Multicomponent Reactions

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A Rearrangement to a Zirconium–Alkenylidene in the Insertion of Dihalocarbenoids and Acetylides into Zirconacycles**

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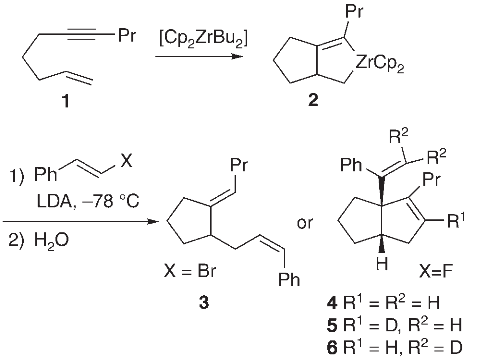
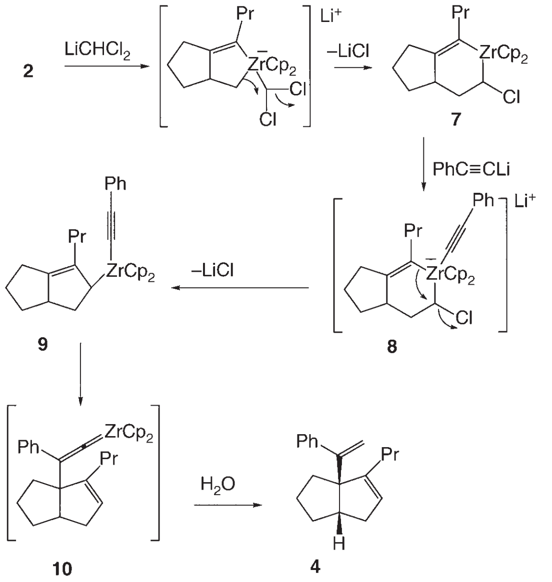
We previously reported that addition of lithium diisopropylamide (LDA) to a mixture of zirconacycle **2**, formed by cocyclization of enyne **1**,[1] and (*E*)-β-bromostyrene leads to insertion of the carbenoid (*E*)-PhCH=CLiBr generated in situ, thus affording alkene **3** on protonolysis.[2] Recently, we attempted to insert the fluoro analogue (*E*)-PhCH=CLiF derived by deprotonation of β-fluorostyrene. Much to our surprise, the main product formed, apart from the protonation product of zirconacycle **2**, was compound **4** (30% yield; Scheme 1).



Scheme 1. An unexpected product from the attempted insertion of (*E*)-PhCH=CLiF into zirconacycle **2**. Cp = cyclopentadienyl.

The additional carbon atom present in **4** was traced to originate from dichloromethane present as an impurity (30 mol%) in the β-fluorostyrene. The use of pure β-fluorostyrene with added CD_2Cl_2 (30 mol%) gave the labeled compound **5** (Scheme 1). In the absence of dichloromethane, no insertion occurred at −78 °C, but **3** was produced by hydrolysis on warming to −20 °C, presumably through the known insertion of phenylacetylide (formed by elimination of HF from (*E*)-PhCH=CHF and deprotonation) into zirconacycle **2**.[3] Evidence that phenylacetylide is also the active species in the formation of **4** came from the failure to trap the carbenoid (*E*)-PhCH=CLiF when generated in the presence of Me_3SiCl—only $PhCCSiMe_3$ was formed. We previously demonstrated that Me_3SiCl is a faster trap for carbenoids than organozirconium species.[4] Evidence for the organometallic precursor of **4** came from workup of the reaction with D_2O to afford the bisdeuterated compound **6** predominantly (77% bisdeuterated; 23% monodeuterated), thus suggesting a zirconium–alkenylidene or 1-metallo-1-zircono–alkene (M = Zr or Li) intermediate. A reasonable mechanism for the formation of **4** is given in Scheme 2.



Scheme 2. Suggested mechanism for the formation of **4**.

The first proposed step is insertion of lithiated dichloromethane into **2** to form the intermediate **7**. After addition of lithiated phenylacetylide to afford the "ate" complex **8**, cyclization occurs to give **9**. We previously reported the insertion of 1-lithio-1,1-dihalocarbenoids into zirconacycles to give cyclized products, although dichloromethane gave rather low yields in this process.[5] We would expect the 1,2-rearrangement of the neutral intermediate **7** to be slow at −78 °C; hence, the requirement for the formation of **8** before rearrangement. There now follows a novel rearrangement to afford the alkenylidene complex **10**: Initially a [3,3] sigmatropic rearrangement was suspected, but successive 1,3-migration of the zirconium atom to the ring junction followed by a 1,3-alkyl shift from the metal center to the β-position of the alkyne unit is an alternative. There is a driving force for the initial 1,3-zirconium rearrangement in release of strain energy, as we have previously observed for a 1,3-amine rearrangement.[6] The only precedent for the second migration is the ring contraction of zirconacycle **11** to afford a zirconium–alkenylidene complex **12** that we recently proposed,[7] although similar transformations are known for mid-/late-transition-metal complexes (Scheme 3).[8]

Having suggested a reasonable mechanism for the formation of **4**, more appropriate conditions for its synthesis could be designed. Thus, the addition of lithium 2,2,6,6-tetramethylpiperidide (LiTMP; 1.1 equiv) to a mixture of

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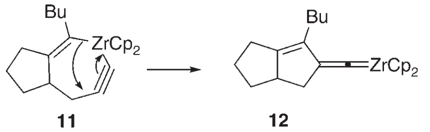
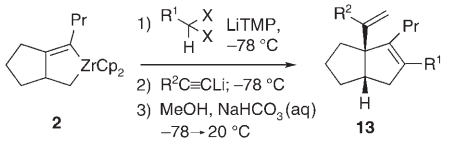


Scheme 3. Zirconocene–alkyne to zirconocene–alkylidene rearrangement.

zirconacycle **2** and dichloromethane (1.1 equiv) at −78 °C, followed by addition of lithium phenylacetylide (1.1 equiv) with warming to room temperature and quenching with water afforded product **4** in 52 % isolated yield (Table 1, entry 1).

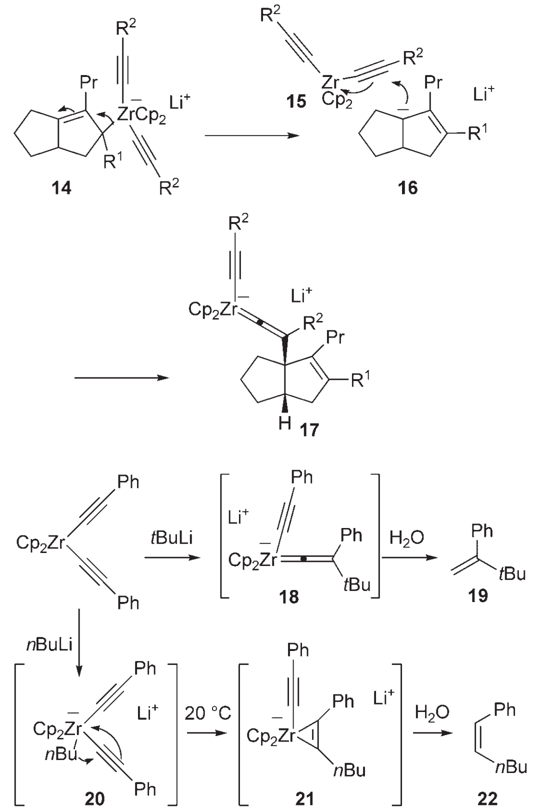
Table 1: Zirconium-mediated multicomponent synthesis.



Entry	R^1	X	R^2	Yield of **13** [%][a]
1	H	Cl	Ph	72 (52[b])
2	Bu	Br	Ph	86 (42[b])
3	$(CH_2)_2Ph$	Br	Ph	72 (54[b])
4	$SiMe_3$	Cl	Ph	55[b]
5	H	Cl	Bu	47[b]
6	Bu	Br	Bu	76

[a] Yield of the isolated product **13** based on **1**, using 2.2 equivalents of the alkynyl lithium reagent. [b] Treatment with 1.1 equivalents of the alkynyl lithium reagent.

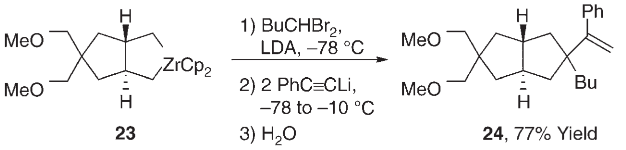
We were able to extend the multicomponent reaction to the use of substituted dihalocarbenoids (Table 1, entries 2–4) and alkyl-substituted alkynes (Table 1, entry 5), but the yields of adducts **13** were only around 50 %. An important observation, with implications for the mechanism, was that the use of two equivalents of the acetylide substantially improved the yields of **13** (Table 1 entries 1–3 and 6), thus suggesting that the final zirconium product might be the "ate" complex **17** (Scheme 4). The formation of **17** also explained why we were unable to trap the supposed zirconium–alkenylidene complex **10** with reagents that might be expected to trap a carbene complex, such as alkynes, ethylene, and acetone.[9] The "ate" complex **17** lacks the empty orbital on the metal center required for normal "carbene"-type reactivity. The extra equivalent of alkynyl lithium reagent could just trap the suggested alkenylidene intermediate **10**, but we favor an alternative mechanism in which the "ate" complex **14**, formed by addition of the lithiated alkyne to **9** eliminates the allyl anion **16**.[10] Readdition of **16** to the β-carbon atom of the bis(alkynyl) zirconocene **15** would then afford **17**. Although such a β-addition to a metal alkyne is unknown for early transition metals, it is an established route for the formation of mid-/late-transition-metal–alkenylidene complexes.[8] An indication that the proposed mechanism is reasonable is the addition of *t*BuLi to bis(phenylethynyl)zirconocene at −78 °C with an immediate protic quench that affords alkene **19** (88 % yield of the isolated product), probably via the alkenylidene ate complex **18**. Addition of *n*BuLi to bis(phenylethynyl)zirconocene gave (*Z*)-1-phenylhexene **22** (73 %) only on warming to room temperature before protonolysis, presumably by initial addition to the metal to afford **20** followed by the type of 1,2-migration previously reported by Negishi and co-workers[11] to afford **21**. The result indicates that a bulky nucleophile is important for successful β-addition to the alkyne to inhibit direct attack on the metal.



Scheme 4. Alternative route to zirconate–alkenylidene complexes.

Finally, reaction of zirconacyclopentane **23**, obtained by zirconium-induced cocyclization[12] of 4,4-bis(methoxymethyl)hepta-1,6-diene, with a dihalocarbenoid and two equivalents of lithium phenylacetylide with aqueous workup afforded the cyclized product **24** in good yield based on the diene (Scheme 5). Warming of the reaction mixture to −10 °C before quenching was required, thereby presumably reflecting the less stable, unconjugated tertiary anion, which needs to undergo the elimination/addition process. In this case, the yield of **24** when only 1.1 equivalents of lithiated phenylacetylene were used was very low.

Overall, we have demonstrated an efficient multicomponent assembly of bicyclo[3.3.0]oct-2-enes and bicyclo[3.3.0]octanes by using stoichiometric zirconium chemistry.



Scheme 5. Multicomponent assembly of bicyclo[3.3.0]octanes.

These compounds will find use as cores for biologically active compounds and in natural product synthesis, for example, angular triquinanes.[13] The proposed mechanism includes facile loss of carbanions from zirconate species, and the first addition of a nucleophile to the β-carbon atom of a zirconium–alkyne complex to afford an alkenylidene–zirconate complex.

Experimental Section

4: *n*BuLi (0.8 mL of a 2.5 M solution in hexane, 2.0 mmol) was added to a stirred solution of [Cp$_2$ZrCl$_2$] (292 mg, 1.0 mmol) and dec-1-en-6-yne (136 mg, 1.0 mmol) in THF (5 mL) dropwise over 5 min at −78 °C. The solution was allowed to warm to room temperature after 25 min and was stirred for 2 h. After cooling the reaction mixture to −78 °C, a solution of CH$_2$Cl$_2$ (64.0 μL, 1.0 mmol) in THF (1 mL) was added, followed by dropwise addition of LiTMP (freshly prepared from 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) and *n*BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) in THF (2 mL) at 0 °C over 30 min) over 15 min. The reaction mixture was stirred at −78 °C for 30 min before dropwise addition of lithium phenylacetylide (freshly prepared from phenylacetylene (0.24 mL, 2.2 mmol) and *n*BuLi (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol) in THF (2 mL) at 0 °C over 15 min) over 15 min. The mixture was stirred at −78 °C for 20 min before addition of MeOH (5 mL) and aqueous NaHCO$_3$ (6 mL) and allowed to warm to room temperature overnight. The mixture was poured into H$_2$O (100 mL) and extracted with Et$_2$O (2 × 100 mL) before washing with aqueous NaHCO$_3$ (150 mL) and brine (150 mL), drying over MgSO$_4$, and concentration in vacuo. Purification by column chromatography on SiO$_2$ with hexane as the eluant gave **4** as a colorless oil (181.0 mg, 72 %). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.19–7.09 (5 H, m), 5.33 (1 H, apparent quintet, J = 2.0 Hz), 5.04 (1 H, d, J = 1.8 Hz), 4.91 (1 H, d, J = 1.8 Hz), 2.39 (1 H, apparent tt, J = 8.8, 2.3 Hz), 2.20 (1 H, m), 1.94–1.84 (1 H, m), 1.83–1.73 (2 H, m), 1.72–1.64 (3 H, m), 1.54–1.42 (3 H, m), 1.34 (1 H, m), 1.24 (1 H, m), 0.89 ppm (3 H, t, J = 7.3 Hz); ^{13}C NMR (100.5 MHz, CDCl$_3$): δ = 155.39 (C), 146.72 (C), 144.53 (C), 128.04 (CH), 127.63 (CH), 126.54 (CH), 124.76 (CH), 113.75 (CH$_2$), 69.14 (C), 46.50 (CH), 40.83 (CH$_2$), 36.62 (CH$_2$), 35.73 (CH$_2$), 29.48 (CH$_2$), 25.71 (CH$_2$), 21.48 (CH$_2$), 14.63 ppm (CH$_3$); IR (thin film): $\tilde{\nu}$ = 2949 (m), 1620 (w), 1491 (m), 1449 (m), 900 cm^{-1} (s); LRMS (EI): m/z: 252 (M^+, 100 %), 237 (56 %), 223 (88 %), 181 (100 %), 149 (95 %); HRMS (EI): m/z calcd for C$_{19}$H$_{24}$: 252.1878; found: 252.1878; elemental analysis (%) calcd for C$_{19}$H$_{24}$: C 90.42, H 9.58; found C 90.83, H 9.47.

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