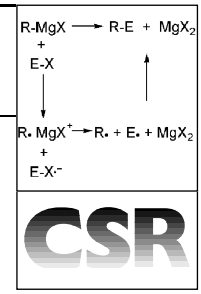
The quest for chiral Grignard reagents



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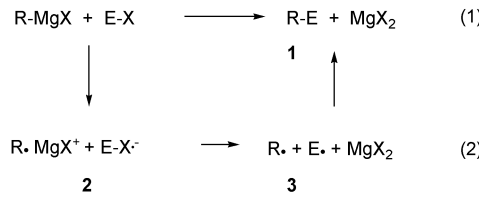
The involvement of single electron transfer, *i.e.* of free radicals in the reactions of organomagnesium reagents could be detected with the aid of a chiral secondary Grignard reagent, in which the magnesium-bearing carbon atom is the sole stereogenic centre. So far, however, such reagents have not been accessible, because the standard preparation of Grignard reagents proceeds *via* free radicals. We review and summarize here our efforts to generate such a Grignard reagent 36 by asymmetric synthesis starting from an enantiomerically pure α-chloroalkyl-sulfoxide 30b using a sulfoxide/magnesium exchange reaction to give 33 followed by a carbenoid homologation reaction. Grignard reagent 36 turned out to be an ideal probe to learn about the extent to which SET is involved in reactions of organomagnesium reagents.

1 Introduction

—To be more precise, the objective of the present study is to generate chiral Grignard reagents, in which the magnesium-bearing carbon atom is the sole stereogenic centre. Why would one be interested in those? Of course, there is the omnipresent interest in chiral building blocks for stereoselective synthesis. But the specific reason to be interested in chiral Grignard reagents has to do with the mechanisms of the reactions of organomagnesium reagents.[1] To probe these, such chiral Grignard reagents would be the perfect tool. Grignard reagents react with electrophiles forming carbon–carbon- or carbon–heteroatom bonds. These reactions are usually pictured as (concerted) polar addition processes. Yet over and over there have been indications that free radicals may be involved in (certain of) these reactions.[2] This has to do with the fact that Grignard reagents are hard nucleophiles with a high negative charge density on carbon, compounds which due to the high lying HOMO are readily subject to one-electron oxidation. In turn, electrophiles have a low lying LUMO. They have a tendency to undergo one-electron reduction. It is therefore quite likely that in addition reactions of organomagnesium reagents electron-motion (single electron transfer SET) precedes nuclear motion. Thus, addition of organomagnesium reagents may either follow a polar pathway (equation (1)) or a SET route (equation (2) in Scheme 1), involving radical pairs **2** and **3**.

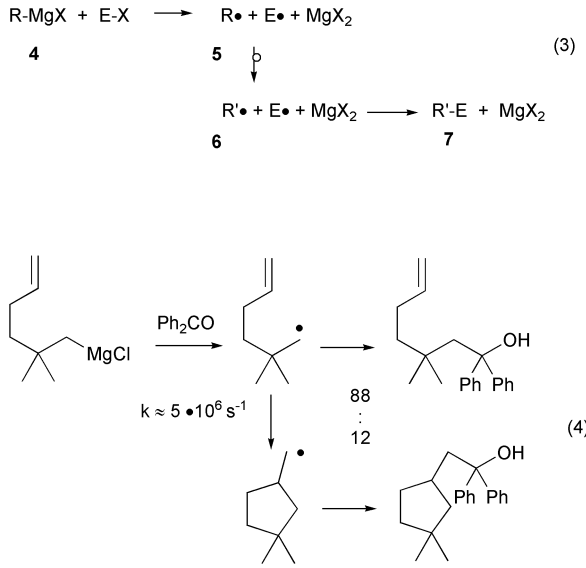


Scheme 1

A distinction between these two mechanistic alternatives has—among other methods[3]—been sought by probing the absence or presence of free radicals[4] as precursors of the products **1** obtained. One way the problem has been addressed is by using a Grignard reagent **4** which is constitutionally stable, but that would give rise on one electron oxidation to a radical **5**, which rearranges to a different radical **6**. The latter would eventually lead to a different product **7** in a diagnostic manner, *cf*. equation (3) in Scheme 2. An example[5] is given in equation (4).

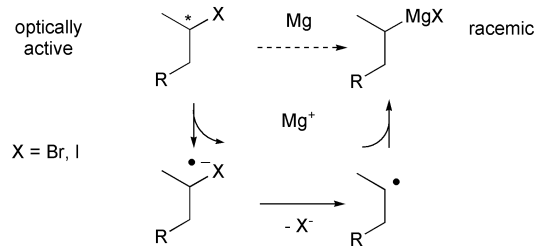
Of course, the rearrangement of R· to R′· has to be more rapid than the combination of R· with E· in the radical pair **5**, in order to be diagnostic. Hence, the formation of a rearranged product R′–E permits clear conclusions, whereas the absence of a product R′–E does not prove the absence of a reaction pathway *via* SET, because recombination of the radical pair **5** may just be faster than the rearrangement R· → R′·. The rates for many radical rearrangements have been determined precisely (radical clocks) to be in the order of 10^1 to 10^{11} s^{-1}.[6] For the purpose of probing the mechanism of Grignard reactions an ultra-fast radical rearrangement would be optimal. Such an ultra-fast "rearrangement" would be the racemisation of a sec-alkyl radical, which has been estimated to have an activation barrier lower than 0.5 kcal mol^{-1}.[7] Therefore sec-alkyl radicals can be considered as being effectively planar, and the rate limiting process in the loss of optical activity in such a process may well be the reorientation of the radical R· with respect to E· in the radical pair **3**.

Professor Hoffmann studied chemistry from 1951 to 1958 at the University of Bonn, finishing with a doctorate under the guidance of Professor B. Helferich. Two years of postdoctoral studies at the Pennsylvania State University were followed by a second postdoctorate with Professor G. Wittig at the University of Heidelberg. Subsequent independent research led to the habilitation of Professor Hoffmann at Heidelberg in 1964. Three years later he was appointed as Dozent at the Technische Hochschule Darmstadt. Since 1970 he has been professor of organic chemistry at the Universität Marburg (emeritus status since 2001). Professor Hoffmann had the pleasure of being visiting professor at the University of Wisconsin, the Universität Bern, the University of California at Berkeley, and Kyoto University



Scheme 2

It thus becomes clear that chiral Grignard reagents, in which the magnesium-bearing carbon atom is the stereogenic centre would be ideal tools to probe the involvement of SET in addition reactions of organomagnesium reagents. The more, since it is known that secondary Grignard reagents are configurationally stable at least up to 0 °C.[8–10] This being so, why have chiral secondary Grignard reagents not been extensively used for this purpose? The reason is that there is hitherto no reliable route to such chiral Grignard reagents. Because the standard route to Grignard reagents is one that proceeds *via* alkyl radicals and, hence, furnishes racemic Grignard reagents even when starting from enantiomerically pure precursor molecules (Scheme 3).[11]

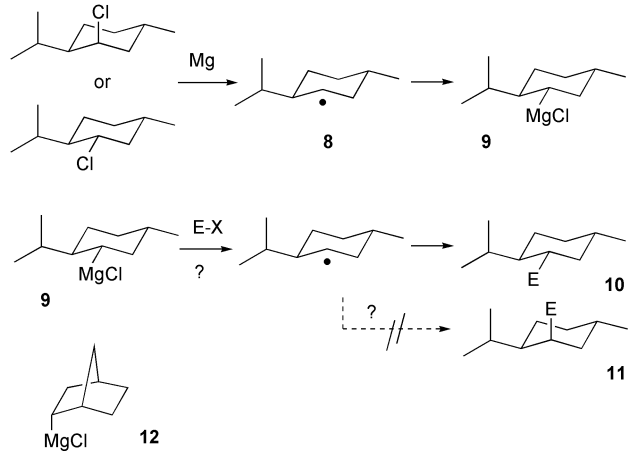


Scheme 3

Recourse was then made to chiral compounds, in which additional stereogenic centres control the stereochemistry of the formation of the carbon–magnesium bond. This way the configurationally defined Grignard reagents **9**[12] and **12**[8] have been generated and used as mechanistic probes for the involvement of SET in reactions of organomagnesium reagents (Scheme 4).[8,10,13] But the stereochemical bias that led to the formation of the carbon–magnesium bond with a distinct configuration during the formation of the Grignard reagent **9** from the radical **8** may also prevail in the combination of the radical pair **3** to give a product **10** of uniform configuration (memory of chirality[14]), concealing the involvement of radicals in this process.

Of course, if significant amounts of a rearranged product **11** are obtained, as for instance in a reaction of **9** with triphenyl-tin chloride,[15] this is a strong indication of involvement of a SET-process and of radicals in this reaction.

This argumentation assumes that a polar (concerted) addition of an organomagnesium reagent proceeds with retention of configuration and that a simultaneous occurrence of a polar addition reaction by a retentive and an inversive pathway[16] is highly unlikely, though not excluded.



Scheme 4

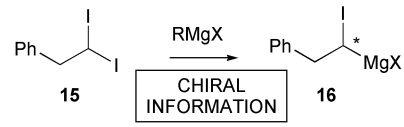
It is clear that most of these ambiguities would be avoided, when chiral Grignard reagents were available, in which the magnesium-bearing carbon atom is the sole stereogenic centre.

2 A route to chiral Grignard reagents by asymmetric synthesis

Any route to enantiomerically enriched chiral secondary Grignard reagents must exclude reactions that proceed *via* radicals. We envisioned the generation of chiral secondary Grignard reagents by asymmetric synthesis using a carbenoid homologation reaction of an α-halo-alkyl Grignard-reagent **13**.[17]

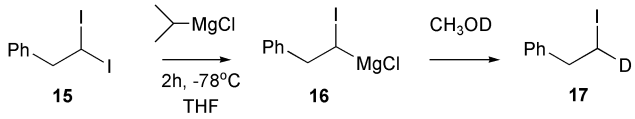
Scheme 5

Several points have to be clarified, though, before this plan could meet with success. Is a Grignard-reagent **13** configurationally stable under the conditions of its generation and reaction towards **14**? Does the carbenoid homologation reaction proceed with α-halo-alkyl Grignard reagents at all, under mild conditions, and in a stereochemically uniform manner? And most important of all, can α-halo-alkyl Grignard reagents **13** be generated in enantiomerically pure form in a reaction not involving free radicals? For this purpose we projected a halogen/magnesium exchange reaction as a process which not necessarily involves free radicals,[18] a fact that would have to proven in the particular example studied. The most direct, but also most challenging route would be an enantioselective exchange of one of the enantiotopic iodine atoms in a 1,1-diiodo alkane such as **15** (Scheme 6).



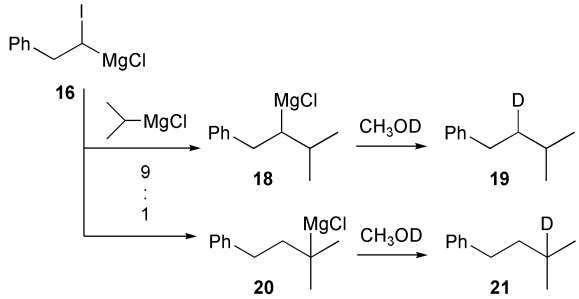
Scheme 6

We therefore started to look into the iodine/magnesium exchange reaction of geminal diiodo alkanes. Reaction of **15** with 1.2 equivalents of isopropylmagnesium halide for 3 h at −78 °C generated the desired α-iodoalkyl Grignard reagent **16** in good yield as evidenced by quenching with CH_3OD to give the deuterated product **17** (Scheme 7).[19]



Scheme 7

^{13}C-NMR data of **16**, especially the chemical shift of the magnesium-bearing carbon atom indicated[20] a substantial carbenoid character (= downfield shift) according to the criterion of Seebach.[21] In line with this finding the carbenoid homologation of **16** to give a secondary Grignard reagent could be effected smoothly by treatment of **16** with an excess (2-fold) of isopropylmagnesium halide at −20 °C for 2 h. This furnished the homologated Grignard reagent **18** as evidenced by quenching with CH_3OD to give **19** (Scheme 8).



Scheme 8

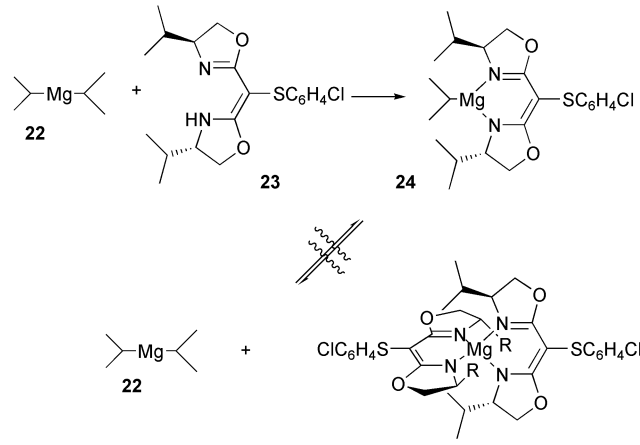
Deuterium-NMR indicated the formation of 10% of an isotopomeric product **21** derived from a tertiary Grignard reagent **20**. A detailed investigation[22] showed that this tertiary Grignard reagent is derived from an intra-aggregate carbenoid C–H-insertion reaction from **16**, a reaction that becomes the main pathway in non-polar solvents. In the present context it is only important that this (undesired) reaction can be suppressed almost completely by carrying out the carbenoid homologation reaction in THF with *ethyl*-magnesium chloride, in which the C–H-bond α to the carbon–magnesium bond is somewhat stronger than that in *isopropyl*-magnesium chloride.

Based on these preliminary results the route to a chiral Grignard reagent **18** appeared to be open, provided that enantioenriched **16** can be generated and is sufficiently configurationally stable. We therefore started to look into an enantioselective exchange of the enantiotopic iodine atoms in **15**. This required an isopropyl- or ethylmagnesium halide reagent, which is loaded with chiral information. We chose the Grignard reagent **24**, in which the chiral information resides in the anionic part, being tied to the magnesium cation by Coulombic attraction. The generation of **24** free of **22** was a project in itself, but could eventually be attained with proper choice (acidity) of the ligand system **23**.[23] The problem was to avoid a Schlenk equilibrium between **24** and the achiral but highly reactive diisopropylmagnesium **22** (Scheme 9).

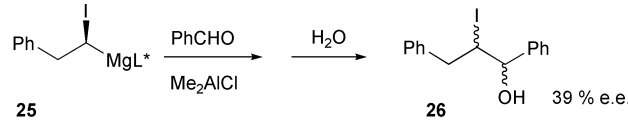
Once we knew how to generate reagent **24**, the iodine magnesium exchange on **15** could be carried out successfully. Trapping of the resulting α-iodoalkyl Grignard reagent **25** with benzaldehyde (activated by dimethylaluminium chloride) gave the iodohydrin **26** in over 90% yield (Scheme 10).

Unfortunately the enantiomeric enrichment in **26** and therefore the diastereomeric enrichment in **25** could not be coaxed to surpass 39% e.e. despite considerable efforts. We clearly did not meet the demands of the project.

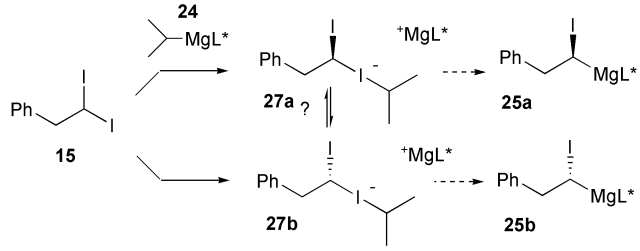
This lack of success has to be seen *vis a vis* a mechanistic uncertainty, regarding the stereochemistry determining step in the iodine/magnesium exchange reaction on **15**. This reaction—as probably all halogen/metal exchange reactions[24]—proceeds *via* iodine ate-complexes **27** as intermediates. If the formation of the ate-complexes is irreversible, this step determines the



Scheme 9



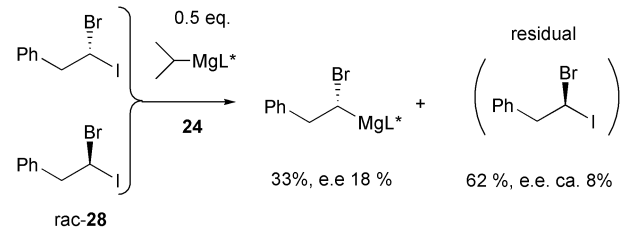
Scheme 10



Scheme 11

enantiomeric purity of the product, and a low asymmetric induction would not be surprising, given the fact, that the incipient stereogenic centre in **27** and the chiral information on the Grignard reagent **24** are in the transition state (not shown) of ate-complex formation on opposite sides of an iodine atom, which effectively shields the transmission of chiral information by it sheer size.

If, however, the diastereomeric ate-complexes **27a** and **27b** were rapidly to equilibrate,[25] dynamic kinetic resolution[26] of the ate-complexes **27** by the chiral cation in the second step, *i.e.* the formation of the α-iodoalkyl Grignard reagents **25a** and **25b** could be expected to be high, as now the magnesium cation with its chiral entourage directly attacks[27] at the new stereogenic centre (Scheme 12).



Scheme 12

As a corollary experiment we looked therefore at a kinetic resolution of the racemic bromo-iodo-alkane **28** by a deficiency of the chiral Grignard-reagent **24** (Scheme 13). This met,

Scheme 13

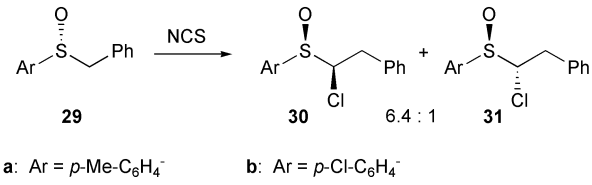
however, again with minimal enantiomeric enrichment in the residual bromo-iodo-alkane. Therefore, it may well be that the first step in the iodine/magnesium exchange on **15** or **28** might be irreversible and, hence, defining the level of asymmetric induction.

In consequence, neither attempt at enantiotopos-selective or enantiomer-selective iodine/magnesium exchange reaction on 1,1-dihalo-alkanes with the reagent **24** provided an α-haloalkyl Grignard reagent **16** of enantiomer enrichment sufficient for this project.

3 Chiral Grignard reagents *via* sulfoxide/magnesium exchange

In order to generate an α-haloalkyl Grignard reagent **16** of high enantiomeric purity, we then looked for a reaction that would be based on a chiral precursor molecule. This led our attention to the sulfoxide/magnesium exchange, a reaction that has been widely applied to the synthesis of enantiomerically pure sulfoxides, but found so far less attention as a method to generate Grignard reagents.[28–30]

The starting material needed for our purpose is an α-haloalkyl-aryl-sulfoxide **30** of high diastereomeric and enantiomeric purity. It could be obtained from the enantiomerically pure sulfoxide **29** by chlorination with *N*-chloro-succinimide,[31] a method that proceeds with complete configurational inversion on sulfur. This reaction provided a mixture of diastereomeric α-chloroalkyl-sulfoxides **30** and **31**, from which the major diastereomer could be obtained pure by crystallisation (Scheme 14). In this respect the use of *p*-chlorophenyl-sulfoxides was advantageous.

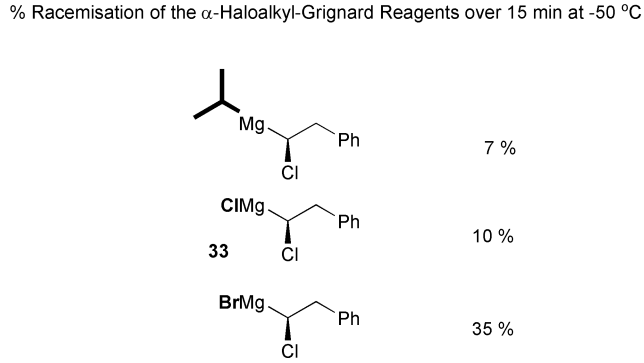


Scheme 14

The sulfoxide/magnesium exchange on **30a** could be effected by treatment with ethyl-magnesium-chloride for 2 h at −78 °C. When the Grignard reagent **33** generated in this manner was quenched with benzaldehyde activated by dimethylaluminium-chloride a chlorohydrin **35** resulted in 70% yield (Scheme 15). The latter was converted to the epoxide **34** in order to determine the enantiomeric purity and to established the absolute configuration by comparison of the sign of the optical rotation with literature data. The epoxide **34** was found to be of 93% e.e.. A corresponding result was obtained when starting from the *p*-chlorophenyl-sulfoxide **30b**.

Thus, the sulfoxide/magnesium exchange proceeded with retention of configuration at carbon to give the Grignard reagent **33** (and with well precedented[32] inversion of configuration at sulfur to give the sulfoxide **32**).

Next, we tested the configurational stability of the Grignard reagent **33** under the reaction conditions. We arbitrarily chose a period of 15 min at −50 °C and found that some racemisation can be observed at this temperature and that the tendency towards racemisation depended on the counter ion of the Grignard reagent (Scheme 16).[33]

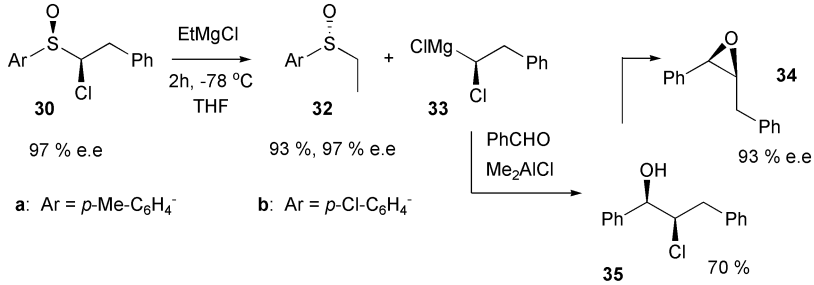


Scheme 16

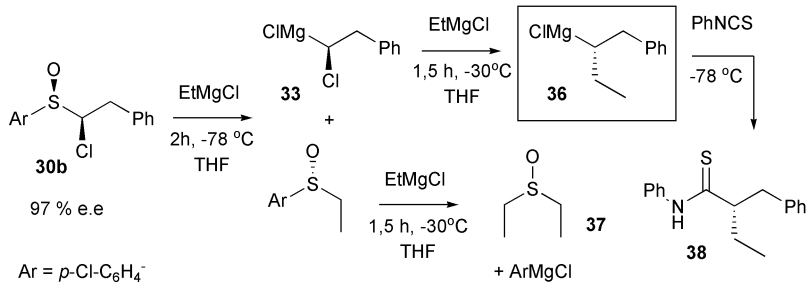
This suggested that the major pathway of racemisation is an S_N2 attack of a halide anion on the α-chloroalkyl Grignard reagent **33**.[28,34] This (slow) racemisation constitutes a limiting factor, which we have to take into account, when carrying out the carbenoid homologation reaction to **36**.

The latter reaction can best be effected by treating the sulfoxide **30b** with 5 equivalents of ethyl-magnesium-chloride at −78 °C followed by briefly warming the solution to −30 °C before it is quenched with an electrophile, such as phenyl-isothiocyanate (Scheme 17).

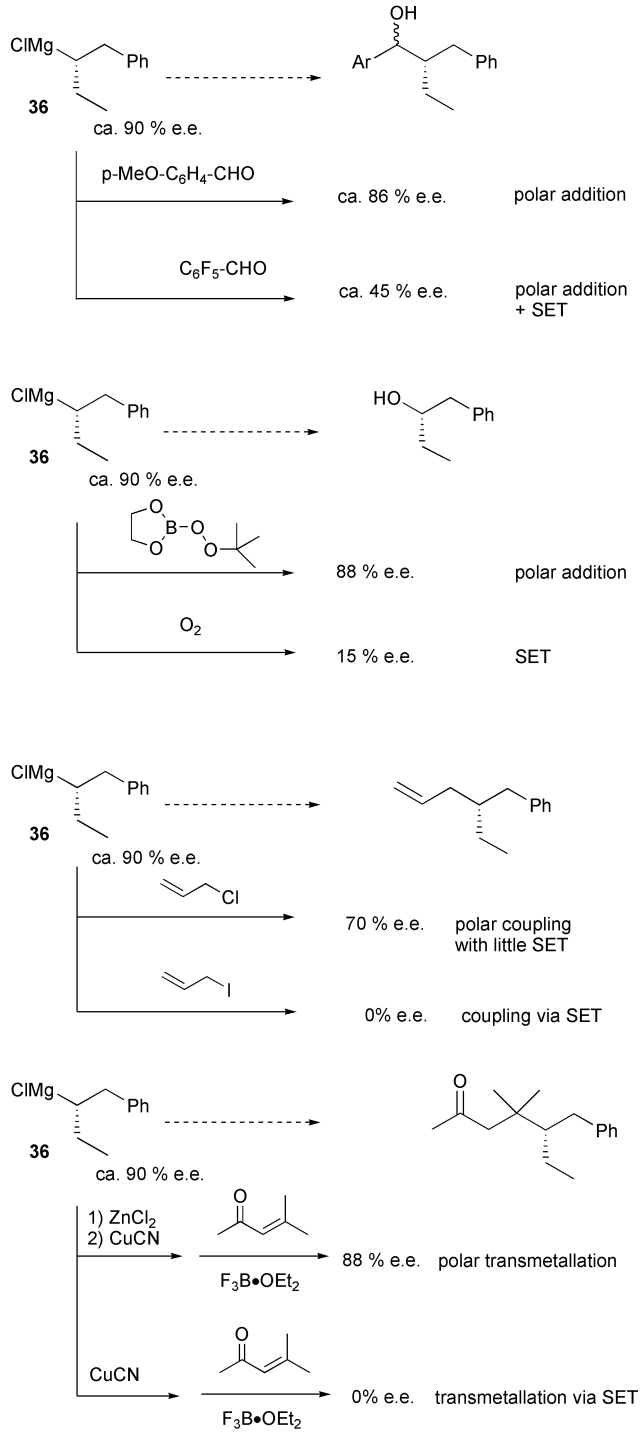
This procedure furnished 56% of the thioamide **38** of 91% e.e..[35] Clearly the desired carbenoid homologation reaction of **33** to **36** had occurred. The absolute configuration of **38** could by determined by X-ray crystallography. Knowing the absolute configuration of the starting sulfoxide **30b** and of the α-chloroalkyl Grignard reagent **33** this indicates the carbenoid homologation to proceed with ≥90% inversion of configuration. The slight loss in enantiomeric purity could be due to a limited configurational stability of **36**, but should probably be ascribed to a competing racemisation of **33** (see above). This is suggested by the finding, that a higher excess of ethyl-magnesium-chloride leads to product of higher e.e.: To speed up the carbenoid homologation reaction relative to the racemisation of **33** we applied ten equivalents of ethyl-magnesium-chloride (actually only three equivalents are needed to convert **30b** into the Grignard reagent **36** and the sulfoxide **37**[30]). This led to the thioamide **38** of 93% e.e., whereas use of only 3 equivalents of ethyl-magnesium-chloride gave **38** of merely 75% e.e.



Scheme 15



Scheme 17



Scheme 18

Any application of the secondary Grignard reagent as a mechanistic probe to study the involvement of SET in addition reactions of organomagnesium reagents requires concise information on the configurational stability of **36**. Since **36** is generated from the sulfoxide **30b** in the above reaction cascade not as a "pure" reagent, but rather as one component in a cocktail of Grignard reagents and sulfoxides (*cf.* Scheme 17) we tested the configurational stability of **36** under just these conditions. Warming the "solution" of **36** for 2 h to −10 °C followed by trapping at −78 °C furnished the thioamide **38** of 79% e.e.. Several experiments of this kind showed that **36** is racemising in this cocktail at −10 °C in a first order process with a half-life of approximately 5 h.[35]

4 Summary and outlook

In consequence, the Grignard reagent **36** can safely be applied as a probe for SET processes if the reaction studied can be carried out in < 5 h at < -30 °C. These conditions can indeed be met by many Grignard reactions. Hence, the reagent **36** put us into a position to map out the extent of SET occurring in oxygenation,[35] amination,[36] allylation[37] and transmetalation of Grignard reagents.[38] (*cf.* Scheme 18)

These expected and unexpected insights regarding the mechanisms of Grignard reactions became possible only after we succeeded in the first asymmetric synthesis of a Grignard reagent[39] (**36**), in which the magnesium-bearing carbon atom is the sole stereogenic centre.

5 Acknowledgements

The results presented in this study are documented in detail in the doctoral theses of V. Schulze (1997), P. Nell (1999), O. Knopff (2000) and B. Hölzer (2001) at the Philipps-Universität Marburg. We thank the Deutsche Forschungsgemeinschaft for generous support (Sonderforschungsbereich 260 and Graduierten-Kolleg, Metallorganische Chemie) of this study.

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