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

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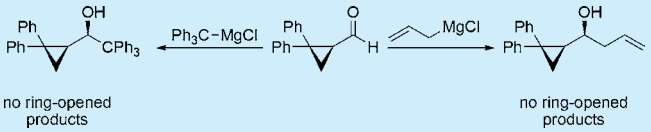
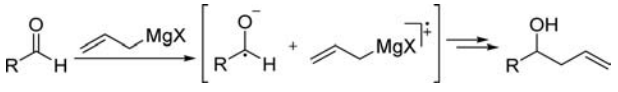
Supporting Information

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.



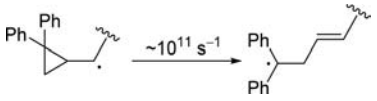
Since its discovery, the Grignard reaction has become one of the more synthetically useful carbon–carbon bond-forming reactions.[1] Additions of allylmagnesium reagents to carbonyl compounds are particularly useful because the products incorporate an alkene functional group that can serve as a useful synthetic handle for further elaboration.[2,3] Although allyl Grignard reagents are used extensively in natural product synthesis and other applications,[4−9] many of their reactions with aliphatic ketones and aldehydes proceed with low selectivity or with selectivity that is distinctly different from other Grignard reagents.[10−13] Predicting these variations in selectivity is difficult because the mechanism by which allylmagnesium reagents react with aliphatic substrates has not been established. Reactions of allylic Grignard reagents with aryl aldehydes may proceed by a single-electron-transfer (SET) mechanism,[14] but no evidence has been provided to establish whether allylmagnesium reagents react with alkyl aldehydes by SET reactions (Scheme 1) or not.[15−17] 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.[18,19] 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

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



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 SmI_2 and tributyltin hydride with aldehydes,[23,26,27] ketones,[28−31] esters,[32−34] amides,[33] and carboxylic acids.[33]

Additions of allylmagnesium reagents to 2,2-diphenylcyclopropane-1-carbaldehyde (**1**) with the radical clock substituent provided no evidence suggesting that single-electron-transfer processes occurred during carbon–carbon bond formation (Table 1).[35] The reaction of commercially available allylmagnesium chloride (2 M in THF) with aldehyde **1** afforded the addition product, alcohol *syn*-**2**, in 83% isolated yield (*syn*/*anti* 68:32). The stereochemical configurations of the products were assigned tentatively on the basis of results with related cyclopropane-substituted carbonyl compounds.[36,37] No ring-opened products, such as aldehydes **3**, **4**, or **5**, were detected by mass spectrometry or ^1H or ^{13}C NMR spectroscopic analysis of the unpurified reaction mixture (Scheme 3).

Under various reaction conditions, 1,2-addition products were the only compounds observed (Table 1). The counterion of the reagent did not influence the outcome of the reaction: reactions of commercially available allylmagnesium bromide and allylmagnesium chloride both afforded similar results with no evidence of rearranged products (Scheme 3). The outcome of the reaction was independent of solvent. The source of the allylmagnesium

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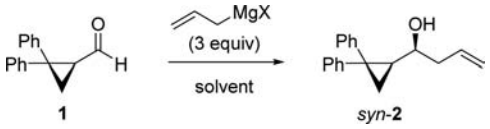
Table 1. Addition of Allyl Grignard Reagent to Aldehyde 1

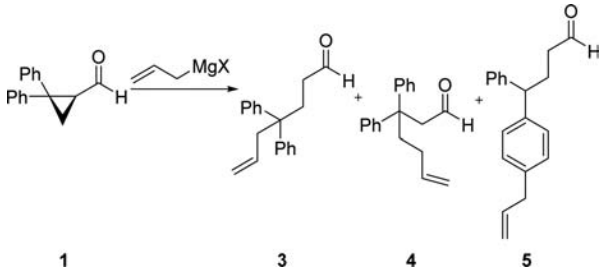


1 *syn*-2

X	solvent	yield **2** (%)[a] (*syn*/*anti*)	starting material (%)
Cl	THF[b]	83 (68:32)	0[e]
Br	Et_2O[b]	83 (72:28)	0[e]
Cl	Et_2O[b]	85 (69:31)	0[e]
Cl	Et_2O[b,c]	74 (70:30)	2
Cl	CH_2Cl_2[b,c]	73 (70:30)	12
Cl	toluene[b,c]	46 (69:31)	34
Cl	THF[d]	83 (68:32)	0[e]

[a]Determined by ^{1}H and ^{13}C NMR spectroscopic analysis of crude reaction mixtures using 1,4-dimethoxybenzene as an internal standard. [b]Purchased. [c]Prepared by concentrating to dryness and adding the appropriate solvent. [d]Grignard reagent prepared before use. [e]Not detected.

Scheme 3. Potential Ring-Opened Products Similar to Those Observed in Other Reactions[31,32]

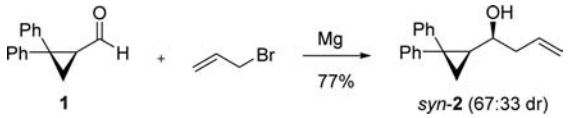


1 3 4 5

reagent was not a significant factor:[38−41] addition of a reagent that had been prepared immediately before use gave results comparable to those obtained using commercially available reagents.

The analogous Barbier reaction[42−44] proceeded similarly. The reaction of allyl bromide and aldehyde **1** in the presence of magnesium turnings afforded allylated product *syn*-**2** with 98% conversion (by NMR spectroscopy) in 77% isolated yield (*syn*/*anti* 67:33, Scheme 4).[45] No ring-opened products were

Scheme 4. Barbier Reaction of Aldehyde 1

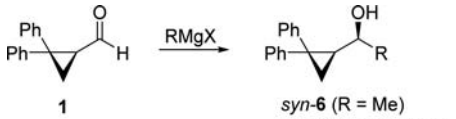


1 *syn*-2 (67:33 dr)

detected. The similarity in outcome (products and stereoselectivity) between this experiment and the reactions involving preformed allylmagnesium reagents (Table 1) suggests that the Grignard reagent was formed in situ under the Barbier conditions. By contrast, in allylations of aryl aldehydes, ketyl radicals have been invoked as reactive intermediates.[46,47]

Experiments with other Grignard reagents and aldehyde **1** also provided no evidence of ring-opened products (Table 2). In all cases, only 1,2-addition products were observed. The reaction with *t*-BuMgCl yielded small amounts of the 1,2-reduction product (12%) and unreacted starting material (18%, Table 2).[48,49] The addition of Ph_3CMgCl, a reagent that generally undergoes single-electron-transfer reactions with aromatic

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



1

syn-**6** (R = Me)
syn-**7** (R = CH=CH_2)
syn-**8** (R = *t*-Bu)
syn-**9** (R = CPh_3)

RMgX	yield (%) (*syn*/*anti*)	starting material (%)
MeMgBr	75 (77:23)[a]	6
H_2C=CHMgBr	78 (83:17)[a]	2
t-BuMgCl	22[b]	18
Ph_3CMgCl	38 (77:23)[a,c]	0

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

carbonyl compounds to give trityl radicals,[50,51] also yielded 1,2-addition products. The lack of ring-opened products with *t*-BuMgCl and Ph_3CMgCl, which would be indicative of the intermediacy of ketyl radicals, contrasts with observations of their reactions with aryl ketones, which react by single-electron processes.[50−52]

In contrast to the reaction with allylmagnesium bromide and Ph_3CMgCl, traces of a compound that was not the 1,2-addition product were observed in the reactions employing methyl-, vinyl-, and *tert*-butylmagnesium halides. Each of the unpurified mixtures was analyzed by ^{1}H NMR spectroscopy, and only when the baseline was amplified considerably could a small amount (<1%) of another compound be identified.[53] In all spectra, this new peak, a triplet (J = 1.4−1.6 Hz), was located in similar positions ($\delta \sim 9.5$ ppm). This resonance is consistent with the presence of a formyl group (CHO) connected to a CH_2 group. No resonances corresponding to the CH_2 group could be identified in the ^{1}H NMR spectra, however, and no corresponding carbon resonances were identifiable by ^{13}C NMR spectroscopy. Careful analysis of mass spectra of unpurified reaction mixtures did not reveal the presence of a product to which this small resonance could be assigned. Too little compound was formed to permit an assignment of the structure of this compound beyond this fragment. This trace component could be formed by ring-opening of the aldehyde by single-electron process, but that ring-opening might or might not be related to the process that forms the carbon−carbon bond in the major products. That the trace impurity was observed in reactions with MeMgBr, which would not form a stable radical, and not observed when allylmagnesium halides and Ph_3CMgCl were used, which would form more stable radicals,[54] suggests that the ring-opening products did not derive from one-electron transfer during carbon−carbon bond formation. Regardless of the structure of these minor products, their presence in trace quantities in these reactions cannot be interpreted as evidence that single-electron pathways are involved in the addition reactions.

The results presented in this paper indicate that allylmagnesium reagents, and Grignard reagents more generally, react with aliphatic aldehyde **1** by mechanisms that do not involve single-electron transfer. It is more likely that a two-electron process gives rise to the addition products. In the case of allylmagnesium

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reagents, those processes could involve six-center (**10**, **11**) or four-center (**12**) transition states (Figure 1);[16,55−57] the radical

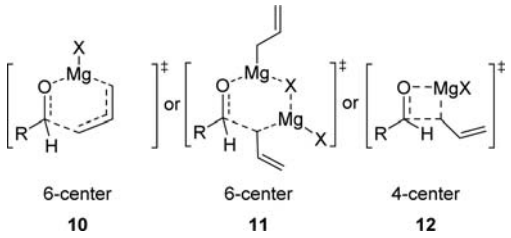

Figure 1. Addition of allyl Grignard reagents involving either six-center or four-center transition states.[16,55−57]

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 alkyl 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).[24,28] In this situation, because the second step is so fast, the stepwise reaction becomes effectively concerted.[58−60]

In summary, studies with an aldehyde substrate bearing a radical clock provide evidence against a single-electron-transfer mechanism for the addition of allylmagnesium reagents to aliphatic aldehydes. A number of other Grignard reagents, including Ph_3CMgCl, which is capable of producing a highly stabilized alkyl radical,[54] also did not provide products consistent with radical intermediates.

■ 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.

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