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The regiochemistry of zirconacycle elaboration

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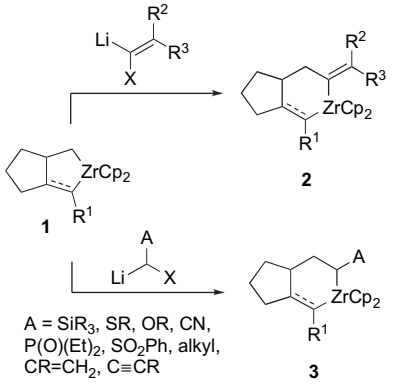
Abstract—The regioselectivity of insertion of carbenoids into a variety of unsymmetrical zirconacyclopentanes is reported. For comparison the regioselectivities of isonitrile insertion and protonation have also been determined.

1. Introduction

A wide variety of five-membered zirconacycles may be readily prepared either by formal co-cyclisation of 1,*n*-dienes, -enynes and -diynes using a zirconocene 'Cp_2Zr'[1] equivalent, or by trapping of zirconocene η^2-alkene, -alkyne and -benzyne complexes with alkenes or alkynes.[2] Methods for further elaboration of these zirconacycles include oxygenation, halogenation[3] and metathesis with a variety of elementodihalides.[4] Carbon–carbon bond forming processes include carbonylation,[5] the insertion of isocyanides and trapping of the resulting zirconocene η^2-imine complexes with unsaturated species,[6] as well as extensively developed copper catalysed 1,1- and 1,2-additions to alkynes,[7] 1,1-additions to acid chlorides[8] and addition to 1,1-, 1,2-, 1,3- or 1,4-dihalides.[9] In all cases the symmetry of the starting zirconacycle is retained so questions of the regiochemistry of addition do not arise. Processes in which the two carbon–zirconium bonds of the zirconacycle are differentially elaborated are also known including monohalogenation,[10] mixed dihalogenation,[11] addition of Ph_2PCl[10a] and R_3SnCl,[10] isocyanide insertion,[6c,10b,12] addition of aldehydes, ketones and nitriles,[13,14] copper catalysed addition of acid chlorides, enones, and allyl-, aryl- and alkynyl-halides,[15] and transmetallation with Grignard reagents.[16,17] We have reported the ring expansion of five-membered zirconacycles **1** by insertion of a range of carbenoids (R^1R^2CXLi) to afford six-membered zirconacycles such as **2** and **3**, which in many cases may be further elaborated (Scheme 1).[18,19]



Scheme 1. Carbenoid insertion into zirconacycles.

Regiocontrolled functionalisation of non-symmetrical zirconacycles is essential for development of their use in synthesis. Several examples of regioselective carbon–zirconium bond elaboration of zirconacyclopentenes have now been reported and selectivity is usually observed for reaction of the alkyl carbon–zirconium bond[5f,6c,10b,12–14] unless the electrophilic reagent may first complex with or add to the double bond (halogens, organocopper species) in which case the selectivity is reversed.[8b,10b,15a,b] We found that in most cases insertion of carbenoids also occurs selectively into the alkyl-zirconium bond of zirconacyclopentenes, the only exception being when the alkene position adjacent to the zirconium is unsubstituted (**1**, R^1=H) when insertion into the alkenyl side was sometimes observed.[18c,20] Only a few examples of differential elaboration of the two carbon–zirconium bonds of unsymmetric saturated zirconacycles are known. Takahashi and Negishi have shown that magnesium/zirconium exchange of monocyclic zirconacyclopentanes is selective for the bond closest to a β-substituent or for the bond adjacent to an α-phenyl substituent[21] and copper catalysed allylation or benzoylation follows a similar selectivity.[15c]

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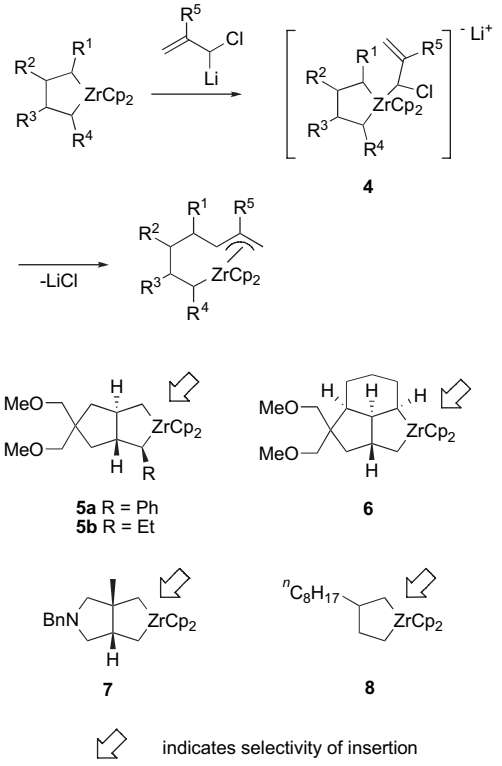
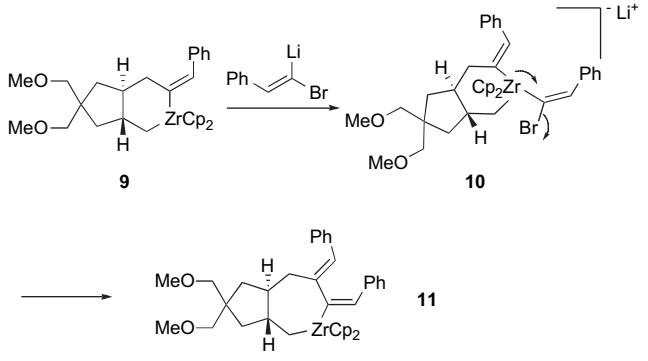
We have reported studies on the regiochemistry of insertion of allyl carbenoids into various non-symmetrical zirconacyclopentanes (Scheme 2)[20] and the results are not readily explained. The mechanism of carbenoid insertion has been generally viewed as initial donation of an electron pair to coordinatively unsaturated zirconium to form an 18-electron zirconate complex (e.g., **4**), which undergoes a carbon–carbon bond forming 1,2-migratory insertion.[22,23] Insertion into **5a/b** occurs into the more accessible side suggesting control by the direction of initial attack of the carbenoid to form the supposed 'ate' complex intermediate **4**; for **6–8** selectivity is for the C–Zr bond with the higher HOMO coefficient suggesting direct attack of the electrophilic carbenoid[24] on the carbon–zirconium bond. Recently we suggested that during the double insertion of an alkenyl carbenoid via **9** fluxionality of, or loss/re-addition of cyclopentadienide to, the intermediate 'ate' complex **10** allowed the selectivity of insertion to be determined in the 1,2-migration step, rather than initial attack (Scheme 3).[18c]



Scheme 2. Regiochemistry of allyl carbenoid insertion.



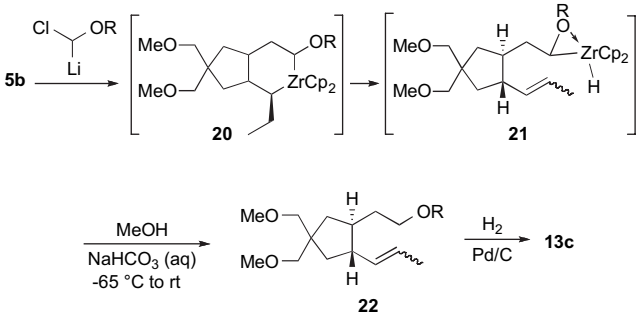
Scheme 3. Alkenyl carbenoid insertion into an α-alkylidene substituted zirconacyclohexane.

In order to better understand the factors, which control regioselectivity of elaboration of zirconacycles we now report the results of a study of insertion of a variety of carbenoids into a selection of non-symmetrical zirconacyclopentanes. We have also examined the regiochemistry of insertion of isonitriles and of zirconacycle protonation.

2. Results and discussion

We chose to use the zirconacycles **5a–c**, **6** and **7** for our studies on the regiochemistry of elaboration, and the carbenoids **12a–d** and **16**. The results are summarised in Table 1.

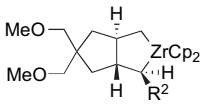
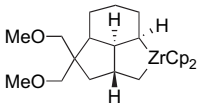
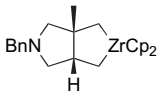
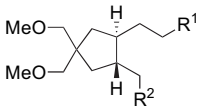
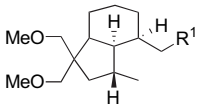
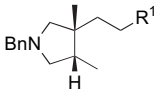
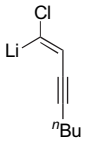
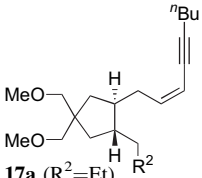
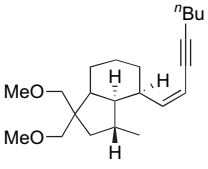
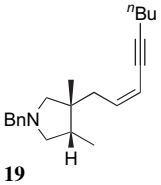
Stereoisomerically pure α-substituted zirconacycles **5a–c** derived from zirconocene (1-butene) mediated co-cyclisation of trans alkenes bearing a terminal phenyl, ethyl or methyl substituent.[25] Regiospecific insertion into the unsubstituted carbon–zirconium bond of **5a–c** was observed for all the carbenoids and suggests steric control of initial carbenoid approach followed by rapid 1,2-migratory insertion, yielding **13a–g** and **17a–b** in moderate to good yields. Negishi has reported that an α-phenyl substituent directs transmetallation (to Mg or Cu) to the substituted carbon–zirconium bond of zirconacyclopentanes,[15c,21] an interesting contrast to our observation of carbenoid insertion into the unsubstituted bond. Insertion of the electron-rich MEM (methoxyethoxymethyl) carbenoid **12b** into **5b** unexpectedly furnished alkene **22** (2:1 *Z*:*E*) on protic quench. A possible explanation is that coordination of oxygen to zirconium favours formation of the zirconium hydride **21** derived from the six-membered zirconacycle **20** by β-H elimination. Hydrogenation of **22** allowed characterisation of **13c** (Scheme 4).



Scheme 4. Alkoxy carbenoid insertion. R=$(CH_2)_2$OMe.

Intramolecular co-cyclisation of a terminal alkene and a cyclohexene furnishes **6**, previously reported,[20] into which exclusive insertion of both alkyl (**12a–d**) and alkenyl (**16**) carbenoids took place into the substituted carbon–zirconium bond to afford **14a–d** and **18**, consistent with our previous observation of the insertion of allyl carbenoid with the same regioselectivity.[20] We attempted to distinguish between the importance of inclusion of the starting alkene in a cyclohexyl ring and its cis geometry by examining insertion into **24** from co-cyclisation of **23a** (Scheme 5). Unfortunately we found the same zirconacycle resulted from co-cyclisation of cis- or trans-disubstituted alkenes **23a** or **23b** (Scheme 5). NMR analysis[26] of the zirconacycle formed identified **5b** in which the ZrCH methine proton is trans to

Table 1. Carbenoid insertion into zirconacyclopentanes

Carbenoid[a]		Starting zirconacyclopentanes[b]					
		 **5a** R^2 = Ph **5b** R^2 = Et **5c** R^2 = Me		 **6**		 **7**	
		Product[c]	Yield (%)	Product[c]	Yield (%)	Product[c]	Yield (%)
	R^1						
12a	$SiMe_3$	**13a** (R^2=Et)	83	**14a**	64	**15a**	63[d]
12a	$SiMe_3$	**13b** (R^2=Ph)	54				
12b	$O(CH_2)_2OMe$	**13c** (R^2=Et)	57[e]	**14b**	49		
12c	$P(O)(OEt)_2$	**13d** (R^2=Me)	73[f]	**14c**	56[f]	**15c**	56[g]
12c	$P(O)(OEt)_2$	**13e** (R^2=Ph)	65[f]				
12d	CN	**13f** (R^2=Me)	51	**14d**	19[h]	**15d**	64
12d	CN	**13g** (R^2=Ph)	59				
							
16		**17a** (R^2=Et)	81	**18**	62	**19**	66[i]
16		**17b** (R^2=Ph)	50				

[a] Carbenoid insertion (**12a**): chloromethyltrimethylsilane, *sec*-BuLi, TMEDA, THF, −78 °C to −65 °C then −78 °C, addition of zirconacycle. Compound **12b**: MEM-Cl added to zirconacycle solution at −100 °C, LiTMP, −100 °C to −65 °C, 1.5 h. Compounds **12c** and **d**: diethylchloromethyl phosphonate or chloroacetonitrile added to zirconacycle solution at −78 °C, LDA, −78 °C to −65 °C, 1.5 h. Compound **16**: (*E*)-(1-chlorooct-1-en-3-yne) added to zirconacycle solution at −78 °C, LiTMP, −78 °C to −65 °C, 1.5 h.

[b] Preparation of zirconacycles: Cp_2ZrCl_2, *n*-BuLi (2 equiv), THF, −78 °C then diene, −78 °C to rt, rt for 2 h.

[c] Quench conditions: MeOH/$NaHCO_3$ (aq) or 2 M HCl (aq) 12–24 h.

[d] By GC–MS contains 2% of an isomer (either diastereoisomer from trans-fused zirconacycle or a regioisomer of carbenoid insertion) and 5% of a bis-inserted product **26**.

[e] Following hydrogenation of **22**.

[f] With 2.0 equiv carbenoid.

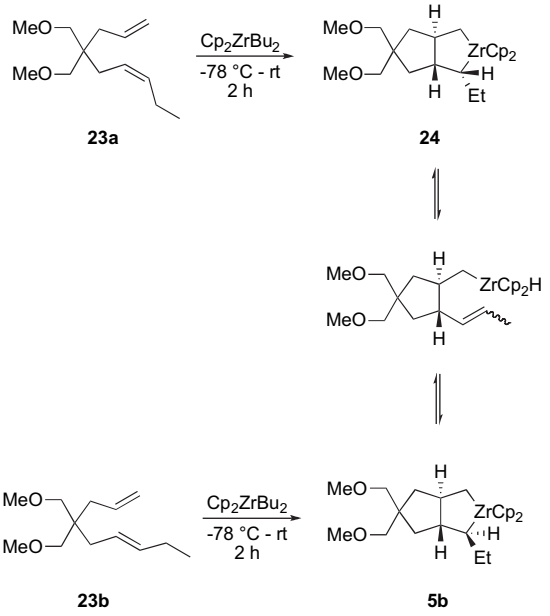
[g] With 5.0 equiv carbenoid.

[h] With 0.5 equiv carbenoid (16% bis-insertion product **25** also formed).

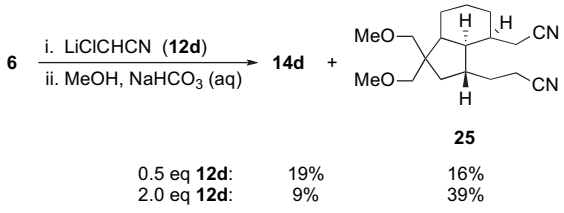
[i] Contained 10% of the bis-insertion product **27**.

the adjacent ring-junction proton. Isomerisation via β-H elimination and re-addition is a likely mechanism.

In **6**, the α-substituent is held away from the plane of lateral nucleophilic attack upon the metal centre. In addition, steric interaction between methylene protons of the cyclohexyl ring and the adjacent cyclopentadiene is manifested as an increased calculated length of the substituted C–Zr bond.[27] However, these steric factors do not convincingly account for the complete regiospecificity of insertion. Electrophilic attack by the carbenoid could account for regioselective insertion into the more electron-rich bond of **6**, however, the nature of substitution on the carbenoid fails to influence the regiochemical outcome, both electron-rich and electron-poor carbenoids showing the same selectivity. In particular, alkoxy-substituted **12b** is strongly nucleophilic but fails to alter the regioselectivity of insertion. Finally, insertion of lithiated chloroacetonitrile into **6** could not be limited to a single insertion, as we have also reported for insertion into symmetrical zirconacyclopentanes.[18c] The regioselectivity of the first insertion for the α-substituted carbon–zirconium bond of **6** was inferred through the use of 0.5 equiv of carbenoid. The single insertion product **14d** was obtained in 19% yield, separable from the product **25** of a second insertion into the opposite side, which was isolated in 16% yield. Unsurprisingly, double insertion was favoured and **25** isolated in higher yield with the use of excess carbenoid (Scheme 6). Following insertion of **12d** into the substituted side of **6** there is no steric hindrance to a second insertion into the unsubstituted C–Zr bond. We do not observe double insertion into **5** as the 'first' insertion is into the unsubstituted side and a second insertion into the opposite side not favoured due to the presence of an α-group in the plane of lateral attack. This result strongly supports a mechanism of insertion into **6** in which initial attack is on the less hindered side and selectivity is determined in the 1,2-migratory step.

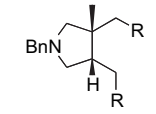


Scheme 5. Interconversion of α-substituted zirconacyclopentanes.



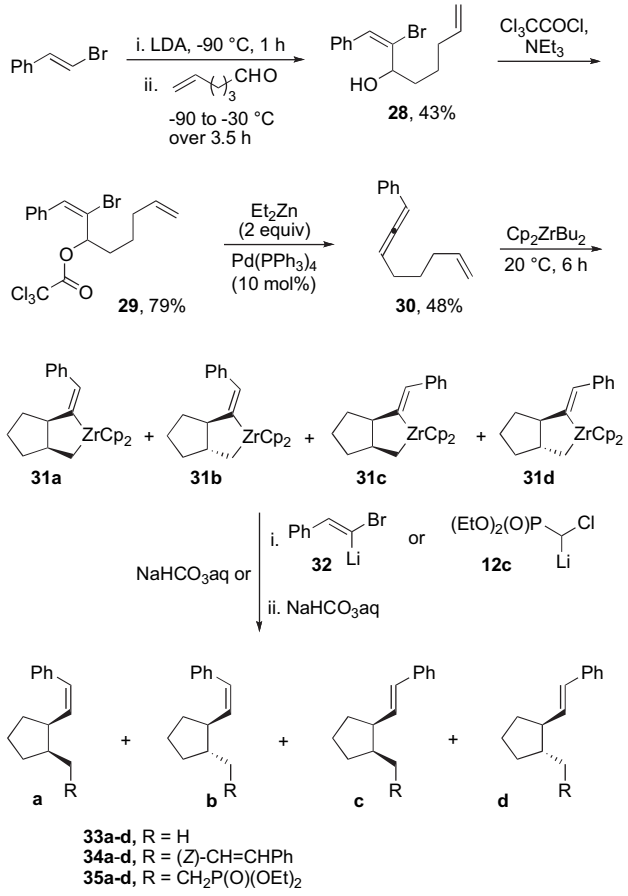
Scheme 6. Double insertion of lithiated chloroacetonitrile.

Insertion of each of the carbenoids **12a**, **12c**, **12d** and **16** into the β-methyl substituted zirconacyclopentane **7** took place regiospecifically into the side closest to the β-substituent to give **15a**, **15c**, **15d** and **19**, respectively. The result is in accordance with our previous observations of the insertion of allyl carbenoids.[20] In the case of insertion of **12a** and **16** significant amounts of the bis-inserted compounds **26** and **27** were formed, and it is possible that these were derived from the opposite regioisomer of the initial insertion. For the insertion of **12a** around 2% of an isomer of **15a** was observed by GC–MS, but this could result from either the opposite regiochemistry of insertion or the formation of a small amount of the transfused isomer of zirconacycle **7**. Five equivalents of the phosphonate substituted carbenoid **12c** were required for high conversion into **15c** and no bis-insertion was observed, probably as coordination of phosphonate oxygen to zirconium in the monoinserted zirconacycle suppresses further addition. Remarkably no double insertion of **12d** into **7** was observed and factors influencing the multiple insertion of lithiated chloroacetonitrile into **6** but not **7** are not understood.



26 R = CH_2SiMe_3
27 R = (*Z*)-CH=CHC≡C^{n}Bu

Finally we wished to examine carbenoid insertion into an α-alkylidene substituted zirconacyclopentane. Our interest was prompted by the remarkably selective insertion of lithiated β-bromostyrene into the more hindered side of the α-alkylidene-zirconacyclohexane **9** shown in Scheme 3. Access to the required α-alkylidene-zirconacyclopentane would be by zirconium induced co-cyclisation between an alkene and an allene. Intramolecular zirconocene induced co-cyclisations to allenes have not been previously reported, but intermolecular dimerisation of allenes to form zirconacycles is known.[28] A suitable cyclisation precursor **30** was synthesised by lithiation of *trans*-β-bromostyrene using LDA, addition of 5-hexenal gave the alcohol **28** in reasonable yield (Scheme 7). Formation of the trichloroacetate ester **29** followed by 1,2-elimination induced by diethylzinc using a palladium catalyst[29] gave 1-(octa-1,2,7-trienyl)-benzene **30**.



33a-d, R = H
34a-d, R = (*Z*)-CH=CHPh
35a-d, R = $CH_2P(O)(OEt)_2$

Scheme 7. Formation and elaboration of α-alkylidene zirconacycle **31**.

Co-cyclisation of **30** using zirconocene (1-butene) resulted in a mixture of four possible diastereoisomers (ring-junction) and geometric isomers **31a–d** as indicated by aqueous quench to afford **33a–d** as an inseparable mixture (Scheme 7 and Table 2, entries 1–4). Interestingly, slow isomerisation of the zirconacycles **31** occurred at room temperature to give predominantly **33a** and **33d** on aqueous quench. Relative energies of the zirconacycles **31** were obtained by DFT calculations[27]: **31a**, 13.2 kJ/mol; **31b**, 17.2 kJ/mol; **31c**, 5.9 kJ/mol; **31d**, 0 kJ/mol. We would expect **31b** to rapidly convert into **31a** via **36**—loss and re-addition of the terminal alkene moiety (Fig. 1), indeed, **31a** and **31b** are formed in equal amounts at very short reaction times and low conversion (Table 2, entry 1). We would expect **31c** to convert into **31d** by the same

Table 2. Elaboration of α-alkylidene zirconacycle **31**

Entry[a]	Product	R	Product ratios of **33**–**35**[b]				Yield[c] (%)
			a	**b**	**c**	**d**	
1[d]	33	H	37	36	16	11	—
2[d]	33	H	55	7	21	17	—
3[d]	33	H	55	3	17	25	53
4[d]	33	H	43	1	9	46	—
5	34	(*Z*)-CH=CHPh	63	22	15[e]		38
6	35	$CH_2PO(OEt)_2$	51	21	25	3	72

[a] Method as in Scheme 7 except as indicated below.
[b] Determined by a combination of GC and NMR.
[c] Isolated yield of given mixture.
[d] Entry 1, zirconacycle formation quenched as soon as 20 °C reached (only ≈10% conversion to cyclised product). Entries 2–4 quenched after 2.5 h (≈70% conversion), 6, and 48 h at room temperature, respectively.
[e] **34c** and **d** could not be distinguished.

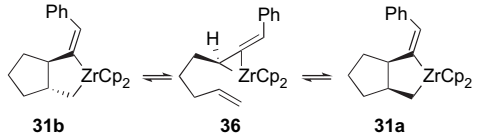
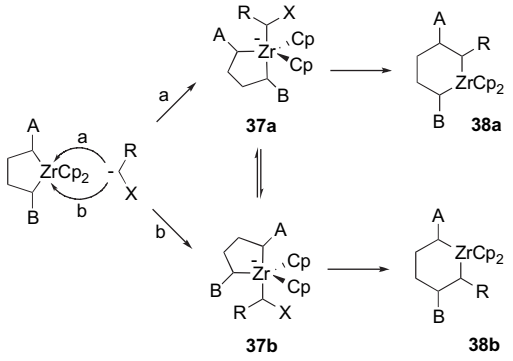


Figure 1. Mechanism of isomerisation of **31**.

mechanism, the observations indicating that this is a much slower process than **31b** to **31a**, perhaps because **31c** is relatively less strained. There may be a very slow interconversion of **31a** and **31b** with **31c** and **31d** occurring, but this would require loss/re-addition of an allene from zirconium—an energetically unfavourable process.[30] Insertion of lithiated (*E*)-β-bromostyrene (**32**) into **31** afforded, after 2 h at room temperature and aqueous quench, the insertion products **34a–d** (Table 2, entry 5). The ratios of products formed and low yield suggest that cyclisation to form **31** was incomplete, however, the key observation was that insertion occurred exclusively into the alkyl-zirconium bond in stark contrast to the formation of **11** (Scheme 3). Similarly, lithiated diethylchloromethyl phosphonate inserted regiospecifically into the alkyl-zirconium bond of **31a–d** to furnish **35a–d**.

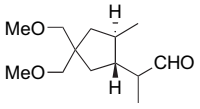
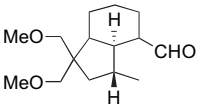
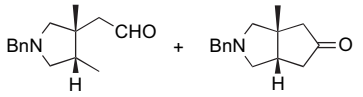
Overall, the regiochemical results we obtained for insertion of the diverse range of carbenoids into zirconacycles **5–7** were the same as those previously noted for the insertion of allyl carbenoids. Whereas control by direction of the initial attack to form an 'ate complex' could explain the results for insertion into **5**, it is unconvincing for insertion into **7**, and cannot explain the insertions into **6**. Direct electrophilic attack of the carbenoid on the more electron-rich carbon–zirconium bond could explain the results for **6** and **7**, but not for **5** (and particularly not the phenyl-substituted case **5a**). We thus favour a mechanism in which the intermediate 'ate' complexes **37a** and **37b**, which could lead to the two regioisomeric insertion products **38a** and **38b**, are in equilibrium so that selectivity may be determined by the rates of the alternative 1,2-metallate rearrangements (Scheme 8). We would postulate that for insertions into **5**, the 1,2-metallate rearrangement is fast so we observed control from the initial direction of attack, whereas for **6** and **7**, the intermediates **37a** and **37b** have time to equilibrate before rearrangement. The facile double insertion of carbenoid **12d** into zirconacycle **6**, but not **5**, provides strong evidence that the direction of initial attack need not be the same as the site of insertion. The mechanism of interconversion of the 'ate' complexes **37a** and **37b** could be via loss/re-addition of cyclopentadienide, but we favour a 'pseudorotation' mechanism.[31] The dramatic difference in the regioselectivity of insertion of the alkenyl carbenoid **32** into zirconacyclohexane **9** and zirconacyclopentane **31** offers some support. Pseudorotation requires substantial bond angle changes around the metal as groups swap 'axial' and 'equatorial' positions so should be inhibited by the angle constraint imposed by the five-membered ring in **31**.



Scheme 8. Possible mechanisms of carbenoid insertion.

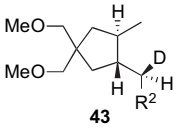
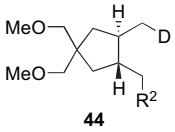
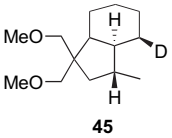
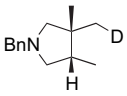
We extended our studies to the insertion of the stable 'carbene' *tert*-butyl isonitrile (Table 3). For insertion into **6** and **7** the same selectivity as for lithium carbenoid insertion was observed but, remarkably, selective insertion into the more hindered side of α-substituted systems **5a**[32] and **5c** occurred. The regiochemistry is consistent with the mechanism suggested in Scheme 8 where the rate of rearrangement of the 'ate' complexes formed by initial attack of the isonitrile on the zirconium is slow, allowing the product to be determined by 1,2-migration of the more electron-rich carbon–zirconium bond, even for insertions into **5**. Low yielding isolation of **41** following insertion into **7** was due to the formation of substantial amounts of the cyclopentanone **42** on work-up. A second 1,2-migration of the iminoacyl complex

Table 3. *tert*-Butyl isonitrile insertion into zirconacyclopentanes

Zirconacycle	Product(s)[a]	Yield (%)
5c	 **39**	48[b]
6	 **40**	56[c]
7	 **41** + **42**	31 (**41**)+30 (**42**)

[a] Reagents and conditions: zirconacycle (**5c**, **6**, **7**) solution in THF, 0 °C, *tert*-butyl isonitrile, 30 min then HCl (2 M aq), room temperature, 24 h.
[b] Major product of a separable 3:1 regioisomeric mix—obtained as a 2:1 mixture of diastereoisomers in which the major isomer was not determined.
[c] Obtained as a 2.7:1 mixture of diastereoisomers in which the major isomer was not determined.

Table 4. Regiochemistry of zirconacyclopentane deuteration

Zirconacycle	Product(s)[a]			Yield (%)
	 **43**	+	 **44**	
5c	**43a** R^2=Me	1:1.16	**44a** R^2=Me	78[b]
5a	**43b** R^2=Ph[c]	6.45:1	**44b** R^2=Ph	82[d]
6	 **45**			71[e]
7	 **46**			61

[a] To zirconacycle (**5a**, **5c**, **6**, **7**) in THF at room temperature was added MeOD (1 equiv). After 1 h excess $NaHCO_3$ (aq) was added and stirred for 16 h.
[b] Combined yield of inseparable monodeuteration product mixture, also containing 20% non- and 2% bis-deuterated products.
[c] Opposite diastereoisomer of 3% at the deuterated carbon also observed. Stereochemistry of major isomer is not proven.
[d] Combined yield of inseparable monodeuteration product mixture, also containing 11% non- and 4% bis-deuterated products.
[e] Stereochemistry of deuterated chiral centre is not proven.

resulting from initial isonitrile insertion, and decomplexation of zirconocene from the η^2-imine complex so formed,[6a] leads to the imine precursor of **42** and may be driven by steric compression induced by the ring-junction methyl group or as a consequence of the cis-ring fusion. Cyclopentanone products have been formed following the insertion of trimethylsilylisonitrile[33] but not previously observed with *tert*-butyl isonitrile. We cannot tell which regioisomer of initial insertion of the isonitrile into **7** leads to **42**.

Finally, we examined the regioselectivity of protonation by quenching zirconacycles **5**–**7** with a single equivalent of MeOD followed by excess H_2O (Table 4). Again the selectivity for zirconacycles **6** and **7** was the same as that observed for carbenoid and isonitrile insertion, and **45** and **46** were each isolated, consistent with electrophilic quench of the more electron-rich carbon–zirconium bond. For the α-substituted systems **5c** and **5a**, regioisomeric product mixtures **43a/44a** and **43b/44b** were obtained perhaps indicating a fine balance between the importance of an electron-rich carbon–zirconium bond and its steric accessibility.

3. Conclusion

We have demonstrated the insertion of both electron-rich and electron-poor carbenoids into non-symmetrical zirconacylopentanes to be highly regiospecific, following the same regioselectivity as previously reported for allyl carbenoids. We favour a mechanism in which the selectivity of insertion may be determined by the rate of 1,2-rearrangement of rapidly interconverting 'ate' complexes.

4. Experimental

4.1. General techniques

All reactions involving air or moisture sensitive compounds were carried out under an atmosphere of argon using standard Schlenk equipment and syringe techniques. All glasswares were dried in a hot oven (>140 °C, for at least 12 h) and cooled in a sealed dessicator over silica gel before assembly.

Unless otherwise stated, reagents were obtained from commercial suppliers and if necessary dried and distilled before use. THF and diethyl ether were freshly distilled from sodium benzophenone ketal under argon. Pentane and dichloromethane were dried over CaH_2 and degassed before use. *n*-Butyllithium was used as a 2.5 mol dm^{-3} solution in hexanes, stored under argon. Lithium diisopropylamide (LDA) was prepared from diisopropylamine (distilled, stored over KOH) in THF by addition of 1.0 equiv of *n*-BuLi at 0 °C. Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was prepared from 2,2,6,6-tetramethylpiperidine (distilled, stored over 4 Å sieves under argon) in THF by addition of 1.0 equiv of *n*-BuLi at 0 °C and stirred for 20 min. Petroleum ether (petrol) refers to the fraction that boils between 40 and 60 °C.

^1H and ^{13}C NMR spectra were recorded on Bruker AV300, AM300 or DPX400 spectrometers. ^1H chemical shifts are reported as values in parts per million referenced to residual solvent. The following abbreviations are used to denote multiplicity and may be compounded: s=singlet, d=doublet, t=triplet, q=quartet, fs=fine splitting. Coupling constants, *J*, are measured in Hertz (Hz). ^{13}C spectra were proton decoupled and referenced to solvent. Signals are reported as s, d, t, q, depending on the number of directly attached protons (0, 1, 2, 3, respectively), this being determined by DEPT experiments. Accurate mass spectra were recorded on a VG analytical 70-250-SE double focussing mass spectrometer using chemical ionisation (CI) (NH_3 reagent gas) or an electron impact ionisation (EI) at 70 eV. LRMS (EI) and (CI) (NH_3 reagent gas) were recorded on a ThermoQuest TraceMS GC–MS. Electrospray mass spectra were recorded using a VG platform quadrupole spectrometer. Values of *m/z* are reported in atomic mass units and the peak intensity

relative to the base peak is reported in parenthesis. Infrared spectra were run as neat films on a Thermo Mattson FTIR Golden Gate spectrometer or ThermoNicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate attachment. Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensities: s=strong, m=medium, w=weak and/or br (broad).

4.2. Synthesis of cyclisation precursors

The general synthetic procedure and full characterisation of malonate derived cyclisation precursors (*E*)-4,4-bis-(methoxymethyl)octa-1,6-diene, (*E*)-4,4-bis(methoxymethyl)nona-1,6-diene, (*Z*)-4,4-bis(methoxymethyl)nona-1,6-diene, (*E*)-(4,4-bis(methoxymethyl)hepta-1,6-dienyl)benzene, 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene, as well as the benzylamine derived precursor *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine, were reported by us previously.[20]

4.3. Zirconacycle formation

4.3.1. Method A. Formation of zirconacycles (5a–c, 6 and 7) using in situ generated zirconocene (1-butene). To a solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) under argon at −78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) and the mixture stirred at −78 °C for 10 min before addition of a solution of the appropriate diene (1 mmol) in THF (1 mL). The reaction mixture was allowed to warm to room temperature before stirring for 2 h to give the zirconacycle as a solution in THF.

4.4. Insertion of carbenoids into zirconacycles

4.4.1. Method B. Insertion of lithiated chloromethyl trimethylsilane (12a). To a stirred solution of chloromethyltrimethylsilane (0.14 mL, 1.0 mmol) in THF (9 mL) at −78 °C was added *sec*-BuLi (0.79 mL of a 1.4 M solution in hexanes, 1.1 mmol) followed by TMEDA (0.17 mL, 1.1 mmol). The mixture was stirred for 30 min, warming to −65 °C during this time, before cooling to −78 °C and slow addition of the zirconacycle solution (6.2 mL, 0.8 mmol). The mixture continued to stir for 1 h, warming to −50 °C before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL). The solution was then stirred for 12 h, warming to room temperature before pouring onto H_2O (150 mL) and extraction with Et_2O (200 mL). The combined extracts were washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), dried over $MgSO_4$ and solvent removed in vacuo to afford the crude product.

4.4.1.1. *rac*-(2-((1*S*,2*R*)-4,4-Bis(methoxymethyl)-2-propylcyclopentyl)ethyl)trimethylsilane (13a). The zirconacycle **5b** was prepared from (*E*)-4,4-bis(methoxymethyl)nona-1,6-diene according to Method A and elaborated using Method B. The crude product was purified by column chromatography (SiO_2 eluted with 10:1 petrol/EtOAc) to afford the title compound as a colourless oil (200 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.38 (4H, br s), 3.22 (6H, m), 2.07 (1H, m), 1.80 (2H, dt, *J*=12.8, 6.3 Hz), 1.59 (2H, m), 1.39 (2H, m), 1.24 (1H, m), 1.01 (4H, m), 0.91 (3H, t, *J*=7.3 Hz), 0.57 (1H, ddd, *J*=12.8, 12.5, 4.3 Hz), 0.41 (1H, ddd, *J*=12.3, 12.6, 5.3 Hz), 0.00 (9H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=77.92 (t), 77.79 (t), 59.24 (q), 59.12 (q), 48.10 (d), 44.45 (d), 44.36 (s), 39.05 (t), 38.39 (t), 35.52 (t), 27.76 (t), 21.46 (t), 14.79 (t), 14.50 (q), −1.70 (q) ppm. IR (film): 2823 (s), 2359 (w), 1247 (s), 837 (s) cm^{-1}. LRMS (CI) *m*/*z* (%): 301 ($M+H^+$, 72), 268 (8), 223 (21). HRMS (EI): $C_{16}H_{32}OSi$ (M^+−MeOH) requires *m*/*z* 268.2222. Found 268.2219.

4.4.1.2. *rac*-(2-((1*S*,2*R*)-2-Benzyl-4,4-bis(methoxymethyl)cyclopentyl)ethyl)trimethylsilane (13b). The zirconacycle **5a** was prepared from (*E*)-(4,4-bis(methoxymethyl)hepta-1,6-dienyl)benzene according to Method A and elaborated using Method B except 1.39 mmol carbenoid and 1.0 mmol zirconacycle were used and the reaction quenched at room temperature. The crude product was purified by column chromatography (SiO_2 eluted with 96:4 petrol/Et_2O) to afford the title compound as a colourless oil (187 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22 (2H, t, *J*=7.3 Hz), 7.14–7.11 (3H, m), 3.30 (3H, s), 3.27 (3H, s), 3.19–3.09 (4H, m), 2.87 (1H, dd, *J*=13.4, 4.1 Hz), 2.28 (1H, dd, *J*=13.4, 9.7 Hz), 1.79 (1H, dd, *J*=13.1, 7.5 Hz), 1.68 (1H, m), 1.64–1.53 (2H, m), 1.48 (1H, m), 1.09 (1H, dd, *J*=13.1, 10.8 Hz), 1.02 (1H, m), 0.99 (1H, dd, *J*=13.1, 10.8 Hz), 0.54 (1H, ddd, *J*=14.3, 12.5, 4.3 Hz), 0.38 (1H, ddd, *J*=14.0, 12.5, 5.02 Hz), −0.05 (9H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.95 (s), 129.02 (d), 128.28 (d), 125.72 (d), 78.01 (t), 77.97 (t), 59.38 (q), 59.33 (q), 47.99 (d), 46.50 (d), 45.06 (s), 40.71 (t), 39.58 (t), 39.05 (t), 27.98 (t), 14.85 (t), −1.56 (q) ppm. IR (film): 2951 (m), 1602 (w), 1247 (m), 861 (s), 831 (s) cm^{-1}. LRMS (CI) *m*/*z* (%): 349 ($M+H^+$, 80), 271 ($M^+-C_6H_5$, 10), 257 ($M^+-C_6H_5CH_2$, 5), 91 ($C_6H_5CH_2^+$, 100), 73 ($Si(CH_3)_3^+$, 85). HRMS (EI): $C_{21}H_{36}SiO_2$ $(M)^+$ requires *m*/*z* 348.2485. Found 348.2487.

4.4.1.3. *rac*-(((3*R*,3a*S*,4*R*,7a*S*)-1,1-Bis(methoxymethyl)-3-methyl-octahydro-1*H*-inden-4-yl)methyl)trimethylsilane (14a). The zirconacycle **6** was prepared from 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene according to Method A and elaborated using Method B except the reaction mixture was quenched at room temperature. The crude product was purified by column chromatography (SiO_2 eluted with 10:1 petrol/EtOAc) to afford the title compound as a colourless oil (160 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.36 (4H, m), 3.27 (2×3H, s), 2.09 (1H, m), 1.73 (5H, m), 1.47 (2H, d(br), *J*=12.8 Hz), 1.26–1.12 (2H, m), 1.09 (3H, d, *J*=6.5 Hz), 1.04 (2H, dt, *J*=12.6, 3.5 Hz), 0.66–0.48 (2H, m), 0.00 (9H, s+fs) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=76.24 (t), 74.77 (t), 59.77 (q), 59.57 (q), 52.80 (d), 49.03 (s), 46.37 (d), 40.64 (t), 36.12 (d), 30.34 (d), 30.22 (t), 26.90 (t), 25.19 (q), 24.51 (t), 24.42 (t), 0.00 (q) ppm. IR (film): 1247 (m), 1106 (s), 1115 (s), 835 (s) cm^{-1}. LRMS (CI) *m*/*z* (%): 313 ($M+H^+$, 60), 281 ([M−OMe]+H^+, 10), 235 (22). HRMS (EI): $C_{17}H_{32}OSi$ (M^+−MeOH) requires *m*/*z* 280.2222. Found 280.2222.

4.4.1.4. *rac*-(3*R*,4*S*)-1-Benzyl-3,4-dimethyl-3-(2-(trimethylsilylethyl)pyrrolidine (15a). The zirconacycle **7** was prepared from *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)-amine according to Method A and elaborated using Method B (but using 1.39 mmol of carbenoid and 1 mmol

zirconacycle). Purification by column chromatography (petrol/diethyl ether/Et_3N 93:5:2) gave a mixture of products as a clear colourless oil (0.206 g) estimated to contain **15a** (0.181 g, 63%), *rac*-(3*R*,4*S*)-1-benzyl-3-methyl-3,4-di-(2-trimethylsilylethyl)pyrrolidine (0.019 g, 5%), and an isomer of **15a** (0.006 g, 2%). 1-Benzyl-3,3,4-trimethylpyrrolidine from protonation of zirconacycle **7** was also recovered (0.025 g, 12%). Further chromatography allowed pure **15a** to be isolated. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.25 (4H, m), 7.23 (1H, t, J=6.9 Hz), 3.66 (1H, d, J=13.3 Hz), 3.60 (1H, d, J=13.3 Hz), 2.96 (1H, dd, J=9.0, 7.5 Hz), 2.47 (1H, d, J=9.3 Hz), 2.37 (1H, d, J=9.3 Hz), 2.21 (1H, t, J=9.0 Hz), 1.95 (1H, sextet, J=7.4 Hz), 1.31 (1H, td, J=13.4, 4.5 Hz), 1.17 (1H, td, J=13.4, 4.5 Hz), 1.00 (3H, s), 0.88 (3H, d, J=7.0 Hz), 0.42 (1H, td, J=13.4, 4.5 Hz), 0.32 (1H, td, J=13.4, 4.5 Hz), 0.00 (9H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.73 (s), 128.73 (d), 128.29 (d), 126.88 (d), 65.36 (t), 61.79 (t), 61.03 (t), 43.43 (s), 43.38 (d), 28.94 (t), 25.16 (q), 13.31 (q), 10.91 (t), −1.67 (q) ppm. IR (film): 2953 (m), 1247 (s), 860 (s), 830 (s), 737 (m) cm^{-1}. LRMS (EI) *m*/*z* (%): 289 (M^+, 100), 274 (M^+-CH_3, 15), 212 ($M^+-C_6H_5$, 18), 91 ($C_6H_5^+$, 90), 73 ($Si(CH_3)_3^+$, 83). HRMS (EI): $C_{18}H_{31}NSi$ $(M)^+$ requires *m*/*z* 289.2226. Found 289.2224.

4.4.2. Method C. Insertion of lithiated 2-methoxyethoxy methyl chloride (12b). The zirconacycle solution (1.0 mmol) was cooled to −100 °C before addition of MEM-Cl (0.11 mL, 1.0 mmol) followed by LiTMP (1.0 mmol) formed from 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) and *n*-BuLi (0.4 mL of a 2.5 M solution, 1.0 mmol) in THF (2.0 mL) at 0 °C. The solution warmed to −65 °C over 1.5 h before addition of MeOH (5.0 mL) and $NaHCO_3$ (aq) (6.0 mL) and was stirred for a further 12 h. The mixture warmed to room temperature during this time and was then extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents in vacuo to afford the crude product.

4.4.2.1. *rac*-(3*S*,4*R*)-3-(2-(2-Methoxyethoxy)ethyl)-1,1-bis(methoxymethyl)-4-propylcyclopentane (13c). The zirconacycle **5b** was prepared from (*E*)-4,4-bis(methoxymethyl)nona-1,6-diene according to Method A and elaborated using Method C. Purification by column chromatography (SiO_2 eluted with 5:1 petrol/EtOAc) yielded a mixture of geometrically isomeric alkenes **22**. To the alkene mixture (175 mg, 0.58 mmol) in MeOH (5 mL) under H_2 gas at room temperature and atmospheric pressure was added Pd/C (≈20 mg). The solution was stirred at room temperature for 20 h before filtration through Celite. Removal of solvents in vacuo gave the title compound as a colourless oil (172 mg, 57% over both steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.47 (3H, m), 3.44–3.33 (3H, m), 3.31 (3H, s), 3.26 (2×3H, s), 3.16–3.08 (4H, m), 1.87 (1H, dddd, J=12.3, 9.5, 7.0, 3.0 Hz), 1.67 (2H, ddd, J=13.1, 6.5, 5.3 Hz), 1.45 (1H, m), 1.38–1.20 (3H, m), 1.14 (1H, m), 0.93 (3H, m), 0.80 (3H, t, J=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=77.88 (2×t), 71.99 (t), 70.73 (t), 69.99 (t), 59.22 (2×q), 59.05 (q), 45.48 (s), 45.09 (d), 41.98 (d), 39.23 (t), 39.09 (t), 36.30 (t), 33.97 (t), 21.33 (t), 14.42 (q) ppm. IR (film): 2957 (s), 2871 (s, br), 1110 (s, br), 1027 (m, br) cm^{-1}. LRMS (CI) *m*/*z* (%): 303 ($M+H^+$, 34), 239 (23), 163 (100). HRMS (EI): $C_{17}H_{34}O_4$ (M^+) requires *m*/*z* 302.2457. Found 302.2459.

4.4.2.2. *rac*-(3*R*,3a*S*,4*R*,7a*S*)-4-((2-Methoxyethoxy)-methyl)-1,1-bis(methoxymethyl)-3-methyloctahydro-1*H*-indene (14b). The zirconacycle **6** was prepared from 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene according to Method A and elaborated using Method C. Purification by column chromatography (SiO_2 eluted with 5:1 petrol/EtOAc) yielded the title compound as a colourless oil (154 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.47 (3H, br s), 3.32–3.15 (16H, m), 2.04–1.87 (3H, m), 1.69–1.62 (3H, m), 1.52 (1H, br d, J=12.8 Hz), 1.44 (1H, m), 1.16–0.95 (4H, m), 0.91 (2H, d, J=6.3 Hz), 0.85 (1H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=76.18 (t), 76.08 (t), 74.43 (t), 72.36 (t), 70.44 (t), 59.60 (q) 59.45 (q), 59.42 (q), 49.18 (s), 47.18 (d), 45.88 (d), 40.27 (t), 39.64 (d), 29.92 (d), 25.95 (t), 25.28 (t), 24.72 (t), 23.63 (q) ppm. IR (film): 2923 (s, br), 2359 (w), 1100 (s, br), 963 (m) cm^{-1}. LRMS (CI) *m*/*z* (%): 315 ($M+H^+$, 100), 251 (9), 207 (47), 175 (100). HRMS (EI): $C_{18}H_{35}O_4$ ($M+H^+$) requires *m*/*z* 315.2535. Found 315.2518.

4.4.3. Method D. Insertion of lithiated diethylchloromethyl phosphonate (12c). The zirconacycle solution (1.0 mmol) was cooled to −78 °C before addition of a solution of diethylchloromethyl phosphonate (0.373 g, 2.0 mmol) in THF (1 mL), followed by addition of LDA (1.8 mL of a 1.1 M solution in THF, 2.0 mmol) dropwise over 10 min. The mixture was allowed to warm to −70 °C before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and then stirred vigorously for 24 h. The product was extracted into Et_2O (3×30 mL) and the combined organic phases were washed with $NaHCO_3$ (aq) solution (30 mL), water (30 mL) and brine (30 mL). Drying over $MgSO_4$ and removal of solvent in vacuo gave the crude product.

4.4.3.1. *rac*-Diethyl-2-((1*S*,2*R*)-2-ethyl-4,4-bis(methoxymethyl)cyclopentyl)ethylphosphonate (13d). The zirconacycle **5c** was prepared from (*E*)-4,4-bis(methoxymethyl)octa-1,6-diene according to Method A and elaborated using Method D. Purification of the crude product by column chromatography (SiO_2 eluted with 7:3 EtOAc/CH_2Cl_2) gave the title compound as a colourless oil (257 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.10–4.01 (4H, m), 3.31 (3H, s), 3.309 (3H, s), 3.19–3.13 (4H, m), 1.85 (1H, m), 1.81–1.58 (6H, m), 1.40–1.20 (2H, m), 1.30 (6H, t, J=7.0 Hz), 0.99 (3H, m), 0.85 (3H, t, J=7.3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=77.84 (t), 77.70 (t), 61.52 (CH_2, d, J=2.8 Hz), 61.42 (CH_2, d, J=2.3 Hz), 59.31 (2×q), 46.62 (d), 45.45 (CH, d, J=16.9 Hz), 45.10 (s), 38.86 (t), 38.81 (t), 26.56 (t), 26.52 (CH_2, d, J=5.7 Hz), 24.47 (CH_2, d, J=140.2 Hz), 16.61 (q), 16.53 (q), 12.58 (q) ppm. IR (film): 1450 (m), 1236 (m), 1199 (m), 1166 (s), 1055 (s), 1027 (s), 729 (s) cm^{-1}. LRMS (EI) *m*/*z* (%): 351 ($M+H^+$, self CI, 76), 335 (M^+-CH_3, 20), 321 ($M^+-C_2H_5$, 10), 286 ($M^+-C_9H_{10}O_2$, 13), 152 ($C_5H_{13}PO_3^+$, 100). HRMS (CI): $C_{17}H_{36}O_5P$ $(M+H)^+$ requires *m*/*z* 351.2300. Found 351.2310.

4.4.3.2. *rac*-Diethyl-2-((1*S*,2*R*)-2-benzyl-4,4-bis(methoxymethyl)cyclopentyl)ethylphosphonate (13e). The zirconacycle **5a** was prepared from (*E*)-(4,4-bis(methoxymethyl)hepta-1,6-dienyl)benzene according to Method A

and elaborated using Method D except LiTMP was used in place of LDA and the reaction mixture was allowed to warm to room temperature overnight before quenching with HCl (6 mL of a 2 M aqueous solution) and stirring for 3 h before work-up. Purification by column chromatography (SiO_2 eluted with EtOAc) gave the title compound as a colourless oil (267 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.24 (2H, t, J=7.4 Hz), 7.14 (1H, t, J=7.4 Hz), 7.13 (2H, d, J=7.4 Hz), 4.24–4.04 (4H, m), 3.30 (3H, s), 3.26 (3H, s), 3.17–3.07 (4H, m), 2.90 (1H, dd, J=13.3, 4.9 Hz), 2.30 (1H, dd, J=13.3, 9.8 Hz), 1.94 (1H, m), 1.84–1.63 (3H, m), 1.80 (1H, dd, J=12.9, 7.5 Hz), 1.61–1.48 (2H, m), 1.57 (1H, dd, J=13.4, 7.3 Hz), 1.31 (6H, t, J=7.0 Hz), 1.12 (1H, dd, J=13.4, 10.8 Hz), 1.03 (1H, dd, J=12.9, 10.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.44 (s), 128.98 (d), 128.32 (d), 125.83 (d), 77.87 (2×t), 61.65 (CH_2, d, J=1.9 Hz), 61.53 (CH_2, d, J=1.5 Hz), 59.34 (q), 59.29 (q), 46.78 (d), 45.61 (CH, d, J=17.0 Hz), 45.21 (s), 40.38 (t), 39.31 (t), 38.70 (t), 26.64 (CH_2, d, J=19.3 Hz), 24.53 (CH_2, d, J=61.2 Hz), 16.65 (q), 16.58 (q) ppm. IR (film): 1452 (m), 1390 (s), 1230 (s), 1200 (m), 1102 (s), 1055 (s), 1027 (s), 958 (s) cm^{-1}. LRMS (ES)$^+$ m/z (%): 413 (M+H$^+$, 100), 435 (M+Na$^+$, 65). HRMS (ES)$^+$: $C_{22}H_{38}NaO_5P$ (M+Na)$^+$ requires m/z 435.2271. Found 435.2264.

4.4.3.3. *rac*-Diethyl-((3*R*,3a*S*,4*R*,7a*S*)-1,1-bis(methoxymethyl)-3-methyloctahydro-1*H*-inden-4-yl)methylphosphonate (14c). The zirconacycle **6** was prepared from 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene according to Method A and elaborated using Method D except the reaction mixture quenched at room temperature. Purification by column chromatography (SiO_2 eluted with 1:1–3:1 EtOAc/petrol) gave the title compound as a colourless oil (212 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.11–4.01 (4H, m), 3.32 (3H, s), 3.27 (3H, s), 3.34–3.17 (4H, m), 2.09 (2H, m), 1.90–1.60 (8H, m), 1.47 (1H, br dd, J=6.3, 3.0 Hz), 1.30 (6H, t, J=7.1 Hz), 1.22–1.06 (3H, m), 1.03 (3H, d, J=6.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=75.85 (t), 74.06 (t), 61.50 (CH_2, d, J=6.8 Hz), 61.33 (CH_2, d, J=6.8 Hz), 59.33 (q), 59.14 (q), 50.57 (CH, d, J=15.0 Hz), 48.46 (s), 45.96 (CH, d, J=1.9 Hz), 40.23 (t), 33.96 (CH, d, J=4.4 Hz), 32.09 (CH_2, d, J=182.7 Hz), 29.92 (d), 27.99 (CH_2, d, J=3.9 Hz), 25.96 (t), 23.89 (q), 23.65 (t), 16.61 (CH_3, d, J=1.9 Hz), 16.54 (CH_3, d, J=1.9 Hz) ppm. IR (film): 1246 (m), 1197 (m), 1101 (s), 1052 (s), 1025 (s), 819 (m), 729 (s) cm^{-1}. LRMS (CI) m/z (%): 377 (M+H$^+$, 35), 361 (M$^+$−Me, 6), 345 (M$^+$−MeO, 5), 286 (M$^+$−$C_4H_{10}O_2$, 20), 152 ($C_5H_{13}O_3P^+$, 100). HRMS (EI): $C_{19}H_{37}O_5P$ (M)$^+$ requires m/z 376.2379. Found 376.2377.

4.4.3.4. *rac*-Diethyl-2-((3*S*,4*R*)-1-benzyl-3,4-dimethylpyrrolidin-3-yl)ethylphosphonate (15c). The zirconacycle **7** was prepared from *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine according to Method A and elaborated using Method D. Purification of the crude product by column chromatography (SiO_2 eluted with 48:50:2 petrol/EtOAc/Et_3N) followed by radial chromatography (SiO_2 eluted with 83:15:2 petrol/EtOAc/Et_3N) gave the title compound as a colourless oil (199 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26–7.17 (5H, m), 4.11–4.01 (4H, m), 3.59 (1H, d, J=13.0 Hz), 3.51 (1H, d, J=13.0 Hz), 2.87 (1H, dd, J=9.0, 7.9 Hz), 2.38 (1H, d, J=9.3 Hz), 2.28 (1H, d, J=9.3 Hz), 2.18 (1H, t, J=9.0 Hz), 1.91 (1H, sextet, J=7.3 Hz), 1.73–1.50 (3H, m), 1.47–1.42 (1H, m), 1.29 (3H, t, J=7.0 Hz), 1.28 (3H, t, J=7.0 Hz), 0.96 (3H, s), 0.86 (3H, d, J=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.79 (s), 128.56 (d), 128.25 (d), 126.83 (d), 65.12 (t), 61.62 (t), 61.55 (t), 61.43 (t), 60.76 (t), 43.40 (d), 42.41 (C, d, J=16.4 Hz), 27.62 (CH_2, d, J=4.5 Hz), 24.86 (q), 21.46 (CH_2, d, J=140.7 Hz), 16.65 (q), 16.58 (q), 13.32 (q) ppm. IR (film): 1250 (m), 1230 (m), 1162 (w), 1055 (s), 1026 (s), 956 (s), 787 (m), 734 (m) cm^{-1}. LRMS (ES)$^+$ m/z (%): 354 (M+H$^+$, 30). HRMS (ES)$^+$: $C_{19}H_{33}NO_3P$ (M+H)$^+$ requires m/z 354.2193. Found 354.2186.

4.4.4. Method E. Insertion of lithiated chloroacetonitrile (12d). The zirconacycle solution (1 mmol) was cooled to −78 °C before addition of chloroacetonitrile (0.083 g, 1.10 mmol) in THF (1 mL) followed by addition of LDA (1.4 mL of a 0.78 M solution in THF, 1.10 mmol) dropwise over 20 min. The reaction mixture typically changed from yellow to red in colour. After stirring for 10 min at −78 °C MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) were added and the mixture then stirred vigorously for 24 h, warming to room temperature during this time. The product was extracted into Et_2O (3×30 mL) and the combined organic phases washed with $NaHCO_3$ (aq) (30 mL), water (30 mL) and brine (30 mL) before drying over $MgSO_4$ and removal of solvent in vacuo to afford the crude product.

4.4.4.1. *rac*-3-((1*R*,2*R*)-2-Ethyl-4,4-bis(methoxymethyl)cyclopentyl)propanenitrile (13f). The zirconacycle **5c** was prepared from (*E*)-4,4-bis(methoxymethyl)octa-1,6-diene according to Method A and elaborated using Method E. Purification of the crude product by column chromatography (SiO_2 eluted with 87.5:12.5 petrol/EtOAc) gave the title compound as a colourless oil (123 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.33 (6H, s), 3.23–3.15 (4H, m), 2.39 (1H, ddd, J=13.8, 8.3, 5.3 Hz), 2.28 (1H, m), 1.96 (1H, tdd, J=11.6, 8.3, 3.1 Hz), 1.82 (1H, dd, J=6.7, 2.6 Hz), 1.77 (1H, dd, J=7.1, 2.2 Hz), 1.63–1.47 (2H, m), 1.45–1.31 (2H, m), 1.06 (1H, d, J=10.9, 7.1 Hz), 1.05 (1H, m), 1.00 (1H, dd, J=10.7, 6.7 Hz), 0.88 (3H, t, J=7.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=120.07 (s), 77.86 (t), 77.81 (t), 59.41 (2×q), 46.77 (CH), 45.37 (s), 43.99 (d), 38.84 (t), 38.62 (t), 29.94 (t), 26.57 (t), 16.23 (t), 12.61 (q) ppm. IR (film): 2244 (w), 1197 (s), 956 (m) cm^{-1}. LRMS (CI) m/z (%): 257 (M+NH_4^+, 5), 240 (M+H$^+$, 100), 208 (M$^+$−MeO, 45), 192 (M$^+$−C_2H_6O, 15), 176 (M$^+$−$C_2H_6O_2$, 100). HRMS (EI): $C_{14}H_{25}NO_2$ (M)$^+$ requires m/z 239.1885. Found 239.1891.

4.4.4.2. *rac*-3-((1*R*,2*R*)-2-Benzyl-4,4-bis(methoxymethyl)cyclopentyl)propanenitrile (13g). The zirconacycle **5a** was prepared from (*E*)-(4,4-bis(methoxymethyl)hepta-1,6-dienyl)benzene according to Method A and elaborated using Method E except LiTMP was used in place of LDA and the reaction mixture was quenched with HCl (6 mL of a 2 M aqueous solution). Purification of the crude product by column chromatography (SiO_2 eluted with 1:1 petrol/Et_2O) gave the title compound as a colourless oil (179 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (2H, t, J=7.3 Hz), 7.16 (1H, t, J=7.3 Hz), 7.12 (2H, d, J=7.3 Hz), 3.31 (3H, s), 3.26 (3H, s), 3.18–3.10 (4H, m), 2.83 (1H,

dd, J=13.3, 4.5 Hz), 2.38 (1H, dd, J=13.3, 9.2 Hz), 2.33 (1H, dd, J=8.1, 5.4 Hz), 2.24 (1H, m), 1.94 (1H, m), 1.83 (1H, dd, J=12.9, 7.4 Hz), 1.77 (1H, m), 1.69 (1H, m), 1.72 (1H, dd, J=13.3, 7.4), 1.38 (1H, m), 1.16 (1H, dd, J=13.3, 10.6 Hz), 1.05 (1H, dd, J=12.9, 10.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.05 (s), 128.95 (d), 128.43 (d), 126.03 (d), 119.87 (s), 77.82 (2×t), 59.36 (q), 59.31 (q), 46.77 (d), 45.45 (s), 44.13 (d), 40.41 (t), 39.35 (t), 38.05 (t), 29.98 (t), 16.13 (t) ppm. IR (film): 2826 (m), 1602 (w), 1495 (m), 1198 (m), 1102 (s), 963 (m) cm^{-1}. LRMS (EI) m/z (%): 301 (M^+, 20), 286 (M^+-Me, 6), 239 ($M^+-C_2H_6O_2$, 36), 224 ($M^+-C_6H_5$, 26), 91 ($C_6H_5CH_2^+$, 100). HRMS (EI): $C_{19}H_{27}NO_2$ $(M)^+$ requires m/z 301.2042. Found 301.2043.

4.4.4.3. *rac*-2-((3*R*,3a*R*,4*S*,7a*S*)-1,1-Bis(methoxymethyl)-3-methyloctahydro-1*H*-inden-4-yl)acetonitrile (14d). The zirconacycle **6** was prepared from 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene according to Method A and elaborated using Method E except that 0.9 mmol of zirconacycle and 1.8 mmol of carbenoid were used. Purification of the crude product by column chromatography (85:15–65:35 petrol/EtOAc) followed by Kugelrohr distillation (140–150 °C/0.8 mmHg) gave the title compound as a colourless oil (20.9 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.38–3.22 (4H, m), 3.35 (3H, s), 3.30 (3H, s), 2.37 (1H, dd, J=16.6, 7.3 Hz), 2.27 (1H, dd, J=16.6, 7.5 Hz), 2.15–2.01 (3H, m), 1.84–1.75 (3H, m), 1.65 (1H, br d, J=10.3 Hz), 1.56 (1H, m), 1.30–1.15 (3H, m), 1.07 (3H, d, J=10.8 Hz), 1.07 (1H, dq, J=13.0, 3.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=119.52 (s), 75.74 (t), 74.05 (t), 59.41 (q), 59.25 (q), 48.86 (s), 48.44 (d), 45.83 (d), 40.02 (t), 36.79 (d), 29.67 (d), 27.67 (t), 25.66 (t), 23.83 (q), 23.80 (t), 23.73 (t) ppm. IR (film): 2245 (w), 1449 (m), 1197 (m), 1099 (s), 958 (m), 732 (m) cm^{-1}. LRMS (CI) m/z (%): 266 (M+H$^+$, 100), 250 (M^+-Me, 5), 234 (38), 218 (10), 202 (70). HRMS (EI): $C_{16}H_{27}NO_2$ $(M)^+$ requires m/z 265.2042. Found 265.2036.

4.4.4.4. *rac*-3-((1*R*,3a*S*,7*S*,7a*R*)-7-(Cyanomethyl)-3,3-bis(methoxymethyl)octahydro-1*H*-inden-1-yl)propanenitrile (25). Isolated from the reaction mixture for preparation of **14d** (above) following purification by column chromatography (85:15–65:35 petrol/EtOAc) as a yellow oil (106 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.36–3.20 (4H, m), 3.33 (3H, s), 3.29 (3H, s), 2.45 (1H, ddd, J=17.1, 7.0, 5.0 Hz), 2.35–2.21 (4H, m), 2.17–2.02 (2H, m), 1.92–1.79 (3H, m), 1.74 (1H, dd, J=14.1, 10.5 Hz), 1.65–1.49 (3H, m), 1.27 (1H, dd, J=14.3, 5.0 Hz), 1.28–1.21 (2H, m), 1.04 (1H, dq, J=12.8, 3.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=119.64 (s), 119.06 (s), 75.33 (t), 73.74 (t), 59.53 (q), 59.22 (q), 49.21 (s), 46.18 (d), 45.26 (d), 36.57 (d), 35.91 (t), 34.19 (d), 33.71 (t), 27.64 (t), 25.42 (t), 23.79 (t), 23.67 (t), 16.65 (t) ppm. IR (film): 2245 (w), 1449 (m), 1197 (m), 1099 (s), 961 (m), 913 (m), 729 (s) cm^{-1}. LRMS (CI) m/z (%): 322 (M+NH_4^+, 25), 305 (M+H$^+$, 100), 289 (5), 273 (25), 257 (10), 241 (65). HRMS (EI): $C_{18}H_{28}N_2O_2$ $(M)^+$ requires m/z 304.2151. Found 304.2159.

4.4.4.5. *rac*-3-((3*S*,4*R*)-1-Benzyl-3,4-dimethylpyrrolidin-3-yl)propanenitrile (15d). The zirconacycle **7** was prepared from *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine according to Method A and elaborated using Method E. Purification of the crude product by column chromatography (SiO_2 eluted with 73:25:2–48:50:2 petrol/Et_2O/Et_3N) gave the title compound as a colourless oil (155 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.19 (5H, m), 3.61 (1H, d, J=13.1 Hz), 3.54 (1H, d, J=13.1 Hz), 2.84 (1H, dd, J=9.5, 8.5 Hz), 2.36 (2H, s), 2.34–2.16 (3H, m), 1.92 (1H, apparent sextet, J=7.7 Hz), 1.78 (1H, ddd, J=13.6, 10.8, 5.5 Hz), 1.58 (1H, ddd, J=13.4, 10.8, 5.8 Hz), 0.99 (3H, s), 0.87 (3H, d, J=7.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.63 (s), 128.56 (d), 128.36 (d), 126.90 (d), 120.69 (s), 64.67 (t), 60.94 (t), 60.57 (t), 43.18 (d), 42.27 (s), 31.16 (t), 24.19 (q), 13.12 (q), 13.07 (t) ppm. IR (film): 2246 (w), 1494 (m), 1453 (s), 1375 (m), 1127 (m), 737 (s) cm^{-1}. LRMS (EI) m/z (%): 242 (M^+, 6), 202 ($M^+-C_2H_2N$, 5), 151 (M^+-PhCH_2, 8), 91 ($PhCH_2^+$, 100). HRMS (ES)$^+$: $C_{16}H_{23}N_2$ $(M+H)^+$ requires m/z 243.1856. Found 243.1857.

4.4.5. Method F. Insertion of (*E*)-(1-chlorooct-1-en-3-ynyl)lithium (16). The zirconacycle solution (1 mmol) was cooled to −78 °C before addition of (1*E*)-1-chloro-1-octen-3-yne (0.1 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and *n*-BuLi (0.4 mL of a 2.5 M solution, 1.0 mmol) in THF (2 mL) at 0 °C for 30 min). The mixture was stirred for 40 min during which time it warmed to −65 °C before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) and stirring at room temperature for 12 h. The mixture was poured onto H_2O (150 mL) and extracted with Et_2O (200 mL) before washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), drying over $MgSO_4$ and removal of solvent in vacuo to afford the crude product.

4.4.5.1. *rac*-(3*R*,4*R*)-1,1-Bis(methoxymethyl)-3-((*Z*)-non-2-en-4-ynyl)-4-propylcyclopentane (17a). The zirconacycle **5b** was prepared from (*E*)-4,4-bis(methoxymethyl)nona-1,6-diene according to Method A and elaborated using Method F. Purification by column chromatography (SiO_2 eluted with 10:1 petrol/Et_2O) yielded the title compound as a pale yellow oil (259 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.75 (1H, dt, J=10.6, 7.5 Hz), 5.36 (1H, br d, J=10.6 Hz), 3.26 (2×3H, s), 3.11 (4H, m), 2.48 (1H, m), 2.27 (2H, dt, J=1.7, 6.8 Hz), 2.04–1.96 (3H, m), 1.74–1.62 (4H, m), 1.48–1.24 (5H, m), 1.22–1.13 (3H, m), 0.88–0.78 (6H, m) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=141.07 (d), 109.82 (d), 94.48 (s), 78.04 (s), 77.77 (2×t), 59.21 (2×q), 45.26 (s), 44.91 (d), 44.49 (d), 39.09 (t), 38.90 (t), 36.38 (t), 33.96 (t), 30.97 (t), 21.97 (t), 21.36 (t), 19.21 (t), 14.46 (q), 13.59 (q) ppm. IR (film): 2916 (s, br), 2060 (w), 1450 (m), 1105 (s), 750 (m) cm^{-1}. LRMS (CI) m/z (%): 321 (M+H$^+$, 23), 288 (M^+-MeOH, 35), 257 (22). HRMS (EI): $C_{20}H_{32}O$ (M^+-MeOH) requires m/z= 288.2453. Found 288.2448.

4.4.5.2. *rac*-(((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-((*Z*)-non-2-en-4-yn-yl)cyclopentyl)methyl)benzene (17b). The zirconacycle **5a** was prepared from (*E*)-(4,4-bis(methoxymethyl)hepta-1,6-dienyl)benzene according to Method A and elaborated using Method F except the reaction mixture stirred at −78 °C for 1.5 h before quenching at this temperature with HCl (6 mL of a 2 M aqueous solution). Purification of the crude product by column chromatography (SiO_2 eluted with 92.5:7.5 petrol/Et_2O) gave the title

compound as a colourless oil (185 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (2H, t, J=7.4 Hz), 7.15–7.12 (3H, m), 5.83 (1H, dt, J=10.5, 7.5 Hz), 5.47 (1H, d, J=10.5 Hz), 3.30 (3H, s), 3.26 (3H, s), 3.17–3.09 (4H, m), 3.00 (1H, dd, J=13.3, 3.6 Hz), 2.60 (1H, m), 2.33 (2H, m), 2.28 (1H, dd, J=13.3, 9.8 Hz), 2.20 (1H, dt, J=14.8, 7.5 Hz), 1.77 (1H, m), 1.74 (1H, dd, J=13.3, 7.3 Hz), 1.65 (1H, m), 1.57 (1H, dd, J=13.3, 7.0 Hz), 1.55–1.48 (2H, m), 1.45–1.38 (2H, m), 1.14 (1H, dd, J=13.3, 10.6 Hz), 1.09 (1H, dd, J=13.3, 10.8 Hz), 0.90 (3H, t, J=7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.76 (s), 140.71 (d), 129.06 (d), 128.29 (d), 125.76 (d), 110.36 (d), 94.86 (s), 77.87 (2×t), 77.69 (s), 59.37 (q), 59.31 (q), 46.58 (d), 45.27 (s), 44.69 (d), 40.43 (t), 39.08 (t), 38.81 (t), 33.93 (t), 31.12 (t), 22.14 (t), 19.39 (t), 13.75 (q) ppm. IR (film): 2824 (m), 1603 (w), 1494 (w), 1453 (m), 1198 (m), 1104 (s), 963 (m), 750 (m) cm^{-1}. LRMS (EI) m/z (%): 368 (M^+, 4), 304 ($M^+-C_6H_5$, 6), 291 ($M^+-C_6H_5CH_2$, 12), 91 ($C_6H_5CH_2^+$, 100), 77 ($C_6H_5^+$, 45). HRMS (EI): $C_{25}H_{36}O_2$ $(M)^+$ requires m/z 368.2715. Found 368.2708.

4.4.5.3. *rac*-(3*R*,3a*R*,4*S*,7a*S*)-1,1-Bis(methoxymethyl)-3-methyl-4-((*Z*)-oct-1-en-3-ynyl)octahydro-1*H*-indene (18). The zirconacycle **6** was prepared from 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene according to Method A and elaborated using Method F. Purification by column chromatography (SiO_2 eluted with 10:1 petrol/EtOAc) gave the title compound as a colourless oil (206 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.70 (1H, t, J=10.5 Hz), 5.28 (1H, br d, J=10.5 Hz), 3.23 (10H, m), 2.88 (1H, tt, J=10.8, 4.3 Hz), 2.28 (2H, dt, J=1.8, 7.0 Hz), 2.07 (1H, m), 1.95 (2H, m), 1.66 (3H, m), 1.05–1.45 (9H, m), 0.92 (3H, d, J=6.5 Hz), 0.87 (3H, t, J=7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=146.21 (d), 106.54 (d), 93.43 (s), 75.84 (s), 73.19 (t), 72.96 (t), 58.04 (q), 57.99 (q), 47.92 (d), 47.75 (s), 44.29 (d), 38.96 (d), 38.57 (t), 29.91 (t), 28.93 (d), 26.27 (t), 24.97 (t), 22.79 (q), 22.59 (t), 20.88 (t), 18.21 (t), 12.60 (q) ppm. IR (film): 2206 (w, br), 750 (m) cm^{-1}. LRMS (CI) m/z (%): 333 ($M+H^+$, 35), 255 (17), 192 (64), 147 (100). HRMS (EI): $C_{22}H_{36}O_2$ (M^+) requires m/z 332.2715. Found 332.2723.

4.4.5.4. *rac*-(3*S*,4*R*)-1-Benzyl-3,4-dimethyl-3-((*Z*)-non-2-en-4-ynyl)pyrrolidine (19). The zirconacycle **7** was prepared from *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine according to Method A and elaborated using Method F. Purification by column chromatography (SiO_2 eluted with 10:1 petrol/Et_3N) yielded a pale yellow oil (255 mg) estimated to contain the title compound (**19**) (204 mg, 66%) and the inseparable bis-addition product *rac*-(3*R*,4*S*)-1-benzyl-3-methyl-3,4-di((*Z*)-non-2-en-4-ynyl)-pyrrolidine **27** (40 mg, 10%). Data for **19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.17 (5H, m), 5.76 (1H, dt, J=10.8, 7.5 Hz), 5.45 (1H, dtt, J=10.8, 2.2, 1.4 Hz), 3.59 (1H, d, J=13.1 Hz), 3.51 (1H, d, J=13.1 Hz), 2.85 (1H, dd, J=9.1, 7.4 Hz), 2.41 (1H, d, J=9.4 Hz), 2.37 (1H, d, J=9.4 Hz), 2.33–2.11 (5H, m), 1.89 (1H, dq, J=8.8, 7.1 Hz), 1.51–1.34 (4H, m), 0.96 (3H, s), 0.86 (3H, d, J=6.8 Hz), 0.84 (3H, t, J=7.7 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.89 (s), 139.66 (d), 128.50 (d), 128.09 (d), 126.63 (d), 111.16 (d), 94.63 (s), 77.71 (s), 65.45 (t), 61.45 (t), 60.82 (t), 43.54 (d), 42.94 (s), 36.00 (t), 30.96 (t), 25.68 (q), 21.95 (t), 19.23 (t), 13.60 (q), 13.10 (q) ppm. The following signals for **27** could be distinguished. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.69 (1H, dt, J=10.5, 7.3 Hz), 5.36 (1H, d, J=10.6, 2.1, 1.4 Hz), 0.99 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.17 (d), 139.36 (d), 128.40 (d), 128.05 (d), 111.33 (d), 110.11 (d), 95.00 (s), 94.67 (s), 77.66 (s), 77.20 (s), 65.54 (t), 60.73 (t), 59.38 (t), 49.08 (d), 43.19 (s), 36.14 (t), 29.53 (t), 25.83 (q), 21.99 (t), 13.52 (q) ppm. IR (film): 2209 (w), 1705 (m), 1119 (s) cm^{-1}. LRMS (CI) m/z (%): 310 ($M+H^+$, 44), 252 (22), 186 (44), 91 (100). HRMS (ES^+): $C_{22}H_{32}N$ ($M+H^+$) requires m/z 310.2529. Found 310.2533. Also observed bis-insertion product **27** at m/z 416.3315 requires m/z 416.3312 for $M+H^+$ ($C_{30}H_{42}N$).

4.4.6. 1-(Octa-1,2,7-trienyl)benzene (30). A solution of β-bromostyrene (1.54 mL, 12.04 mmol) in THF (10 mL) was cooled to −90 °C before addition of LDA (10 mL, 12.04 mmol) over 30 min. After stirring at −90 °C for 30 min a solution of hex-5-enal (1.18 g, 12.04 mmol) in THF (4 mL) was added to the reaction mixture over 30 min. The solution was allowed to warm to −30 °C over 3.5 h before addition of $NaHCO_3$ (aq) (30 mL). The products were extracted into diethyl ether (3×50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 4:1 hexane/Et_2O) gave (*E*)-2-bromo-1-phenyl-octa-1,7-dien-3-ol **28** as a clear oil (1.445 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.50–7.30 (6H, m), 5.89 (1H, ddt, J=17.0, 10.3, 6.7 Hz), 5.09 (1H, d+fs, J=17.0 Hz), 5.07 (1H, d+fs, J=10.3 Hz), 4.66 (1H, t, J=6.9 Hz), 2.16 (2H, apparent q, J=6.9 Hz), 1.92–1.77 (3H, m), 1.56 (2H, apparent pentet, J=7.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.39 (d), 135.82 (s), 134.19 (d), 134.03 (s), 128.75 (2×d), 128.41 (2×d), 128.00 (d), 115.03 (t), 69.95 (d), 36.09 (t), 33.46 (t), 24.56 (t) ppm. IR (film): 3571 (m, br), 1639 (m), 1443 (s), 1261 (m), 805 (m), 756 (s) cm^{-1}.

According to the method of Tanaka[29] a solution of (*E*)-2-bromo-1-phenyl-octa-1,7-dien-3-ol **28** (0.70 g, 2.50 mmol) and triethylamine (3.48 mL, 25.00 mmol) in THF (20 mL) was cooled to 0 °C before the dropwise addition of trichloroacetylchloride (1.40 mL, 15.00 mmol). After stirring for 30 min, $NaHCO_3$ (aq) (30 mL) was added. The products were extracted into diethyl ether (3×50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 9:1 hexane/Et_2O) gave (*E*)-2-bromo-1-phenylocta-1,7-dien-3-yl 2,2,2-trichloroacetate **29** as a clear oil (0.847 g, 79%).[30] ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.42–7.22 (6H, m), 5.74 (1H, ddt, J=18, 9.5, 6.5 Hz), 5.67 (1H, dd, J=8.4, 6.0 Hz), 4.97 (1H, m), 4.92 (1H, m), 2.07–1.96 (3H, m), 1.85 (1H, dddd, J=14, 8.5, 7.5, 6.2 Hz), 1.43 (2H, apparent pentet, J=7.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.92 (s), 137.73 (d), 137.59 (d), 135.30 (s), 128.92 (2×d), 128.43 (d), 128.21 (2×d), 124.95 (s), 115.52 (t), 77.10 (d), 33.05 (t), 32.58 (t), 23.98 (t) ppm.

To a stirred solution of (*E*)-2-bromo-1-phenylocta-1,7-dien-3-yl 2,2,2-trichloroacetate **29** (0.840 g, 1.98 mmol) and tetrakispalladiumtriphenyl phosphine (0.229 g, 0.20 mmol) in

THF (10 mL), under argon, was added diethylzinc (3.96 mL of a 2 M solution in benzene, 3.96 mmol). The solution changed from cloudy to clear yellow. After stirring for 2 h at room temperature the reaction remained incomplete but work-up was carried out due to concern for the stability of the allene formed. NH_4Cl (aq) (30 mL of a saturated solution) was added and the products were extracted into diethyl ether (3×100 mL), the combined organic phases washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with hexane) gave the title compound **30** as a colourless oil (175 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.30 (4H, m), 7.21 (1H, m), 6.17 (1H, dt, J=6.4, 3.1 Hz), 5.84 (1H, ddt, J=17.1, 10.3, 6.8 Hz), 5.60 (1H, apparent q, J=6.4 Hz), 5.03 (1H, d+fs, J=17.1 Hz), 4.98 (1H, d+fs, J=10.3 Hz), 2.22–2.12 (4H, m), 1.62 (2H, apparent pentet, J=7.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.40 (s), 138.62 (d), 135.19 (s), 128.69 (2×d), 126.80 (2×d), 126.73 (d), 114.89 (t), 94.90 (2×d), 33.40 (t), 28.54 (t), 28.28 (t) ppm. IR (film): 1947 (m), 1638 (m), 1596 (m), 875 (s) cm^{-1}. LRMS (EI) m/z (%): 184 (M^+, 74), 169 (M^+-Me, 58), 155 ($M^+-C_2H_5$, 64), 141 (100), 115 (100). HRMS (EI): $C_{14}H_{16}$ $(M)^+$ requires 184.1252. Found 184.1257.

4.4.6.1. (*E*)- and (*Z*)-(2-(2-Methylcyclopentyl)vinyl)-benzene (33a–d). To a solution of zirconocene dichloride (0.146 g, 0.50 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (0.40 mL of 2.5 M solution in hexanes, 1.00 mmol). After 5 min a solution of octa-1,2,7-trienyl benzene (**30**) (0.092 mg, 0.50 mmol) in THF (1 mL) was added. On warming to room temperature the solution changed from yellow to dark brown, and after stirring for 6.5 h was quenched with $NaHCO_3$ (aq) (5 mL) and MeOH (5 mL) and stirred for 16 h. The products were extracted into diethyl ether (3×50 mL), the combined organic phases washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography (SiO_2 eluted with hexane) to yield the title compounds, a clear colourless oil (49 mg, 53%), as a 55:3:17:25 mixture of **33a/33b/33c/33d** as determined by a combination of NMR and GC. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.22 (3H, m), 7.21–7.11 (2H, m), 6.42 (0.6H, d, J=11.5 Hz, **33a** and **33b**), 6.34 (0.4H, d, J=15.8 Hz, **33c** and **33d**), 6.18 (0.2H, dd, J=15.8, 8.5 Hz, **33c**), 6.08 (0.25H, dd, J=15.8, 8.4 Hz, **33d**), 5.60 (0.55H, t, J=11.2 Hz, **33a**), 5.47 (~0.03H, t, J=10.9 Hz, **33b**), 3.01 (0.55H, dq, J=10.7, 7.3 Hz, **33a**), 2.62 (0.2H, pentet, J=7.5 Hz, **33c**), 2.48 (~0.03H, m, **33b**), 2.11 (1H, m), 2.01 (0.25H, pentet, J=8.4 Hz, **33d**), 1.94–1.70 (2H, m), 1.69–1.44 (2H, m), 1.35 (1H, m), 1.17 (1H, m), 0.97 (0.75H, d, J=6.8 Hz, **33d**), 0.91 (1.6H, d, J=7.0 Hz, **33a**), 0.87 (0.55H, d, J=7.0 Hz, **33c**). ^{13}C NMR (100 MHz, $CDCl_3$) compound **33a**: δ=138.16 (s), 135.28 (d), 128.55 (d), 128.83 (d), 128.60 (d), 128.23 (d), 126.85 (d), 126.51 (d), 126.12 (d), 126.10 (d), 41.82 (d), 38.48 (d), 34.03 (t), 32.77 (t), 23.76 (t), 16.28 (q) ppm. Compound **33d**: δ=138.13 (s), 135.05 (d), 129.17 (d), 52.39 (d), 41.44 (d), 34.68 (t), 33.37 (t), 23.75 (t), 18.59 (q) ppm. Compound **33c**: δ=138.25 (s), 133.04 (d), 129.42 (d), 47.49 (d), 38.66 (d), 33.59 (t), 30.98 (t), 23.45 (t), 16.35 (q) ppm. IR (film): 3023 (w), 2949 (s), 2866 (m), 1599 (w), 1492 (m), 1461 (m), 1446 (m), 962 (s), 743 (s) cm^{-1}. LRMS (EI) m/z (%): 186 (M^+, 54), 157 ($M^+-C_2H_5$, 6), 143 ($M^+-C_3H_7$, 30), 129 ($M^+-C_4H_9$, 100), 104 (90). HRMS (EI): $C_{14}H_{18}$ (M^+) requires 186.1409. Found 186.1401.

4.4.6.2. (*E*)- and (*Z*)-*rac*-(2-(2-((*Z*)-3-Phenylallyl)cyclopentyl)vinyl)benzene (34a–d). To a solution of zirconocene dichloride (0.356 g, 1.22 mmol) in THF (5 mL) under argon at −78 °C was added *n*-BuLi (0.98 mL of a 2.5 M solution in hexanes, 2.44 mmol) and the mixture stirred at −78 °C for 10 min, followed by a solution of 1-(octa-1,2,7-trienyl)benzene **30** (0.206 g, 1.12 mmol) in THF (1 mL). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The mixture was then split into two equal portions. One portion was then re-cooled to −78 °C. (*E*)-β-Bromostyrene (72 μL, 0.58 mmol) was added followed by LiTMP (0.90 mL of a 0.64 M solution in THF, 0.58 mmol) dropwise over 15 min. The solution warmed slowly to −70 °C over 2 h before addition of $NaHCO_3$ (aq) (5 mL) and MeOH (5 mL). The mixture was now stirred for 16 h before extraction into Et_2O (3×50 mL), washing with water (50 mL) and brine (50 mL), drying over $MgSO_4$ and removal of the solvent in vacuo. Purification by column chromatography (SiO_2 eluted with hexane) gave the title compounds as a colourless oil (61 mg, 38%) as mixture of **35a** (63%), **35b** (22%) and **35c+35d** (15% combined—probably just **35c** but we cannot be certain) as determined by a combination of NMR and GC. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.17 (10H, m), 6.44–6.32 (1.85H, m), 6.11 (0.15H, dd, J=15.8, 8.8 Hz, **34c** and/or **34d**) 5.64–5.49 (2H, m), 3.14 (0.85H, dq, J=10.8, 6.8 Hz, **34a** and **34b**), 2.76 (0.15H, apparent pentet, J=6.8 Hz, **34c** and/or **34d**), 2.61 (0.3H, apparent pentet, J=9.1 Hz **34c** and/or **34d**), 2.45 (1.7H, m, **34a** and **34b**), 2.27 (1H, m), 2.09 (1H, m), 1.94–1.80 (2H, m), 1.74–1.38 (2.3H, m), 1.21 (0.7H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) compound **34a**: δ=138.00 (s), 134.49 (d), 132.69 (d), 129.22 (d), 128.90 (d), 128.86 (4×d), 128.25 (4×d), 126.58 (d), 126.54 (d), 44.97 (d), 41.07 (d), 33.29 (t), 31.13 (t), 30.16 (t), 23.70 (t) ppm. Compound **34b**: δ=138.10 (s), 132.12 (d), 129.18 (d), 129.05 (d), 128.95 (d), 128.77 (d), 128.17 (d), 126.50 (d), 48.43 (d), 45.01 (d), 33.70 (t), 33.21 (t), 32.06 (t), 23.94 (t) ppm. Compound **34c** or **34d**: δ=137.90 (s), 137.49 (d), 132.62 (d), 132.21 (d), 129.80 (d), 129.15 (d), 128.54 (d), 126.88 (d), 126.17 (d), 46.43 (d), 45.42 (d), 31.45 (t), 30.75 (t), 30.30 (t), 23.19 (t) ppm. IR (film): 1598 (w), 1491 (m), 1445 (m), 794 (m), 767 (s) cm^{-1}. LRMS (CI) m/z (%): 306 ($M+NH_4^+$, 64), 289 ($M+H^+$, 10), 211 ($M^+-C_6H_5$, 30), 197 ($M^+-C_7H_7$, 86), 184 (100). HRMS (EI): $C_{22}H_{24}$ (M^+) requires m/z 288.1878. Found 288.1877.

4.4.6.3. (*E*)- and (*Z*)-*rac*-Diethyl-2-(2-styrylcyclopentyl)ethyl phosphonate (35a–d). To a solution of the zirconacycles **31** (0.56 mmol) at −78 °C, prepared as described in the synthesis of **34**, was added a solution of diethylchloromethyl phosphonate (0.208 g, 1.12 mmol) in THF (1 mL), followed by LiTMP (1.5 mL of a 0.75 M solution in THF, 1.12 mmol) dropwise over 30 min. The solution was warmed slowly to room temperature over 16 h before addition of $NaHCO_3$ (aq) (5 mL) and MeOH (5 mL), and then stirred for a further 5 h. The products were extracted into Et_2O (3×50 mL) and the combined organic phases washed with water (50 mL) and brine (50 mL) before drying over

$MgSO_4$ and removal of solvent in vacuo. Purification by column chromatography (SiO_2 eluted with 1:1 hexane/EtOAc) followed by Kugelrohr distillation (190 °C/10 mmHg) gave the title compound as a 51:21:25:3 mixture of **35a**, **35b**, **35c** and **35d**, respectively, determined by a combination of NMR and GC, as a clear colourless oil (136 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.16 (5H, m), 6.44 (0.5H, d, J=11.3 Hz, **35a**), 6.42 (0.2H, d, J=11.4 Hz, **35b**), 6.36 (0.3H, d, J=15.8 Hz, **35c** and **35d**), 6.13 (0.25H, dd, J=15.8, 9.3 Hz, **35c**), 6.07 (~0.03H, dd, J=15.8, 8.5 Hz, **35d**), 5.60 (0.5H, t, J=11.3 Hz, **35a**), 5.50 (0.2H, dd, J=11.4, 10.3 Hz, **35b**), 4.12–3.92 (4H, m), 3.11 (0.5H, dtd, J=11.3, 6.9, 5.2 Hz, **35a**), 2.74 (0.25H, dtd, J=9.3, 6.8, 4.6 Hz, **35c**), 2.57 (0.2H, pentet, J=9.0 Hz, **35b**), 2.15 (~0.03H, pentet, J=8.8 Hz, **35d**), 1.98–1.71 (4H, m), 1.70–1.47 (6H, m), 1.42–1.16 (7H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.90 (s), 137.85 (s), 137.78 (s), 137.34 (d), 134.61 (d), 133.82 (d), 131.53 (d), 130.04 (d), 129.05 (d), 128.98 (2×d), 128.80 (2×d), 128.67 (2×d), 128.56 (2×d), 128.23 (2×d), 127.01 (d), 126.63 (d), 126.14 (2×d), 126.10 (d), 63.51 (2×CH_2, d, J=6.8 Hz), 61.47 (2×CH_2, d, J=5.8 Hz), 61.45 (2×CH_2, d, J=5.8 Hz), 48.45 (CH, d, J=16.5 Hz), 46.15 (d), 45.28 (CH, d, J=16.5 Hz), 45.03 (d), 45.00 (CH, d, J=16.5 Hz), 40.48 (d), 33.90 (2×t), 33.37 (2×t), 32.03 (2×t), 31.90 (t), 30.86 (t), 30.62 (t), 27.05 (t), 26.99 (t), 25.63 (t), 25.53 (t), 25.36 (t), 24.24 (t), 24.18 (t), 24.13 (t), 24.06 (t), 24.01 (t), 23.97 (t), 23.85 (t), 23.65 (t), 23.21 (t), 16.60 (q), 16.54 (q), 16.46 (q) ppm. The extra CH_2 signals between 27.05 and 23.65 ppm are accounted for as part of $^2J_{CP}$ doublets—splitting indistinct. IR (film): 1239 (s), 1054 (s), 1024 (s), 953 (s), 789 (s), 731 (s) cm^{-1}. LRMS (ES)$^+$ m/z (%): 337 ($M+H^+$, 100), 359 ($M+Na^+$, 43), 673 ([2M+H]$^+$, 30), 695 ([2M+Na]$^+$, 45). HRMS (ES)$^+$: $C_{19}H_{30}O_3P$ $(M+H)^+$ requires m/z 337.1927. Found 337.1924.

4.5. Insertion of *tert*-butyl isonitrile into zirconacycles

4.5.1. Method G. Insertion of *tert*-butyl isonitrile with hydrolytic work-up. The zirconacycle solution (1.0 mmol) was cooled to 0 °C and *tert*-butyl isocyanide (0.10 mL, 1.0 mmol) was added. The solution was stirred at 0 °C for 30 min before addition of HCl (5 mL of a 2 M aqueous solution) and was then stirred for 24 h. The products were extracted into Et_2O (3×30 mL) before the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and solvent removed in vacuo to give the crude product.

4.5.1.1. *rac*-(*S*)-2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methyl cyclopentyl)propanal (39). The zirconacycle **5c** was prepared from (*E*)-4,4-bis(methoxymethyl)octa-1,6-diene according to Method A and elaborated using Method G. Purification of the crude product by column chromatography (SiO_2 eluted with 8:2 petrol/Et_2O) gave the title compound as a 2:1 mixture of inseparable diastereoisomers (108 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.72 (0.33H, d, J=1.8 Hz), 9.63 (0.66H, d, J=1.8 Hz), 3.32 (6H, s+fs), 3.21–3.16 (4H, m), 2.44 (1H, t+fs, J=6.2 Hz), 1.84 (1H, m), 1.79–1.59 (4H, m), 1.53 (0.66H, dd, J=13.0, 7.5 Hz), 1.27 (0.33H, m), 1.17 (0.66H, t, J=12.3 Hz), 1.09 (1H, d, J=7.0 Hz), 1.05 (2H, m), 1.00 (2H, d, J=7.0 Hz), 0.94 (3H, d, J=5.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.7 (d, minor), 205.4 (d, major), 78.01 (t), 77.76 (t), 60.94 (2×q), 47.81 (d, minor), 47.79 (d, major), 47.63 (d, minor), 46.04 (d, major), 45.16 (s), 41.76 (t, minor), 41.37 (t, major), 36.83 (d, major), 36.56 (t, minor), 36.13 (d, minor), 34.22 (t, major), 18.73 (q, minor), 18.09 (q, major), 11.35 (q, minor), 8.85 (q, major) ppm. IR (film): 1724 (s), 1451 (m), 1104 (s), 964 (m) cm^{-1}. LRMS (CI) m/z (%): 229 ($M+H^+$, 100), 213 (M^+-Me, 2), 166 ($M^+-C_2H_6O_2$, 10), 138 ($M^+-C_4H_{10}O_2$, 40), 137 (85).

4.5.1.2. *rac*-(3*R*,3a*S*,4*R*,7a*S*)-1,1-Bis(methoxymethyl)-3-methyl octahydro-1*H*-indene-4-carbaldehyde (40). The zirconacycle **6** was prepared from 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene according to Method A and elaborated using Method G. Purification of the crude product by column chromatography (SiO_2 eluted with 3:1 petrol/Et_2O) gave the title compound as a colourless oil (143 mg, 56%) as 2.7:1 mixture of isomers. With further purification by column chromatography (SiO_2 eluted with 3:1 petrol/Et_2O) a small portion of the major isomer was isolated pure for characterisation. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.69 (1H, s), 3.32 (3H, s), 3.31–3.16 (4H, m), 3.26 (3H, s), 3.25 (1H, d, J=5.5 Hz), 2.11–2.03 (2H, m), 1.97 (1H, d+fs, J=13.8 Hz), 1.69–1.63 (2H, m), 1.58–1.46 (3H, m), 1.17–1.06 (3H, m), 0.95 (3H, d, J=6.3 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.03 (d), 76.84 (t), 73.93 (t), 59.30 (q), 59.04 (q), 49.01 (s), 47.51 (d), 44.13 (d), 41.92 (d), 38.54 (t), 33.12 (d), 23.28 (t), 22.33 (t), 21.21 (t), 19.59 (q) ppm. IR (film): 1724 (s), 1451 (m), 1100 (s), 961 (m) cm^{-1}. LRMS (CI) m/z (%): 255 ($M+H^+$, 100), 240 ($M+H^+-Me$, 5), 233 ($M+H^+-MeOH$, 50), 164 ($C_{11}H_{16}O^+$, 30), 149 ($C_{10}H_{13}O^+$, 28). HRMS (EI): $C_{15}H_{26}O_3$ $(M)^+$ requires m/z 254.1882. Found 254.1882.

4.5.1.3. *rac*-2-((3*S*,4*R*)-1-Benzyl-3,4-dimethylpyrrolidin-3-yl)acetaldehyde (41). The zirconacycle **7** was prepared from *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine according to Method A and elaborated using Method G. Purification by column chromatography (SiO_2 eluted with 88:10:2 petrol/Et_2O/Et_3N) failed to separate *rac*-2-((3*S*,4*R*)-1-benzyl-3,4-dimethylpyrrolidin-3-yl)acetaldehyde (**41**) from contaminant ketone *rac*-(3a*R*,6a*S*)-2-benzyl-3a-methylhexahydrocyclopenta[*c*]pyrrol-5(1*H*)-one (**42**).[34] Reduction of the mixture was therefore carried out and permitted separation and characterisation of the primary alcohol *rac*-2-((3*S*,4*R*)-1-benzyl-3,4-dimethyl pyrrolidin-3-yl)ethanol as follows. A solution of the aldehyde and ketone mixture **41+42** prepared above (0.080 g, 0.35 mmol) in ethanol (2 mL) was added slowly to a suspension of sodium borohydride (0.026 g, 0.70 mmol) in ethanol (2 mL). The reaction mixture was stirred for 2 h before addition of HCl (3 mL of a 2 M aqueous solution) at 0 °C. The reaction mixture was basified by addition of NaOH (10 mL of a 2 M aqueous solution). The products were extracted into Et_2O (3×30 mL) and the combined organic phases washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 48:50:2 petrol/Et_2O/Et_3N) gave *rac*-2-((3*S*,4*R*)-1-benzyl-3,4-dimethyl pyrrolidin-3-yl)ethanol as a colourless oil (20 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31–7.21 (5H, m), 3.73 (1H, d, J=12.8 Hz), 3.71 (1H, m), 3.58 (1H, m), 3.57 (1H, d, J=12.8 Hz), 2.85 (1H, d, J=9.0 Hz), 2.74 (1H, t, J=10.3 Hz), 2.70 (1H, t,

J=10.3 Hz), 2.30 (1H, d, J=9.0 Hz), 1.98 (1H, m), 1.64–1.51 (3H, m), 0.97 (3H, s), 0.90 (3H, d, J=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.52 (s), 128.89 (d), 128.60 (d), 127.34 (d), 66.48 (t), 61.08 (t), 60.84 (t), 60.72 (t), 43.02 (s), 42.59 (d), 39.62 (t), 26.74 (q), 12.18 (q) ppm. IR (film): 3500–3200 (m, br), 1453 (s), 1373 (s), 1263 (m), 1047 (s), 976 (m), 737 (s) cm^{-1}. LRMS (CI) m/z (%): 234 (M+H$^+$, 5). HRMS (EI): $C_{15}H_{23}NO$ (M)$^+$ requires m/z 233.1779. Found 233.1778.

4.6. Deuteration of zirconacycles

4.6.1. Method H. Monodeuteration of zirconacycles. A solution of CD_3OD (41 μL, 1.00 equiv, 1.00 mmol) in THF (1 mL) was added to the zirconacycle solution at room temperature and stirred for 1 h. The reaction was then quenched by addition of satd $NaHCO_3$ aq solution (5 mL) and MeOH (5 mL) and stirred vigorously for 16 h. The product was extracted into diethyl ether (3×30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed in vacuo.

4.6.1.1. Deuteration of zirconacycle 5c. Zirconacycle **5c** was prepared from 4,4-bis-methoxymethyl-octa-1,6-diene by Method A and deuterated by Method H. The crude product was purified column chromatography (SiO_2 eluted with 95:5 petrol/Et_2O) to yield a mixture of *rac*-(3*R*,4*R*)-3-ethyl-1,1-bis(methoxymethyl)-4-methylcyclopentane (**47**, 20%), *rac*-(3*R*,4*R*)-3-ethyl-1,1-bis(methoxymethyl)-4-deuteriomethylcyclopentane (**44a**, 42%), *rac*-(3*R*,4*R*)-3-(1-deuterioethyl)-1,1-bis(methoxymethyl)-4-methylcyclopentane (**43a**, 36%) and *rac*-(3*R*,4*R*)-3-(1-deuterioethyl-1,1-bis-(methoxymethyl)-4-deuteriomethylcyclopentane (**48**, 2%) (0.105 g, 53%). The ratio of **44a** to **43a** was determined by ^{13}C NMR. Mass spectrometry (CI) was used to determine the ratio of **43a**+**44a** to **47** and **48**. Relevant carbon-13 signals (cf. the known undeuterated compound **47**[18c]) are given. ^{13}C NMR (100 MHz, $CDCl_3$): δ=48.52 (d, *C*HCH$_2$D, **44a**), 48.46 (d, *C*HMe, **43a**), 39.65 (d, *C*HCHDMe), 39.58 (d, *C*HEt), 26.54 (t, *C*H$_2$Me), 26.16 (CHD, CHDMe, t, J=19.2 Hz), 18.29 (q, *C*H$_3$CH), 17.99 (CH$_2$D, *C*H$_2$DCH, t, J=19.2 Hz), 12.75 (q, *C*H$_3$CH$_2$), 12.65 (q, *C*H$_3$CHD) ppm.

4.6.1.2. 1-{[4,4-Di(methoxymethyl)-2-methylcyclopentyl]methyl}benzene (49). Zirconacycle **5a** was prepared from (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene according to Method A, then the reaction was quenched by the addition of HCl (6 mL, 2 M aqueous solution) and stirred vigorously for 3 h. The product was extracted into diethyl ether (3×30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed in vacuo. Purification by column chromatography (SiO_2 eluted with 92:8 petrol/Et_2O) gave the title compound **49** as a clear colourless oil (0.208 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (2H, t, J=7.5), 7.15–7.12 (3H, m), 3.30 (3H, s), 3.26 (3H, s), 3.18–3.07 (4H, m), 2.89 (1H, dd, J=13.3, 3.2 Hz), 2.28 (1H, dd, J=13.3, 8.9 Hz), 1.74 (1H, dd, J=13.3, 6.6 Hz), 1.61–1.54 (3H, m), 1.11–0.96 (2H, m), 0.96 (3H, d, J=5.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.90 (s), 129.02 (2×d), 128.27 (2×d), 125.71 (d), 78.08 (t), 78.00 (t), 59.36 (q), 59.09 (q), 48.66 (d), 45.20 (s), 41.92 (t), 40.33 (t), 39.81 (d), 39.54 (t), 18.33 (t) ppm. IR (film): 3026 (w), 2957 (w), 2949 (m), 2921 (m), 2870 (m), 2823 (m), 1453 (m), 1376 (w), 1198 (m), 1105 (s), 964 (m) cm^{-1}. LRMS (CI) m/z (%): 262 (M$^+$, 45), 231 (M+H$^+$−MeOH, 12), 185 (M$^+$−C$_6$H$_5$, 57), 138 (91), 91 ($C_7H_7^+$, 100). HRMS (EI): $C_{17}H_{26}O_2$ requires m/z 262.1933. Found 262.1935.

4.6.1.3. Deuteration of zirconacycle 5a (43b and 44b). The zirconacycle **5a** was prepared from (4,4-bis-methoxymethyl-hepta-1,6-dienyl)-benzene according to Method A and monodeuterated by Method H. The crude product was purified by chromatography (SiO_2 eluted with 92:8 petrol/Et_2O) to yield a clear colourless oil (0.202 g, 77%). A combination of ^{13}C NMR (particularly the shift of a carbon when the adjacent carbon is deuterated), ^{2}H NMR spectroscopy and mass spectrometry (EI and CI) were used to calculate the approximate composition of the mixture of isomers as **43b** (major diastereoisomer) (71%), **43b** (minor diastereoisomer) (3%), **44b** (11%), **49** (11%) and 1-{[4,4-di(methoxymethyl)-2-deuteriomethylcyclopentyl]deuteriomethyl}benzene (**50**) (4%). The key signals observed (cf. **49** above) were: ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.87 (dd, J=13.3, 3.0 Hz, CHPh not deuterated in major isomer of **43b**), 2.28 (dd, J=13.3, 8.5 Hz, CHPh deuterated in major diastereoisomer of **43b**), 0.96 (d, J=5.5 Hz, Me, monodeuterated in **44b**). ^{13}C NMR (100 MHz, $CDCl_3$): δ=48.66 (CHCH$_2$Ph), 48.60 (CHCHDPh), 40.32 (CH$_2$Ph), 40.06 (CHDPh, t, J=17.9 Hz), 39.78 (CHMe), 39.72 (CHCH$_2$D), 18.33 (CH$_3$), 18.03 (CH$_2$D, t, J=19.2 Hz) ppm. LRMS (EI) m/z (%): 263(M$^+$, 30), 232 (M$^+$−CH$_3$O, 5), 186 (M$^+$−C$_6$H$_5$, 35), 92 (C$_6$H$_5$CHD$^+$, 100).

4.6.1.4. 3-Methyl-1,1-bis(methoxymethyl)-octahydro-indene (51). The zirconacycle **6** was prepared from 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene according to Method A, then quenched by addition of MeOH (5 mL) and satd $NaHCO_3$ aqueous solution (5 mL) and stirred vigorously for 16 h. The product was extracted into diethyl ether (3×30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 95:5 petrol/Et_2O) gave the title compound **51** as a clear colourless oil (0.181 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.34 (3H, s), 3.33–3.14 (4H, m), 3.31 (3H, s), 2.02 (1H, m), 1.75–1.63 (5H, m), 1.52–1.42 (3H, m), 1.26 (1H, m), 1.18–1.09 (2H, m), 1.07 (1H, dd, J=14.0, 8.1 Hz), 0.92 (3H, d, J=6.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=76.98 (t), 74.34 (t), 59.35 (q), 59.15 (q), 48.82 (s), 45.32 (d), 44.28 (d), 39.48 (t), 31.17 (d), 26.11 (t), 25.16 (t), 24.08 (t), 21.43 (t), 19.90 (q) ppm. IR (film): 2974 (w), 2921 (m), 2888 (m), 2865 (m), 2806 (w), 1451 (m), 1389 (w), 1373 (w), 1196 (m), 1156 (w), 1102 (s), 960 (m) cm^{-1}. LRMS (CI) m/z (%): 227 (M+H$^+$, 90), 195 (M+H$^+$−MeOH, 10), 180 (M$^+$−C$_2$H$_5$O, 3), 164 (M$^+$−C$_2$H$_6$O$_2$, 8), 150 (M$^+$−C$_3$H$_8$O$_2$, 6). HRMS (EI): $C_{14}H_{26}O_2$ (M$^+$) requires m/z 226.1933. Found 226.1936.

4.6.1.5. 4-Deuterio-3-methyl-1,1-bis(methoxymethyl)-octahydro-indene (45). The zirconacycle **6** was prepared from 3-(1,1-bis-methoxymethyl-but-3-enyl)-cyclohexene according to Method A and monodeuterated by Method H. The crude product was purified by chromatography (SiO_2

eluted with 95:5 petrol/Et_2O) to yield a mixture of **51** and monodeuterated compound **45** as a clear colourless oil (162 mg, 71% yield, 60% deuterium incorporation). Deuterium incorporation was determined from the ^{13}C NMR spectrum by integration of the peaks of the carbons adjacent to the deuterated positions. Relevant carbon-13 signals are: ^{13}C NMR (75 MHz, $CDCl_3$): δ=45.31 (CH, C3a, C4 non-deuterated), 45.23 (CH, C3a, C4 deuterated), 44.28 (CH, C7a, C4 non-deuterated), 44.25 (CH, C7a, C4 deuterated), 26.10 (CH_2, C6, C4 non-deuterated), 26.06 (CH_2, C6, C4 deuterated), 25.14 (CH_2, C4 non-deuterated), 24.76 (CHD, t, J=19.3 Hz, C4 deuterated), 21.42 (CH_2, C5, C4 non-deuterated), 21.30 (CH_2, C5, C4 deuterated) ppm. LRMS (CI) m/z (%): 228 ($M+H^+$, 100—deuterated), 227 ($M+H^+$, 68 non-deuterated).

4.6.1.6. 1-Benzyl-3-deuteromethyl-3,4-dimethyl-pyrrolidine (46). The zirconacycle **7** was prepared from *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)-amine according to Method A and deuterated by Method H to afford a clear colourless oil (0.124 g, 61%) with 86% deuterium incorporation—determined by ^{13}C NMR integrals of the carbon adjacent to the deuterated position. The protonated compound, 1-benzyl-3,3,4-trimethylpyrrolidine is known.[20,34] ^1H NMR (400 MHz, $CDCl_3$): δ=7.33–7.24 (5H, m), 3.67 (1H, d, J=13.1 Hz), 3.57 (1H, d, J=13.1 Hz), 2.89 (1H, dd, J=9.0, 7.7 Hz), 2.58 (1H, d, J=9.0 Hz), 2.30 (1H, d, J=9.0 Hz), 2.24 (1H, t, J=9.0 Hz), 1.90 (1H, m), 1.03 (3H, s), 0.90 (2H, m, CH_2D), 0.87 (3H, d, J=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.02 (s), 128.70 (2×d), 128.24 (2×d), 126.77 (d), 68.92 (t), 61.77 (t), 61.11 (t), 42.56 (d), 39.55 (s), 28.48 (t), 22.82 (CH_2D, t, J=19.2 Hz), 13.26 (q) ppm.

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References and notes

1. (a) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829; (b) Negishi, E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 1163.
2. (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687; (b) Xi, Z. F.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444; (c) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696; (d) Erker, G. *J. Organomet. Chem.* **1977**, *134*, 189; (e) Kropp, K.; Erker, G. *Organometallics* **1982**, *1*, 1246; (f) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7411; (g) Buchwald, S. L.; Broene, R. D. *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982–1994*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 771–784.
3. Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435; Xi, C. J.; Huo, S. Q.; Afifi, T. H.; Hara, R.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 4099; Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870; Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797.
4. Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880; Spence, R. E. V.; Hsu, D. P.; Buchwald, S. L. *Organometallics* **1992**, *11*, 3492; Buchwald, S. L.; Fisher, R. A.; Foxman, B. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 771; Buchwald, S. L.; Qun, F. *J. Org. Chem.* **1989**, *54*, 2793; Ura, Y.; Li, Y. Z.; Xi, Z. F.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 2787.
5. (a) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521; (b) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105; (c) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336; (d) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N.; Nakajima, K. *Organometallics* **1994**, *13*, 4183; (e) Takahashi, T.; Huo, S. Q.; Hara, R.; Noguchi, Y.; Nakajima, K.; Sun, W. H. *J. Am. Chem. Soc.* **1999**, *121*, 1094; (f) Barluenga, J.; Sanz, R.; Fananas, F. J. *Chem.—Eur. J.* **1997**, *3*, 1324.
6. (a) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Tetrahedron Lett.* **1992**, *33*, 5655; (b) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Tetrahedron Lett.* **1994**, *35*, 1445; (c) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *Synlett* **1994**, 111.
7. Takahashi, T.; Xi, Z. F.; Yamazaki, A.; Liu, Y. H.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672; Liu, Y. H.; Shen, B. J.; Kotora, M.; Takahashi, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 949; Kotora, M.; Xi, C. J.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 4321; Takahashi, T.; Sun, W. H.; Xi, C. J.; Kotora, M. *Chem. Commun.* **1997**, 2069.
8. (a) Takahashi, T.; Xi, Z. F.; Kotora, M.; Xi, C. J.; Nakajima, K. *Tetrahedron Lett.* **1996**, *37*, 7521; (b) Takahashi, T.; Kotora, M.; Xi, Z. F. *J. Chem. Soc., Chem. Commun.* **1995**, 1503.
9. Takahashi, T.; Hara, R.; Nishihara, Y.; Kotora, M. *J. Am. Chem. Soc.* **1996**, *118*, 5154; Takahashi, T.; Sun, W. H.; Liu, Y. H.; Nakajima, K.; Kotora, M. *Organometallics* **1998**, *17*, 3841; Kotora, M.; Umeda, C.; Ishida, T.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 8355; Duan, Z.; Sun, W.-H.; Liu, Y.; Takahashi, T. *Tetrahedron Lett.* **2000**, *41*, 7471.
10. (a) Nishihara, Y.; Aoyagi, K.; Hara, R.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1996**, *252*, 91; (b) Aoyagi, K.; Kasai, K.; Kondakov, D. Y.; Hara, R.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **1994**, *220*, 319.
11. Ubayama, H.; Xi, Z. F.; Takahashi, T. *Chem. Lett.* **1998**, 517.
12. Cuny, G. D.; Gutierrez, A.; Buchwald, S. L. *Organometallics* **1991**, *10*, 537.
13. Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695.
14. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.
15. (a) Kasai, K.; Kotora, M.; Suzuki, N.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 109; (b) Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407; (c) Takahashi, T.; Nishihara, Y.; Hara, R.; Huo, S. Q.; Kotora, M. *Chem. Commun.* **1997**, 1599; (d) Takahashi, T.; Sun, W. H.; Xi, C. J.; Ubayama, H.; Xi, Z. F. *Tetrahedron* **1998**, *54*, 715.
16. Uesaka, N.; Mori, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4542.
17. Mori, M.; Imai, A. E.; Uesaka, N. *Heterocycles* **1995**, *40*, 551.
18. (a) Fillery, S. M.; Gordon, G. J.; Luker, T.; Whitby, R. J. *Pure Appl. Chem.* **1997**, *69*, 633; (b) Dixon, S.; Whitby, R. J. *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 86–109; (c) Dixon, S.; Fillery, S. M.; Kasatkin, A.; Norton, D.; Thomas, E.; Whitby, R. J. *Tetrahedron* **2004**, *60*, 1401.

19. (a) Baldwin, I. R.; Whitby, R. J. *Chem. Commun.* **2003**, 2786; (b) Dixon, S.; Gordon, G. J.; Whitby, R. J. *Chem. Commun.* **2005**, 4303.
20. Gordon, G. J.; Luker, T.; Tuckett, M. W.; Whitby, R. J. *Tetrahedron* **2000**, *56*, 2113.
21. Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*.
22. Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933.
23. Negishi, E.; Akiyoshi, K.; O'Connor, B.; Takagi, K.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 3089.
24. Boche, G.; Lohrenze, J. C. W. *Chem. Rev.* **2001**, *101*, 697.
25. (a) Negishi, E. I.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917; (b) Negishi, E. I.; Choueiry, D.; Nguyen, T. B.; Swanson, D. R.; Suzuki, N.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 9751.
26. NMR of **5b**: ^{1}H (400 MHz, C_6D_6): δ=5.81 (10H, s), 3.32 (4H, br s), 3.28 (6H, s), 2.37–2.25 (2H, m), 2.20 (1H, m), 1.76 (1H, ddd, J=11.5, 11.5, 4.5 Hz, ZrCH proton identified by C–H correlation), 1.64 (1H, ddq, J=13, 11.5, 7.3 Hz, C*H*HMe), 1.24–1.20 (3H, m), 1.14–0.97 (3H, m), 0.79 (3H, t, J=7.3 Hz) ppm. ^{13}C (100 MHz, C_6D_6): δ=108.69 (d), 108.41 (d), 77.64 (t), 65.16 (d), 57.66 (q), 49.24 (t), 45.78 (t), 45.07 (s), 41.44 (t), 39.02 (d), 33.19 (d), 31.24 (t), 15.41 (q) ppm.
27. Molecular modelling studies were performed with Spartan 04 or Spartan 06 (Wavefunction Inc.). Conformational searches were carried out using molecular mechanics (MMFF94 force field extended to include transition metals and cyclopentadiene ligands). Final minimizations of likely global minima were carried out using the hybrid DFT/HF B3LYP method using the 6-31G* basis set, and core electron approximation for zirconium.[35]
28. Yin, Y. G.; Jones, W. M. *Tetrahedron* **1995**, *51*, 4395; Duggan, D. M. *Inorg. Chem.* **1981**, *20*, 1164.
29. Ohno, H.; Miyamura, K.; Tanaka, T.; Oishi, S.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **2002**, *67*, 1359.
30. The ratio of isomers **33a–d**, and by implication **31a–d**, formed at particular times varied in different experiments, though the trends observed were consistent. This is similar to what we have observed for the isomerisation of *cis*-8-biscyclopentadienylzirconabicyclo[4.3.0]nonane to the trans isomer where the time/temperature needed to obtain the reported >97% trans isomer varies greatly between similar preparations, and suggests catalysis by an unknown and variable component.
31. (a) Berry, R. S. *J. Chem. Phys.* **1960**, *32*, 933; (b) Lauterbur, P. C.; Ramirez, F. *J. Am. Chem. Soc.* **1968**, *90*, 6722.
32. The iminoacyl species resulting from *tert*-BuNC insertion into **5a** was unexpectedly resistant to acid hydrolysis and the corresponding aldehyde product was therefore not obtained. However, NMR analysis of the (iminoacyl) zirconacycle indicated regioselective insertion into the α-substituted C–Zr bond.
33. Probert, G. D.; Whitby, R. J. *Tetrahedron Lett.* **1995**, *36*, 4113.
34. Yamaura, Y.; Hyakutake, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615.
35. Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, D.; Adam-son, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwalt-ney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y. H.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W. M.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C. P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Comput. Chem.* **2000**, *21*, 1532.