Evidence that Additions of Grignard Reagents to Aliphatic Aldehydes Do Not Involve Single-Electron-Transfer Processes

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Supporting Information

ABSTRACT: Addition of allylmagnesium reagents to an aliphatic aldehyde bearing a radical clock gave only addition products and no evidence of ring-opened products that would suggest single-electron-transfer reactions. The analogous Barbier reaction also did not provide evidence for a single-electron-transfer mechanism in the addition step. Other Grignard reagents (methyl-, vinyl-, t-Bu-, and triphenylmethylmagnesium halides) also do not appear to add to an alkyl aldehyde by a single-electron-transfer mechanism.

Since its discovery, the Grignard reaction has become one of the more synthetically useful carbon–carbon bond-forming reactions. Additions of allylmagnesium reagents to carbonyl compounds are particularly useful because the products incorporate an alkene functional group that can serve as a useful synthetic handle for further elaboration.1-9 Although ally Grignard reagents are used extensively in natural product syntheses,10-12 many of their reactions with aliphatic ketones and aldehydes proceed with low selectivity or with selectivity that is distinctly different from other Grignard reagents.13-15 Predicting these variations in selectivity is difficult because the mechanism by which allylmagnesium reagents react with aliphatic ketones and aldehydes proceed with low selectivity or with selectivity that is distinctly different from other Grignard reagents. In this paper, we provide evidence that radical intermediates are unlikely to be reactive intermediates in additions of allylmagnesium reagents to aliphatic aldehydes.

Scheme 1. Addition of Allylmagnesium Halide Depicted As Involving a Single-Electron-Transfer Process

Our approach to discovering whether radical intermediates were present during the carbon–carbon bond-forming step of the addition of an allylmagnesium reagent to a nonaromatic aldehyde involved the use of a radical clock. The 2,2-diphenylcyclopropylcarbinyl system (Scheme 2), one of the fastest radical clocks known, was chosen to maximize the chance of observing products derived from single-electron-transfer reactions.16-19 The 2,2-diphenylcyclopropylcarbinyl radical undergoes ring opening at a rate of 5 × 10^11 s⁻¹,19-21 and oxygen-containing substituents have been shown to have little effect on this rate.20,22 Consequently, if a radical intermediate were formed, it should undergo ring opening at a rate that is competitive with the rate of geminate radical pairs undergoing recombination.23,24 Cyclopropane-derived radical clocks have been used to provide evidence for radical intermediates.24,25 These radical clocks have been used to identify ketyl radicals as intermediates in reactions of reagents such as SmI₂ and tributyltin hydride with aldehydes,26,27 ketones,28-31 esters,32-34 amides,33 and carboxylic acids.33

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Scheme 2. Unimolecular Ring Opening of 2,2-Diphenylcyclopropylcarbinyl Radical Clock

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Table 1. Addition of Allyl Grignard Reagent to Aldehyde 1

<table>
<thead>
<tr>
<th>X</th>
<th>solvent</th>
<th>yield (%)</th>
<th>starting material (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>THF</td>
<td>83 (68:32)</td>
<td>0°</td>
</tr>
<tr>
<td>Br</td>
<td>Et₂O</td>
<td>83 (72:28)</td>
<td>0°</td>
</tr>
<tr>
<td>Cl</td>
<td>Et₂O</td>
<td>85 (69:31)</td>
<td>0°</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl₂</td>
<td>74 (70:30)</td>
<td>2</td>
</tr>
<tr>
<td>Cl</td>
<td>CH₂Cl₂</td>
<td>73 (70:30)</td>
<td>12</td>
</tr>
<tr>
<td>Cl</td>
<td>toluene</td>
<td>46 (69:31)</td>
<td>34</td>
</tr>
<tr>
<td>Cl</td>
<td>THF</td>
<td>83 (68:32)</td>
<td>0°</td>
</tr>
</tbody>
</table>

“Détermined by ¹H and ¹³C NMR spectroscopic analysis of crude reaction mixtures using 1,4-dimethoxybenzene as an internal standard. “Purchased. “Prepared by concentrating to dryness and adding the appropriate solvent. “Grignard reagent prepared before use. “Not detected.

Table 2. Other Grignard Reagents Investigated for Evidence of a SET Mechanism

<table>
<thead>
<tr>
<th>RMgX</th>
<th>yield (%)</th>
<th>starting material (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeMgBr</td>
<td>75 (77:23)</td>
<td>6</td>
</tr>
<tr>
<td>H₂C=C=CHMgBr</td>
<td>78 (83:17)</td>
<td>2</td>
</tr>
<tr>
<td>t-BuMgCl</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Ph₃CMgCl</td>
<td>38 (77:23)</td>
<td>0</td>
</tr>
</tbody>
</table>

“Détermined by ¹H NMR spectroscopic analysis of crude reaction mixtures using 1,4-dimethoxybenzene as an internal standard. “Syn/anti not determined. The yield was determined by ¹H NMR spectroscopic analysis of the purified reaction mixture. 1,2-Reduction product (12%) was also isolated. “Results were comparable at −78 and 35 °C.

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reagents, those processes could involve six-center (10, 11) or four-center (12) transition states (Figure 1).\textsuperscript{16,55–57} The radical clock experiments cannot differentiate between these possibilities. We cannot discount a stepwise single-electron mechanism completely, however. If the addition of a Grignard reagent to an alky aldehyde proceeded by one-electron reduction of the aldehyde to form a ketyl radical and an alkyl radical and then recombination of these two radicals (Scheme 1), the rate constant of the two radicals recombining would need to be faster than the rate of the particularly fast ring-opening rearrangement (Scheme 2). In this situation, because the second step is so fast, the stepwise reaction becomes effectively concerted. In summary, studies with an aldehyde substrate bearing a radical clock provide evidence against a single-electron-transfer reaction (ref 14a). The carbon–carbon bond-forming step in reactions of Grignard reagents with aromatic aldehydes and ketones can involve a single-electron-transfer (SET) process, depending on the substrate: Hoffmann, R. W.; Holzer, B. Chem. Commun. 2001, 491.

The additions to both alkyl methyl ketones and alkyl trifluoromethyl ketones have been proposed to involve polar mechanisms, not single-electron-transfer reactions: Felix, C.; Laurent, A.; Mison, P. J. Fluorine Chem. 1995, 70, 71.

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(1) Grignard, V. Compt. Rend. 1900, 130, 1322.
(15) Kinetic isotope effect studies suggest that allyllithium reagents react with alkyl aldehydes by a polar mechanism (ref 14a).
(17) The additions to both alkyl methyl ketones and alkyl trifluoromethyl ketones have been proposed to involve polar mechanisms, not single-electron-transfer reactions: Felix, C.; Laurent, A.; Mison, P. J. Fluorine Chem. 1995, 70, 71.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01893.

Experimental data and NMR spectra (PDF)

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Notes
The authors declare no competing financial interest.

Figure 1. Addition of allyl Grignard reagents involving either six-center or four-center transition states.\textsuperscript{6,55–57}
(53) Assuming this peak represented one hydrogen atom, it accounted for <1% yield.