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Carbenoid insertion into alkenylzirconocenes—a convergent synthesis of functionalised allylmetallics

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Abstract

Insertion of lithium alkylcarbenoids RC(A)LiX, A = CN, P(O)(OEt)₂, SO₂Ph, OMe into alkenylzirconocene chlorides derived by hydrozirconation of terminal alkynes affords functionalised allylzirconium reagents which may be further elaborated. © 2000 Elsevier Science Ltd. All rights reserved.

An important aim of synthetic organic chemistry is to develop new methods for forming carboncarbon bonds. Efficient synthesis of complex molecules requires methods which form several carbon-carbon bonds in one operation. Within organometallic chemistry a hardly investigated reaction—the insertion of lithium carbenoids into metal–carbon bonds via a 1,2-metallate rearrangement (Eq. (1))¹—holds particular promise for the above since the product retains the organometallic functionality of the starting material, i.e. the process is inherently iterative. We now describe one application of this idea with the convergent formation of allylzirconium compounds by insertion of an alkyl carbenoid into a alkenylzirconocene, and their further elaboration.

$$R^{1}-M + \frac{R^{2}}{R^{3}} \xrightarrow{X}_{Li} \longrightarrow \begin{bmatrix} R^{3}R^{2}C \xrightarrow{X} \\ R^{1} \xrightarrow{M^{-}Li^{+}} \end{bmatrix} \xrightarrow{-LiX} R^{1} \xrightarrow{R^{2}} M$$
(1)

Allylmetallic reagents are generally highly reactive towards electrophiles and have an important place in organic synthesis.² The possibility of controlling regio- and stereochemistry when using allyl organometallics has prompted the investigation of many metal systems, and those of the group IV transition metals have proven extremely useful.² The normal route to allyl organometallics is from the allyl halide by oxidative addition reaction, or by transmetallation from a species so formed. The use of low valent metal complexes $Cp_2Zr(1-butene)$ and $(^{i}PrO)_2Ti(propene)$ allows

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allyl alcohol derivatives to be used as precursors.³ Hydrozirconation of allenes is another route to allylzirconocene reagents.⁴ A particularly attractive route to allylmetallic species, which provides an easy access to a wide range of previously inaccessible reagents, is the insertion of a saturated metal carbenoid into an alkenyl-metal bond. However, this 'homologation' approach is almost unexplored, the insertion of LiCH₂Cl, LiCHCl₂ and LiCH(Cl)SiMe₃ into alkenyl boronates,⁵ LiCH(Cl)SiMe₃ into (*E*)-1-octenylzirconocene chloride,^{1b} LiCH(Cl)SiMe₂Ph into (*E*)-1-nonenyl(diisobutyl)aluminium,^{1b} and ICH₂ZnI into alkenylcopper species⁶ are the only examples of which we are aware. Following our interest in the insertion of carbenoids into alkenylzirconocene chlorides,⁸ recently we communicated the high yielding formation of silyl-substituted allylzirconium compounds by insertion of silylated lithium carbenoids into alkenylzirconocene chlorides.⁹ We now report an extension of this work to form a range of functionalised allylzirconium species.

Deprotonation of methyl chloromethyl ether (MOM-chloride) with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at -100° C in the presence of (*E*)-1-octenylzirconocene chloride (1) (readily formed by hydrozirconation of 1-octyne) followed by warming to -60° C and hydrolysis gave the (*E*)-allyl ether **4a** indicating intermediate formation of the methoxy-substituted allylzirconocene **3a** (Scheme 1, Table 1, entry 1). The carbenoid **2b** derived by deprotonation of 2-methoxyethyl chloromethyl ether (MEM-chloride) afforded a mixture of the allyl ether **4b** (*E*isomer) and the alkenyl ether **5b** (*Z*-isomer) in 59% total yield (entry 2), higher than in the



Scheme 1.

 Table 1

 Protonation products from allylzirconocences 3 (Scheme 1)^a

Entry	2	3 – 5	А	Х	\mathbb{R}^2	Ratio 4 ^b : 5	Yield %	
1	а	а	OMe	Cl	Н	>95 : 5	42 ^c	
2	b	b	O(CH ₂) ₂ OMe	Cl	Н	80 : 20	59	
3	с	а	OMe	SO_2Ph	Н	93 ^d : 7	78	
4	d	d	SO_2Ph	Cl	Н	>95 : 5	48	
5	e	e	P(O) (OEt) ₂	Cl	Н	>95 ^e : 5	64	
6	f	f	CN	Cl	Н	>95 : 5	73	
7	g	g	CN	Cl	Me	>95 : 5	58	

^a Preparation of **3** (entries 1-3): slow addition of LiTMP (1.3 equiv.) to a mixture of **1** and the carbenoid precursor (1.3 equiv.) in THF at -100 °C followed by warming to -60 °C over 1 h; (entries 4-7): as above but LDA was used instead of LiTMP. ^b Only (*E*)-isomer except stated otherwise. ^c 11% of 1-methoxymethyl-2-methoxy-3-hexylcyclopropane was also isolated. ^d E : Z = 93:7. ^e E : Z = 82:18.

reaction with **2a**. We were delighted to find that the easily formed and relatively stable carbenoid (MeO)CH(PhSO₂)Li (**2c**)¹⁰ inserted into **1** to form the allylzirconocene **3a** in excellent yield judging from the hydrolysis products (entry 3). In contrast to **2c**, lithiated phenyl methyl sulphone failed to insert, suggesting that a sulphone only acts as a leaving group when the carbon–sulphone bond is weakened by the anomeric effect of an adjacent alkoxy-fragment.¹¹ Unfortunately, the substituted α -alkoxysulphones **6** and **7**, and the α -acyloxysulphones **8** did not react with **1** in the presence of LiTMP under conditions described above. Previously some alkoxy-substituted allylzirconocenes have been formed by the reaction of acetals derived from α , β -unsaturated aldehydes with Cp₂ZrBu₂.¹²



Successful insertion of the carbenoid **2c** prompted us to examine other lithium carbenoids stabilised by electron withdrawing groups. We were delighted to find that the PhSO₂-, (EtO)₂P(O)- and CN-substituted lithium carbenoids **2d**–**g**¹³ reacted with **1** to afford the corresponding functionalised allylzirconium compounds **3d**–**g** in good yield. In all cases hydrolysis of the zirconium reagents gave only the β , γ -unsaturated products **4** as exclusively (Table 1, entries 4, 6, 7) or predominately (entry 5) (*E*)-isomers. The 'one pot' procedure provides a very convenient route to β , γ -unsaturated sulphones, phosphonates and nitriles widely used in organic synthesis.



Scheme 2.

 Table 2

 Reaction of oxygen-substituted allylzirconocenes 3a,b with aldehydes (Scheme 2)

Entry	3	\mathbf{R}^2	9 ª	9 ^b							Yield %	10 ^c	10 ^b			Yield %
				anti			syn				trans	:	cis			
				Ε	:	Ζ	:	Ε	:	Ζ						
1	b	Ph	а	56	:	31	:	0	:	13	50	а	100	:	0	83
2^d	b	Ph	а	20	:	0	:	80	:	0	34	а	25	:	75	82
3	b	Pr	b	56	:	39	:	0	:	5	23	b	92	:	8	80
4	а	Ph	c	59	:	28	:	0	:	13	70	а	89	:	11	85
5	а	Pr	d	38	:	56	:	0	:	6	83	b	95	:	5	55

^a Preparation of **9**: **3**, R²CHO (1.5-3 equiv.), -78 to 20 °C, 3 h, then NaHCO₃ aq. ^b According to ¹H NMR spectroscopy.

^c Preparation of **10**: i. **9**, 15 mol.% Me₃SiCl, MeOH, 20 °C; ii. MCPBA (1.2 equiv.), $BF_3 \cdot Et_2 O$ (20 mol.%), $CH_2 Cl_2$, 20 °C. ^d 1 equiv. of $BF_3 \cdot Et_2 O$ with respect to PhCHO was added.

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To make best use of the synthetic method we needed to elaborate the intermediate allylzirconocenes with electrophiles other than H⁺. Addition of benzaldehyde to **3b** followed by hydrolysis gave the homoallylic alcohol **9a** in reasonable yield and good *anti*-diastereoselectivity (Scheme 2, Table 2, entry 1). The stereochemistry of **9a** was proven by its conversion to the *trans*- γ -lactone **10a**.¹⁴ Reaction with an aliphatic aldehyde gave similar stereochemical results but the expected alcohol **9b** was obtained in lower yield (entry 3). Remarkably, the addition of benzaldehyde to **3b** in the presence of BF₃·Et₂O afforded predominantly the *syn*-(*E*)-stereoisomer of **9a**, absent in the uncatalysed reaction (entry 2).¹⁵ Subsequent treatment with acidic MeOH followed by oxidation led to predominantly the *cis*- γ -lactone.¹⁴ The methoxy-substituted allylzirconocene **3a** formed by the insertion of **2c** reacted with both benzaldehyde and propanal to give the corresponding alcohols **9c** and **9d** in excellent yield (entries 5, 6). The stereochemical results were similar to those

Although the reaction of the PhSO₂- and (EtO)₂P(O)-substituted allylzirconium reagents **3d**,**e** with benzaldehyde gave a complex mixture of products, the addition of PhCHO to the cyano-substituted allylzirconocenes **3f** and **3g** led to the β , γ -unsaturated β' -hydroxynitriles **11** (a mixture of diastereoisomers in both cases) in good yield (Scheme 3). The lack of diastereocontrol, and the fact that the regiochemistry does not depend on the presence of an α -substituent in **3** (A = CN, R² = H or Me) is interesting and might be explained by localisation of the zirconium on the nitrogen. We have previously noted that in similar silicon-substituted systems (**3**, A = SiMe₃) the presence of an α -substituent (R² \neq H) reversed the regiochemistry of the reaction with aldehydes.⁹ Elimination of water from **11** (R² = H) gave the 2-cyano-1,3-diene **12** as a mixture of (*Z*,*E*)- and (*E*,*E*)-isomers.



Overall we have shown that the insertion of readily available functionalised lithium carbenoids into alkenylzirconocene chlorides represents an efficient and practical route to a range of allyl-zirconium compounds; the RO- and CN-substituted allylzirconocenes can be further elaborated by the reaction with aldehydes.¹⁶

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in the elaboration of **3b**.

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- The stereochemistry of the *cis* and *trans*-γ-lactones 11 was determined by comparison of their ¹H NMR data with those of *cis* and *trans*-4-propyl-5-phenyltetrahydro-2-furanones (for 11a, see: Sekine, M.; Nakajima, M.; Kume, A.; Hashizume, A.; Hata, T. *Bull. Chem. Soc. Jpn.* 1982, 55, 224), and *cis* and *trans*-4-pentyl-5-propyltetrahydro-2-furanones (for 11b, see: Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* 1989, 935).
- 15. A similar reversal of diastereoselectivity in the reaction of alkoxy-substituted allylzirconocene species with aldehydes has been reported, see Ref. 12.
- 16. The following procedure for the preparation of 9c (entry 4 in Table 2) is representative: A solution of 1 was prepared by addition of 1-octyne (94 mg, 0.85 mmol) to a suspension of Cp₂Zr(H)Cl (253 mg, 0.98 mmol) in THF (3.5 mL) followed by stirring at 20°C for 1 h. The reaction mixture was cooled to -100°C, and a solution of methoxymethyl phenyl sulphone (206 mg, 1.11 mmol) in THF (4.0 mL) was added followed by slow addition of a solution of LiTMP [preformed from TMP (157 mg, 1.11 mmol) and BuLi (0.44 mL, 2.5 M in hexanes, 1.11 mmol) in THF (2.5 mL) at 0°C]. After warming to -60°C over 1 h benzaldehyde (180 mg, 1.70 mmol) was added, the mixture was allowed to warm to room temperature, stirred for 3 h and hydrolysed with sat. NaHCO₃ aq. (10 mL). The products were extracted into ether (3×6 mL), the organic layer was washed with brine (2×10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel,

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20% ethyl acetate in 40–60 petrol ether) to afford 1-phenyl-2-hexyl-4-methoxy-3-buten-1-ol (**9c**) (156 mg, 70% yield) as a mixture of three stereoisomers. ¹H NMR (300 MHz, CDCl₃): $\delta = 0.82$ (m, 3H), 1.05–1.50 (m, 10H), 2.15 (m, 1H), 2.37 (br. s, OH), 3.58 (s, 3H), 4.33 (m, 1H), 4.52 (dd, J = 15.5 and 9.8 Hz, 1H), 6.40 (d, J = 15.5 Hz, 1H), 7.36 (m, 5H) (*anti*,*E*-isomer); 2.48 (br. s, OH), 2.78–2.95 (m, 1H), 3.55 (s, 3H), 4.24 (dd, J = 9.9 and 6.3 Hz, 1H), 6.20 (d, J = 6.3 Hz, 1H) (*anti*,*Z*-isomer); 2.90 (m, 1H), 3.46 (s, 3H), 3.95 (dd, J = 9.9 and 6.3 Hz, 1H), 4.58 (m, 1H), 5.90 (d, J = 6.3 Hz, 1H) (*syn*,*Z*-isomer). ¹³C NMR (75 MHz, CDCl₃): $\delta = 14.23$, 22.76, 27.38, 29.25, 31.53, 31.90, 47.66, 56.31, 77.51, 102.97, 127.20, 127.69, 128.33, 142.82, 150.22 (*anti*,*E*-isomer); 27.29, 29.31, 43.22, 59.82, 78.00, 107.36, 127.53, 128.22, 143.26, 149.49 (*anti*,*Z*-isomer).