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

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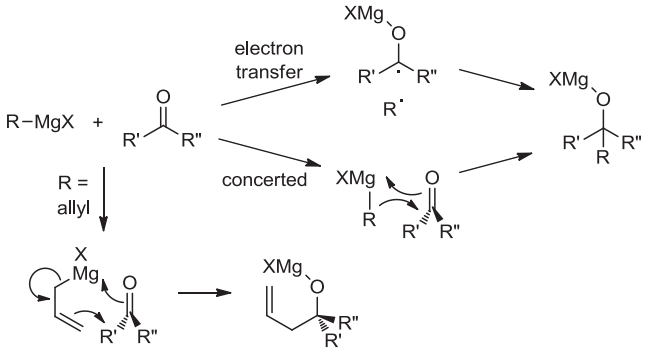
ABSTRACT

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.

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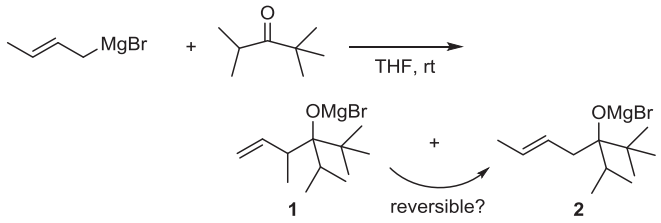
came from the observation that crotylmagnesium bromide, in the reaction with *tert*-butyl isopropyl ketone, gave the α-methallyl addition product **1** initially, while after a period of time the crotyl addition product **2** dominated (Scheme 2).[5]



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]

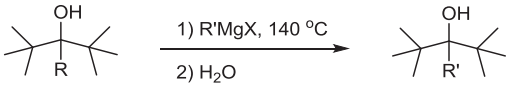
So far, however, the reversal has only been described with allylic substrates and no studies have been carried out with other Grignard reagents. Thus, the purpose of the present study is to investigate whether the reverse Grignard addition reaction is possible with other alkylmagnesium halides.

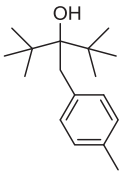
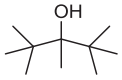
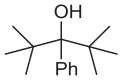
2. Results and discussion

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	*p*MeBnMgCl[b]	3		51
2	Bn	*p*MeBnMgCl[b]	10		77
3	Bn	MeMgBr[c]	6		75
4	Bn	PhMgBr[d]	10		7
5	Ph	*p*MeBnMgCl[b]	3	—	0
6	Ph	MeMgBr[c]	3	—	0

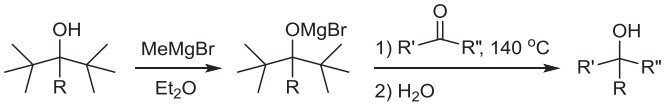
[a] Determined by GC.
[b] 0.67 M solution in THF.
[c] 3.0 M solution in Et_2O.
[d] 1.0 M solution in THF.

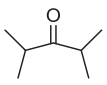
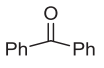
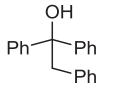
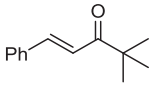
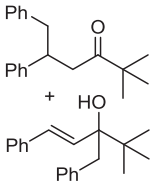
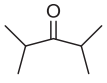
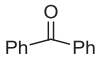
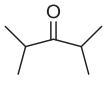
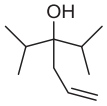
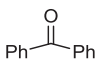
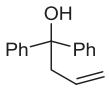
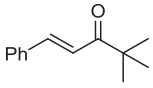
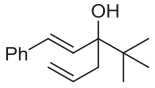
A similar crossover reaction was observed when the added Grignard reagent was changed to methyl- and phenylmagnesium bromide. With the former, the methyl addition product was generated in 75% yield after 6 days with some unreacted starting alcohol remaining (entry 3). With the latter, only 7% yield of 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).

Thus, the benzyl group can be detached from a tertiary magnesium alkoxide, but in order to substantiate this as a retro Grignard addition reaction it is also important to trap the benzyl moiety with a ketone. Otherwise, the observed reaction could in principle be a result of alkoxide decomposition by a different mechanism. In fact, when the tertiary magnesium alkoxide was heated to 140 °C for 8 days in the absence of a Grignard reagent, di-*tert*-butyl ketone was formed in 62% yield. The driving force is the release of strain by converting the sp^3-hybridized alcoholate into the sp^2-hydridized ketone, but the pathway could potentially be different from a retro Grignard addition.

Therefore, the exchange of ketone was investigated next. The tertiary alcohol was treated with 1 equiv of methylmagnesium bromide to form the corresponding magnesium alkoxide, which was followed by addition of the ketone and heating to 140 °C (Table 2). No crossover occurred with diisopropyl ketone, which remained completely unreacted after 3 days (entry 1). However, with benzophenone the exchange product could be observed in 40% yield after the same period along with 60% of di-*tert*-butyl ketone (entry 2). A similar exchange was observed with benzalpinacolone, which afforded a mixture of the 1,4- and the 1,2-addition products in a combined 16% yield (entry 3). Together with the Grignard crossover experiment this verifies the reversibility of the benzylmagnesium bromide addition reaction at 140 °C. No exchange was observed when 2,2,4,4-tetramethyl-3-phenylpentan-3-ol was subjected to the same experiments, which again confirms the non-reversibility of the phenyl addition reaction (entries 4 and 5). For comparison, the corresponding allyl adduct was also included in the study since this particular crossover experiment has not previously been performed with the unsubstituted allyl moiety. As anticipated, the allyl exchange took place at a much lower temperature and in a shorter time than with the benzyl reagent and diisopropyl ketone, benzophenone, and benzalpinacolone could all be employed as the acceptor (entries 6–8).

Table 2
Retro Grignard by exchange of ketone

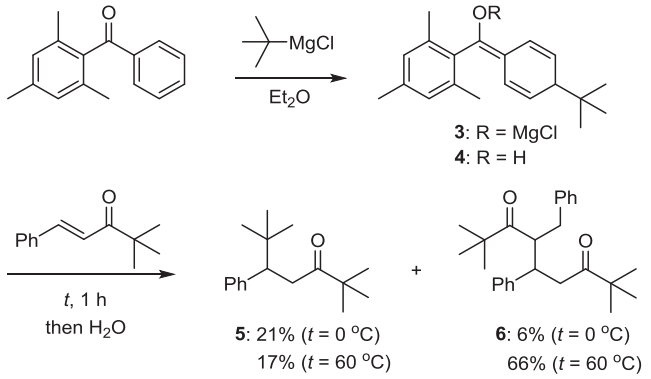


Entry	R	Ketone	Time (d)	Product	Yield (%)[a]
1	Bn		3	—	0
2	Bn		3		40
3	Bn		3		11+5
4	Ph		3	—	0
5	Ph		3	—	0
6[b]	Allyl		0.75		34
7[b]	Allyl		0.75		32
8[b]	Allyl		0.75		50

[a] Determined by GC.
[b] Exchange performed at 70 °C.

Grignard additions by an electron transfer mechanism may also be reversible although this scenario is more complicated since two consecutive steps are involved. To simplify the picture *tert*-butylmagnesium chloride was selected in this case together with mesityl phenyl ketone and benzalpinacolone. Both ketones are known to react with *tert*-butylmagnesium chloride and afford only one product. Benzalpinacolone gives exclusively the 1,4-addition product in this case,[13] while mesityl phenyl ketone only furnishes the corresponding 1,6-adduct.[14] The latter is strained and lacks aromatic stabilization making it a good candidate for a reverse addition reaction.

Thus, a small excess of mesityl phenyl ketone was reacted with *tert*-butylmagnesium chloride at room temperature for 30 min to furnish the intermediate 1,6-adduct **3** (Scheme 3). The identity of this was confirmed by careful workup at 0 °C in the absence of air, which allowed the enol **4** to be characterized by NMR. Without workup the 1,6-adduct **3** was treated directly with 1 equiv of benzalpinacolone and the outcome of the subsequent reaction turned out to depend on the temperature. Upon additional stirring at 0 °C for 1 h the 1,4-addition product **5** was obtained in 21% yield together with 6% of diketone **6**. However, at 60 °C the ratio between the two products changed and diketone **6** was obtained in 66% yield along with 17% of **5**.

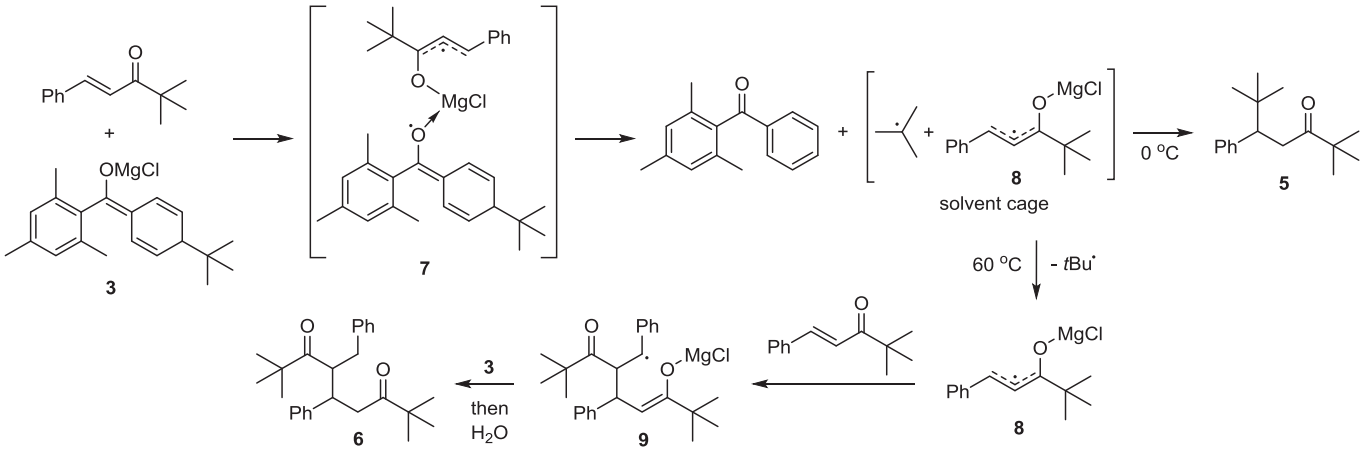


Scheme 3. Addition of *tert*-butyl Grignard.

These results were not due to unreacted *tert*-butylmagnesium chloride from the initial addition to mesityl phenyl ketone. This was confirmed by repeating the sequence with a significantly larger excess of mesityl phenyl ketone, which still produced a mixture of **5** and **6** after addition of benzalpinacolone. Hence, if the formation of these is caused by a retro Grignard addition reaction it should also be possible to perform a Grignard exchange experiment with adduct **3**. Therefore, *tert*-amylmagnesium chloride and allylmagnesium chloride were both allowed to react with **3**, but even after 3 days at 60 °C no exchange was observed at all in either of these two cases. This complete lack of reactivity came as a surprise since especially the highly reactive allylmagnesium chloride should capture even the slightest amount of mesityl phenyl ketone. Consequently, there appears to be no reversal of the *tert*-butyl Grignard addition reaction and the formation of products **5** and **6** in Scheme 3 must be due to a different pathway.

This pathway is believed to involve a slightly different electron transfer route than the classical *tert*-butyl Grignard addition

reaction (Scheme 4). Initially, benzalpinacolone coordinates to adduct **3** and then receives an electron to afford allyl radical **7**.[15] Mesityl phenyl ketone is regenerated by release of the *tert*-butyl radical into the solvent cage with allyl radical **8**.[16] At low temperature, these will combine to form **5** after workup. At higher temperature, however, allyl radical **8** can diffuse out of the cage and react with a second molecule of benzalpinacolone to form the new benzyl radical **9**,[17] which then accepts an electron from **3** to give **6** after workup.



Scheme 4. Mechanism for formation of ketones **5** and **6**.

In summary, we have demonstrated that the Grignard addition reaction is also a reversible process with benzylmagnesium halides. The reversibility was shown with a ketone, which becomes strained upon reaction with the Grignard reagent since this transformation is less exothermic and has a lower heat of activation than other Grignard addition reactions. On the other hand, the same reversibility was not observed with the less reactive phenyl- and *tert*-butylmagnesium halides.

3. Experimental section

3.1. General methods

Ketones were purchased from Sigma–Aldrich and used as received. Benzylic Grignard reagents were prepared in ampoules by slow addition of the benzylic halide to a magnesium suspension in freshly distilled THF under an argon atmosphere. The remaining Grignard reagents were purchased from Sigma–Aldrich and used as received. The base concentration was determined by quenching 1.0 mL of the solution in H_2O followed by addition of a few drops of phenolphthalein and then titrating with nitric acid until a color shift from pink to colorless occurred.[18] THF was distilled from sodium and benzophenone while Et_2O was dried over sodium. NMR spectra were recorded on a Varian Mercury 300 or a Bruker Ascend 400 spectrometer with residual solvent signals as reference. Melting points were measured on a Stuart SMP30 melting point apparatus and are uncorrected. Gas chromatography was performed on a Shimadzu QP5000 GC–MS instrument fitted with an Equity 5, 30 m×0.25 mm×0.25 μm column. High resolution mass spectra were recorded on an Agilent 1100 LC system, which was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a lock mass probe.

3.2. General procedure for synthesis of tertiary alcohols

The ketone was dissolved in Et_2O and a small excess of the Grignard solution in Et_2O or THF was added under an argon atmosphere. The reaction was stirred overnight at room temperature. The mixture was diluted with Et_2O and quenched with H_2O. The organic layer was separated and washed with saturated aqueous NH_4Cl and H_2O. The organic phase was dried with $MgSO_4$, filtered, and concentrated. Further purification was performed either by vacuum distillation or by column chromatography (heptane/ethyl acetate or heptane/toluene).

3.3. General procedure for Grignard exchange reactions

3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (65 mg, 0.28 mmol) was added to a 5 mL screw-top vial, which was flushed with argon. The Grignard solution (4.0 mL of 0.67 M *p*-methylbenzylmagnesium chloride in THF, or 4.0 mL of 1.0 M phenylmagnesium bromide in THF, or 2.5 mL of 3.0 M methylmagnesium bromide in Et_2O) was then added and the vial sealed. The solution was heated to 140 °C for the indicated time. The mixture was then allowed to reach room temperature and the reaction diluted with Et_2O and quenched with H_2O. The organic layer was separated and washed with saturated aqueous NH_4Cl and H_2O. Samples for GC analysis were taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

3.4. General procedure for ketone exchange reactions

The tertiary alcohol (0.34 mmol) was placed in a 5 mL screw-top vial, which was flushed with argon. Et_2O (1.0 mL) and methylmagnesium bromide (0.11 mL, 3.0 mL in Et_2O, 0.33 mmol) were added. When the gas evolution had ceased the ketone (1.43 mmol) was added. The vial was sealed and heated to the indicated temperature for the time stated. Then the mixture was allowed to reach room temperature and the reaction was diluted with Et_2O and quenched with H_2O. The organic layer was separated and washed with saturated aqueous NH_4Cl and H_2O. A sample for GC analysis was taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

3.5. General procedure for *tert*-butyl exchange reactions

To mesityl phenyl ketone (525 mg, 2.34 mmol) in dry Et_2O (10.0 mL) was added *tert*-butylmagnesium chloride (1.5 mL, 1.25 M in Et_2O, 1.90 mmol) under an argon atmosphere. The light brown suspension was stirred at room temperature for 30 min. The reaction was set to the indicated temperature and benzalpinacolone (358 mg, 1.90 mmol) was added. The reaction was stirred at this

temperature for 1 h. The mixture was diluted at room temperature with Et_2O and quenched with H_2O. The organic layer was separated and washed with saturated aqueous NH_4Cl and H_2O. The organic phase was dried with $MgSO_4$, filtered, and concentrated. A sample for GC analysis was taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

3.6. Di-*tert*-butyl ketone

3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (68 mg, 0.29 mmol) was placed in a 5 mL screw-top vial, which was flushed with argon. Et_2O (2.0 mL) and methylmagnesium bromide (0.09 mL of a 3.0 M solution in Et_2O, 0.27 mmol) were added. When the gas evolution had ceased the vial was sealed and heated to 140 °C for 8 days. The mixture was allowed to reach room temperature, diluted with Et_2O and quenched with H_2O. The organic layer was separated and washed with saturated aqueous NH_4Cl and H_2O. A sample for GC analysis was taken out and a yield of 62% was determined by using a calibration curve with *n*-nonane as internal standard.

3.7. 3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (Table 1, entries 1–4)

δ_H (300 MHz, $CDCl_3$) 7.43–7.18 (m, 5H), 3.06 (s, 2H), 1.50 (s, 1H, OH), 1.17 (s, 18H); δ_C (75 MHz, $CDCl_3$) 139.8, 131.6, 128.0, 125.9, 80.0, 42.9, 38.5, 29.5; ν_{max} (film) 3598, 3085, 3061, 2959, 2916, 2878, 1493, 1481, 1452, 1393, 1086, 1001 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{26}O$ $[M+Na]^+$ *m/z* 257.1876, found 257.1875. ^1H NMR data are in accordance with literature values.[19]

3.8. 2,2,4,4-Tetramethyl-3-(*p*-methylbenzyl)pentan-3-ol (Table 1, entries 1 and 2)

δ_H (300 MHz, $CDCl_3$) 7.32 (d, *J*=8.0 Hz, 2H), 7.17 (d, *J*=8.0 Hz, 2H), 3.06 (s, 2H), 2.40 (s, 3H), 1.54 (s, 1H, OH), 1.21 (s, 18H); δ_C (75 MHz, $CDCl_3$) 136.4, 135.3, 131.4, 128.8, 79.8, 42.8, 38.0, 29.4, 21.3; HRMS (ESI) calcd for $C_{17}H_{28}O$ $[M+Na]^+$ *m/z* 271.2032, found 271.2032.

3.9. 2,2,3,4,4-Pentamethylpentan-3-ol (Table 1, entry 3)

Mp 39–41 °C, lit.[12] 39–41 °C; δ_H (300 MHz, $CDCl_3$) 1.26 (s, 1H, OH), 1.14 (s, 3H), 1.05 (s, 18H); δ_C (75 MHz, $CDCl_3$) 79.5, 41.1, 28.9, 21.7; ν_{max} (film) 3506, 2983, 2960, 2916, 2876, 1371, 1106, 1065 cm^{-1}. NMR data are in accordance with literature values.[20]

3.10. 2,2,4,4-Tetramethyl-3-phenylpentan-3-ol (Table 1, entry 4)

Bromobenzene (3.0 mL, 29 mmol) was added dropwise to a suspension of lithium metal (500 mg, 72 mmol) in dry Et_2O (20 mL) under an argon atmosphere. The concentration was measured to 1.39 M by the phenolphthalein titration method.[18] The phenyllithium solution, thus obtained, was added dropwise to 2,2,4,4-tetramethylpentan-3-one (1.24 g, 8.7 mmol) under an argon atmosphere and stirred for 10 min. The mixture was diluted with Et_2O and quenched with H_2O. The organic layer was separated and washed with saturated aqueous NH_4Cl and H_2O. The organic phase was dried with $MgSO_4$, filtered, and concentrated. No further purification was needed. δ_H (300 MHz, $CDCl_3$) 7.77–7.72 (m, 1H), 7.64–7.58 (m, 1H), 7.41–7.33 (m, 1H), 7.29–7.23 (m, 2H), 1.98 (s, 1H, OH), 1.15 (s, 18H); δ_C (75 MHz, $CDCl_3$) 145.6, 128.0, 127.6, 127.4, 126.0, 125.8, 83.2, 41.7, 29.8; ν_{max} (film) 3624, 3057, 2961, 2913, 2877, 1483, 1392, 1370, 1053 cm^{-1}. NMR data are in accordance with literature values.[21]

3.11. 1,1,2-Triphenylethan-1-ol (Table 2, entry 2)

δ_H (300 MHz, $CDCl_3$) 6.95–7.45 (m, 13H), 6.95–6.89 (m, 2H), 3.56 (s, 2H), 2.23 (s, 1H, OH); δ_C (75 MHz, $CDCl_3$) 146.7, 135.9, 131.0, 128.2, 127.0, 126.9, 126.3, 78.0, 48.1; ν_{max} (film) 3548, 3086, 3060, 3027, 2956, 2910, 2856, 1492, 1446, 1199 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{18}O$ $[M-H_2O+H]^+$ *m/z* 257.1325, found 257.1325. NMR data are in accordance with literature values.[22]

3.12. 2,2-Dimethyl-5,6-diphenylhexan-3-one (Table 2, entry 3)

Mp 82–84 °C; δ_H (300 MHz, $CDCl_3$) 7.39–6.96 (m, 10H), 3.52 (quint, *J*=7.2 Hz, 1H), 3.02–2.81 (m, 3H), 2.74 (dd, *J*=17.2, 6.3 Hz, 1H), 1.00 (s, 9H); δ_C (75 MHz, $CDCl_3$) 214.4, 144.5, 140.1, 129.3, 128.4, 128.2, 127.8, 126.4, 126.1, 44.2, 42.7, 42.7, 42.6, 26.2; ν_{max} (neat) 3024, 2969, 2919, 1694, 1601, 1494, 1452, 1366, 1073 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}O$ $[M+H]^+$ *m/z* 281.1905, found 281.1905.

3.13. (*E*)-3-Benzyl-4,4-dimethyl-1-phenylpent-1-en-3-ol (Table 2, entry 3)

Mp 103–105 °C; δ_H (300 MHz, $CDCl_3$) 7.41–7.06 (m, 10H), 6.41 (d, *J*=16.0 Hz, 1H), 6.19 (d, *J*=16.0 Hz, 1H), 3.03 (d, *J*=13.1 Hz, 1H), 2.97 (d, *J*=13.0 Hz, 1H), 1.35 (s, 1H, OH), 1.09 (s, 9H); δ_C (75 MHz, $CDCl_3$) 137.5, 137.0, 134.0, 131.1, 129.6, 128.6, 128.2, 127.2, 126.7, 126.42, 79.2, 41.8, 38.4, 25.9; ν_{max} (neat) 3560, 3025, 2966, 2937, 2909, 2872, 1493, 1454, 1393, 1359, 1203, 1105, 1069, 1010 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}O$ $[M+H]^+$ *m/z* 281.1905, found 281.1900.

3.14. 3-Allyl-2,2,4,4-tetramethylpentan-3-ol (Table 2, entries 6–8)

δ_H (300 MHz, $CDCl_3$) 5.93 (ddt, *J*=17.5, 10.2, 7.5 Hz, 1H), 5.18–5.00 (m, 2H), 2.45 (d, *J*=7.5 Hz, 2H), 1.55 (s, 1H, OH), 1.05 (s, 18H); δ_C (75 MHz, $CDCl_3$) 137.4, 118.7, 78.9, 42.4, 38.0, 28.9; ν_{max} (film) 3581, 3076, 2960, 2918, 2878, 1482, 1392, 1370, 1001 cm^{-1}. NMR data are in accordance with literature values.[23]

3.15. 3-Allyl-2,4-dimethylpentan-3-ol (Table 2, entry 6)

δ_H (300 MHz, $CDCl_3$) 5.85 (ddt, *J*=17.5, 10.1, 7.4 Hz, 1H), 5.11–5.00 (m, 2H), 2.28 (dt, *J*=7.4, 1.3 Hz, 2H), 1.89 (sept, *J*=6.9 Hz, 2H), 1.26 (s, 1H, OH), 0.92 (d, *J*=6.9 Hz, 12H); δ_C (75 MHz, $CDCl_3$) 135.2, 117.7, 76.9, 38.4, 34.2, 17.6, 17.4; ν_{max} (film) 3500, 3077, 2964, 2880, 1468, 1385, 991 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{20}O$ $[M-H_2O+H]^+$ *m/z* 139.1481, found 139.1482. ^1H NMR data are in accordance with literature values.[24]

3.16. 1,1-Diphenylbut-3-en-1-ol (Table 2, entry 7)

δ_H (300 MHz, $CDCl_3$) 7.61–7.53 (m, 4H), 7.45–7.28 (m, 6H), 5.78 (ddt, *J*=17.2, 10.1, 7.2 Hz, 1H), 5.40–5.22 (m, 2H), 3.18 (d, *J*=7.2 Hz, 2H), 2.75 (s, 1H, OH); δ_C (75 MHz, $CDCl_3$) 146.5, 133.5, 128.2, 126.9, 126.0, 120.4, 76.9, 46.7; ν_{max} (film) 3554, 3475, 3059, 3025, 2978, 2923, 1493, 1446, 1345, 1166, 990 cm^{-1}. NMR data are in accordance with literature values.[23]

3.17. (*E*)-3-(*tert*-Butyl)-1-phenylhexa-1,5-dien-3-ol (Table 2, entry 8)

δ_H (300 MHz, $CDCl_3$) 7.16–7.46 (m, 5H), 6.58 (d, *J*=16.0 Hz, 1H), 6.35 (d, *J*=16.0 Hz, 1H), 5.89–5.67 (m, 1H), 5.20–5.17 (m, 1H), 5.16–5.12 (m, 1H), 2.66–2.51 (m, 1H), 2.40 (dd, *J*=13.5, 9.3 Hz, 1H), 1.74 (s, 1H, OH), 1.05–1.01 (m, 9H); δ_C (75 MHz, $CDCl_3$) 137.3, 134.6, 133.5, 129.5, 128.7, 127.3, 126.5, 119.7, 78.2, 40.1, 38.1, 25.7; ν_{max}

(film) 3554, 3079, 3060, 3026, 2958, 2873, 975 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O$ $[M-H_2O+H]^+$ m/z 213.1638, found 213.1638. NMR data are in accordance with literature values.[25]

3.18. (4-(*tert*-Butyl)cyclohexa-2,5-dien-1-ylidene)(mesityl) methanol (4)[14]

To mesityl phenyl ketone (222 mg, 0.99 mmol) in dry Et_2O (10 mL) was added *tert*-butylmagensium chloride (1.0 mL of 1.25 M solution in Et_2O, 1.25 mmol) under an argon atmosphere. The light brown suspension was stirred at room temperature for 30 min. The mixture was quenched with an ice-cold solution of saturated aqueous NH_4Cl. The organic layer was removed with an air-tight syringe and washed inside the syringe with H_2O. The organic phase was transferred to a pear-shaped flask under argon followed by removal of the solvent by a flow of argon. The remaining colorless oil was dissolved in $CDCl_3$ and added to an NMR tube inside an argon-filled Schlenk flask. δ_H (400 MHz, $CDCl_3$) 6.90 (s, 2H), 6.83 (dt, J=10.3, 1.7 Hz, 1H), 5.86 (ddd, J=10.3, 4.4, 1.9 Hz, 1H), 5.64 (dt, J=10.3, 1.6 Hz, 1H), 5.54 (ddd, J=10.3, 4.2, 1.9 Hz, 1H), 4.01 (s, 1H), 2.80 (tt, J=4.3, 1.5 Hz, 1H), 2.21 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 0.84 (s, 9H); δ_C (100 MHz, $CDCl_3$) 144.4, 138.6, 137.8, 137.5, 132.7, 128.5, 128.4, 127.0, 125.4, 125.2, 122.0, 110.9, 48.9, 35.9, 27.4, 21.3, 19.62, 19.60.

3.19. 2,2,6,6-Tetramethyl-5-phenylheptan-3-one (5)

Following the general procedure for *tert*-butyl exchange, mesityl phenyl ketone and *tert*-butylmagnesium chloride were reacted at 0 °C for 1 h. After workup ketone **5** was purified by column chromatography (1:50 ethyl acetate/pentane) and recrystallization from toluene/methanol. Mp 99–100 °C, lit.[26] 100–101 °C; δ_H (300 MHz, $CDCl_3$) 7.25–7.10 (m, 5H), 3.09–3.15 (m, 2H), 2.71 (dt, J=10.8, 8.9, 8.9 Hz, 1H), 1.01 (s, 9H), 0.88 (s, 9H); δ_C (75 MHz, $CDCl_3$) 214.5, 143.0, 129.4, 127.6, 126.1, 50.4, 44.4, 37.9, 33.7, 28.4, 26.5; MS m/z 246 $[M^+]$; ν_{max} (neat) 2959, 2915, 2867, 1699, 1472, 1365, 1342 cm^{-1}. ^{13}C NMR data are in accordance with literature values.[27]

3.20. 4-Benzyl-2,2,8,8-tetramethyl-5-phenylnonane-3,7-dione (6)

Following the general procedure for *tert*-butyl exchange, mesityl phenyl ketone and *tert*-butylmagnesium chloride were reacted at 60 °C for 1 h. After workup diketone **6** was obtained as a 3:1 diastereomeric mixture, which were separated and purified by column chromatography (1:50 ethyl acetate/pentane and then 1:1 toluene/heptane) and recrystallization from heptane. For major diastereomer: Mp 94–95 °C; δ_H (300 MHz, $CDCl_3$) 7.07–7.35 (m, 8H), 6.90–6.93 (m, 2H), 3.76 (dt, J=6.7, 4.5 Hz, 1H), 3.44 (ddd, J=11.1, 4.5, 3.3 Hz, 1H), 3.11 (d, J=6.7 Hz, 2H), 2.94 (dd, J=12.6, 11.1 Hz, 1H), 2.71 (dd, J=12.6, 3.3 Hz, 1H), 1.10 (s, 9H), 0.74 (s, 9H); δ_C (75 MHz, $CDCl_3$) 217.2, 213.7, 143.5, 140.0, 129.4, 128.6, 128.3, 128.1, 126.8, 126.3, 54.0, 44.7, 44.2, 41.1, 35.9, 34.0, 26.6, 26.0; ν_{max} (neat) 3062, 3027, 2968, 1707, 1682, 1476, 1454, 1364 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{34}O_2$ $[M+Na]^+$ m/z 401.2451, found 401.2452; HRMS (ESI) calcd for $C_{26}H_{34}O_2$ $[M+H]^+$ m/z 379.2632, found 379.2633.

For minor diastereomer: δ_H (300 MHz, $CDCl_3$) 7.25–7.02 (m, 8H), 6.97–6.84 (m, 2H), 3.56 (ddd, J=9.1, 7.4, 5.1 Hz, 1H), 3.49–3.37 (ddd, J=10.0, 6.7, 3.4 Hz, 1H), 3.10 (dd, J=17.2, 10.0 Hz, 1H), 2.77–2.46 (m, 3H), 0.92 (s, 9H), 0.68 (s, 9H); δ_C (75 MHz, $CDCl_3$) 219.0, 213.2, 142.4, 139.6, 129.3, 128.5, 128.4, 128.4, 126.8, 126.5, 52.9, 44.8, 44.2, 43.4, 39.8, 38.2, 26.3, 26.2.

Supplementary data

^1H and ^{13}C NMR spectra of all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.070.

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