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Grignard-type Addition of Alkenyl- and Alkylzirconocene Chloride to Aldehyde: Remarkable Catalytic Acceleration Effect of $AgClO_4$

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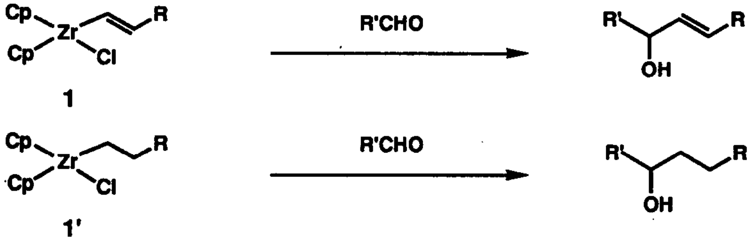
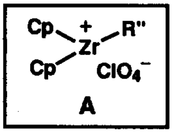
Abstract: Nucleophilic addition of alkenylzirconocene chloride [$Cp_2Zr(Cl)CH{=}CHR$] to aldehyde, which is ordinarily a slow reaction, is remarkably accelerated by a catalytic amount of $AgClO_4$. The rate acceleration effect is also valid for the alkyl congener, $Cp_2Zr(Cl)R$.

Organozirconium compounds are gaining increasing importance in organic synthesis.[1)] Due to the inherently mild reactivity of organozirconium species in general, their utilization calls for the finding of effective *catalyst* or *promoter*. Such aspects are well illustrated by the synthetic utility of alkenylzirconocene chloride **1** in conjugate addition[2a,b)] or olefin cross-coupling reactions,[2c)] where the key point is the efficient transmetalation to other transition metals such as Cu and Ni. Due to the ready accessibility of **1**, i.e., via hydrozirconation of 1-alkyne with Schwartz reagent,[3)] these reactions are currently serving as new methods for C-C bond formation. In sharp contrast, the Grignard-type reactivity of **1** (or its alkyl counterpart **1'**), even though fundamental, has been virtually unexploited so far, which would obviously of great value to expand the scope of organozirconium chemistry.



1

1'



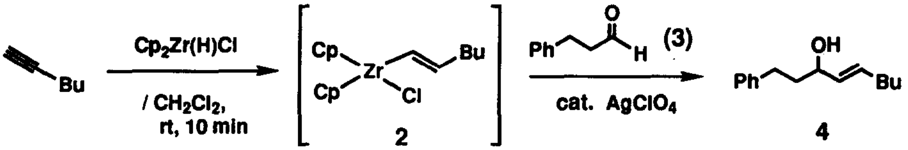
A

In this context, we were particularly interested in the use of silver salt such as $AgClO_4$, which would generate cationic zirconocene species such as A from **1** (or **1'**). What we expected was the pronounced reactivity of such species, documented in our glycosidation chemistry[4)] and also in the polymerization chemistry,[5)] which would activate the carbonyl group of the aldehyde to enhance its electrophilicity.[6)]

Herein, we wish to describe that *a catalytic amount of $AgClO_4$ indeed dramatically accelerates the Grignard-type addition of organozirconocene chloride to aldehyde, thereby offering a new possibility for C-C bond formation.*

The feature is represented by the reaction of 3-phenylpropanal (3) with 1-hexenylzirconocene chloride (2). Treatment of a suspension of $Cp_2Zr(H)Cl^{3,7)}$ with 1-hexyne at room temperature (10 min, CH_2Cl_2) gave a slightly yellow solution of **2**. Subsequent reaction with aldehyde **3**, however, gave rise to only sluggish addition and the alcohol **4** was obtained in low yield even after prolonged reaction time (runs 1, 2; Table 1). In sharp contrast, addition of 5 mol% of $AgClO_4$ remarkably accelerated the reaction to give adduct **4** in 90% yield after 10 min (run 3). The amount of $AgClO_4$ was reducible to 1 mol% or even to 0.1 mol% without losing the reasonable reaction rate (runs 4, 5). Choice of the silver salt was crucial. AgOTf exhibited a slightly inferior rate acceleration effect, while other silver salts were considerably less effective. Order of the reactivity is as follows: $AgClO_4 \geq AgOTf > AgSbF_6 > AgPF_6 >> AgBF_4$.

Table 1. Rate acceleration by $AgClO_4$.8)



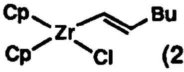
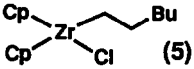
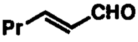
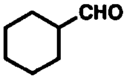
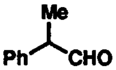
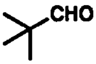
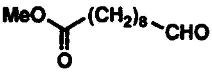
Run	$AgClO_4$	Time	Yield / %
1	none	2 h	17
2	none	overnight	23
3	5 mol%	10 min	90
4	1 mol%	30 min	90
5	0.1 mol%	2.5 h	84

Typical procedure is as follows: A mixture of $Cp_2Zr(H)Cl$ (401 mg, 1.55 mmol) and 1-hexyne (132 mg, 1.61 mmol) in CH_2Cl_2 (4.0 mL) was stirred at room temperature for 10 min. To the resulting solution was added 3-phenylpropanal (**3**) (174 mg, 1.30 mmol) in CH_2Cl_2 (4.0 mL) followed by $AgClO_4$ (13 mg, 63 μmol, 5 mol%). The reaction mixture gradually turned dark brown. After stirring for 10 min, the mixture was poured into sat. $NaHCO_3$ aqueous solution. Extractive workup (EtOAc) followed by purification with preparative TLC (hexane/EtOAc = 80/20) gave allylic alcohol **4** as colorless oil (255 mg, 90%).8)

Under the similar conditions, reaction of **2** with some other aldehydes were examined in the presence of 5 mol% of $AgClO_4$ (Table 2; the left column). All reactions proceeded rapidly to give the corresponding alcohols in high yield (CH_2Cl_2, rt, 10 min). The reaction with an α,β-unsaturated aldehyde **7** gave the corresponding bis-allylic alcohol without any indication of competing 1,4-addition. 2-Phenylpropanal (**10**) also reacted smoothly, although essentially no diastereoselectivity was observed. Furthermore, the reaction went chemoselectively with the aldehyde **12** having an ester group. It should be noted that the reaction goes efficiently by utilizing alkenylzirconocene chloride in slight excess, which makes this alkenyl-transfer reaction synthetically attractive.

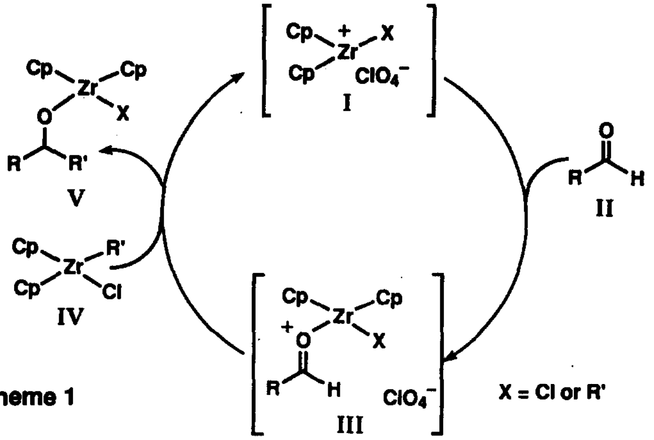
Moreover, this rate acceleration effect was also valid for alkylzirconocene chloride. The right column in Table 2 shows the results of the reaction of hexylzirconocene chloride (**5**), generated from $Cp_2Zr(H)Cl$ and 1-hexene,3) with the aldehydes **6**–**12**. The reactivity was inferior to the alkenyl counterpart and employment of **5** in 2 equivalents and 10 mol% of $AgClO_4$ proved to be necessary for achieving reasonable rate. Furthermore, this alkyl transfer was sensitive to the steric hindrance as shown in the case of the aldehydes **9** and **11**. These features make this alkyl transfer less attractive than the alkenyl transfer stated above.

Table 2. Reaction of organozirconcene chloride.

Run	Aldehyde	 (2) Yield / % a) (reaction time)	 (5) Yield / % a) (reaction time)
1	PhCHO **6**	92 (10 min)	84 (1 h)
2	 **7**	88 (10 min)	81 (3 h)
3	n-C_8H_{17}CHO **8**	93 (10 min)	90 (5 h)
4	 **9**	90 (10 min)	64 (10 h)
5	 **10**	94b) (10 min)	77b) (6 h)
6	 **11**	63c) (10 min)	27 (15 h)
7	 **12**	93 (10 min)	79 (6 h)

a) Yields refer to isolated, purified products.
b) The product was ca. 1:1 diastereomeric mixture.
c) The product was highly volatile. GC-Analysis (tetralin as standard) showed 98% yield.

The catalytic activity of $AgClO_4$ in this addition reaction could be explained by considering the following catalytic cycle (Scheme 1). The cationic zirconocene species **I**, generated by the action of silver salt, is capable of the carbonyl activation as shown in **III**. This encourages the transfer of the R'-group from **IV** to give **V**. Irrespective as to whether the transfer is intra- or intermolecular in nature, the cationic complex **I** is regenerated, so that a catalytic amount of silver salt suffices for the overall rate enhancement.[9]



Scheme 1

In summary, we described the remarkable rate acceleration effect of $AgClO_4$ on the Grignard-type addition of alkenyl- and alkylzirconocene chloride to aldehyde. Application of this reaction to a new method for 1,3-diene synthesis is the subject of the following paper.[10]

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8. All new compounds were fully characterized by ^1H-, ^{13}C NMR, IR, and HRMS.
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10. Maeta, H.; Suzuki, K. the following paper in this issue.

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