Volume 13
Number 1
7 January 2022
Pages 1–304

Chemical Science

rsc.li/chemical-science

ISSN 2041-6539

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

Paul Knochel *et al.*

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

Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2022, **13**, 44

All publication charges for this article have been paid for by the Royal Society of Chemistry

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

Alexander Kremsmair,‡ Henrik R. Wilke,‡ Matthias M. Simon, Quirin Schmidt, Konstantin Karaghiosoff and Paul Knochel *

A general preparation of enantiomerically and diastereomerically enriched secondary alkylmagnesium reagents was reported as well as their use for performing highly stereoselective transition-metal free electrophilic aminations leading to α-chiral amines in up to 97% ee. Thus, the reaction of *t*-BuLi (2.2 equiv.) with a mixture of chiral secondary alkyl iodides and the commercially available magnesium reagent Me_3SiCH_2MgCl in a 2 : 1 mixture of pentane and diethyl ether at up to −50 °C provided optically enriched secondary mixed alkylmagnesium species of the type alkyl(Me)CHMgCH$_2$SiMe$_3$ with high retention of configuration (up to 99% ee). The resulting enantiomerically enriched dialkylmagnesium reagents were trapped with electrophiles such as non-enolizable ketones, aldehydes, acid chlorides, isocyanates, chlorophosphines and *O*-benzoyl hydroxylamines providing α-chiral tertiary alcohols, ketones, amides, phosphines and tertiary amines in up to 89% yield (over three reaction steps) and up to 99% ee.

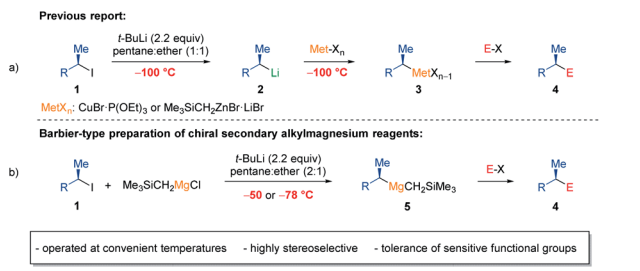
Received 24th September 2021
Accepted 18th October 2021

DOI: 10.1039/d1sc05315a

rsc.li/chemical-science

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- norbornylmagnesium bromide using benzophenone[3] or exploiting the different reactivities of menthylmagnesium chloride epimers[4] have been reported. Recently, we have shown that various enantiomerically enriched secondary alkyl iodides of type **1** underwent an I/Li-exchange[5] at −100 °C in pentane:ether mixtures furnishing the corresponding chiral alkyllithiums 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,[7d,g,h] such reaction sequences required very low temperatures (−100 °C) due to the occurrence of configurationally labile alkyllithium reagents (**2**), which epimerized readily at temperatures above −100 °C (ref. 6*b*) 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 alkyllithiums.[8] Recently, we have shown that Barbier conditions were broadly applicable for the directed lithiation of (hetero)aromatics with



Scheme 1 (a) Previous preparation of chiral secondary alkyl organometallics of type **3** *via* I/Li-exchange and subsequent transmetalation at −100 °C; (b) Barbier-type preparation of chiral secondary alkylmagnesium reagents (**5**) *via* I/Li-exchange and *in situ* transmetalation with Me_3SiCH_2MgCl at −50 °C or −78 °C.

Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, 81377 München, Germany. E-mail: paul.knochel@cup.uni-muenchen.de

† Electronic supplementary information (ESI) available. CCDC 2110720. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc05315a

‡ These authors contributed equally.

TMPLi (TMP = 2,2,6,6,-tetramethylpiperidyl) in the presence of various salts.[9]

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 alkyllithiums 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 iodides in the presence of commercially available Me_3SiCH_2-MgCl 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 α-chiral tertiary alcohols, 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

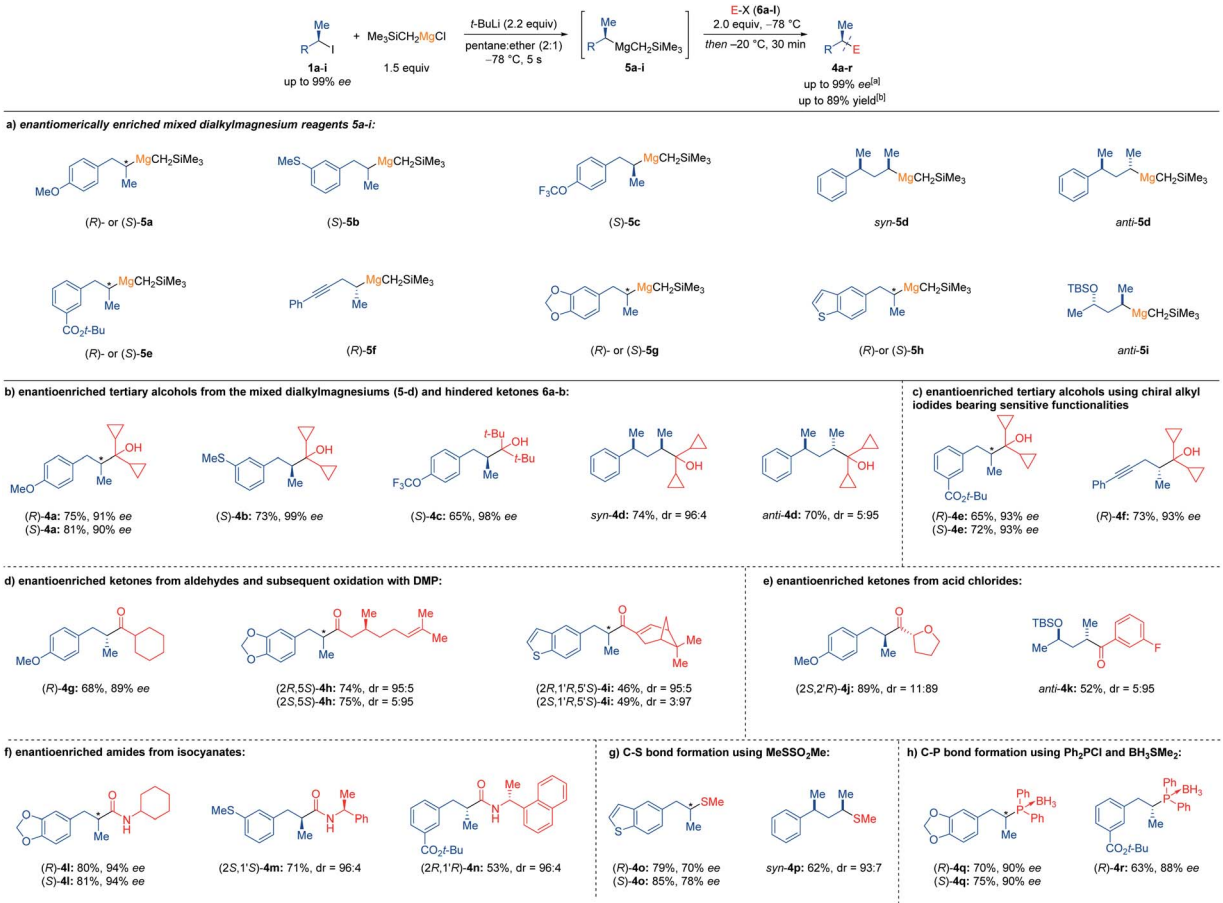
Thus, in preliminary experiments, we have mixed the chiral secondary alkyl iodide (*R*)-**1a** with Me_3SiCH_2MgCl and have subsequently added *t*-BuLi (2.2 equiv.) at various temperatures (see Table 1). The resulting secondary alkylmagnesium species (*R*)-**5a** was quenched with dicyclopropyl ketone (**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 I/Li-exchange at −78 °C (entry 2). As expected, if the reaction was performed at −78 °C without Me_3SiCH_2MgCl, (*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 Me_3SiCH_2MgCl 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 Me_3SiCH_2MgCl 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.[10] 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 alkyllithium reagents (configurationally stable only below −100 °C for some minutes)[6] were better suited for synthetic applications.

With these optimized conditions in hand (Table 1, entry 2), we have prepared chiral Grignard reagents (**5a–i**) with high retention of configuration starting from the corresponding enantiomerically enriched secondary alkyl iodides (**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 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*)-**4e** (72% yield, 93% ee) and

Table 1 Optimization of reaction conditions[a]

Entry	Temperature [°C]	Yield of (*R*)-**4a**[b]	ee of (*R*)-**4a**[c]
(a) Reaction condition optimization			
1	−100	80%	91%
2	**−78**	**80% (75%)[d]**	**91%**
3	−78	78%[e]	12%
4	−60	73%	90%
5	−40	71%	82%
6	−20	59%	52%
7	−20[f]	52%	78%
8	−40[f]	67%	84%
(b) Configurational stability evaluation of (R)-5a			
9	−78[g]	75%	91%
10	**−50[g]**	**71%**	**86%**
11	−50[h]	64%	69%
12	−20[g]	66%	60%

[a] Stereoselective preparation of (*R*)-**5a** at various reaction temperatures under Barbier conditions. [b] The yield was determined by GC-analysis of reaction aliquotes. [c] The enantiomeric excess (% ee) was determined by chiral HPLC-analysis. [d] Yield of analytically pure isolated product. [e] The reaction was performed without Me_3SiCH_2MgCl. [f] Me_3SiCH_2MgCl (2.0 equiv.) was used. [g] The chiral Grignard reagent (*R*)-**5a** was kept for 1 h at this temperature before quenching. [h] The chiral Grignard reagent (*R*)-**5a** was kept for 3 h at this temperature before quenching.



Scheme 2 Scope of optically enriched secondary alkylmagnesium reagents **5a-i** and subsequent reactions with electrophiles (**6a–l**). Enantiomerically and diastereomerically enriched secondary alkylmagnesium reagents **5a–i** prepared by an I/Li-exchange in the presence of Me_3SiCH_2MgCl and their reactions with electrophiles (**6a–l**) leading to the corresponding optically and diastereomerically enriched products **4a–r**. [a]The enantiomeric excess (% ee) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr; *syn*/*anti* ratio) was determined by ^{1}H-NMR spectroscopy and GC-analysis. [b]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 (1*R*)-(−)-myrtenal (**6e**) afforded after Dess–Martin oxidation the corresponding ketones (*R*)-**4g** (68%, 89% ee), (2*R*,5*S*)-**4h** (74%, dr = 95 : 5), (2*S*,5*S*)-**4h** (75%, dr = 5 : 95) as well as (2*R*,1′*R*,5′S)-**4i** (46%, dr = 95 : 5) and (2*S*,1′*R*,5′S)-**4i** (49%, dr = 3 : 97). Performance of acylations did not require Weinreb amides as used for the acylation of chiral alkyllithiums,[6c] but commercially available acid chlorides were employed. Thus, (*R*)-**5a** reacted with (*S*)-tetrahydrofuran-2-carbonyl chloride (**6f**) affording (2*S*,2′*R*)-**4j** in 89% yield and dr = 11 : 89. Similarly, acylation of *anti*-**5i** with 3-fluorobenzoyl 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*)-**5b** and (*S*)-**5e** to cyclohexyl isocyanate (**6h**) and the commercial chiral (*S*)-(−)-α-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 (2*S*,1′*S*)-**4m** (71%, dr = 96; 4) and (2*R*,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 alkyllithiums.[6] We observed that the coupling of (*R*)- or (*S*)-**5h** and *syn*-**5d** with $MeSO_2SMe$ (**6k**) led to the thioethers (*R*)- or (*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 Ph_2PCl (**6l**) reacted with high stereoretention with chiral Grignard reagents. Thus, (*R*)- and (*S*)-**5g** or (*R*)-**5e** led, after protection with $BH_3 \cdot SMe_2$,[12] to a practical synthesis of chiral phosphine BH_3-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.

α-Chiral alkyl amines are of considerable interest due to their presence in natural products, pharmaceuticals and other biologically active molecules.[13] Inspired by pioneering work of Johnson,[14] we envisioned using *O*-benzoyl hydroxylamines[15] 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 α-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)[16] 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,[17] was successfully aminated *via* **7b** and (*S*)-**5a** using this procedure, giving (2′*S*,1*S*,4*S*)-**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(4*H*)-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.[18] 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)[19] confirming the (*S*)-configuration of **8g** as well as the retention of configuration of this electrophilic amination (Fig. 1).

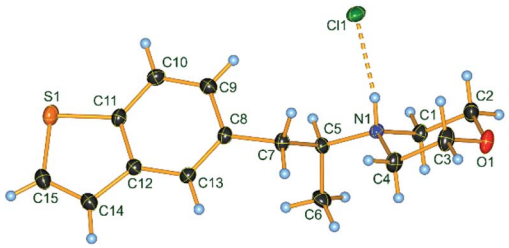
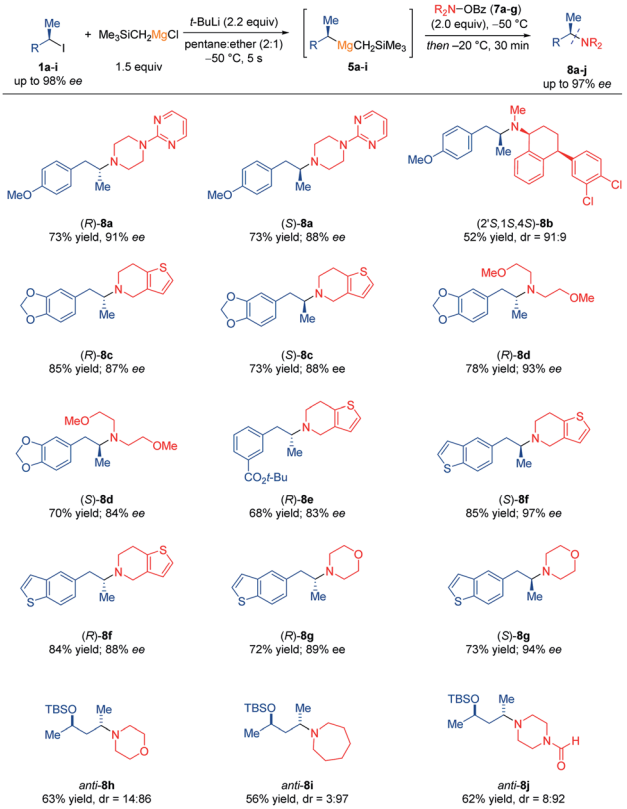


Fig. 1 X-ray structure of (*S*)-**8g** crystallized as the corresponding amine hydrochloride as a representative example of the overall stereoretention of the electrophilic amination.



Scheme 3 Scope of prepared enantiomerically and diastereomerically enriched α-chiral tertiary amines. Enantiomerically and diastereomerically enriched tertiary amines **8a–j** obtained by electrophilic amination of secondary alkylmagnesium reagents **5a–i** with *O*-benzoyl hydroxylamines (**7a–g**). The enantiomeric excess (% ee) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr; *syn*/anti ratio) was determined by ^{1}H-NMR spectroscopy and GC-analysis.

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 Me_3SiCH_2MgCl at convenient temperatures. The resulting new chiral alkylmagnesium reagents of the type $AlkCH(Me)MgCH_2SiMe_3$ (**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 ESI.†

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.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG) and the Ludwig-Maximilians-Universität München for financial support. We also thank Albemarle for the generous gift of chemicals. We thank Dr J. Skotnitzki for fruitful discussions and K. Kublik, Y. Gong and R. Traber for preliminary experiments.

Notes and references

1 (*a*) H. G. Richey, *Grignard Reagents: New Developments*, John Wiley & Sons, Ltd. New York, 1999; (*b*) Z. Rappoport and I. Marek, *PATAI's Chemistry of Functional Groups: The Chemistry of Organomagnesium Compounds*, John Wiley & Sons, Ltd., New York, 2008; (*c*) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn and I. Sapountzis, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302–4320; (*d*) B. Haag, M. Mosrin, H. Ila and V. Malakhov, *Angew. Chem., Int. Ed.*, 2011, **50**, 9794–9824; (*e*) A. Kremsmair, J. H. Harenberg, K. Schwärzer, A. Hess and P. Knochel, *Chem. Sci.*, 2021, **12**, 6011–6019.

2 (*a*) R. W. Hoffmann, B. Hölzer, O. Knopff and K. Harms, *Angew. Chem., Int. Ed.*, 2000, **39**, 3072–3074; (*b*) R. W. Hoffmann and B. Hölzer, *Chem. Commun.*, 2001, 491–492; (*c*) R. W. Hoffmann, B. Hölzer and O. Knopff, *Org. Lett.*, 2001, **3**, 1945–1948; (*d*) R. W. Hoffmann and B. Hölzer, *J. Am. Chem. Soc.*, 2002, **124**, 4204–4205; (*e*) B. Hölzer and R. W. Hoffmann, *Chem. Commun.*, 2003, 732–733.

3 (*a*) F. R. Jensen and K. L. Nakamaye, *J. Am. Chem. Soc.*, 1966, **88**, 3437–3438; (*b*) J. San Filippo and J. W. Nicoletti, *J. Org. Chem.*, 1977, **42**, 1940–1944.

4 J. Beckmann, D. Dakternieks, M. Dräger and A. Duthie, *Angew. Chem., Int. Ed.*, 2006, **45**, 6509–6512.

5 We used 2.2 equiv. of *t*-BuLi for best results (formation of lithium reagent and formation of isobutylene and isobutene as side-products); see: M. Schlosser, *Organometallics in Synthesis: Third Manual*, John Wiley & Sons, Ltd., New York, 2013.

6 (*a*) S. Seel, G. Dagousset, T. Thaler, A. Frischmuth, K. Karaghiosoff, H. Zipse and P. Knochel, *Chem.–Eur. J.*, 2013, **19**, 4614–4622; (*b*) G. Dagousset, K. Moriya, R. Mose, G. Berionni, K. Karaghiosoff, H. Zipse, H. Mayr and P. Knochel, *Angew. Chem., Int. Ed.*, 2014, **53**, 1425–1429; (*c*) K. Moriya, D. Didier, M. Simon, J. M. Hamann, G. Berionni, K. Karaghiosoff, H. Zipse, H. Mayr and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, **54**, 10963–10967; (*d*) J. Skotnitzki, A. Kremsmair and P. Knochel, *Synthesis*, 2020, **52**, 189–196.

7 For transmetalations to alkylcopper reagents: (*a*) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, **54**, 10963–10967; (*b*) V. Morozova, K. Moriya, P. Mayer and P. Knochel, *Chem.–Eur. J.*, 2016, **22**, 9962–9965; (*c*) J. Skotnitzki, V. Morozova and P. Knochel, *Org. Lett.*, 2018, **20**, 2365–2368; (*d*) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5515–5519; (*e*) J. Skotnitzki, A. Kremsmair, D. Keefer, F. Schüppel, B. Le Cacher de Bonneville, R. de Vivie-Riedle and P. Knochel, *Chem. Sci.*, 2020, **11**, 5328–5332; (*f*) A. Kremsmair, J. Skotnitzki and P. Knochel, *Chem.–Eur. J.*, 2020, **26**, 11971–11973For transmetalations to mixed alkylcopper-zinc reagents: (*g*) J. Skotnitzki, L. Spessert and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 1509–1514; (*h*) J. Skotnitzki, A. Kremsmair, B. Kicin, R. Saeb, V. Ruf and P. Knochel, *Synthesis*, 2020, **52**, 873–881For transmetalations to alkylzinc reagents see: (*i*) J. Skotnitzki, A. Kremsmair, D. Keefer, Y. Gong, R. de Vivie-Riedle and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 320–324.

8 (*a*) C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springer-Verlag, Berlin Heidelberg, 1993; (*b*) S. Goto, J. Velder, S. El Sheikh, Y. Sakamoto, M. Mitani, S. Elmas, A. Adler, A. Becker, J.-M. Neudörfl, J. Lex and H.-G. Schmalz, *Synlett*, 2008, **9**, 1361–1365.

9 A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2014, **53**, 7928–7932.

10 For a detailed screening table, see ESI.†

11 The enantiopurity was estimated based on the enantiopurity of the obtained tertiary alcohols after reaction with the ketones **6a** or **6b**.

12 F. Langer and P. Knochel, *Tetrahedron Lett.*, 1995, **36**, 4591–4594.

13 (*a*) N. E. Lee and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 5985–5986; (*b*) T. C. Nugent and M. El-Shazly, *Adv. Synth. Catal.*, 2010, **352**, 753–819; (*c*) G.-H. Hou, J.-H. Xie, P.-C. Yan and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2009, **131**, 1366–1371; (*d*) D. Matheau-Raven, P. Gabriel, J. A. Leitch, Y. A. Almehmadi, K. Yamazaki and D. J. Dixon, *ACS Catal.*, 2020, **10**, 8880–8897; (*e*) A. Trowbridge, S. M. Walton and M. J. Gaunt, *Chem. Rev.*, 2020, **120**, 2613–2692.

14 (*a*) A. M. Berman and J. S. Johnson, *J. Am. Chem. Soc.*, 2004, **126**, 5680–5681; (*b*) A. M. Berman and J. S. Johnson, *J. Org. Chem.*, 2005, **70**, 364–366; (*c*) A. M. Berman and J. S. Johnson, *J. Org. Chem.*, 2006, **71**, 219–224.

15 (*a*) S. L. McDonald, C. E. Hendrick and Q. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4667–4670; (*b*) K. Shen and Q. Wang, *Chem. Sci.*, 2015, **6**, 4279–4283; (*c*) B. N. Hemric, K. Shen and Q. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 5813–5816; (*d*) C. E. Hendrick, K. J. Bitting, S. Cho and Q. Wang, *J. Am. Chem. Soc.*, 2017, **139**, 13110–13116; (*e*) Y.-H. Chen, S. Graßl and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 1108–1111; (*f*) S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann and P. Knochel, *Org. Lett.*, 2019, **21**, 494–

497; (*g*) Z. Xiong, P. Cai, Y. Mei and J. Wang, *RSC Adv.*, 2019, **9**, 42072–42076; (*h*) V. A. Van der Puyl, J. Derosa and K. M. Engle, *ACS Catal.*, 2019, **9**, 224–229; (*i*) S. Graßl and P. Knochel, *Org. Lett.*, 2020, **22**, 1947–1950; (*j*) J. He, Y. Xue, B. Han, C. Zhang, Y. Wang and S. Zhu, *Angew. Chem., Int. Ed.*, 2020, **59**, 2328–2332; (*k*) Y. Kwon and Q. Wang, *Org. Lett.*, 2020, **22**, 4141–4145; (*l*) B. N. Hemric, C. K. Ku and Q. Wang, *Encyclopedia of Reagents for Organic Synthesis*, Wiley VCH 2020, DOI: 10.1002/047084289X.rn02290.

16 M. J. Campbell and J. S. Johnson, *Org. Lett.*, 2007, **9**, 1521–1524.

17 M. W. Welch, A. R. Kraska, R. Sarges and B. K. Koe, *J. Med. Chem.*, 1984, **27**, 1508–1515.

18 For a detailed comparison of electrophilic and nucleophilic aminations see ESI.†

19 (*a*) H. D. Flack, *Acta Crystallogr.*, 1983, **39**, 876–881; (*b*) E. C. Constable and C. E. Housecroft, *Chemistry*, 2020, **2**, 759–776.