EDGE ARTICLE
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General stereoretentive preparation of chiral secondary mixed alkylmagnesium reagents and their use for enantioselective electrophilic aminations
Introduction

Organomagnesium reagents are key intermediates in organic synthesis, which have found numerous applications.¹ Nevertheless, a general and practical enantioselective preparation of secondary alkylmagnesium reagents is still pending. To date, only one example of a non-heteroatom-stabilized α-chiral Grignard reagent has been reported, which was prepared via a sulfoxide-magnesium exchange.² Furthermore, deracemization of a mixture of endo- and exo-norbormynagnesium bromide using benzophenone³ or exploiting the different reactivities of menthylmagnesium chloride epimers⁴ have been reported. Recently, we have shown that various enantiomerically enriched secondary alkyl iodides of type 1 underwent an I/Li-exchange⁵ at −100 °C in pentane:ether mixtures furnishing the corresponding chiral alkylolithiums of type 2 with retention of configuration (Scheme 1a).⁶ After transmetalations with appropriate ether soluble Cu and Zn salts at −100 °C, chiral organometallics of type 3 were obtained, which reacted with various electrophiles providing products of type 4 with high retention of configuration.⁷ Although chiral building blocks and natural products were available by these procedures,⁸ such reaction sequences required very low temperatures (−100 °C) due to the occurrence of configurationally labile alkylolithium reagents (2), which epimerized readily at temperatures above −100 °C (ref. 6b) and tolerated no sensitive functional groups. Thus, Barbier-conditions involving the generation of the organometallic species in the presence of an electrophile or transmetalation reagent might circumvent the configurational lability and high reactivity of these secondary alkylolithiums.⁹ Recently, we have shown that Barbier conditions were broadly applicable for the directed lithiation of (hetero)aromatics with...
TMPLi (TMP = 2,2,6,6-tetramethylpiperidil) in the presence of various salts.

With these previous reports in mind, we have envisioned Barbier conditions, that would overcome the use of unpractical very low temperatures for the preparation of chiral secondary alkylmagnesium reagents (5) by generating the chiral secondary alkylolithium in the presence of an appropriate magnesium transmetalation reagent.

Herein, we report a general and practical preparation of non-stabilized enantiomerically enriched mixed alkylmagnesium reagents of type 5 from optically enriched secondary alkyl iodoines in the presence of commercially available Me₃SiCH₂MgCl using t-BuLi at convenient temperatures of up to −50 °C (Scheme 1b). These enantiomerically enriched Grignard reagents (5) reacted with a range of eletrophiles including ketones, aldehydes, acid chlorides, isocyanates, S-methyl methanethiosulfonate, chlorophosphines and O-benzoyl hydroxylamines providing products of type 4 such as z-chiral tertiary alkylmagnesium reagents, ketones, amides, thioethers, phosphines and tertiary amines in up to 89% yield (over 3 reaction steps) with high retention of configuration (up to 99% ee).

Results and discussion

Thus, in preliminary experiments, we have mixed the chiral secondary alkyl iodide [R]-1a with Me₃SiCH₂MgCl and have subsequently added t-BuLi (2.2 equiv.) at various temperatures (see Table 1). The resulting secondary alkylmagnesium species ([R]-5a) was quenched with dicyclopropyl ketone (6a) and stirred at −20 °C for 30 min. The desired tertiary alcohol ([R]-4a) was obtained in 80% yield and 91% ee at a reaction temperature of −100 °C (entry 1). To our delight, the same enantioselectivity was achieved by performing the 1/Li-exchange at −78 °C (entry 2). As expected, if the reaction was performed at −78 °C without Me₃SiCH₂MgCl, ([R]-4a) was obtained in comparable yield (78%) but only with 12% ee (entry 3). A slight erosion of enantioselectivity was observed if the reaction was carried out at −60 °C (73% yield; 90% ee, entry 4). However, higher temperatures led to a significant loss of enantiomeric purity as a reaction at −40 °C afforded ([R]-4a) in 71% yield and 82% ee (entry 5).

Further raising the reaction temperature and performing the exchange at −20 °C gave ([R]-4a) in 59% yield with 52% ee (entry 6). Interestingly, using 2.0 equiv. of Me₃SiCH₂MgCl considerably reduced the racemization rate at −20 °C, since the tertiary alcohol ([R]-4a) was obtained in 78% ee and 52% yield (entry 7). Lowering the reaction temperature to −40 °C again and using 2.0 equiv. of Me₃SiCH₂MgCl did not give any improved result (67% yield, 84% ee, entry 8). Alternative transmetalating reagents may also be used for this reaction, however with less satisfactory results. Next, we have examined the configurational stability of such chiral secondary alkylmagnesium reagents of type 5. Therefore, we have generated the mixed dialkylmagnesium reagent ([R]-5a) at −78 °C and kept it at this temperature for 1 h before adding 6a, yielding the corresponding alcohol ([R]-4a) in 75% yield and 91% ee (entry 9). A detectable racemization was observed after stirring the reaction mixture of ([R]-5a) for 1 h (71% yield, 86% ee; entry 10) or 3 h (64% yield, 69% ee; entry 11) at −50 °C. Furthermore, a large loss of enantioselectivity was observed by keeping ([R]-5a) for 1 h at −20 °C (66% yield, 60% ee, entry 12). These results indicated, that mixed non-stabilized secondary alkylmagnesium reagents of type 5 were configurationally stable up to ca. −50 °C for ca. 1 h and in comparison with the corresponding alkyl lithium reagents (configurationally stable only below −100 °C for some minutes) were better suited for synthetic applications.

With these optimized conditions in hand (Table 1, entry 2), we have prepared chiral Grignard reagents ([S]-5a-i) with high retention of configuration starting from the corresponding enantiomerically enriched secondary alkyl iodoines (1a-i; Scheme 2a). Thus, using ([S]-5a) (ca. 92–94% ee (ref. 11) instead of ([R]-5a) described in Table 1) obtained from the alkyl iodide ([S]-1a) (95% ee), gave the alcohol ([S]-4a) after quenching with 6a in 81% yield and 90% ee. Related Grignard reagents such as ([S]-5b) (ca. 99% ee) or ([S]-5c) (ca. 98% ee) add similarly to 6a or 6b providing the alcohols ([S]-4b) and ([S]-4c) in 65–73% yield and 98–99% ee. Also, diastereomerically enriched chiral Grignard reagents syn-5d (dr = 99 : 1) and anti-5d (dr = 1 : 99) provided after addition to 6a the alcohols syn- and anti-4d respectively in 74% yield and dr = 96 : 4 as well as 70% yield and dr = 5 : 95. Remarkably, functionalized alkylmagnesium species bearing a tert-butyl ester function such as ([R]- and ([S]-5e or an alkynyl group like ([R]-5f reacted with excellent stereoretention with 6a giving the alcohols ([R]-4e (65% yield, 93% ee) or ([S]-4c (72% yield, 93% ee) and
SiCH₂MgCl and their reactions with electrophiles (NMR spectroscopy and GC-analysis). Yield refers to isolated analytically pure compounds.

Scope of optically enriched secondary alkylmagnesium reagents

Scheme 2  Scope of optically enriched secondary alkylmagnesium reagents 5a-i and subsequent reactions with electrophiles (6a–l). Enantio-merically and diastereomerically enriched secondary alkylmagnesium reagents 5a–l prepared by an I/Li-exchange in the presence of Me₂-SiCH₂MgCl and their reactions with electrophiles (6a–l) leading to the corresponding optically and diastereomerically enriched products 4a–r.

The enantiomeric excess (% ee) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr; syn/anti ratio) was determined by 1H-NMR spectroscopy and GC-analysis. Yield refers to isolated analytically pure compounds.

(R)-4f (73% yield, 93% ee). Although enolizable ketones did not give satisfactory results, addition of Grignard reagents (R)-5a, (R)- and (S)-5g and (R)-5h to aldehydes such as c-hexylcarboxaldehyde (6c), (S)-citronellal (6d) and (1R)-(−)-myrtenal (6e) afforded after Dess–Martin oxidation the corresponding ketones (R)-4g (68%, 89% ee), (2R,5S)-4h (74%, dr = 95 : 5), (2S,5S)-4h (75%, dr = 5 : 93) as well as (2R,1R,5'S)-4i (46%, dr = 95 : 5) and (2S,1R,5'S)-4i (49%, dr = 3 : 97). Performance of acylations did not require Weinreb amides as used for the acylation of chiral alkylolithiums, but commercially available acid chlorides were employed. Thus, (R)-5a reacted with (S)-tetrahydrofuran-2-carboxyl chloride (6f) affording (2S,2'R)-4j in 89% yield and dr = 11 : 89. Similarly, acylation of anti-3i with 3-fluorobenzyl chloride (6g) led to anti-4k in 52% yield and dr = 5 : 95. Further functionalizations of these optically enriched Grignard reagents were realized by addition of (R)- and (S)-5g, (S)-5h and (S)-5e to cyclohexyl isocyanate (6h) and the commercial chiral (S)-(−)-z-methylbenzyl isocyanate (6i, 96% ee) or (R)-(−)-1-(1-naphthyl)ethyl isocyanate (6j, 95% ee) providing under our standard conditions, the chiral amides (R)-4l (80%, 94% ee) or (S)-4l (81%, 94% ee) as well as the diastereomerically enriched amides (2S,1'S)-4m (71%, dr = 96 : 4) and (2R,1'R)-4n (53%, dr = 96 : 4). The enantioselective preparation of carbon-sulfur bonds was briefly examined since it proceeded also directly with chiral secondary alkylolithiums. We observed that the coupling of (R)- and (S)-5h and syn-5d with MeSO₂SMe (6k) led to the thiocyclos (R)- and (S)-4o and syn-4p in up to 85% yield, but moderate stereoselectivity (up to 78% ee or dr = 93 : 7). However, phosphorus electrophiles such as Ph₂PCl (6l) reacted with high stereoretention with chiral Grignard reagents. Thus, (R)- and (S)-5g or (R)-5e led, after protection with BH₃·SMe₂, to a practical synthesis of chiral phosphine BH₃ complexes (R)- and (S)-4q as well as (R)-4r in up to 75% yield and up to 90% ee. These optically enriched phosphines could be of interest for asymmetric catalysis.

z-Chiral alkyl amines are of considerable interest due to their presence in natural products, pharmaceuticals and other biologically active molecules. Inspired by pioneering work of Johnson, we envisioned using O-benzoyl hydroxylamines as electrophilic amination reagents with chiral dialkyl Grignard reagents of type 5. After optimization, we have found that at a reaction temperature of −50 °C, the desired z-chiral amines
8a–j were obtained with high stereoretention (Scheme 3). Remarkably, all these reactions occurred chemoselectively without any transition metal additive and only minimal amounts of usual side-products (ketone) were observed. Thus, (R)- and (S)-5a reacted with 4-(pyrimidin-2-yl)piperazin-1-yl benzoate (7a) affording the corresponding α-chiral tertiary amines (R)- and (S)-8a in 73% yield and 88–91% ee. Furthermore, sertraline, a commercially available drug molecule, was successfully aminated via 7b and (S)-5a using this procedure, giving (2S,1S,4S)-8b in 52% yield and dr = 91 : 9. Also, the chiral Grignard reagents (R)- and (S)-5g were generated at −50 °C and trapped with 6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl benzoate (7c) and non-cyclic O-benzoyl-N,N-bis(2-methoxyethyl) hydroxylamine (7d) yielding (R)- and (S)-8c as well as (R)- and (S)-8d in 70–85% yield and 84–93% ee. The functionalized secondary alkylmagnesium reagent (R)-5e was also aminated with 7c providing (R)-8e in 68% yield and 83% ee. Additionally, the aminated benzothiophene derivatives (R)- and (S)-8f–g were prepared in up to 85% yield and up to 97% ee from optically enriched Grignard reagents (R)- and (S)-5h and the O-benzoyl hydroxylamines 7c and N-morpholino benzoate (7e).

Also, the diastereomerically enriched secondary alkylmagnesium reagent anti-5i was successfully quenched with 7e, azepan-1-yl benzoate (7f) and even the sensitive formamide 4-formylpiperazin-1-yl benzoate (7g) affording anti-8h–j in 56–63% yield and up to dr = 3 : 97. This preparation of tertiary amines was found to be superior to standard nucleophilic substitutions of chiral secondary alkyl iodides, phosphates and tosylates by metallic amides, which gave erratic results in our hands. The determination of the absolute configuration was made in the case of the amine hydrochloride derivative of (S)-8g using X-ray diffraction (Flack parameter method) confirming the (S)-configuration of 8g as well as the retention of configuration of this electrophilic amination (Fig. 1).

Fig. 1 X-ray structure of (S)-8g crystallized as the corresponding amine hydrochloride as a representative example of the overall stereoretention of the electrophilic amination.

Conclusions

In summary, we have prepared a broad range of functionalized enantiomerically enriched non-stabilized secondary alkylmagnesium reagents from the corresponding alkyl iodides via I/Li-exchange and in situ transmetalation with Me3SiCH2MgCl at convenient temperatures. The resulting new chiral alkylmagnesium reagents of the type AlkCH(Me)MgCH2SiMe3 (5) were trapped with ketones, aldehydes, acid chlorides, isocyanates, S-methyl methanethiosulfonate and chlorophosphines providing the corresponding tertiary alcohols, ketones, amides, thioethers and phosphines with high retention of configuration (up to 99% ee). These mixed Grignard reagents were found to be configurationally stable up to −50 °C (for ca. 1 h) and allowed a convenient preparation of enantiomerically enriched α-chiral tertiary amines starting from O-benzoyl hydroxylamines in the absence of a transition metal catalyst, which demonstrated a valuable alternative to nucleophilic substitutions of secondary alkyl iodides, phosphates and tosylates with metallic amides. Further applications of these new chiral magnesium intermediates are currently underway.

Data availability

All experimental and crystallographic data is available in the ESL.

Author contributions

A. K., H. R. W., M. M. S. and Q. S. performed and analyzed the experiments. K. K. measured and analyzed X-ray crystal
structures. A. K., H. R. W. and P. K. designed the experiments. A. K., H. R. W. and P. K. prepared the manuscript with contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

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