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Cp_2TiCl_2-CATALYZED GRIGNARD REACTIONS. 2. REACTIONS WITH KETONES AND ALDEHYDES[1]

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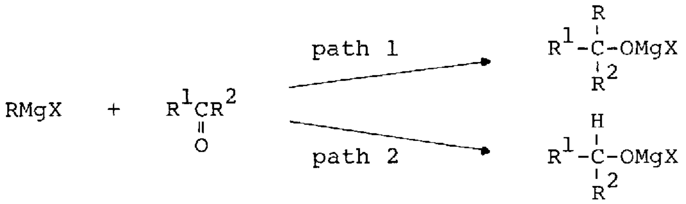
Summary: The reaction of Grignard reagents with ketones or aldehydes in the presence of a catalytic amount of Cp_2TiCl_2 leads to the corresponding reduction products in high yields. Cp_2TiH intermediate was proposed to account for this observation.

Since the two pioneering works of Kharasch, Cu(I)-catalyzed 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds[2] and Co(II)-catalyzed reaction of Grignard reagents with organic halides[3], the transition metal-catalyzed reactions of Grignard reagents have been attracting a great deal of interest. Especially over the last 15 years, many new reactions useful in organic synthesis have been developed[4].

Ashby and Wiesemann recently reported that the addition of a catalytic amount of $FeCl_3$ to the reaction of tert-butylmagnesium chloride with acetone leads to a high yield of reduction products[5]. However, the application of this reaction to organic synthesis have not been developed.

We report here our discovery that when the reaction of Grignard reagents with ketones or aldehydes is carried out in the presence of a catalytic amount of Cp_2TiCl_2, reduction (path 2 in eq. 1) becomes dominant and the usual 1,2-addition (path 1) is suppressed. Thus this new development provides a simple and general method for reduction of alkyl ketones and aldehydes.



$$RMgX + R^1\underset{\overset{\|}{O}}{C}R^2 \begin{cases} \xrightarrow{\text{path 1}} R^1\text{-}\overset{R}{\underset{R^2}{C}}\text{-OMgX} \\ \xrightarrow[\text{path 2}]{} R^1\text{-}\overset{H}{\underset{R^2}{C}}\text{-OMgX} \end{cases} \qquad (1)$$

The following reaction is representative and illustrates the drastic change in reaction path by the catalysis of Cp_2TiCl_2: After stirring an ether solution of iso-propylmagnesium bromide (30 ml of 1.0 M solution, 30 mmol) and Cp_2TiCl_2 (0.19 g, 0.76 mmol) for 5 min at 0°C, 2-hexanone (2.5 g, 25 mmol) was added dropwise over about 5 min, and then the reaction mixture was stirred for 10 min at 0°C followed by another 10 min at room temperature. The reaction mixture was decomposed with 2N-HCl, extracted with ether, dried over $MgSO_4$, and then the solvent was removed by rotary evaporation. Elution of the product mixture with hexane-ether from a column of silica gel afforded a clear liquid (2.57 g, 99% yield) composed of 2-hexanol (91%) and 2,3-dimethyl-3-heptanol (9%).
Without the catalyst the same reaction gave 97% of 2,3-dimethyl-3-heptanol and 3% of 2-hexanol in 98% total yield.

Table 1 summarizes the results of the reactions of various ketones and aldehydes with Grignard reagents.
Many Grignard reagents with hydrogen atom in the β-position, such as propyl, iso-propyl, 2-methylbutyl and hexyl Grignard reagent, can reduce alkyl ketones to secondary alcohols in excellent yields. However, methyl and phenyl Grignard reagents, and, despite the hydrogen atom on its β-carbon, ethyl Grignard reagent did not reduce ketones in higher yields than in the absence of Cp_2TiCl_2.
Though various alkyl ketones were reduced to the secondary alcohols as stated, aromatic ketones and α,β-unsaturated ketones were not reduced to the corresponding secondary alcohols (entries 11 and 12). Aldehydes were reduced to the primary alcohols similarly, but yields were lower than ketones indicating that the reaction is sensitive to steric effects to some extent.
Noteworthy also is the fact that, though $TiCl_4$ showed catalytic activity, its activity was far lower than Cp_2TiCl_2 (entry 6). In addition, the choice of solvent plays an important role. Switching from ether to THF lowered the yield of the reduced products (entry 7).

By analogy from the mechanism suggested for Cp_2TiCl_2-catalyzed Grignard reactions, such as exchange reactions with olefins[6] or conjugated diolefins[1] and reduction of bromides[7] and for Cp_2TiCl_2-catalyzed hydromagnesation[8], we propose the mechanism shown in Scheme 1 for the present reaction.
In the first step the Grignard reagent (RMgX) reacts with Cp_2TiCl_2 to form Cp_2TiR (1)[9] followed by elimination of a β-hydrogen to afford Cp_2TiH (2) and olefin. The compound 2 reacts with ketones or aldehydes to form an alkoxytitanium compound 3 in the next step, and then, in the last step, 3 exchanges with RMgX to give the alkoxymagnesium halide reproducing 1.
Reduction of the carbonyl group via direct transfer of a β-hydrogen atom in the alkyl group of the compound 1, which is the generally accepted mechanism for ketone reductions by Grignard reagent[10], was ruled out because no asymmetric ketone reduction was observed when (+)-2-methylbutylmagnesium chloride was used as the reagent (entry 17).

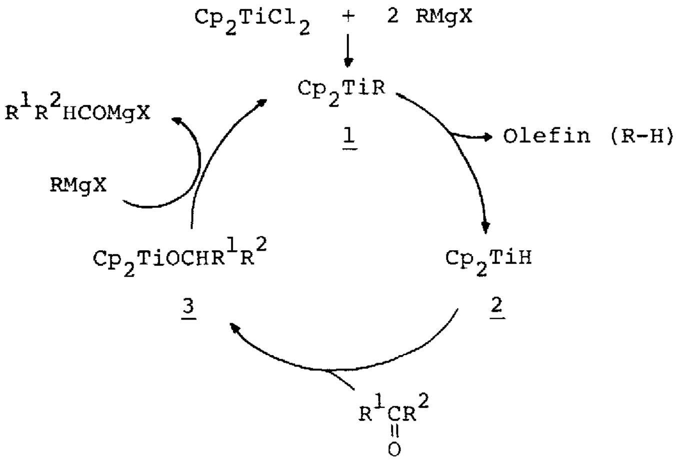
Table 1. PRODUCTS OF GRIGNARD REACTIONS WITH KETONES AND ALDEHYDES

Entry	Starting Material RMgBr R	$R^1C(O)R^2$ R^1	 R^2	Reaction conditions[a]	Ratio of Products R^1R^2CHOH / R^1R^2RCOH [b]	Total yield[c] %
1	CH_3	CH_3	C_4H_9	A	0 / 100	d
2	C_2H_5	CH_3	C_4H_9	A	trace / 100	d
3	C_3H_7	CH_3	CH_3	A	83 / 17	94[e]
4	$(CH_3)_2CH$	CH_3	CH_3	A	96 / 4 (2 / 98)	95[e]
5		CH_3	C_4H_9	A	91 / 9 (3 / 97)	99
6				B	10 / 90	96
7				C	20 / 80	94
8		C_2H_5	C_2H_5	A	98 / 2	97
9		$-CH_2-(CH_2)_3-CH_2-$		A	91 / 9 (13 / 87)	96
10		CH_3	$(CH_3)_2CH$	A	98 / 2	83
11		CH_3	C_6H_5	A	0 / 100	d
12		CH_3	$CH_2{=}CH$	A	0 / 100	d
13		CH_3	$CH_2{=}CHCH_2CH_2$	A	99[f] / 1 (4 / 96)	98
14		C_2H_5	H	A	48 / 52 (0 / 100)	95[e]
15		$C_3H_7(CH_3)CH$	H	A	52 / 48 (2 / 98)	98
16	$(CH_3)_2CHCH_2$	CH_3	C_4H_9	A	98 / 2	98
17	$(+)-C_2H_5CH(CH_3)CH_2$[g]	CH_3	$(CH_3)_3C$	A	100[h] / 0	99
18	C_6H_{13}	CH_3	CH_3	A	84 / 16	97[e]
19	C_6H_5	CH_3	CH_3	A	0 / 100	d

[a] All reactions were performed in the same manner (scale, addition and reaction periods, temp., workup). See the Representative method in the paper. Solvent and catalyst are as follows, A: solvent; ether, catalyst; Cp_2TiCl_2. B: solvent; ether, catalyst; $TiCl_4$. C: solvent; THF, catalyst; Cp_2TiCl_2. [b] Determined by GLC. The ratio of products for reaction without catalyst is presented in the parentheses. [c] Isolated by column chromatography. [d] Not determined. [e] GLC yield. [f] Product is cis and trans-4-hexen-2-ol, no 5-hexen-2-ol was detected by NMR. [g] $(+)-C_2H_5CH(CH_3)CH_2MgCl$ was used. [h] No asymmetric reduction was observed.

The existence of 2 explains the production of 4-hexen-2-ol from 5-hexen-2-one (entry 13) via isomerization of the double bond by metal hydride addition-elimination mechanism.

Scheme 1



The application of these Cp_2TiCl_2-catalyzed Grignard reductions of ketones and aldehydes in synthetic chemistry are apparent; however, the more remarkable is the fact that the present work strongly suggests that other Grignard reactions which proceed readily under mild conditions would similarly be influenced by Cp_2TiCl_2.

References and notes

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