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Reactions of acylzirconocene chloride with nucleophiles: bimodal reactivity at β- and acyl carbons of α,β-unsaturated acylzirconocene chloride

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Abstract

Reactions of α,β-unsaturated acylzirconocene chloride with nucleophiles showed novel bimodal reactivity at the β- and acyl carbons depending upon the nucleophile employed, and the formation of ketone α,β-dianionic species was also observed. © 2000 Elsevier Science Ltd. All rights reserved.

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Recent studies on the reactivity of acylzirconocene chloride derivatives (**1** and **2**) indicated their usefulness as an 'unmasked' acyl anion donor in organic synthesis.[1] Herein we report the reactions of α,β-unsaturated acylzirconocene chloride **2** with nucleophiles and the bimodal (nucleophilic or electrophilic) reactivity at both the acyl and β-carbons in **2** (Fig. 1).

Reactions of **2** with stable carbon nucleophiles (sodium salt of dimethyl malonate and malononitrile) at 0°C in THF afforded Michael addition products **4** in good yields (Eq. (1))

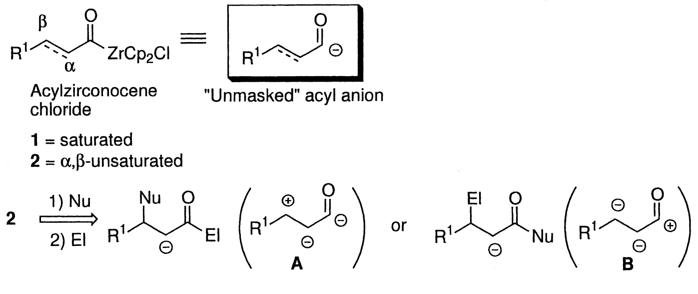

Figure 1. Electronic duality of α,β-unsaturated acylzirconocene chloride **2**

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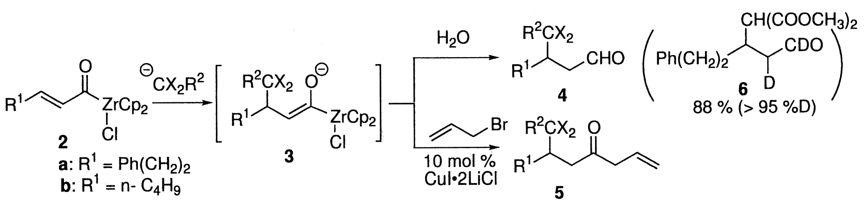
(entries 1–5, Table 1).[2] Direct treatment of the intermediate **3** with allyl bromide in the presence of a catalytic amount of CuI·2LiCl (10 mol%) at 0°C gave allylic ketone **5** in one-pot (Eq. (1)) (entries 6–8, Table 1).[3,4] In the reaction of **2a** with dimethyl malonate anion, D_2O-work-up gave α-deuterated deutero aldehyde **6** in 88% yield (>95 D%). The transformation of **2** into **5** implies that the electronic nature of **2** is to be **A** shown in Fig. 1.



(1)

Table 1
Reactions of **2** with stable carbon nucleophiles and the subsequent Cu(I)-catalyzed coupling reaction with allyl bromide[a]

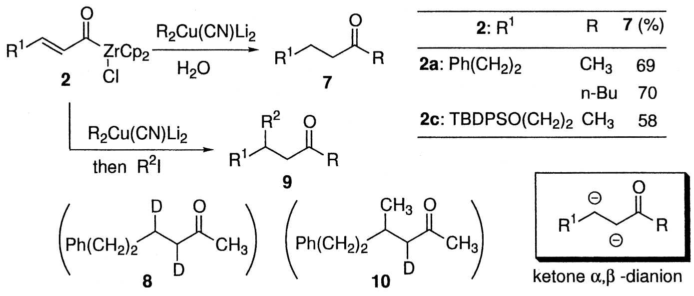
Entry	**2**	Nucleophile		Yield (%)[b]	
		R^2	X	**4**	**5**
1	**2a**	H	$COOCH_3$	88	
2	**2a**	CH_3	$COOCH_3$	84	
3	**2b**	H	$COOCH_3$	81	
4	**2b**	CH_3	$COOCH_3$	72	
5	**2b**	H	CN	52	
6	**2a**	H	$COOCH_3$		81
7	**2b**	H	$COOCH_3$		75
8	**2b**	CH_3	$COOCH_3$		68

[a] Reaction conditions for the formation of **4**:**2** 1.5 equiv.; NAH (1.1–1.5 equiv.); R^2CHX_2 (1 equiv.); 0°C, 2 h. Reaction conditions for **5**:**2** 1.5 equiv.: (i) NaH (1.1–1.5 equiv.); R^2CHX_2 (1 equiv.); 0°C, 2 h and (ii) CuI·2LiCl (10 mol%), allyl bromide (1.3 equiv.) 0°C, 1 h.

[b] Isolated yield.

However, the reaction of **2** with a higher-order cyanocuprate reagent,[5] $R_2Cu(CN)Li_2$, at −78°C in THF afforded, contrary to our expectation, saturated ketone **7** by aqueous work-up (Eq. (2)). No trace of a Michael addition product was observed in the reaction mixture. In the reaction of **2a** and $(CH_3)_2Cu(CN)Li_2$, D_2O treatment of the reaction mixture gave α,β-didueterated ketone **8** (the undetermined stereochemistry) in 69% yield, and the deuterium content at each position was over 95%. The formation of **8** suggests the presence of ketone α,β-dianion equivalent[6] from **2** under the reaction conditions. An addition of an excess of organic halides to the reaction mixture of **2** and $R_2Cu(CN)Li_2$ afforded ketone derivatives **9**. D_2O-treatment of the reaction mixture, which is derived from **2a**, $(CH_3)_2Cu(CN)Li_2$ and CH_3I, afforded α-deuterated **10** in 65% yield (Eq. (2)). Attempts to react the α-carbanion with electrophiles, however, ended with synthetically little success.[7] The results of the reactions of **2a** with higher-order cyanocuprate and the following reaction with organic halides are shown in Table 2.

The facts that (i) the reaction of saturated acylzirconocene chloride **1a** with $(CH_3)_2Cu(CN)Li_2$ gave alcohol **12** (73%), and (ii) D_2O work-up of the reaction gave d-**12** suggest the formation of



2: R¹	R	7 (%)
2a: Ph(CH₂)₂	CH₃	69
	n-Bu	70
2c: TBDPSO(CH₂)₂	CH₃	58

(2)

Table 2
The formation of **9** by the treatment of **2a** with $R_2Cu(CN)Li_2$ and R^2I[a]

Entry	R^2X	R	**9** Yield (%)[b]
1	CH_3I	CH_3	68
2	allyl chloride	CH_3	71
3	Propargyl chloride	CH_3	22[c]
4	PhCOCl	CH_3	68
5	CH_3COCl	CH_3	46
6	2-Naphthoyl chloride	n-C_4H_9	50

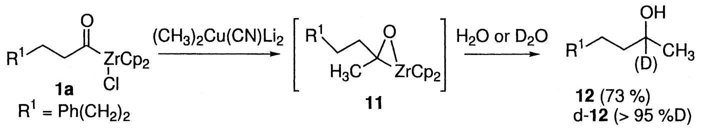
[a] Reaction conditions: **2a** 1.5 equiv., $R_2Cu(CN)Li_2$ (2.0 equiv.) in THF, −78°C, 0.5 h then R^2X (3 equiv.) −78°C, 0.5 h.

[b] Isolated yield.

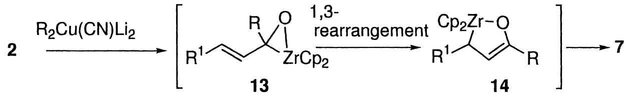
[c] Allenyl product.

ketone–zirconocene intermediate **11** (Eq. (3)).[8] Thus, in the case of **2**, oxazirconacyclopentene **14**,[9] a ketone α,β-dianion equivalent, would be formed through the formation of unsaturated ketone–zirconocene complex **13** followed by 1,3-rearrangement of the zirconocene moiety (Eq. (4)). Although the intermediate **14** proved difficult to isolate and characterize,[10] the 1,3-rearrangement of the zirconocene portion in the nitrogen analogue of **11** has been well established in the formation of zirconaazacycle, the nitrogen analogue of **14**.[9b] The formation of ketone **15** or d_2-**15** (Eq. (5)) by the reaction of saturated acylzirconocene chloride **1a** with higher-order vinyl cyanocuprate would support the postulated process.

In the present reactions of **2** with nucleophiles, the dichotomous reactivity (**A** and **B** in Fig. 1) at both the β- and acyl carbons in **2** was brought about by our choice of nucleophilic reagents (stable carbon nucleophiles or $R_2Cu(CN)Li_2$).



(3)



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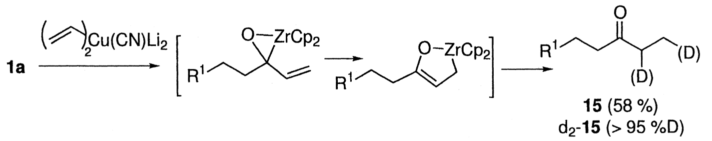

(5)

In summary, we have shown that an electronic nature at the β- and acyl carbons of the α,β-unsaturated acylzirconocene chloride **2** depends on the employed nucleophile. Generation of the ketone α,β-dianion species, oxazirconacyclopentene derivative **14**, through the reaction of α,β-unsaturated acylzirconocene chloride **2** with $R_2Cu(CN)Li_2$ and the efficient reaction of **14** toward electrophiles has opened up a new synthetic possibility of the acylzirconocene complex.

Preparation of **9**: To a solution of **2a** (2.0 mmol) in THF (5 mL) [prepared by (i) stirring with $Cp_2Zr(H)Cl$ (1.3 mmol) and 4-phenyl-1-butyne (2.1 mmol) in CH_2Cl_2 (4 mL) at ambient temperature for 0.5 h, (ii) stirring under CO atmosphere (1 atm) for 2 h and (iii) concentration to dryness in vacuo and addition of THF (5 mL)] was added a solution of $(CH_3)_2Cu(CN)Li_2$ (4 mmol) in THF–ether (8: 5) (13 mL) at −78°C. After the mixture was stirred for 0.5 h at the same temperature, CH_3I (6 mmol) was added and the stirring was continued for 0.5 h at −78°C. The reaction was quenched by the addition of sat. aq. NH_4Cl and extracted with ether. After the usual procedures, the crude material was purified by silica gel column chromatography (hexane:ethyl acetate = 80:1) to give **9** [$R^1 = Ph(CH_2)_2$, $R^2 = CH_3$, $R = CH_3$] (68%).

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