Concerted and stepwise Grignard additions, probed with a chiral Grignard reagent

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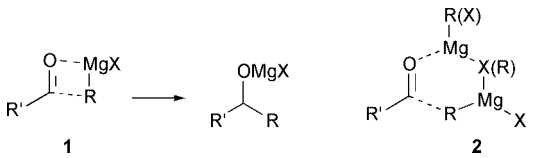
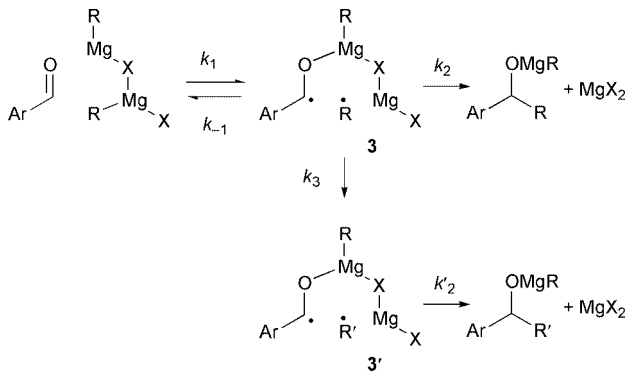
The Grignard reagent 6, in which the magnesium-bearing carbon atom is the sole stereogenic centre has been added to CO_2, PhNCO, PhNCS and certain aldehydes with full retention of configuration. Reaction with benzophenone, electron-deficient aldehydes and several allyl halides proceeded with partial or complete racemization. The findings are discussed with respect to a dichotomy between concerted polar and stepwise SET reaction pathways.

Grignard reagents are among the oldest organometallic reagents known.[1] Their chemistry has evolved as the prototype of polar organometallic compounds. Yet, despite the enormous body of polar addition reactions recorded,[2] the mechanism of these additions cannot be considered as settled.[3] Most textbooks describe the addition of Grignard reagents to aldehydes—being representative of carbonyl compounds—as a simple addition, *cf.* **1**. Evidence has however been provided[4] that it is a Grignard dimer (halogen-bridged or alkyl-bridged) that enters into the reaction with the carbonyl group, *cf.* **2**.



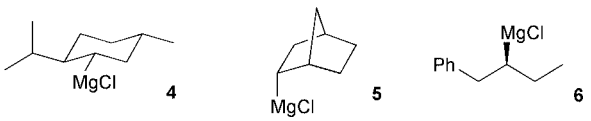
1 **2**

But still, this says little about the nature of the C–C bond forming step. At least in some cases it has been shown that electron transfer precedes the C–C bond formation, especially in addition reactions to carbonyl compounds with a low reduction potential, such as benzophenone.[5,6] While it is tempting to formulate[5,7,8] all polar additions as being initiated by an electron-transfer step, there is at the moment no meaningful way to address the question to what extent electron motion precedes nuclear motion in the formation of the new C–C bond. Rather we have to be content with the heuristic approach that a two-step process can be considered as established, if it is possible to prove the existence of an intermediate (likely the radical R· or radical pair **3**).[9]



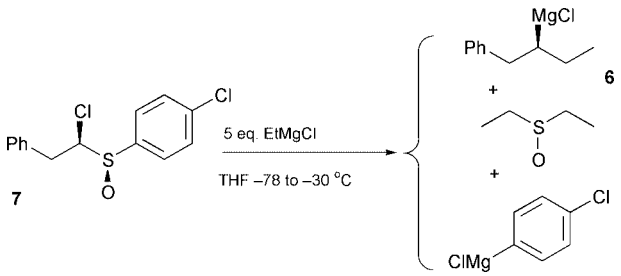
3 **3′**

This is usually done by diverting the radical R· to give another radical R′·, a process that becomes manifest if the rate of conversion (k_3) of R· into R′· is similar to or larger than the rate of collapse (k_2) of the postulated radical pair **3**. Radical rearrangements of known k_3 (radical clocks) have been studied in this context.[5] It is clear, that an ultrafast radical reorganization reaction would enlarge the scope of this approach.[10] This would hold *e.g.* for the conversion of a chiral carbon radical R· to its enantiomer R′·. The barrier to the inversion of the *tert*-butyl radical has been experimentally bracketed to be < 0.5 kcal mol^{-1}.[11] For most practical purposes alkyl radicals can be considered as being planar, that is prochiral. Therefore, the stereochemical probes such as **4**[12,13] and **5**[14] have been used to probe the mechanism of Grignard additions.[15,16]



4 **5** **6**

Yet in the case of **4** and **5** it is a moot point, to what extent the stereochemical outcome is influenced by the presence of the additional stereogenic centres (only one case of epimerisation[13] has been so far observed). The ideal probe would be a Grignard reagent such as **6**, in which the magnesium-bearing carbon atom is the sole stereogenic centre. We have recently described an access to such a species of *ca.* 90% ee by asymmetric synthesis.[17] We report here on the use of this reagent as a mechanistic probe in Grignard additions to carbonyl compounds and in Grignard-substitution reactions.



7

The reagent **6** is generated in *ca.* 90% ee from the enantiomerically and diastereomerically pure sulfoxide **7**.[17] Due to the mode of generation, the solution of **6** contains *ca.* 2 equiv. of EtMgCl, one equiv. of *p*-Cl-C_6H_4-MgCl and one equiv. of diethyl sulfoxide. The reagent **6** is configurationally stable in this cocktail in THF solution up to −30 °C; racemization proceeds with $t_{1/2}$ = 5 h at −10 °C.

Therefore those polar additions can be investigated that proceed readily at −30 °C or below. This holds *e.g.* for the addition of **6** to CO_2, PhNCO, or PhNCS which provides the adducts **8**, **9**, and **10**. The same level of enantiomeric purity of these adducts suggests that the value of 90 ± 2% ee represents the enantiomeric purity of **6** and that the addition proceeds without racemization (Table 1).

The absolute configuration of compounds **8**[18] and **10**[17] is known, that of **9** has been established by chemical correlation

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Table 1 Trapping of the Grignard reagent **6** (*ca.* 90% ee) with various electrophiles

Electrophile	Product(s)	Configuration[a]	Yield (%)	ee (%)
CO_2	HOOC-CH(Et)Bn **8**	*S*	80	92
PhNCO	PhNHCO-CH(Et)Bn **9**	*S*	60	89
PhNCS	PhNHCS-CH(Et)Bn **10**	*S*	56	91
ArCHO[b]	ArCHOH-CH(Et)Bn	n.d.	41	D1: 89 D2: 84
PhCHO	PhCHOH-CH(Et)Bn	*S*	42	D1: 88 D2: 84
C_6F_5CHO **11**	C_6F_5CHOH-CH(Et)Bn	n.d.	45	D1: 43 D2: 47
Ph_2CO **12**	Ph_2COH-CH(Et)Bn	—	85	12

[a] At the former Grignard C-atom. [b] Ar = *p*-MeO-C_6H_4—. n.d.: not determined.

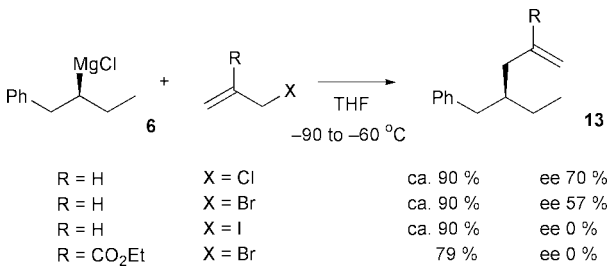
with compound **8**. This establishes that the addition reactions proceeded with retention of configuration. This is in line with the finding for the carboxylation of **5**.[14] As the addition of formaldehyde to **5** proceeded as well without epimerisation,[15] we looked at the addition of **6** to aromatic aldehydes, where the intervention of electron transfer steps is more likely. Addition of **6** to aldehydes generates two diastereomeric adducts (D1; D2), which were derivatized with Mosher's reagent and analysed by ^{1}H-NMR spectroscopy. Both for addition to benzaldehyde and *p*-methoxybenzaldehyde the formation of the major diastereomer proceeded without loss in enantiomeric purity. There is a slight decrease in enantiomeric purity of the minor diastereomer, a fact of uncertain significance. Addition to the more electron deficient pentafluorobenzaldehyde clearly led to partially racemized adducts. On addition to benzophenone, which has a reduction potential that is by +0.20 V more positive than that of benzaldehyde,[19] racemization is extensive but not complete.

The partial racemization observed in the addition to **11** and **12** can be interpreted in terms of a competition between a concerted polar addition and a SET initiated process. This would imply that even benzophenone undergoes a polar addition to the extent of 12%. One could also argue that all of these reactions proceed by SET[5,8] and that rotation of R· within the radical pair **3** is only in few instances faster than the collapse of the radical pair.

We then turned our attention to the reaction of Grignard reagent **6** with allylic halides, which proceeds in high yield even at −90 °C and therefore intuitively suggests an SET process.

While allylation with allyl iodide led indeed to racemic product **13** (R = H) we were surprised to find sizeable enantiomeric enrichment when allyl bromide or allyl chloride were allowed to react with **6**. We tend to interprete this as being caused by a competition between a polar S_N2-reaction and an SET process. This is in line with the ordering of the reduction potentials recorded for allyl chloride, bromide and iodide (−1.91; −1.29; −0.23 V *vs.* Hg).[20] The SET process should be faster with ethyl α-bromomethylacrylate and indeed, this gave rise to 79% of racemic product, **13** (R = COOEt).

Thus, with the chiral Grignard reagent **6** it was possible to probe the mechanism of Grignard addition to carbonyl compounds and Grignard substitution reactions with respect to the competition between polar concerted and stepwise SET pathways.



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