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Pentamethylcyclopentadienide in organic synthesis: nucleophilic addition of lithium pentamethylcyclopentadienide to aromatic aldehydes and carbon–carbon bond cleavage of the adducts affording the parent aldehydes

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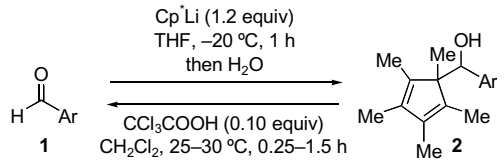
Abstract—Treatment of aromatic aldehyde with lithium pentamethylcyclopentadienide provided the corresponding carbinol in excellent yield. The carbinol returns to the parent aldehyde and pentamethylcyclopentadiene upon exposure to an acid or due to heating. The combination of the two reactions can represent a protection of aromatic aldehyde.

One cannot overestimate the importance of pentamethylcyclopentadienide ($Me_5C_5^-$, Cp^{*-}) as a ligand in transition metal chemistry.[1,2] Its steric bulkiness as well as delocalized 6π-electron system provides coordinated metals with a unique environment and, as a result, the complexes with interesting reactivity, enhanced solubility, and crystallizability. In the field of organic synthesis, Cp^{*-} serves as a ligand of transition metal catalysts. However, there are few reports on useful reactions of Cp^{*-} itself.[3] Here we report an example, wherein Cp^{*-} adds to aromatic aldehydes to temporarily protect the aldehyde moiety, taking advantage of formally reversible carbon–carbon bond formation/cleavage.[4]

Nucleophilic addition of Cp^{*-} to aromatic aldehydes proceeded in excellent yield.[5] Treatment of *p*-bromobenzaldehyde (**1a**, 2.0 mmol) with Cp^*Li (2.4 mmol, generated from ^{n}BuLi and Cp^*H) in THF at −20 °C for 1 h afforded the corresponding carbinol **2a** in 95% isolated yield (Table 1, entry 1, from **1** to **2**). Higher temperature led to the concurrence of a side reaction, Meerwein–Ponndrof–Verley reduction/Oxpenauer oxidation to form *p*-bromobenzyl alcohol and *p*-Br–$C_6H_4C(=O)Cp^*$. Use of methylmagnesium bromide to abstract the acidic proton of Cp^*H also enhanced the reduction/oxidation side reaction. The attempted nucleophilic addition reaction resulted in no or little conversion under Cs_2CO_3/DMSO, $KN(SiMe_3)_2$/THF, or $NaN(SiMe_3)_2$/THF deprotonation conditions.

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



Entry	Ar	From **1** to **2** (%)	From **2** to **1** (%)
1	*p*-BrC_6H_4 (**a**)	95	92
2	2-$C_{10}H_7$ (**b**)	88	87
3	*p*-$PhC(=O)C_6H_4$ (**c**)	85	87
4	*p*-$MeOC(=O)C_6H_4$ (**d**)	87	91
5	*p*-NCC_6H_4 (**e**)	95	79
6	*p*-$BuOC_6H_4$ (**f**)	98	87
7	*p*-^{i}PrC(=O)C_6H_4 (**g**)	84	93
8	*o*-$MeOC_6H_4$ (**h**)	97	69

Keywords: Pentamethylcyclopentadiene; Nucleophilic addition; Carbon–carbon bond cleavage; Protection; Aldehydes.
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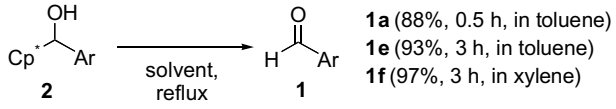
A variety of aromatic aldehydes underwent the nucleophilic addition (Table 1, from **1** to **2**). The reaction was highly chemoselective. Keto (entries 3 and 7), ester (entry 4), and cyano (entry 5) moieties did not interfere with the reaction. Despite its steric factor, *ortho*-substitution did not retard the reaction (entry 8). Unfortunately, the reaction with dodecanal failed to yield a satisfactory amount of the corresponding adduct (ca. 50% yield), instead furnishing several aldol adducts. Different from the reactions with **1c** and **1g**, enolization of *p*-formylacetophenone took place to yield the expected adduct in less than 30% yield.

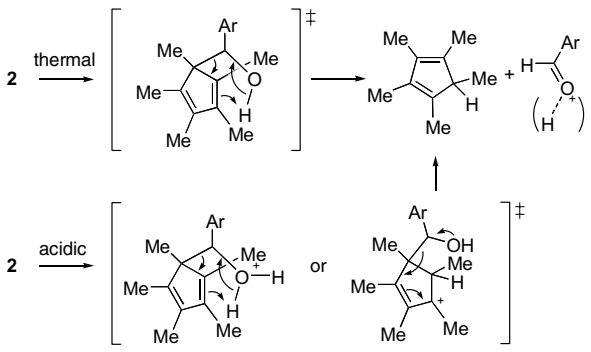
Carbinols **2** were unstable under acidic conditions and were transformed into the parent aldehydes via carbon–carbon bond cleavage.[6,7] Treatment of **2a** with 10 mol % of trichloroacetic acid in dichloromethane at 25–30 °C for 1.5 h provided **1a** in 92% isolated yield (entry 1, from **2** to **1**). Concomitant recovery of a quantitative amount of Cp^*H is advantageous since Cp^*H is costly. Other acids such as trifluoroacetic acid, camphorsulfonic acid monohydrate, *p*-toluenesulfonic acid monohydrate also effected the carbon–carbon bond cleavage under the otherwise same reaction conditions, although the yields of **1a** were lower by ca. 20% because of several unidentified by-products. Use of acetic acid promoted the elimination very slowly. Silica gel in dichloromethane did not work at all. In polar coordinating solvents such as THF and methanol, acid-catalyzed cleavage was not observed. Under the standard reaction conditions, all the carbinols **2** were transformed into the parent aldehydes without any difficulty (Table 1, from **2** to **1**).

A similar carbon–carbon bond cleavage was observed in the absence of acid. Heating **2a** and **2e** in toluene at reflux provided aldehydes **1a** and **1e** in 88% and 93% yields, respectively (Scheme 1). Electron-rich carbinol **2f** required a higher temperature to return efficiently to **1f** in boiling xylene. Complete conversion of **2f** in refluxing toluene took more than 20 h, albeit the yield was quantitative.

A retro-carbonyl-ene mechanism can rationalize the fragmentation reaction (Scheme 2).[8] The thermal reaction would proceed via a concerted mechanism although thermal retro-carbonyl-ene reactions generally require higher temperature, most of which were performed in a gas phase.[8e] The reaction temperatures used herein are extremely low as being a temperature for a retro-carbonyl-ene reaction. Since a number of acids catalyze carbonyl-ene reactions, trichloroacetic acid can lower the barrier of activation of the present retro-reaction based on the principle of microscopic reversibility. Alternatively, protonation at the Cp^* group can facilitate the carbon–carbon bond cleavage. The solvent effect



Scheme 1.

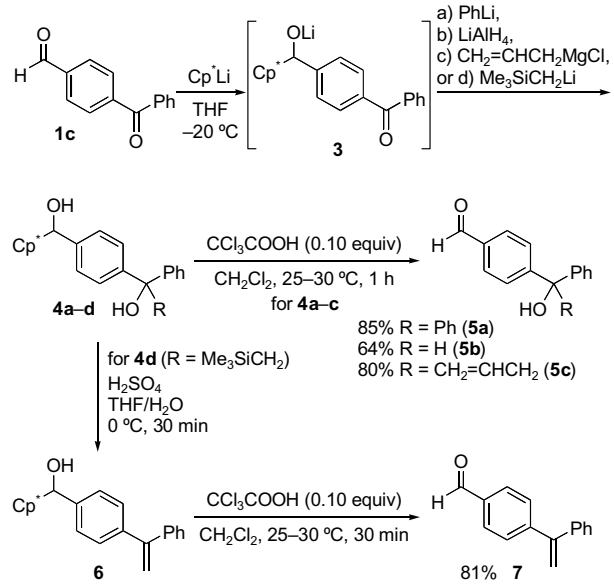


Scheme 2.

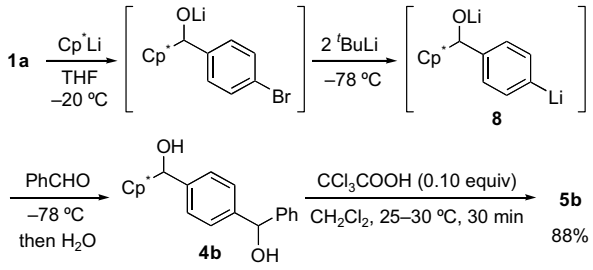
on the acid-catalyzed cleavage can be rationalized by specific acid catalysis. To clarify the reaction course, further investigation is necessary.

The utility of the Cp^* group as a protective group is demonstrated in Scheme 3. After Cp^* had masked the aldehyde moiety of **1c** in situ, the keto group was subjected to nucleophilic addition reaction with phenyllithium to afford diol **4a**. The crude oil was exposed to the acidic conditions to produce hydroxy aldehyde **5a** in 85% overall yield. Chemoselective reduction and allylation were also successful to furnish **5b** and **5c**, respectively.[9,10] Attempted Wittig reaction of **3** with $CH_2{=}PPh_3$ failed, and the methylenation of the aldehyde moiety that must be masked was partly observed. Instead, addition of trimethylsilylmethyllithium to **3** followed by acid-catalyzed olefination in aqueous THF yielded the carbinol **6**. Treatment of **6** under the deprotection conditions afforded **7** in 81% overall yield. All the procedures proceeded so cleanly that no purification of the intermediates such as **4** and **6** was necessary.

The in situ protection made preparation of a formyl-substituted phenyllithium equivalent feasible (Scheme 4). Nucleophilic addition of Cp^*Li to **1a** fol-



Scheme 3.



Scheme 4.

lowed by bromine–lithium exchange furnished aryllithium **8**. The lithium reagent **8** could be trapped with benzaldehyde to yield crude diol **4b**. Subsequent removal of Cp^*H afforded **5b** in 88% overall yield.

In summary, pentamethylcyclopentadiene or its anionic form has now participated in organic synthesis as a new 'reagent', taking advantage of the facile cleavage of the carbon–carbon bond, specifically the Cp^*–CAr(H)OH bond. The in situ protection of an aldehyde moiety has realized a new chemoselective reaction and generation of an organometallic reagent having a masked aldehyde group.

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Supplementary data

Supplementary data including experimental details and characterization data for new compounds can be found with this article in the online version at doi:10.1016/j.tetlet.2005.05.094.

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