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Chlorodimethylaluminum-promoted nucleophilic addition of lithium pentamethylcyclopentadienide to aliphatic aldehydes and DDQ-mediated carbon–carbon bond cleavage of the adducts providing the parent aldehydes

Minoru Uemura, Hideki Yorimitsu* and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

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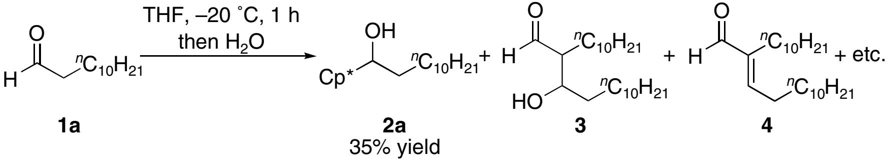
Abstract—Treatment of aliphatic aldehyde with lithium pentamethylcyclopentadienide in the presence of chlorodimethylaluminum provided the corresponding carbinol in excellent yield. The carbinol returns to the parent aldehyde and pentamethylcyclopentadiene by the action of a catalytic amount of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

We have been interested in the use of pentamethylcyclopentadiene (Me_5C_5H, Cp*H) and its anionic form ($Me_5C_5^-$, Cp^{*-}) as reagents in organic synthesis. In the previous report,[1] we demonstrated that Cp*Li adds to aromatic aldehydes to yield the corresponding alcohols[2] and that the adducts return to the parent aldehydes and Cp*H via carbon–carbon bond cleavage upon heating or treatment with acid. On the other hand, several attempted reactions of aliphatic aldehydes with Cp*Li resulted in failure. For instance, treatment of dodecanal (**1a**) with Cp*Li yielded the corresponding adduct **2a** in only 35% yield (Eq. 1). The byproducts comprised β-hydroxy aldehyde **3** and α,β-unsaturated aldehyde **4**. The formation of the byproducts means that Cp*Li unfortunately worked as a bulky base to generate the lithium enolate of **1a**. To overcome the limitation, a number of additives are examined to attain selective nucleophilic attack to the carbonyl group of aliphatic aldehyde. We luckily found that chlorodimethylaluminum assists the addition reaction of Cp^{*-} to aliphatic aldehydes, which is disclosed herein.

Chlorodimethylaluminum (6.0 mmol) was added to a suspension of Cp*Li (6.0 mmol, generated from ^{n}BuLi and Cp*H) in THF at −20 °C, and the resulting suspension was stirred for 30 min. Aldehyde **1a** (5.0 mmol) was added, and the mixture was stirred at −20 °C for 1 h. After aqueous workup, purification on silica gel yielded the desired alcohol **2a** in 92% yield (Table 1, entry 1, from **1** to **2**). Trace amounts of **3** and **4** were detected



(1)

Keywords: Pentamethylcyclopentadiene; Nucleophilic addition; Carbon–carbon bond cleavage; Chlorodimethylaluminum.

* Corresponding authors. Tel.: +81 75 383 2441; fax: +81 75 383 2438; e-mail addresses: yori@orgrxn.mbox.media.kyoto-u.ac.jp; oshima@orgrxn.mbox.media.kyoto-u.ac.jp

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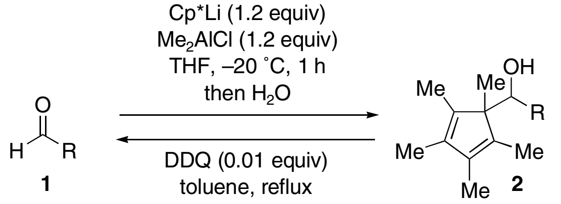
Table 1. Nucleophilic addition of Cp*Li to aliphatic aldehydes and carbon–carbon bond cleavage of the adducts affording the parent aldehydes and Cp*H



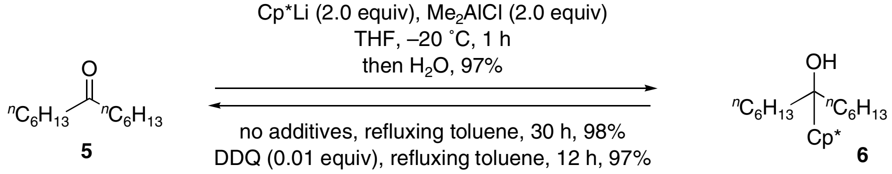
Entry	R	From **1** to **2** (%)	From **2** to **1**[a] (%)
1	CH$_3$(CH$_2$)$_{10}$ (**a**)	92	92 (12 h)
2	PhCH$_2$CH$_2$ (**b**)	94	80 (12 h)
3[b]	*cyclo*-C$_6$H$_{11}$ (**c**)	97	82 (24 h)[c]
4	^{t}C$_4$H$_9$ (**d**)	<10	—
5	NC(CH$_2$)$_5$ (**e**)	89	75 (24 h)
6	Cl(CH$_2$)$_9$ (**f**)	93	95 (12 h)
7	CH$_3$OC(=O)(CH$_2$)$_4$ (**g**)	82	81 (36 h)

[a] The reaction time of each run is in parentheses.

[b] To complete the reaction, 1.5 equiv of Cp*Li and Me$_2$AlCl were used.

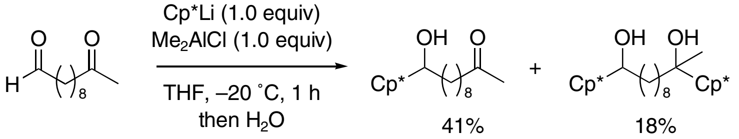
[c] Isolated as 1-cyclohexylpentanol after treatment of the crude oil with *n*-butyllithium.

in the crude oil. The role of chlorodimethylaluminum is unclear. Chlorodimethylaluminum can serve as a Lewis acid, activating the carbonyl group. Alternatively, Me_2Cp^*Al reagent would be formed via transmetalation and can enable the selective nucleophilic attack. Other Lewis acids such as chlorotrimethylsilane, triethylaluminum, and magnesium dibromide were much less effective than chlorodimethylaluminum. Titanium tetraisopropoxide comparably promoted the addition (81% yield).



(3)

A variety of aliphatic aldehydes were subjected to the nucleophilic addition (Table 1, from **1** to **2**). The reaction of cyclohexanecarbaldehyde (**1c**) provided **2c** in excellent yield. Sterically demanding pivalaldehyde (**1d**) resisted the reaction, and **1d** remained untouched. The reaction was highly chemoselective. Cyano, chloro, and ester moieties did not interfere with the reaction (entries 5–7). When catalytic amounts (10 mol %, for instance) of chlorodimethylaluminum were used, the reactions did not go to completion and ca. 20% of **1** was left. The reaction with keto aldehyde, 11-oxo-2-undecanone, exhibited unsatisfactory chemoselectivity (Eq. 2).

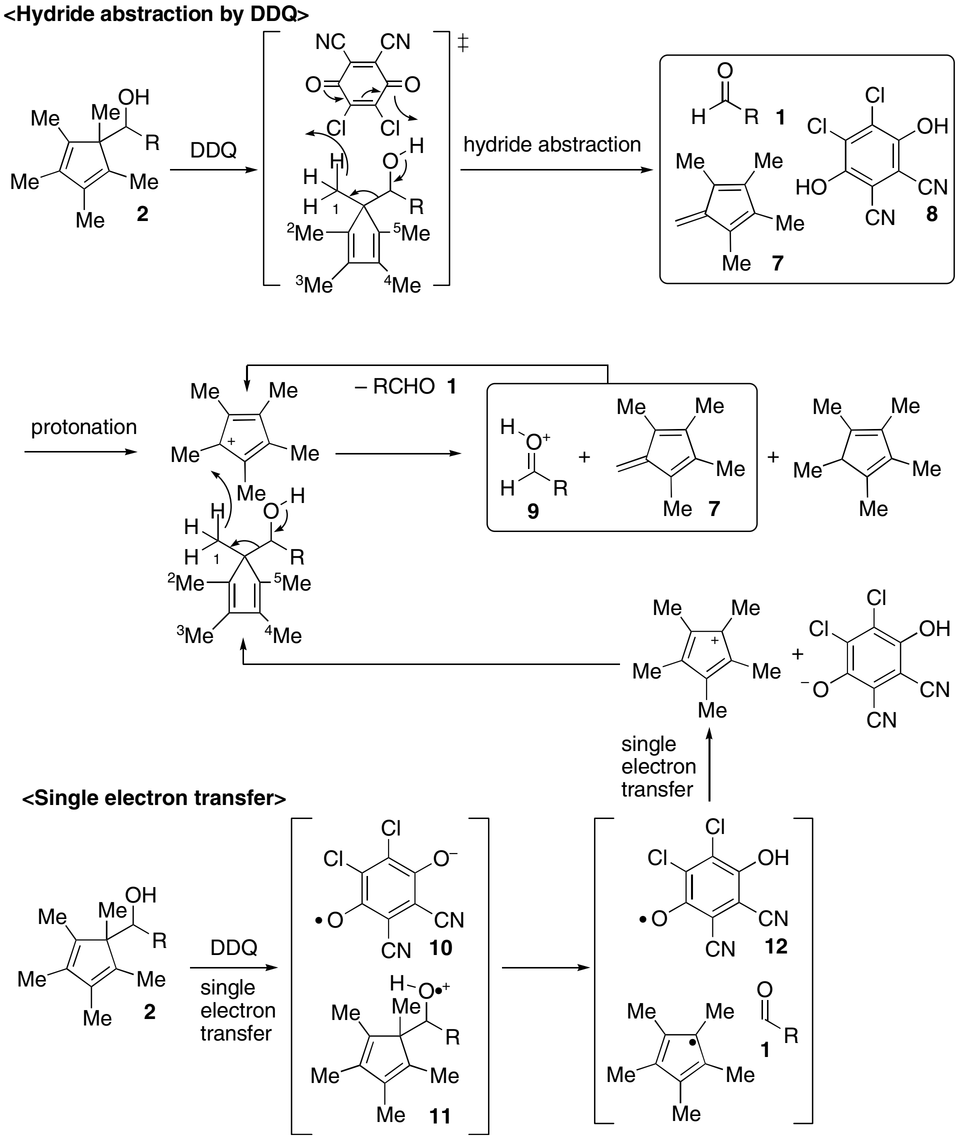


(2)

Removal of the Cp* group of **2**, which results in recovery of **1**, can represent a protective method of aliphatic aldehydes. Contrary to the previous report,[1] carbinols **2** were stable under acidic conditions or at high temperature. By extensive screening of reaction conditions, a strong oxidant, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), proved to effect smooth carbon–carbon bond cleavage[3] to afford the parent aldehyde **1** and Cp*H. Treatment of **2a** with 1 mol % of DDQ in refluxing toluene for 12 h furnished **1a** in 92% isolated yield (entry 1, from **2** to **1**), with concomitant production of quantitative Cp*H. In the presence of DDQ, all the carbinols **2** were transformed into the parent aldehydes (Table 1, from **2** to **1**). Carbinols **2e** and **2g** having polar cyano and ester moieties underwent the removal of the Cp* group more slowly. The sterically hindered cyclohexyl group of **2c** also retarded the reaction. Other organic oxidants such as chloranil, 2,3-dichlorobenzoquinone, trityl tetrafluoroborate (Ph$_3$C$^+$BF$_4$$^-$) also promoted the removal albeit the efficiency was much lower.

Chlorodimethylaluminum also facilitated the addition of Cp*Li to dihexyl ketone (**5**) (Eq. 3). Without the additive, none of the adduct **6** was obtained. Interestingly, heating **6** in toluene at reflux for 30 h afforded **5** in 98% yield, along with Cp*H. It is worth noting that DDQ accelerated the transformation (reflux, 12 h).

Although the mechanism operating in the DDQ-promoted carbon–carbon bond cleavage is not clear at this stage, we are tempted to assume two possible mechanisms (Scheme 1). One mechanism involves hydride abstraction by DDQ, a strong hydride acceptor.[4] DDQ would abstract the hydride at the 1-methyl group of the Cp* group,[5] which leads to the generation of aldehyde **1**, tetramethylfulvene (**7**), and **8**. Protonation of **7** with **8** would produce unstable pentamethylcyclopentadienyl cation (Cp^{*+}). The cyclic 4π-electronic cation Cp^{*+} would be a hydride acceptor powerful enough to abstract hydride from **2** to give oxonium cation **9**, **7**, and Cp*H. The combination of the oxonium cation **9**



Scheme 1.

and fulvene **7** again generates Cp^{*+} to complete the catalytic cycle. Alternatively, a mechanism involving single electron transfer is probable.[6] Single electron transfer from **2** to DDQ generates radical anion **10** and radical cation **11**. The latter undergoes fragmentation into pentamethylcyclopentadienyl radical (Cp$^{*\bullet}$) and **1**. Cp$^{*\bullet}$ would be oxidized by **12** into Cp^{*+}. The cation Cp^{*+} participates in the same catalytic cycle in the hydride abstraction mechanism. Noteworthy is the fact that no deuterium incorporation was observed in the cleavage reaction in deuterated toluene, which eliminates the possibility of hydrogen abstraction of the intermediary radicals from solvent.

The hydroxy group of **2** plays a key role in the carbon–carbon bond cleavage process. Additional polar groups such as cyano and ester groups in **2e** and **2g** would prevent the weak interaction between the hydroxy group and electron deficient species such as DDQ and Cp^{*+}. The bulkier cyclohexyl group of **2c** hampered the access of the electron deficient species to the hydroxy group of **2c**. Namely, rate-determining hydride abstraction or single electron transfer would be retarded. It is worth noting that the silyl ether of **2b** completely resisted the cleavage upon treatment with DDQ in boiling toluene.

In summary, we found that chlorodimethylaluminum facilitates nucleophilic addition of lithium pentamethylcyclopentadienide to aliphatic aldehydes. The adducts return to their parent aldehydes by the DDQ-mediated cleavage of the Cp*–CR(H)OH bond. Metal-mediated carbon–carbon bond cleavage is a transformation that is attracting increasing attention.[3] The DDQ-mediated cleavage provides a new protocol for carbon–carbon bond cleavage without metal reagents.

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Supplementary data

Supplementary data including experimental details and characterization data for new compounds can be found online. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.159.

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