

On the mechanism of the zirconium-catalysed addition of ethyl Grignard reagents to imines

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Abstract – Ethyl Grignard reagents undergo the Cp_2ZrCl_2 -catalysed addition to imines. We have studied the mechanism of this reaction and demonstrated that two overlapped catalytic cycles coexist, leading to mono- and dimagnesated products (before hydrolysis). *To cite this article:* V. Gandon et al., C. R. Chimie 5 (2002) 127–130 © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

mechanism / deuteration / zirconium / catalysis / Grignard reagents / imines

Résumé – Mécanisme de l'addition des éthylmagnésiens aux imines sous catalyse au zirconium. L'addition des éthylmagnésiens aux imines peut s'effectuer par catalyse au Cp_2ZrCl_2 . Nous avons étudié le mécanisme de cette réaction et mis en évidence la coexistence de deux cycles catalytiques imbriqués, conduisant, avant hydrolyse, à un monomagnésien et à un dimagnésien. *Pour citer cet article:* V. Gandon et al., C. R. Chimie 5 (2002) 127–130 © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

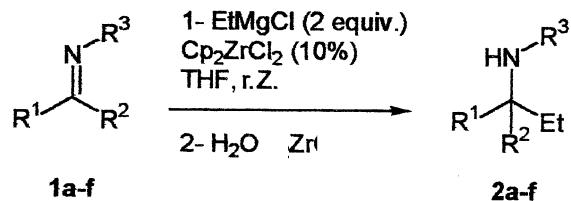
mécanisme / deutération / zirconium / catalyse / Grignard / imines

1. Introduction

The zirconium-catalysed ethylmagnesianation of terminal alkenes attracted great interest [1]. Similarly to alkenes, imines readily give addition products with ethyl Grignard reagents (EtMgX , $\text{X} = \text{Cl}, \text{Br}, \text{Et}$) in the presence of a catalytic amount of Cp_2ZrCl_2 ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) [2,3]. Since imines are weakly electrophilic, the direct addition of organomagnesium reagents in mild conditions is somewhat difficult [4], and consequently the catalysed reaction favourably competes with the non-catalysed one (see Table 1).

In the case of aldimines, the non-catalysed alkylation reaction can take place either slowly (**1a–b**) or not at all (**1c**) [5]. On the other hand, when a catalytic amount of Cp_2ZrCl_2 was used (10 mol%), the formation of addition products became much easier. In the case of ketimines, the title reaction is also effective [2]. This application is particularly interesting

Table 1. Catalytic ethylmagnesianation of imines.



Imine	R ¹	R ²	R ³	Time (h)	Yield (%) ^{a,b}
1a	Ph	H	Ph	1.5	69 (16)
1b	Ph	H	Bn	8	90 (12)
1c	Ph	H	<i>t</i> Bu	8 ^c	61 (0)
1d	Ph	Me	Ph	1.5	78 (0)
1e	<i>n</i> C ₆ H ₁₃	Me	Ph	1.5	86 (0)
1f	Ph	Me	Bn	1.5	50 (0)

^a Yields refer to isolated compounds. ^b Yields for the reactions without Cp_2ZrCl_2 are given in parentheses. ^c 4 equiv of EtMgCl .

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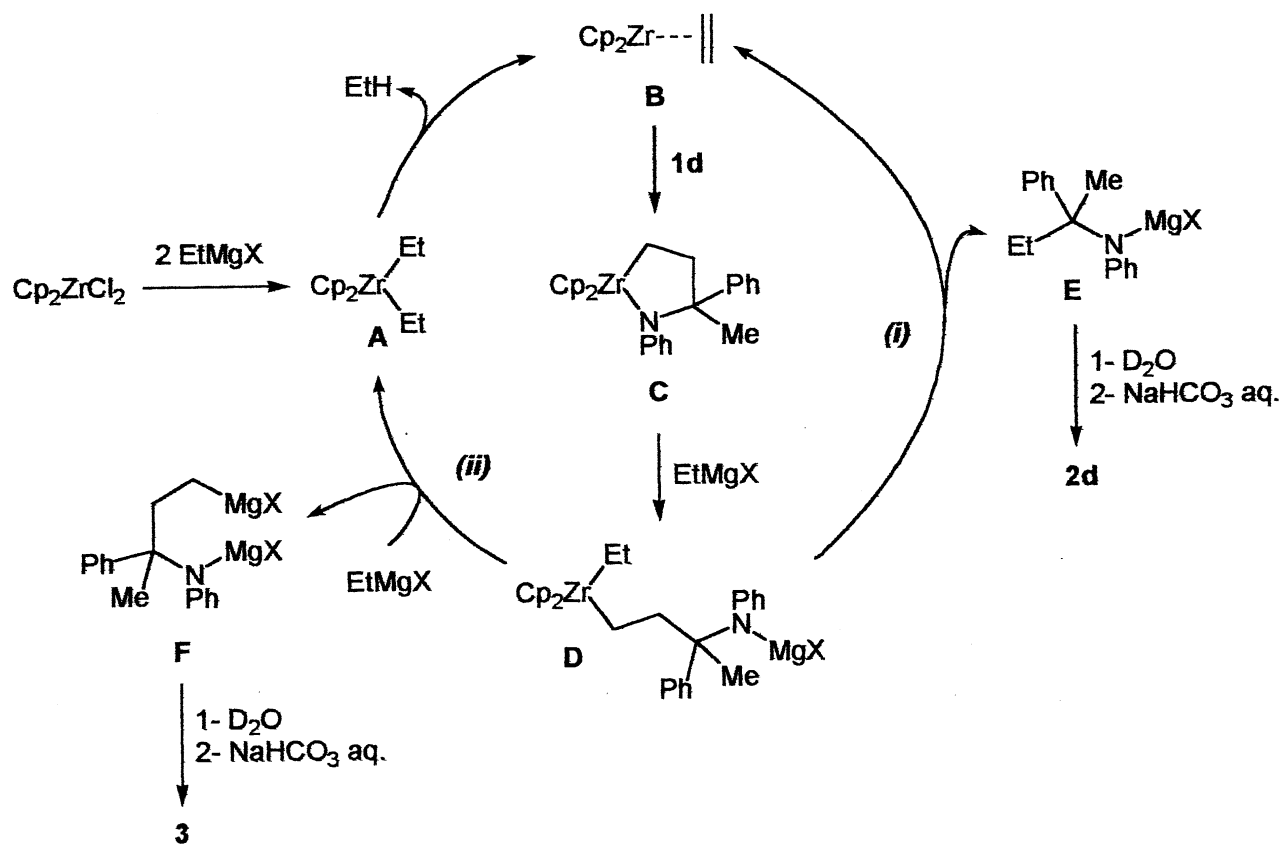


Fig. 1. Proposed catalytic cycle for zirconium catalyzed ethylmagnesation of imines.

since the direct addition of Grignard reagents to ketimines is generally not possible (**1d–f**) [6].

2. Results and discussion

Fig. 1 shows a proposed catalytic cycle consistent with what it was postulated for alkenes [7]. The initial step involves the typical formation of zirconocene–ethylene complex **B** via β -H abstraction of the unstable intermediate **A** [8]. Ethane is eliminated through this process. In the next step, the insertion of the imine **1d** into **B** gives metallacycle **C**. The formation of **C** is supported by the complete deuterium incorporation at the terminal carbon of the amine **3**, which was obtained via the stoichiometric reaction of **B** (prepared from Cp_2ZrCl_2 (1 equiv) and EtMgBr (2 equiv) from -78 to 0°C) [9] with the imine **1d** (1 equiv) followed by quenching with $\text{D}_2\text{O}/\text{D}_2\text{SO}_4$ (Fig. 2).

Starting from **C**, the transmetalation by EtMgX would result in the selective Zr–N bond cleavage to provide the new intermediate **D**. The complex **D** undergoes a specific β -H abstraction that regenerates **B** and affords the monomagnesated product **E** (path (i)). On the other hand, the transmetalation of **D** with

EtMgX gives the dimagnesated product **F** and regenerates **A** (path (ii)).

The coexistence of these two competing pathways is supported by deuteration and gas monitoring experiments. First, the treatment of **1d** with 10 mol% Cp_2ZrCl_2 and 2 equiv EtMgBr and quenching with $\text{D}_2\text{O}/\text{D}_2\text{SO}_4$ led to a mixture of **2d** and **3** in a 1:1.5 ratio (Fig. 3).

Second, in the course of the reaction of **1d** with EtMgX ($\text{X} = \text{Cl}, \text{Br}, \text{Et}, 2$ equiv) and Cp_2ZrCl_2

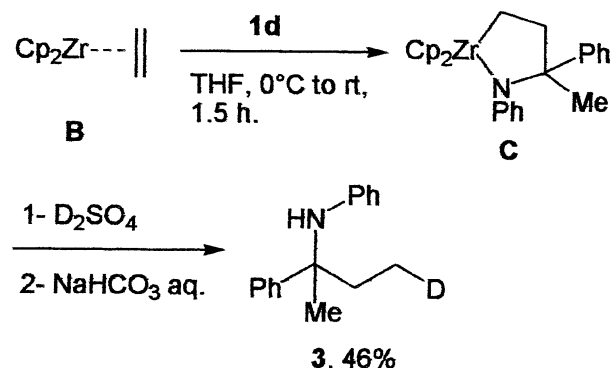


Fig. 2. Synthesis of **3** via the stoichiometric reaction of **B** with the amine **1d** (1 equiv), followed by quenching with $\text{D}_2\text{O}/\text{D}_2\text{SO}_4$.

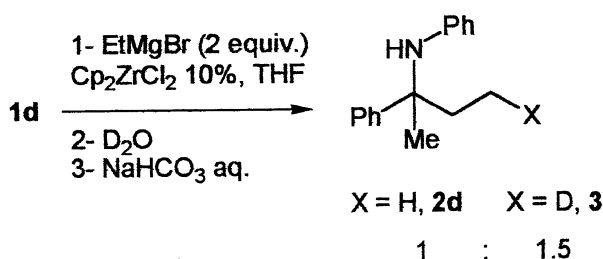


Fig. 3. Treatment of **1d** with 10 mol% Cp_2ZrCl_2 and 2 equiv EtMgBr and quenching with $\text{D}_2\text{O}/\text{D}_2\text{SO}_4$, leading to a mixture of **2d** and **3** in a 1:1.5 ratio.

(10 mol%), ethane was detected (benzene- d_6 was saturated with the contents of the collecting gas burette) supporting the formation of **B** from **A**. As shown in Fig. 4, the molar quantity of ethane collected is much higher than that of the catalyst. This suggests that **A** is regenerated during the catalytic cycle. It is also noteworthy that the molar quantity of ethane is lower than that of the amine **2d**; this suggests that **2d** is reached through both pathways.

Additional experiments were carried out to support the mechanism. First, treatment of **1d** with $\text{CD}_3\text{CH}_2\text{MgBr}$ and Cp_2ZrCl_2 (10 mol%) followed by quenching with water gave a mixture of two dimagnesated compounds (**4** and **5**) and two trimagnesated compounds (**6** et **7**) in a 6:6:1:1 estimated ratio (Fig. 5, equation (1)). On the other hand, quenching with $\text{D}_2\text{O}/\text{D}_2\text{SO}_4$ led to a 1:1 mixture of **5** and **7**. This deuterium scrambling is in favour of an intermediate metallacycle and inconsistent with a direct alkylation (**7** should be the only product). With the presence of trideuterated products after hydrolysis, the $\beta\text{-D}$ abstraction comes to light. The comparison of the H_2O and $\text{D}_2\text{O}/\text{D}_2\text{SO}_4$, quenching indicates that the formation of **4** and **5** is due to the hydrolysis of the dideuterated regioisomers derived from **F**, whereas the formation of **6** and **7** is due to the hydrolysis of the

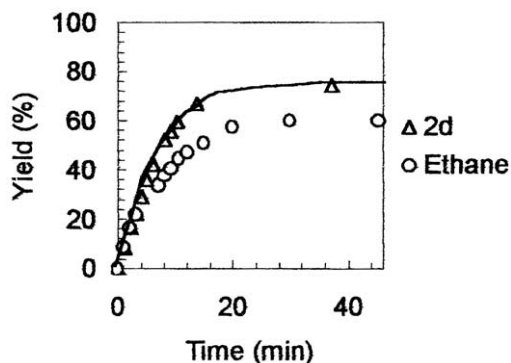


Fig. 4. GC and ethane monitoring during the reaction of **1d** [200 mmol l^{-1}] with EtMgCl [400 mmol l^{-1}] and Cp_2ZrCl_2 [20 mmol l^{-1}].

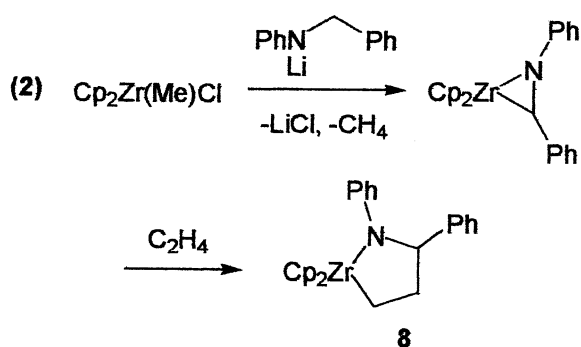
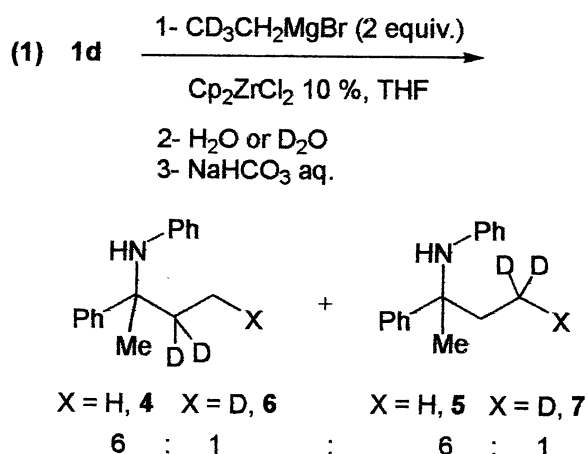


Fig. 5. (1) Treatment of **1d** with $\text{CD}_3\text{CH}_2\text{MgBr}$ and Cp_2ZrCl_2 followed by quenching with water, leading to a mixture of **4**, **5**, **6** and **7** in a 6:6:1:1 estimated ratio. (2) Synthesis of **8** by the reaction of $\text{Cp}_2\text{Zr(Me)Cl}$ with benzylphenylamine lithium salt, followed by insertion of ethylene into the intermediate zirconaaziridine.

trideuterated regioisomers derived from **E**. The difference between the product ratios in Figs 3 (1:1.5) and 5 (6:1) is likely due to a primary isotope effect, which slows the $\beta\text{-D}$ abstraction down. Consequently, the selective Zr-N bond cleavage of metallacycle **C** is emphasized. The isotope effect can be estimated to $k_{\text{H}}/k_{\text{D}} = 4.3$, which is consistent with other values reported for related reactions [6]. Second, complex **8** was prepared by the reaction of $\text{Cp}_2\text{Zr(Me)Cl}$ with benzylphenylamine lithium salt, followed by insertion of ethylene into the intermediate zirconaaziridine (equation (2)) [10]. Metallacycle **8**, whose structure is very similar to the one of **C**, proved to be catalytically active in the reaction of **1d** with ethyl Grignard reagents.

Third, the Zr -catalysed ethylmagnesylation of **1d** was carried out using various concentrations of EtMgCl . As shown above, quenching with $\text{D}_2\text{O}/\text{D}_2\text{SO}_4$ led to a mixture of **3** and **2d**. As expected, the selectivity $S = [\mathbf{3}]/[\mathbf{2d}]$, estimated by NMR, increases linearly as a function of the concentration (Fig. 6). Path (ii) is thus promoted by a high concentration of the ethylmagnesium compound.

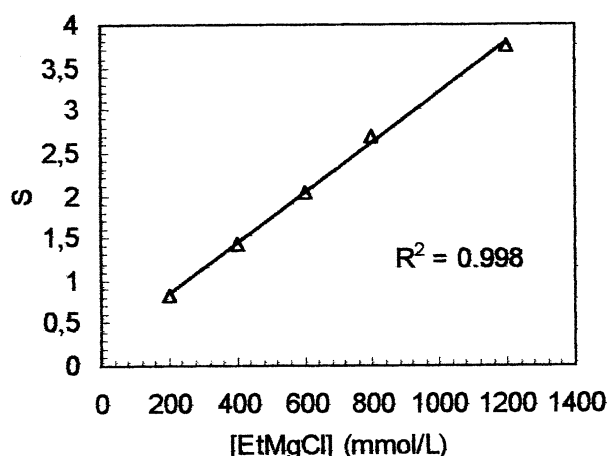


Fig. 6. Reaction of **1d** [100 mmol l⁻¹] with Cp₂ZrCl₂ [10 mmol l⁻¹]. S = [3]/[2d].

3. Conclusion

On the basis of deuterium labelling experiments, analysis of by-products, as well as the catalytic activity of an independently prepared intermediate, we have proposed a mechanism for the Zr-catalyzed addition of ethyl Grignard reagents to imines. We have

demonstrated the coexistence of two competing ethyl- and (2-magnesio)ethylmagnesium pathways that involve a common intermediate resulting from the selective cleavage of an azazirconacyclopentane.

4. Typical experimental procedure of the Zr-catalyzed alkylation of imines

Under an argon atmosphere, a dry Schlenk flask was charged with Cp₂ZrCl₂ (146 mg, 0.5 mmol) and the imine (5 mmol). THF (20 ml) was added, followed by the ethyl Grignard reagent (1 M in THF, 2 equiv). The reaction mixture was allowed to stir for 1.5 hours. The reaction mixture was carefully quenched with 15% NaOH (2 ml). After dilution with 15% NaOH, the phases were separated and the aqueous phase was extracted three times with ether. The combined organic layers were washed with a saturated solution of Na₂CO₃, dried over Na₂SO₄ and concentrated. Amines of greater than 95% purity were obtained by flash chromatography on silica.

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