



The retro Grignard addition reaction revisited: the reversible addition of benzyl reagents to ketones



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ABSTRACT

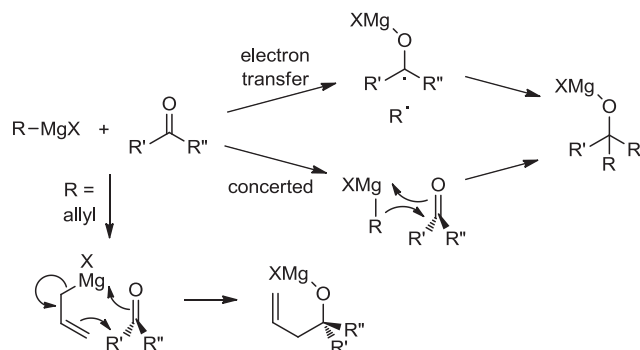
The Grignard addition reaction is known to be a reversible process with allylic reagents, but so far the reversibility has not been demonstrated with other alkylmagnesium halides. By using crossover experiments it has been established that the benzyl addition reaction is also a reversible transformation. The retro benzyl reaction was shown by the addition of benzylmagnesium chloride to di-*tert*-butyl ketone followed by exchange of both the benzyl and the ketone moiety with another substrate. Similar experiments were performed with phenylmagnesium bromide and *tert*-butylmagnesium chloride, but in these two cases the Grignard addition reaction did not show any sign of a reverse transformation.

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1. Introduction

The addition of Grignard reagents to carbonyl compounds is one of the fundamental reactions in synthetic organic chemistry.¹ The transformation is highly favored since the two bonds formed (C–C and O–Mg) are much stronger than the two bonds broken (C–Mg and C=O). The mechanism has been thoroughly studied and it has been found that the reaction takes place by two rather different pathways depending on the nature of the reagent and the substrate (Scheme 1).² Electron transfer reactions are observed if the substrate is easily reduced by the acceptance of an electron and the reagent has an alkyl group, which may form a stabilized radical by donating an electron to the substrate. Steric hindrance is of little importance in this stepwise mechanism and the reactivity series for the Grignard reagents is often *tert*-butyl>isopropyl>*n*-butyl>ethyl>methyl.² If radical formation is not facilitated, the reaction takes place by a synchronous shift of the electron pairs. This four-centered concerted mechanism is highly dependent on steric factors since the electron shifts require a close approach of the reacting atoms. The reactivity series is often phenyl>ethyl>*n*-butyl>isopropyl>>*tert*-butyl.²

Allylic Grignard reagents are special, since by electron donation they may form the highly stabilized allyl radical and therefore react very fast by electron transfer mechanisms.³ At the same time



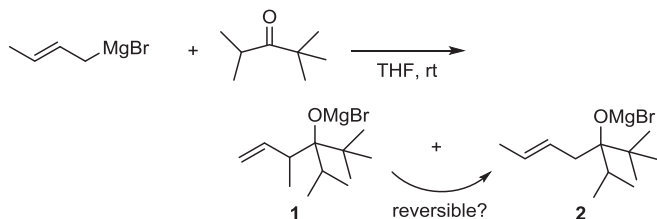
Scheme 1. Mechanism of Grignard addition reaction.

allylmagnesium halides are extremely well suited for reaction in a concerted way since the normal high steric requirements of the magnesium atom with its coordination sphere of solvent molecules may be circumvented by conjugate addition of the naked γ -carbon in a cyclic six-center mechanism (Scheme 1). The reactions of allylmagnesium halides with many substrates therefore have half lives in the microsecond range.³ In fact, allylations are so fast that they may compete with protonations by water making it possible to achieve certain allylic Grignard additions in aqueous media.⁴

Due to the high reactivity of Grignard reagents the addition is commonly viewed as being irreversible. However, this is not always completely true. The first suggestion of a retro Grignard addition

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came from the observation that crotylmagnesium bromide, in the reaction with *tert*-butyl isopropyl ketone, gave the α -methallyl addition product **1** initially, while after a period of time the crotyl addition product **2** dominated (Scheme 2).⁵



Scheme 2. α -Methallyl versus crotyl adduct.

The process took place at room temperature and the result was interpreted as a rearrangement of the α -methallyl adduct **1** into the crotyl product **2**. The rearrangement was postulated to take place by allylic transposition of **1** into a *tert*-butyl isopropyl ketone–crotylmagnesium bromide complex, which then collapses through a four-centered transition state to the thermodynamically more stable crotyl product **2**.^{5,6} However, it is unlikely that this rearrangement takes place by a true retro Grignard addition at ambient temperature. The heat of reaction for the addition of crotylmagnesium bromide to *tert*-butyl isopropyl ketone is 105 kJ/mol and the activation energy for the process is of the order of 30 kJ/mol.⁷ The reverse reaction must then overcome a barrier of 135 kJ/mol and even with a favorable entropy of reaction, the reaction at room temperature would require hundreds of years, while the observed rearrangement occurs within a few hours.

That a retro Grignard addition is indeed possible was shown by another approach where two different crossover experiments were designed independently at the same time.^{7,8} In the first, 1,3-dimethylallylmagnesium bromide was reacted with di-*tert*-butyl ketone and the initial adduct split into two batches and treated with *tert*-butyl isopropyl ketone and allylmagnesium bromide, respectively.⁷ In both cases, significant allyl transfer occurred within an hour at 80 °C.⁷ An essential requirement for this experiment is that both the added ketone and the Grignard reagent are more reactive than the original reactants, which makes the crossover a favorable transformation when the initial addition is a reversible reaction. In the second crossover experiment, two different Grignard adducts were mixed and heated to 65 °C.⁸ The first was prepared from di-*tert*-butyl ketone and allylmagnesium bromide while the second was obtained from *tert*-butyl isopropyl ketone and crotylmagnesium bromide. Again, allyl crossover was observed indicating that the addition is reversible.⁸

The reversal process has found synthetic applications since sterically encumbered homoallylic tertiary alcohols have been used as allyl transfer reagents in the presence of various metals and bases.^{9,10} First, the retro allylation transfers the allyl group to the metal, which is then followed by allylation of an aldehyde or an imine. This retro allylation/allylation sequence from homoallylic alcohols has been mediated by copper, gallium, and rhodium complexes at temperatures ranging from 25 to 130 °C.^{9,10}

So far, however, the reversal has only been described with allylic substrates and no studies have been carried out with other Grignard reagents. Thus, the purpose of the present study is to investigate whether the reverse Grignard addition reaction is possible with other alkylmagnesium halides.

2. Results and discussion

The studies were performed by crossover experiments in line with the earlier work from one of us.⁷ First, a concerted reaction

was investigated where it is important that the Grignard reagents have little steric requirements and react rapidly with the carbonyl compounds. This is true for benzylic reagents, which are some of the most reactive Grignard reagents after the allylic compounds. In fact, the half life for the addition of benzylmagnesium bromide to acetone is about 5 ms,³ while the same value for methylmagnesium bromide is around 0.2 s.¹¹ In the same way, the ketones should be sterically encumbered and non-enolizable in order to avoid protonation of the Grignard reagent. Therefore, benzyl Grignard and di-*tert*-butyl ketone were selected for the crossover experiments.

First, the exchange of Grignard reagent was investigated starting from 3-benzyl-2,2,4,4-tetramethylpentan-3-ol (Table 1). The tertiary alcohol was reacted with a large excess of the Grignard reagent, which immediately formed the corresponding alkoxide salt. The mixture was then heated in a sealed vial and the exchange monitored by GC. With *p*-methylbenzylmagnesium chloride no reaction occurred at 100 °C while a very low conversion was observed at 120 °C after 2 days. However, upon heating to 140 °C for 3 days the crossover product, 2,2,4,4-tetramethyl-(*p*-methylbenzyl)pentan-3-ol, was obtained in 51% yield after workup together with 48% of the starting alcohol (entry 1). Complete conversion was observed when the reaction was extended to 10 days where 77% yield of the exchange product was obtained (entry 2). This may indicate that the benzyl Grignard addition reaction is a reversible process although the temperature is significantly higher than for the corresponding allyl reagent.

Table 1
Retro Grignard by exchange of Grignard reagent

Entry	R	R'MgX	Time (d)	Product	Yield (%) ^a
1	Bn	<i>p</i> MeBnMgCl ^b	3		51
2	Bn	<i>p</i> MeBnMgCl ^b	10		77
3	Bn	MeMgBr ^c	6		75
4	Bn	PhMgBr ^d	10		7
5	Ph	<i>p</i> MeBnMgCl ^b	3	—	0
6	Ph	MeMgBr ^c	3	—	0

^a Determined by GC.

^b 0.67 M solution in THF.

^c 3.0 M solution in Et₂O.

^d 1.0 M solution in THF.

A similar crossover reaction was observed when the added Grignard reagent was changed to methyl- and phenylmagnesium bromide. With the former, the methyl addition product was generated in 75% yield after 6 days with some unreacted starting alcohol remaining (entry 3). With the latter, only 7% yield of the phenyl addition product was formed after 10 days, which may be due to the lower reactivity of phenylmagnesium bromide towards di-*tert*-butyl ketone (entry 4).¹² Attempts were also made to react 2,2,4,4-tetramethyl-3-phenylpentan-3-ol with Grignard reagents, but in this case no conversion was observed indicating that the phenyl Grignard addition reaction is not a reversible process at 140 °C (entries 5 and 6).

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