting of some of the ^{13}C NMR signals - the ratios were not determined. The ratio of the four side chain isomers were obtained by integration of the distinct benzyl proton signals. The alkene signals gave the *Z* : *E* ratio of the *erythro*-isomers. The overall *erythro* : *threo* ratio was proven by ozonolysis / reduction to give the *erythro* and *threo* diols **20** and **21** which were identified by NMR studies on their acetonides (Tsukuda, T.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 4245). Although the *threo*-isomer was present as a 3 : 2 mixture of double bond isomers we did not determine which was the major.



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