Synthesis of carbocycles by insertion of 1,1-dihalo-1-lithio species into zirconacycles

Nicolas Vicart[†] and Richard J. Whitby*

Department of Chemistry, Southampton University, Southampton, UK SO17 1BJ. E-mail: rjw1@soton.ac.uk

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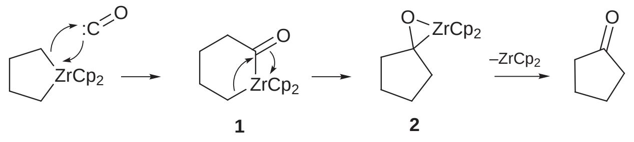
1,1-Dihalo-1-lithio species (halogenocarbenoids) undergo double insertion into the carbon–zirconium bonds of a zirconacyclopent-ane or -ene to produce, after hydrolysis, bicyclo[3.3.0]oct-anes and -enes.

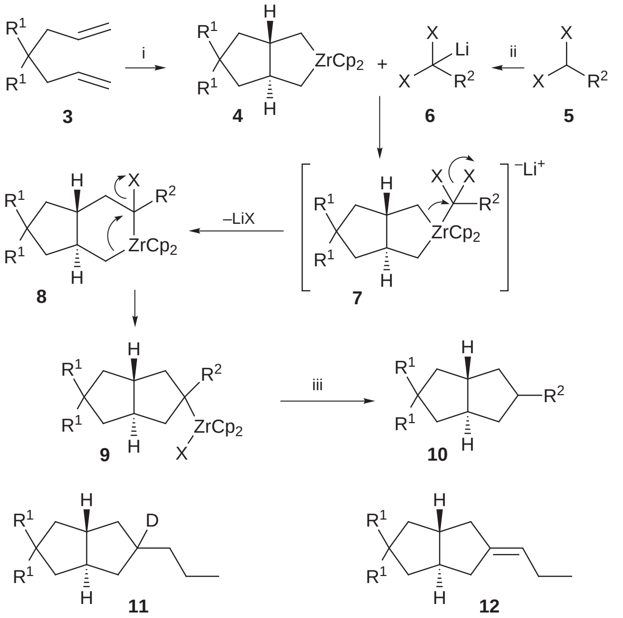
The intramolecular coupling of 1,*n*-dienes and -enynes induced by the zirconocene ('Cp_2Zr') equivalent zirconocene(but-1-ene) (generated *in situ* from dibutylzirconocene[1]) is a powerful method for ring construction.[2] It is important for efficient use of the transition metal to develop elaboration methods for the zirconacycles formed as intermediates. Of particular interest is their transformation into carbocycles by replacement of zirconium with carbon. Carbonylation to form cyclopent-anones and –enones by the mechanism shown in Scheme 1 is one method.[3] We extended this to the addition of isocyanides, where the zirconocene η^2-imine complex analogous to **2** could be trapped by insertion of a variety of alkenes, alkynes, and carbonyl compounds.[4] The direct formation of five-membered carbocyclic rings from zirconacycles has also been observed in a tandem allenyl carbenoid/aldehyde addition.[5] Takahashi has formed cyclopentadiene products from zirconacyclopentadienes by 1,1-addition to propynoates and copper catalysed addition to 3-iodopropenoates, and from zirconacyclopentenes by copper catalysed addition to acyl chlorides.[6]

We have developed a range of ring expansions of five-membered zirconacycles to six-membered homologues through the insertion of carbenoids (1-lithio-1-halo species), analogous to the formation of **1** (Scheme 1).[7] Here we describe how the insertion of 1,1-dihalo-1-lithio species allows the formation of five-membered carbocycles in a fashion analogous to the formation of **2** (Scheme 1).

Our first experiments were performed using the simplest halocarbenoid, lithiodichloromethane (**6a**).[8] Negishi has reported the formation of diphenylmethane from diphenylzirconocene and $LiCHCl_2$.[9] A solution of the zirconacyclopentane **4** in THF was formed from the diene **3** by the usual method.[1] Addition of CH_2Cl_2 followed by the slow addition of LDA at −78 °C and then hydrolysis gave a mixture of the protonolysis product of **4** and the anticipated product **10a** (Scheme 2 and Table 1, entry 1). Increasing the excess of $LiCHCl_2$ gave complete reaction of the zirconacycle **4**, but afforded **10a** mixed with products in which more than one molecule of the carbenoid had been incorporated. By using the bulkier carbenoid, $LiBr_2CPr$ (**6b**), generated *in situ* by deprotonation of 1,1-dibromobutane,[8] the multiple insertion pathway was eliminated and compound **10b** was isolated as the single product in good yield (Table 1, entry 2).[‡] The likely mechanism is shown in Scheme 2. Deprotonation of **5b** by LDA gave the halogenocarbenoid **6b** which adds to **4** to produce the ate-complex **7b**. A 1,2-metallate rearrangement[9,10] to afford **8b** is followed by a diotropic rearrangement[11] to give **9b**. The formation of **9b** was confirmed by quenching the reaction at −78 °C with D_2O to afford the deuterated product **11** in 71% yield (Scheme 3). It is notable that both the formation of **8b** and its rearrangement to **9b** are fast at −78 °C. For the clean synthesis of **10b** it was important to maintain the reaction temperature below −50 °C until quenching, otherwise the by-product **12** was formed. We were pleased to find that allowing the reaction mixture to warm to room temperature before quenching gave **12** (86%) as the only product. Quenching with D_2O confirmed that the metal had



Scheme 1



R^1—R^1 = $CH_2OCMe_2OCH_2$

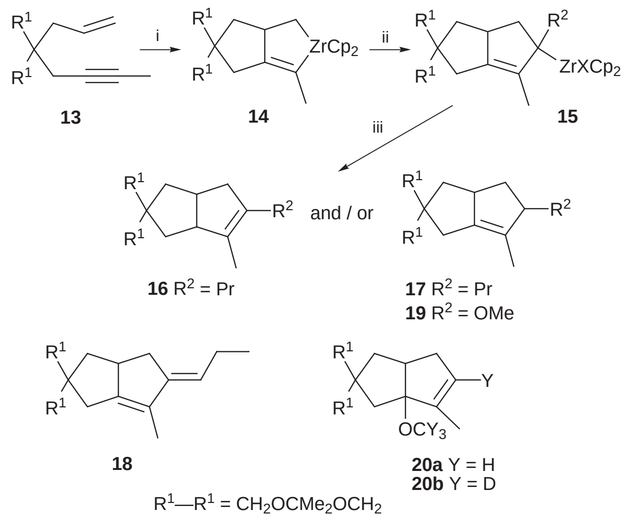
Scheme 2 *Reagents and conditions:* i, Cp_2ZrCl_2, BuLi (2 equiv.), −78 °C to room temp., THF; ii, R^2X_2CH (**5**) (1.5 equiv.), LDA (1.7 equiv.), −78 °C (−95 °C for **5e**) to −55 °C over 2 h; iii, MeOH, $NaHCO_3$ −78 °C to room temp., then room temp., 16 h.

Table 1 Reaction of dihalogenocarbenoids with zirconacyclopentane **4**

Entry	Dihalide **5**	R^2	X	Product	Yield (%)[a]
1	**5a**	H	Cl	**10a**	< 15[b]
2	**5b**	Pr	Br	**10b**	66
3	**5c**	OMe	Cl	**10c**	68
4	**5d**	$SiMe_2Ph$	Cl	**10d**	71
5	**5e**	CN	Cl	**10e**	48

[a] Yields of isolated product after chromatography based on **3**. [b] Not separated from the hydrolysis product of **4**.

[†] Present address: Laboratoire des fonctions azotées et oxygénés complexes, Université de Rouen, IRCOF, UPRES A 6014, F76821 Mt. St. Aignan Cedex, France.



Scheme 3 *Reagents and conditions:* i, Cp_2ZrCl_2, BuLi (2 equiv.), −78 °C to room temp., THF; ii, R^2X_2CH (**5b** or **5c**) (1.5 equiv.), LDA (1.7 equiv.), −78 to −55 °C over 2 h, iii, hydrolysis as in Table 2.

Table 2 Reaction of dihalogenocarbenoids **5b** and **c** with **14**

Entry	5	Hydrolysis conditions	Products (ratios)[a]	Yield (%)[b]
1	**5b**	AcOH, −78 °C	**16** + **17** (36:64)	75
2	**5b**	MeOH–aq. $NaHCO_3$, 20 °C	**16** + **17** + **18** (29:44:27)	81
3	**5c**	AcOH, −78 °C	**19a**[c]	77
4	**5c**	MeOH–aq. $NaHCO_3$, −78 °C	**19a** + **20a** (47:53)	64
5	**5c**	$CD_3OD–D_2O$, −78 °C	**19b** + **20b** (45:55)	55

[a] Product ratios by NMR. [b] Isolated yields after chromatography based on **13**. [c] 72:28 ratio of diastereoisomers.

been lost by this stage, and a reasonable mechanism is a β-hydride elimination process (dehydrozirconation).

Metallation of dichloromethyl methyl ether **5c** with LDA in the presence of **4** gave the methoxy-substituted cyclopentane **10c** in good yield after protonolysis (Table 1, entry 3). Attempts to insert the carbenoid derived by lithiation of dichloromethyl(trimethyl)silane failed due to self condensation[12] and only the hydrolysis product of **4** was recovered. We found that the lithium derivative **6d** of the bulkier dichloromethyl(dimethyl)phenylsilane inserted into **4** efficiently to give silane **10d** (Table 1, entry 4) on protonolysis.

To avoid self condensation of the carbenoid precursor dichloroacetonitrile **5e** we added it to a mixture of LDA and the zirconacycle **4** in THF at −95 °C.[13] The cyanide **10e** was then isolated in moderate yield on hydrolysis (Table 1, entry 5).

When zirconacyclopentene **14** was treated with 1.5 equiv. of the *in situ* generated lithium carbenoid **6b** an inseparable mixture of **16** and **17** was formed (Scheme 3, Table 2, entry 1). Both **16** and **17** were formed as single diastereoisomers (estimated > 93:7 detection limits). The formation of the mixture of **16** and **17** is easily rationalised by rapid allylic rearrangement of the initially formed organozirconium species **15**, indeed an η^3-allylzirconocene representation is probably most accurate. There is little to differentiate the two ends of the allylic system so a mixture of hydrolysis products is to be expected. Hydrolysis at 20 °C gave the diene **18** as a side product (Table 2, entry 2) presumably formed by a similar mechanism to the formation of **12**. The small amount of **18** produced compared with the formation of **12** is a reflection of the greater stability towards β-hydride elimination of the η^3-allyl *cf.* η^1-tertiary alkyl bonded zirconium.

Using dichloromethyl methyl ether **5c** as the carbenoid precursor, acidic quench of the reaction gave the single regioisomeric product **19** as a separable 72:28 mixture of diastereoisomers in good yield (Table 2, entry 3). When MeOH was used during the quench, we isolated a mixture of one diastereoisomer of **19** (the major one of the preceding experiment) and one diastereoisomer of **20a** (Table 2, entry 4). Quenching with CD_3OD gave a mixture of deuterated **19** and **20b** (Table 2, entry 5). Moreover, treatment of a sample of the minor diastereoisomer of **19** in THF with MeOH in the presence of Cl_2ZrCp_2 induced its fast transformation into **20a**. Formation of **20** is then due to an acid catalyzed $S_{N'}$ substitution of the methoxy group of **19** by the alcohol, probably *via* a carbocation. We have previously observed the 1,3-transposition of an amino group and the $S_{N'}$ replacement of an amino group by a hydroxy group in similar systems.[4a]

In conclusion, we have shown that selected halogenocarbenoids insert into a zirconacyclopentane to produce the related five-membered carbocyclic rings *via* sequential 1,2-metallate, and diotropic rearrangements. The yields are good for a tandem reaction sequence in which three carbon–carbon bonds are formed. Extension of the methodology to a zirconacyclopentene was complicated by poor regio- and/or diastereo-selectivity.

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Notes and references

‡ All compounds gave satisfactory ^1H and ^{13}C NMR (300 MHz), FTIR and LRMS spectra together with correct HRMS or microanalysis. All compounds were obtained pure except **10a** (mixture with hydrolysis product of **4**) and the regioisomers **16**/**17** which were characterised as the mixture.

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