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Grignard reagent mediated reaction of Cp_2Zr(II)–ethylene complex with imines†

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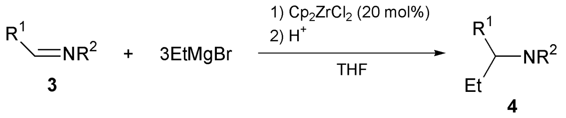
Imines which do not react with Grignard reagents reacted with EtMgBr in the presence of a catalytic amount of Cp_2ZrCl_2 to give ethylated products in excellent yields; the stoichiometric reaction of the imines and the zirconocene–ethylene complex did not give the ethylated product, whereas addition of MeMgBr or BuMgCl to the mixture afforded the ethylated product after hydrolysis.

We have found that a zircononcene–ethylene complex $Cp_2Zr(CH_2{=}CH_2)$ (**2**)[1] and its ate complex $[Cp_2ZrEt(CH_2{=}CH_2)]MgBr$[2] prepared from Cp_2ZrEt_2 (**1**) and zirconacyclopentanes[1] were involved in the zirconium-catalysed reaction of olefins with EtMgBr[3] which was first reported by Dzhemilev.[4] In order to extend this type of reaction we investigated a catalytic and a stoichiometric reaction of imine with EtMgBr in the presence of zirconocene. In this paper we would like to report a zirconium-catalysed reaction of imine with EtMgBr and the unusual effect of addition of Grignard reagents on the formation of a new C–C bond in the stoichiometric reaction of imines with the zirconocene–ethylene complex.

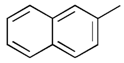
Imines **3a**–**d**, easily prepared from the corresponding aldehydes and amines, do not react with EtMgBr in THF at even 50 °C to give addition products. When 20 mol% Cp_2ZrCl_2 was added to the mixture of the imines and EtMgBr in THF, the reaction proceeded smoothly at rt to produce substituted amine derivatives **4** in excellent yields after hydrolysis. The results are shown in Table 1. At least 3 eq. of EtMgBr was needed to finish the reaction, and the use of 10 mol% of Cp_2ZrCl_2 decreased the yield of products **4** [eqn. (1)].



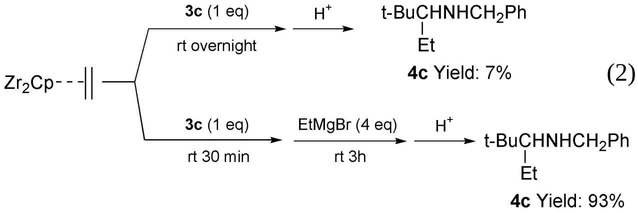
(1)

We investigated the stoichiometric reactions of imines with the zirconocene–ethylene complex. And quite surprisingly, we found that the stoichiometric reaction of **3c** with **2** did not give the coupling product (only 7% of **4c**) after hydrolysis. It puzzled us, however, that when an additional amount of EtMgBr (1 eq.) was added to the reaction mixture, the desired product **4c** was obtained in 64% yield. Moreover, addition of 4 eq. of EtMgBr to the mixture gave an excellent yield of **4c** (93%) [eqn. (2)].

Table 1 Zirconium-catalysed addition of EtMgBr to imines[a]

Imines	R¹	R²	*T*/°C	*t*/h	Products	Yield (%)[b]
3a	Ph	Bn	20	1	**4a**	96
3b	Ph	Bu	20	12	**4b**	89
3c	t-Bu	Bn	20	1	**4c**	97
3d		Bn	20	1	**4d**	(87)

[a] 20 mol% Cp_2ZrCl_2 and 3 eq. of EtMgBr were used. [b] GC yields: isolated yield is given in parenthesis.



(2)

It is noteworthy that the use of different Grignard reagents also afforded only the same ethylated product **4c**, with improved yields as shown in Table 2.

It is interesting that the reaction of **3a** with **2** gave the ethylated product **4a** in 57% yield after hydrolysis. This indicates that the azazirconacylopentane **5a** was formed in the case of **3a**. A similar effect of addition of a Grignard reagent was also observed. In fact, addition of 1 eq. of MeMgBr to the mixture of **3a** and **2** afforded **4a** in 75% yield after hydrolysis. When 4 eq. of EtMgBr was added to the mixture of **3a** and **2**, the product **4a** was formed in 97% yield after hydrolysis.

These results suggest that there is an equilibrium between azazirconacyclopentane **5** and imine **3** and that the position of the equilibrium lies to the left under the conditions used here. If an irreversible step such as ring-opening and β-hydrogen abstraction is involved in the reaction, in other words, when additional Grignard reagents are added, the reaction goes to the right as expected to give the ethylated products. Deuterolysis instead of hydrolysis of the reaction mixture after addition of 4 eq. of MeMgBr to a mixture of **3c** and **2** afforded deuterated product **4c** $DCH_2CH_2(t\text{-}Bu)CHNDCH_2Ph$ (65% D) [eqn. (3)]. This strongly suggests that the complex **6c** is the reaction product of MeMgBr with a mixture of **3c** and **2**. When **6c** was treated with 2 eq. of CuCl for 6 h at rt, ethylated imine tBu(Et)CHN=CHPh (**7**) was obtained in 48% yield after hydrolysis.

We also carried out the reactions of a mixture of Cp_2ZrEt_2 and imine **3a** with various electrophiles[5,6] and the results are summarized in Table 3.

Table 2 The effect of addition of Grignard reagents under stoichiometric conditions

Grignard reagents	Yield of **4c** (%)[a] 1 eq. of RMgX[b]	Yield of **4c** (%)[a] 4 eq. of RMgX[b]
MeMgBr	40	70[a]
EtMgBr	64	93
n-BuMgCl	38	64
sec-BuMgCl	22	96
t-BuMgCl	7	15

[a] GC yields of ethylated product **4c**. [b] Amount of addition of RMgX.

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† Electronic supplementary information (ESI) available: reaction procedures and NMR data. See http://www.rsc.org/suppdata/cc/b0/b007456j/

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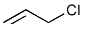
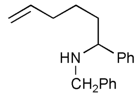
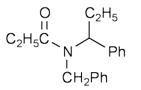
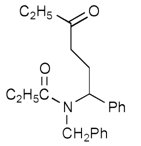
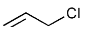
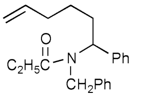
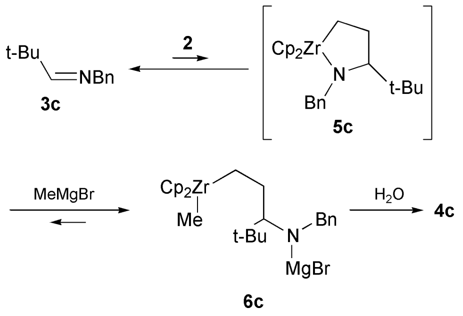
Table 3 Reactions of a mixture of Cp_2ZrEt_2 and **3a** with electrophiles[a]

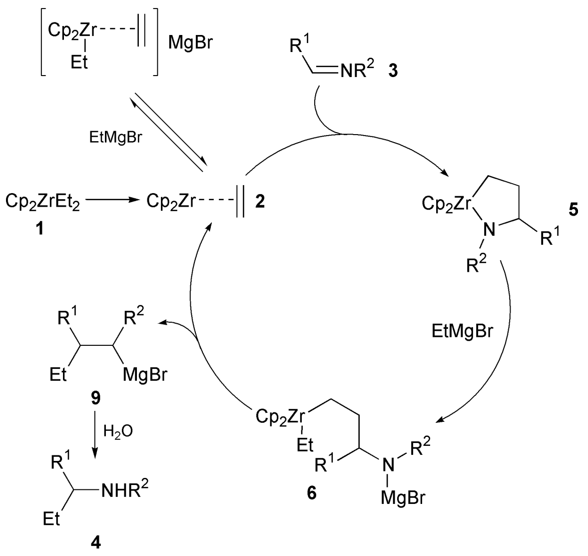
Entry	Additives	Electrophile	T/°C	t/h	Product[a]		Yield (%)[b]
1	CuCl		r.t.	3		(**8a**)	56 (48)
2	—	C_2H_5COCl	0	1		(**8b**)	79 (57)
3[c]	(1) — (ii) CuCl	C_2H_5COCl (2 eq) —	0 50	1 12		(**8c**)	70 (56)
4[c]	(i) — (ii) CuCl	C_2H_5COCl 	0 r.t.	1 6		(**8d**)	82 (63)

[a] GC yields; isolated yields are given in parenthesis. [b] Reaction products were isolated after hydrolysis. [c] The mixture was treated with (i) and then (ii).



(3)

We have developed several zirconium-catalyzed reactions, in which a zirconocene–olefin complex acts as the key catalytic species. In the light of our previous work, a plausible mechanism for this catalytic addition of EtMgBr to imines is shown in Scheme 1, which involves: (1) generation of zirconocene–ethylene complex **2** from Cp_2ZrCl_2 and two eq. of EtMgBr; (2) coupling with imine **3** to form azazirconacyclopentane **5**; (3) ring-opening reaction by EtMgBr; and (4) β-elimination to regenerate zirconocene–ethylene complex **2** and to release metalated amine **9**.[7] The ring-opening reaction occurred exclusively on the Zr–N bond, because no deuterium incorporation was found in the Et group of products **4** in the catalytic reaction when the reaction mixture was quenched with MeOD. As expected, this catalytic reaction did not proceed with MeMgBr. When higher magnesium alkyls, namely, n-PrMgBr and n-BuMgCl, were used, the formation of addition products was not observed from the reaction with imine **3a**, indicating no coupling reaction between the zirconocene-substituted olefin complex and the imine.



Scheme 1

Notes and references

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