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Preparation and Reactions of Enantiomerically Pure α-Functionalised Grignard Reagents

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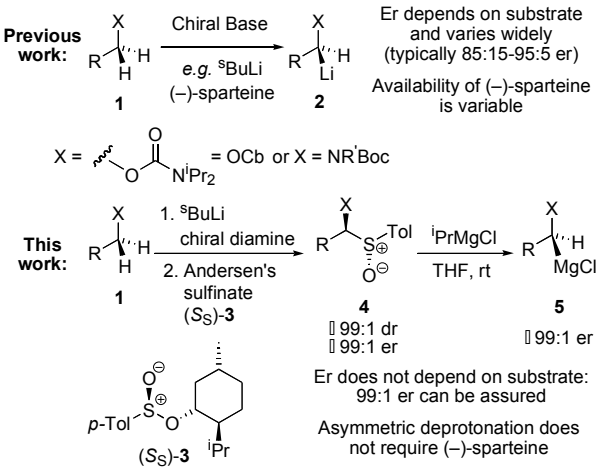
ABSTRACT: A strategy for the generation of enantiomerically pure α-functionalised chiral Grignard reagents is presented. The approach involves the synthesis of α-alkoxy- and α-amino sulfoxides in ≥99:1 dr and ≥99:1 er *via* asymmetric deprotonation (*s*-BuLi/chiral diamine) and trapping with Andersen's sulfinate (menthol-derived). Subsequent sulfoxide → Mg exchange (room temperature, 1 minute) and electrophilic trapping delivers a range of enantiomerically pure α-alkoxy- and α-amino substituted products. Using this approach, either enantiomer of products can be accessed in 99:1 er from asymmetric deprotonation protocols without the use of (–)-sparteine as the chiral ligand. Two additional discoveries are noteworthy: (i) for the deprotonation and trapping with Andersen's sulfinate, there is a lack of stereospecificity at sulfur due to attack of a lithiated intermediate onto the α-alkoxy- and α-amino sulfoxides as they form and (ii) the α-alkoxy-substituted Grignard reagent is configurationally stable at room temperature for 30 minutes.

Introduction

Asymmetric deprotonation α to oxygen[1] or nitrogen[2] in carbamates **1** using a chiral base (*e.g. s*-BuLi/(–)-sparteine) is an established method for the generation of enantioenriched α-functionalised organolithium reagents **2** (Scheme 1).[3] Such methodology has been widely-used in synthesis: for example, Aggarwal *et al.* have developed molecular assembly lines using *O*-alkyl carbamates [4] and scientists at Merck scaled up the asymmetric deprotonation of *N*-Boc pyrrolidine to prepare ~0.7 kg of a glucokinase activator.[5] However, two key limitations with this methodology remain. First, enantiomer ratios (ers) of the products from asymmetric deprotonations vary widely. This is especially true for *N*-Boc heterocycles which typically range from 85:15-95:5 er. Indeed, the only examples which consistently give 99:1 er are Hoppe-style deprotonations of *O*-alkyl carbamates using *s*-BuLi/(–)sparteine,[3] and are thus limited to one enantiomeric series. Second, over the last two years, the commercial availability of (–)-sparteine has been variable. This is of much concern as (–)-sparteine generally gives the highest enantioselectivity over a wide range of reaction types.

To address these two limitations, we set out to develop a new approach in which the asymmetric deprotonation of carbamates **1** using *s*-BuLi/chiral diamine (ideally not (–)-sparteine) would be merged with electrophilic trapping using Andersen's chiral sulfinate (S_S)-**3**[6] (Scheme 1). In this way, we would improve on the moderate enantioselectivity (85:15-95:5 er typically) engendered by the chiral base through the generation of α-alkoxy and α-amino sulfoxides **4** in ≥99:1 dr and ≥99:1 er. Subsequent sulfoxide → Mg exchange on α-functionalised sulfoxides **4** would then generate chiral α-functionalised Grignard reagents **5** (analogous to organolithiums **2**) in ≥99:1 er (Scheme 1). Crucially, as well as delivering substituted products in ≥99:1 er, it was anticipated that our methodology would not rely on (–)-sparteine for high enantioselectivity.

Scheme 1. Comparison of asymmetric deprotonation with asymmetric deprotonation-chiral sulfinate trapping.



A conceptually related approach to organolithiums **2** would be to carry out Sn → Li exchange on enantiopure α-alkoxy and α-amino-stannanes. Such an approach was used by Still in pioneering studies on the configurational stability of α-alkoxy organolithiums[7] and has been employed more recently by Hammerschmidt[8] and Aggarwal.[9] However, these methods do not represent a general route to organolithiums **2** of 99:1 er, especially for *N*-Boc heterocycles, and it is necessary to carry out the Sn → Li exchange at low temperaures (–78 °C) due to the configurational or chemical instability of the organolithiums **2**.[10] In contrast, our approach should deliver a wide range of α-functionalised

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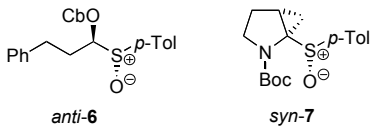
Grignard reagents **5** in ≥99:1 er *via* the same general strategy. It was also envisioned that sulfoxide → Mg exchange should be possible at temperatures above –78 °C as α-functionalised Grignard reagents have a higher degree of configurational stability than their organolithium counterparts.[11] Whilst there are some related sulfoxide → Li exchanges[12] (especially in the area of chiral ferrocene synthesis[12a,12c]), we know of only two specific cases where enantioenriched α-functionalised Grignards like **5** have been directly prepared by sulfoxide → Mg exchange: α-aziridino Grignards (Satoh[13]) and α-halo-substituted Grignards (Hoffmann[14] and Blakemore[15]).[16] In related work, Blakemore has also reported a sulfoxide → Mg exchange route to stereodefined α-magnesiated S,O-acetals[17] and Bull has recently described the synthesis and reactions of α-aziridino Grignard reagents.[18]

Our approach to enantiopure Grignard reagents **5** is summarised in Scheme 1: asymmetric deprotonation of carbamates **1** using *s*-BuLi/chiral diamine and trapping with Andersen's sulfinate (S_S)-**3** should generate α-alkoxy and α-amino sulfoxides **4** in ≥99:1 dr and ≥99:1 er. We anticipated needing to carry out the lithiation reaction only once on each substrate to generate **4**. Subsequent sulfoxide → Mg exchange on **4** would then deliver the Grignard reagents **5** on demand, potentially under mild conditions and in ≥99:1 er, ready for electrophilic trapping to give a wide range of products from just one asymmetric deprotonation reaction. In this paper, we present the implementation of this strategy with two examples: the preparation and reactions of enantiomerically pure α-functionalised Grignard reagents derived from sulfoxides *anti*-**6** and *syn*-**7** (Figure 1), the synthesis of which does not require (–)-sparteine.

Figure 1. α-Substituted sulfoxides *anti*-6 and *syn*-7.

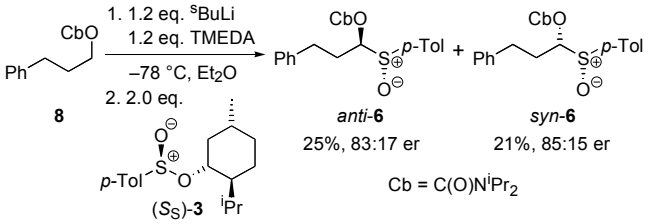


Results and Discussion

Preparation and Reactions of Enantiopure α-Alkoxy Grignard Reagents

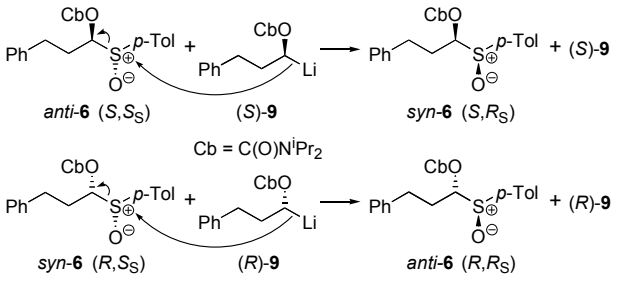
The asymmetric deprotonation of *O*-alkyl carbamates, first reported by Hoppe in 1990,[1] is now recognised as an important synthetic method due primarily to Aggarwal's recent extensive studies on boronate rearrangement methodology.[4,9,19] As a result, we commenced our studies with *O*-alkyl carbamates. Thus, racemic deprotonation of *O*-alkyl carbamate **8** using 1.2 eq. of *s*-BuLi/TMEDA in Et_2O at –78 °C and addition of 2.0 eq. of Andersen's sulfinate (S_S)-**3**[6] to the solution of the organolithium reagent gave, after warming to room temperature over 18 h, a separable mixture of sulfoxides *anti*-**6** (25%) and *syn*-**6** (21%) (Scheme 2). The assignment of configuration in sulfoxides *anti*-**6** and *syn*-**6** is presented later (*vide infra*). From this initial experiment, we expected stereospecific substitution at sulfur (with inversion of configuration[6]) to deliver the products in high er. Disappointingly, sulfoxides *anti*-**6** (83:17 er) and *syn*-**6** (85:15 er) were isolated with only moderate enantioselectivity indicating a lack of stereospecificity at sulfur in the trapping with (S_S)-**3**. Although there is some limited precedent[20] for this, no explanation has previously been forwarded. Of note, there was no epimerisation of Andersen's sulfinate (S_S)-**3** during the reaction as the excess (S_S)-**3** was recovered unchanged.

Scheme 2. Racemic deprotonation of *O*-alkyl carbamate 8 and trapping with Andersen's sulfinate (S_S)-3.



Our proposed mechanism to account for the lack of stereospecificity in the trapping step is shown in Scheme 3. Deprotonation of *O*-alkyl carbamate **8** using *s*-BuLi/TMEDA will generate a 50:50 mixture of lithiated carbamates (*S*)-**9** and (*R*)-**9**. As an example, reaction of organolithium (*S*)-**9** with sulfinate (S_S)-**3** would give sulfoxide *anti*-(*S*,S_S)-**6** and, as the amount of *anti*-(*S*,S_S)-**6** increases, we suggest that competitive sulfoxide → Li exchange mediated by lithiated carbamate (*S*)-**9** as shown in Scheme 3 could occur to give diastereomeric sulfoxide *syn*-(*S*,R_S)-**6**. An analogous process (using (*R*)-**9**) would convert *syn*-(*R*,S_S)-**6** into *anti*-(*R*,R_S)-**6** (Scheme 3). Such sulfoxide → Li exchange processes (attack of lithiated carbamates onto the sulfoxides) could account for the generation of *syn*-(*S*,R_S)-**6** and *anti*-(*R*,R_S)-**6**, the enantiomers of the expected major products *anti*-(*S*,S_S)-**6** and *syn*-(*R*,S_S)-**6**, and would thus account for the lack of stereospecificity at sulfur in the trapping with sulfinate (S_S)-**3**.

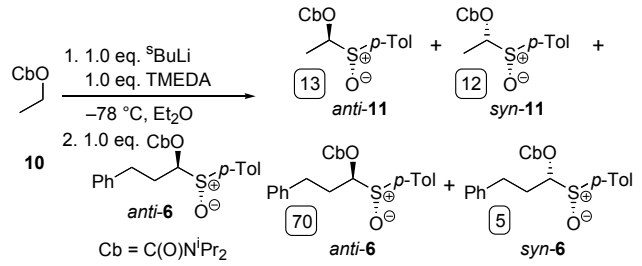
Scheme 3. Proposed mechanism to account for lack of stereospecificity in trapping with sulfinate (S_S)-3.



To establish that the sulfoxide → Li exchange was occurring, a crossover-type experiment using two different *O*-alkyl carbamates was devised. Thus, ethyl *O*-alkyl carbamate **10** was deprotonated using 1.0 eq. of *s*-BuLi/TMEDA in Et_2O at –78 °C and then 1.0 eq. of sulfoxide *anti*-**6** (racemic) was added. After 1 h at –78 °C, the reaction was quenched with MeOH. Purification by chromatography gave a 96% yield (based on *anti*-**6**) of a 13:12:70:5 mixture of sulfoxides *anti*-**11**, *syn*-**11**, *anti*-**6** and *syn*-**6** (Scheme 4). Crucially, the product mixture contained *anti*-**11** and *syn*-**11** (separately synthesised and characterised, see Supporting Information) indicating that the proposed sulfoxide → Li

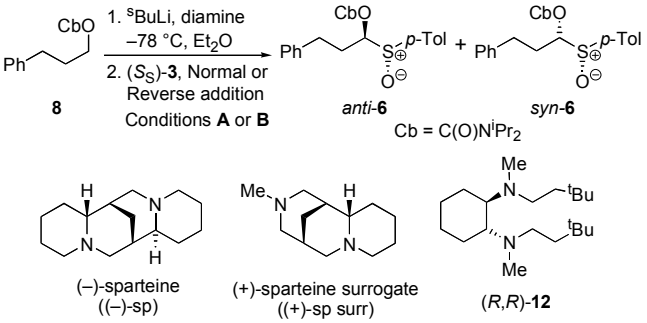
exchange was occurring, even at –78 °C. It is also notable that some *syn*-**6** was also present. This suggests that lithiated carbamates (*S*)-**9** and (*R*)-**9** are formed in the solution, as necessitated by the sulfoxide → Li exchange.

Scheme 4. Crossover-type experiment to establish the viability of the proposed sulfoxide → Li exchange process.



With a mechanism for the lack of stereospecifity at sulfur established, we then attempted to minimise the loss of er in the trapping with Andersen's sulfinate (*S*S)-**3**. The reaction time was reduced from warming to room temperature over 18 h (conditions A) to 5 min at –78 °C (MeOH quench, conditions B). We compared the reaction under normal addition (addition of (*S*S)-**3** to the lithiated carbamate) and reverse addition (addition of lithiated carbamate to sulfinate (*S*S)-**3**) which should mean that the organolithium reagent is not present in excess. The results are summarised in Table 1. Use of both –78 °C for 5 min (conditions B) and reverse addition of the lithiated carbamate to Andersen's sulfinate (*S*S)-**3** led to increases in er of *anti*-**6** and *syn*-**6** (87:13-91:9 er) (entries 2/3) compared to the original result (83:17-85:15 er, entry 1, Scheme 2).

Table 1. Synthesis of α-alkoxy sulfoxides *anti*-6 and *syn*-6.



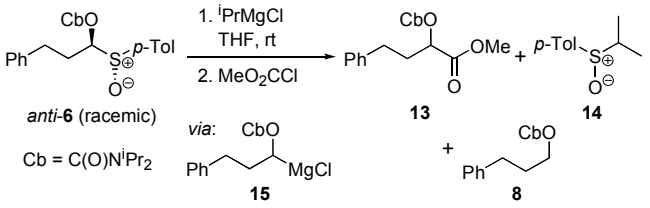
Entry	Diamine[a]	Trapping conditions[b]	*anti*-**6** %,[c] er[d]	*syn*-**6** %,[c] er[d]
1	TMEDA	Normal, **A**	25, 83:17	21, 85:15
2	TMEDA	Normal, **B**	23, 88:12	32, 91:9
3	TMEDA	Reverse, **B**	25, 87:13	29, 90:10
4	(–)-sp	Normal, **A**	53, 99:1	0.2, nd
5	(+)-sp surr	Normal, **A**	7, 87:13	45, 99:1
6	(*R*,*R*)-**12**	Reverse, **B**	56, 99:1	14, 93:7
7	(*S*,*S*)-**12**	Reverse, **B**	17, 95:5	54, 99:1

[a] 1.2 eq. *s*-BuLi/diamine, Et_2O, –78 °C, 1 h. [b] Normal = addition of (*S*S)-**3** to organolithium; Reverse = addition of organolithium to (*S*S)-**3**; Trapping conditions **A**: –78 °C → rt and then 18 h at rt; Trapping conditions **B**: –78 °C for 5 min. [c] % Yield after chromatography. [d] Er determined by chiral stationary phase (CSP)-HPLC.

Next, we explored the use of chiral diamines with the intention that high enantioselectivity in the asymmetric deprotonation could be coupled with ~90:10 stereospecificity at sulfur in trapping with (*S*S)-**3** to deliver the major diastereomer in 99:1 er (together with reduced er of the minor diastereomeric sulfoxide). For comparison, the previously reported *enantioselectivity* for the deprotonation (–78 °C, Et_2O) and trapping of *O*-alkyl carbamate **8** are as follows: (–)-sparteine (99:1 er, Bu_3SnCl);[21] (+)-sparteine surrogate (94:6 er, Bu_3SnCl)[21] and diamine (*R*,*R*)-**12**[22] (82:18 er, CO_2). To our delight, use of all three diamines gave the major diastereomeric sulfoxide in 99:1 er (entries 4-7). Sulfoxide *anti*-**6** (99:1 er) was isolated in 53-56% yield using (–)-sparteine or (*R*,*R*)-**12** (entries 4/6) whereas *syn*-**6** (99:1 er) with opposite configuration at the *O*-alkyl carbamate stereogenic centre was accessible in 45-54% yield using the (+)-sparteine surrogate or (*S*,*S*)-**12** (entries 5/7). The known asymmetric induction with these diamines[1,21,22] and the predominance for inversion of configuration at sulfur in trapping with (*S*S)-**3**[6,20] allowed assignment of the configurations in *anti*-**6** and *syn*-**6**. Given the recent variability in the availability of (–)-sparteine, it is significant and synthetically useful that sulfoxides *anti*-**6** and *syn*-**6** can be accessed in 99:1 er using the commercially available diamines (*R*,*R*)-**12** and (*S*,*S*)-**12** (entries 6/7).

With *anti*-**6** and *syn*-**6** of 99:1 er in hand, we then explored the sulfoxide → Mg exchange and trapping. Optimisation was carried out using racemic *anti*-**6** which was treated with 1.3-2.5 eq. of *i*-PrMgCl in THF at room temperature before trapping with MeO_2CCl. This gave ester **13** together with the sulfoxide **14**, the by-product of the sulfoxide exchange process. In addition, some of *O*-alkyl carbamate **8** and starting material, *anti*-**6**, were also isolated (Table 2).

Table 2. Optimisation of sulfoxide → Mg exchange with *anti*-6.



Entry	Eq. of *i*-PrMgCl	Time min	**13** %[a]	**14** %[a]	**8** %[a]	*anti*-**6** %[a]
1	1.3	5	48	81	14	4
2	1.3	1	65	73	6	8
3	1.5	5	42	82	17	0
4	1.5	1	67	84	9	0
5	2.5	1	75	84	5	0

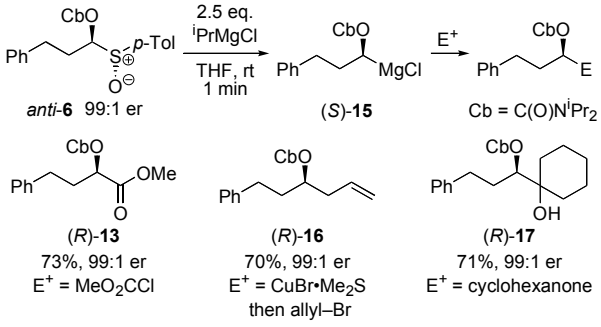
[a] % Yield after chromatography.

Using 1.3 eq. of *i*-PrMgCl and trapping after 5 min gave a moderate 48% yield of ester **13** even though the sulfoxide → Mg exchange must have been efficient, as shown by the formation of sulfoxide **14** in 81% yield (entry 1). Better

results were obtained if the exchange time was reduced to just 1 min: 65% yield of **13** (entry 2). To explain these results, we suggest that the intermediate Grignard reagent **15** is chemically unstable either by deprotonation of sulfoxide **14** or *via* intramolecular nucleophilic attack onto the C=O of the carbamate group, a known process for the organolithium analogue at temperatures above –20 °C.[4] Use of 1.5 eq. or 2.5 eq. of *i*-PrMgCl and 1 min reaction times ensured that no starting *anti*-**6** remained (entries 3-5). The best results were obtained using 2.5 eq. of *i*-PrMgCl in THF at room temperature for 1 min: after trapping, ester **13** was isolated in 75% yield (entry 5). This 75% yield of **13** is similar to the 84% yield of sulfoxide exchange by-product **14** indicating that any side-reactions of Grignard reagent **15** can be minimised with a 1 min reaction time.

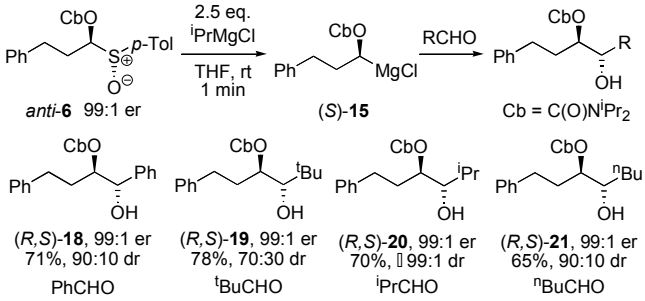
Significantly, we then showed that the Grignard reagent (*S*)-**15** was configurationally stable at room temperature during the sulfoxide → Mg exchange and trapping. Three examples are shown in Scheme 5. Sulfoxide *anti*-**6** of 99:1 er was treated with *i*-PrMgCl in THF at room temperature for 1 min (to give Grignard reagent (*S*)-**15**) and then reacted with MeO_2CCl, CuBr•SMe_2/allyl bromide or cyclohexanone to give (*R*)-**13** (of known configuration[21d]), (*R*)-**16** and (*R*)-**17** respectively, each in 99:1 er. The enantiomers of the products depicted in Scheme 5 are equally accessible starting from *syn*-**6**: for example, sulfoxide → Mg exchange on *syn*-**6** and trapping gave (*S*)-**17** in 74% yield and 99:1 er.

Scheme 5. Synthesis of trapped products in 99:1 er *via* sulfoxide → Mg exchange with *anti*-6.



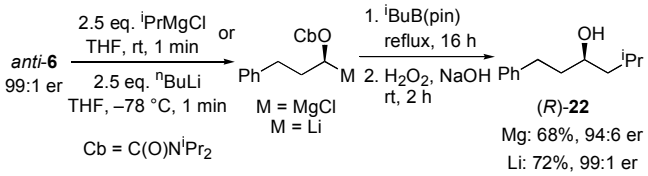
Reaction of the Grignard reagent (*S*)-**15** derived from *anti*-**6** with aldehydes was also explored (Scheme 6). These reactions gave protected diols (*R*,*S*)-**18**-**21** with *anti*-diastereoselectivity (70:30 to ≥99:1 dr, inseparable mixtures) in 65-78% yields, each diastereomer being formed in 99:1 er. The relative configuration of (*R*,*S*)-**21** was assigned by conversion (using $LiAlH_4$) into the known[23] *anti*-diol with (*R*,*S*)-**18**-**21** assigned by analogy. This methodology represents a new, connective strategy for the asymmetric synthesis of *anti*-1,2-diols[24] which are typically synthesised in two steps (Wittig reaction and asymmetric dihydroxylation).

Scheme 6. Synthesis of monoprotected diols in 99:1 er *via* sulfoxide → Mg exchange with *anti*-6.



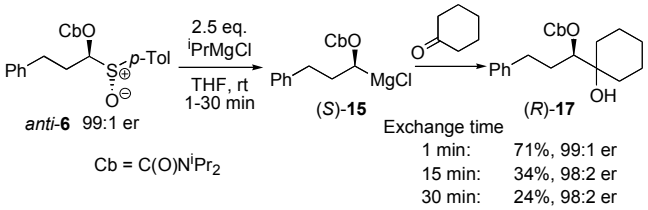
We also explored the use of sulfoxide *anti*-**6** (99:1 er) in Aggarwal-style boronate rearrangement chemistry.[4,9,19] Trapping Grignard reagent (*S*)-**15** derived from *anti*-**6** with *i*-BuB-pinacolate and subsequent oxidation (H_2O_2, NaOH) gave alcohol (*R*)-**22** in 68% yield but only 94:6 er (Scheme 7). Such a lack of stereospecificity in the rearrangement with Mg is precedented[15,19a] and we turned to Li to solve the problem. Thus, sulfoxide → Li exchange of sulfoxide *anti*-**6** using *n*-BuLi (THF, –78 °C, 1 min) and reaction with *i*-BuB-pinacolate (reflux, 16 h) followed by oxidation gave alcohol (*R*)-**22** in 72% yield and 99:1 er (Scheme 7).

Scheme 7. Use of sulfoxide *anti*-6 in boronate rearrangement chemistry to give alcohol (*R*)-22 in 99:1 er.



Finally, with simple access to Grignard reagent (*S*)-**15** (of 99:1 er), we were in a position to investigate its configurational stability over longer times than 1 min. With sulfoxide → Mg exchange reaction times of 15 and 30 min, trapping with cyclohexanone gave alcohol (*R*)-**17** in 98:2 er (34% and 24% yield respectively) (Scheme 8). The low yields with extended sulfoxide → Mg exchange times are due to the chemical instability of Grignard reagent (*S*)-**15** (as discussed previously). From this marginal loss of er (within the error limits of HPLC detection), we conclude that α-functionalised Grignard reagent (*S*)-**15** is configurationally stable at room temperature for 30 min. This is a significant observation in the context of configurational stability of α-functionalised organometallic reagents.

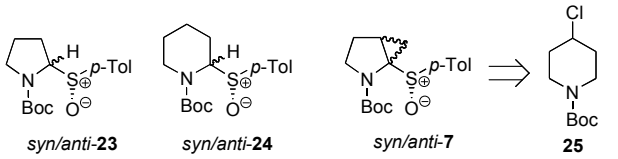
Scheme 8. Investigation of the configurational stability of α-functionalised Grignard reagent (*S*)-15.



Preparation and Reactions Enantiopure of α-Amino Grignard Reagents

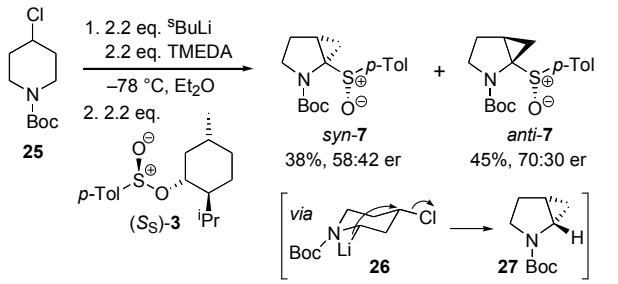
Our attention then switched to *N*-Boc heterocycles. Unfortunately, attempts to prepare α-amino sulfoxides *syn*/*anti*-**23** and *syn*/*anti*-**24** (Figure 2) by deprotonation (*s*-BuLi, TMEDA, –78 °C) and sulfinate trapping of *N*-Boc pyrrolidine and *N*-Boc piperidine respectively were unsuccessful. Other routes to *syn*/*anti*-**23** and *syn*/*anti*-**24** (*e.g.* oxidation of the sulfides) were explored with no success. We suspect that α-amino sulfoxides *syn*/*anti*-**23** and *syn*/*anti*-**24** are unstable due to α-elimination of the sulfoxide promoted by the nitrogen lone pair. Our attention thus focused on α-amino sulfoxides *syn*/*anti*-**7** (derived from *N*-Boc chloropiperidine **25** as reported by Beak,[25] Figure 2) since α-elimination should be disfavoured by the [3.1.0] bicyclic system. Furthermore, the highest enantioselectivity reported for the *s*-BuLi/(–)-sparteine-mediated desymmetrisation of 4-chloro and 4-tosyl *N*-Boc piperidines was only 78:22 er.[25b,25c] Our sulfoxide methodology could thus provide a significant improvement by generating products in 99:1 er.

Figure 2. α-Amino sulfoxides *syn*/*anti*-23, *syn*/*anti*-24 and *syn*/*anti*-7.



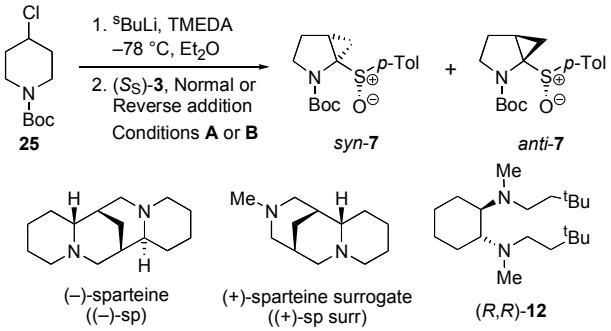
To start with, racemic deprotonation of 4-chloro *N*-Boc piperidine **25** was carried out using 2.2 eq. of *s*-BuLi/TMEDA (Scheme 9). Mechanistically, the reaction proceeds *via* cyclisation of α-lithiated piperidine **26** to cyclopropane **27** which undergoes a second α-lithiation before electrophilic trapping. In this case, addition of 2.2 eq. of Andersen's sulfinate (S_S)-**3** to the solution of the organolithium reagent gave, after warming to room temperature over 18 h, sulfoxides *syn*-**7** (38%, 58:42 er) and *anti*-**7** (45%, 70:30 er) (Scheme 9). Notably, α-amino sulfoxides *syn*/*anti*-**7** were stable, isolable compounds unlike their more simple pyrrolidine analogues *syn*/*anti*-**23**. The lack of stereospecificity at sulfur was more pronounced with α-amino sulfoxides *syn*-**7** and *anti*-**7** compared to the corresponding α-alkoxy carbmates *anti*-**6** and *syn*-**6** (Scheme 2). This probably reflects the fact that the lithated cyclopropyl *N*-Boc pyrrolidine is the better leaving group in the sulfoxide → Li exchange process that results in the loss of er. The configurational assignment of sulfoxides *syn*-**7** and *anti*-**7** is presented later (*vide infra*).

Scheme 9. Racemic deprotonation of *N*-Boc chloropiperidine 25 and trapping with Andersen's sulfinate (S_S)-3.



As with the *O*-alkyl carbamates, we explored shorter reaction times, reverse addition and chiral diamines in order to prepare α-amino sulfoxide *syn*-**7** in 99:1 er (Table 3). Using TMEDA and reverse addition with a 5 min trapping time at –78 °C, better results were obtained: sulfoxide *syn*-**7** was formed in 39% yield and 89:11 er and sulfoxide *anti*-**7** was isolated in 44% yield and 88:12 er (entry 3). Before investigating the chiral diamines in the synthesis of α-amino sulfoxides *syn*-**7** and *anti*-**7**, we explored their inherent *enantioselectivity* in the deprotonation-cyclisation-trapping of 4-chloro *N*-Boc piperidine **25** (trapping with PhNCO, see Supporting Information): (–)-sparteine gave 56:44 er;[26] (+)-sparteine surrogate gave 54:46 er and diamine (*S*,*S*)-**12** gave the highest enantioselectivity of 67:33 er. Not surprisingly, low enantioselectivity with (–)-sparteine and the (+)-sparteine surrogate led to moderate yields and only slightly improved ers of the expected major diastereomers *syn*-**7** (27%, 96:4 er) and *anti*-**7** (27%, 93:7 er) respectively upon trapping with (S_S)-**3** (entries 4/5). However, the combination of diamine (*R*,*R*)-**12** and (S_S)-**3** was optimal and gave sulfoxide *syn*-**7** in 53% yield and 99:1 er (entry 6). Notably, this synthesis of sulfoxide *syn*-**7** in 99:1 er does not rely on the use of (–)-sparteine. Finally, starting from **25**, use of diamine (*S*,*S*)-**12** and trapping with (S_S)-**3** gave sulfoxide *anti*-**7** in only 87:13 er (54% yield). Unlike the *O*-alkyl carbamates, it was not possible to access both α-amino sulfoxides *syn*-**7** and *anti*-**7** in 99:1 er. Presumably, the diamine plays a role in facilitating loss of er at sulfur by sulfoxide → Li exchange, especially if the initial enantioselectivity from the asymmetric deprotonation step is moderate (67:33 er with diamine (*R*,*R*)-**12** or (*S*,*S*)-**12**). Nonetheless, (+)-menthol is commercially available and thus would allow access to *ent*-*syn*-**7** in 99:1 er *via* deprotonation of 4-chloro *N*-Boc piperidine **25** using diamine (*S*,*S*)-**12** and trapping with sulfinate (R_S)-**3**.

Table 3. Synthesis of α-amino sulfoxides *syn*-7 and *anti*-7.

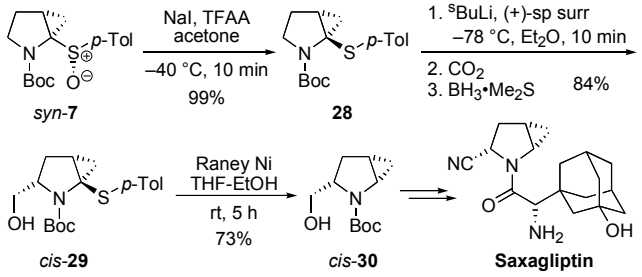


Entry	Diamine[a]	Trapping conditions[b]	*syn*-7 %,[c] er[d]	*anti*-7 %,[c] er[d]
1	TMEDA	Normal, **A**	38, 58:42	45, 70:30
2	TMEDA	Normal, **B**	36, 80:20	47, 78:22
3	TMEDA	Reverse, **B**	39, 89:11	44, 88:12
4	(–)-sp	Reverse, **B**	27, 96:4	24, 89:11
5	(+)-sp surr	Reverse, **B**	26, 99:1	27, 93:7
6	(*R*,*R*)-**12**	Reverse, **B**	51, 99:1	25, 87:13
7	(*S*,*S*)-**12**	Reverse, **B**	12, 89:11	54, 87:13

[a] 2.2 eq. *s*-BuLi/diamine, Et_2O, –78 °C, 1 h. [b] Normal = addition of (S_S)-**3** to organolithium; Reverse = addition of organolithium to (S_S)-**3**; Trapping conditions **A**: –78 °C → rt and then 18 h at rt; Trapping conditions **B**: –78 °C for 5 min. [c] % Yield after chromatography. [d] Er determined by chiral stationary phase (CSP)-HPLC.

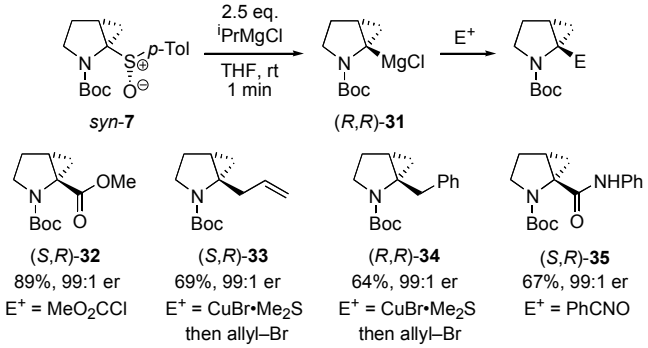
The configuration of sulfoxide *syn*-**7** was assigned based on the known[25c] deprotonation-cyclisation of 4-chloro *N*-Boc piperidine **25** using *s*-BuLi/(–)-sparteine, the known[27] deprotonation of *N*-Boc piperidine using *s*-BuLi/(*R*,*R*)-**12** and the conversion of *syn*-**7** into known[28] amino alcohol *cis*-**30** (Scheme 10). Thus, the sulfoxide in *syn*-**7** was reduced to the sulfide **28** (using NaI and trifluoroacetic anhdyride). Then, ligand-controlled diastereoselective lithiation[22] (*s*-BuLi/(+)-sparteine surrogate), carbon dioxide trapping and borane reduction gave alcohol *cis*-**29** as a single diastereomer. Use of *s*-BuLi/TMEDA gave *cis*-**29** in only 68:32 dr. Finally, reductive cleavage of the sulfide gave amino alcohol *cis*-**30**. The relative and absolute configuration was established by comparison of spectroscopic and optical rotation data with known *cis*-**30**.[28] The preparation of *cis*-**30** also completes a formal synthesis of saxagliptin, a drug for the treatment of type 2 diabetes.[28,29]

Scheme 10. Synthesis of known amino alcohol *cis*-30 from sulfoxide *syn*-7 and formal synthesis of saxagliptin.



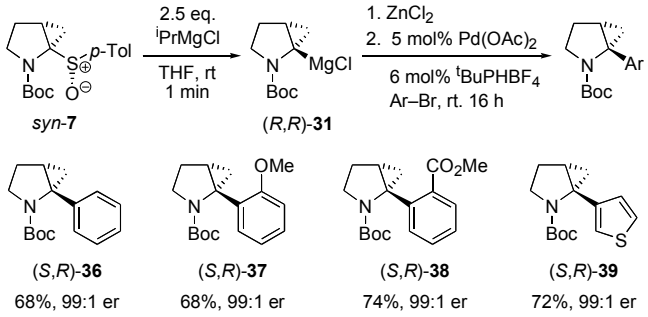
With ready access to α-amino sulfoxide *syn*-**7** in 99:1 er, sulfoxide → Mg exchange and subsequent trapping of α-functionalised Grignard reagent (*R*,*R*)-**31** with electrophiles was explored. The sulfoxide → Mg exchange on sulfoxide *syn*-**7** (99:1 er) worked well using 2.5 eq. of *i*-PrMgCl in THF at room temperature for 1 min. Direct electrophilic trapping delivered (*S*,*R*)-**32**-**33**, (*R*,*R*)-**34** and (*S*,*R*)-**35** in 99:1 er (64-89% yield) using MeO_2CCl, allyl bromide/CuBr•SMe_2, benzyl bromide/CuBr•SMe_2 and PhNCO respectively (Scheme 11). In these cases, due to the bicyclic system, configurational stability of the intermediate Grignard reagent (*R*,*R*)-**31** is assured.

Scheme 11. Synthesis of trapped products in 99:1 er *via* sulfoxide → Mg exchange with *syn*-7.



Finally, we also showed that α-functionalised Grignard reagent (*R*,*R*)-**31** derived from *syn*-**7** could be coupled with aryl bromides (*via* transmetallation to Zn and Pd-mediated Negishi coupling[18,24]). In this way, arylated heterocycles (*S*,*R*)-**36**-**39** were generated in 99:1 er (Scheme 12). Thus, a wide range of substituted *N*-Boc cyclopropyl pyrrolidines are now accessible in 99:1 er *via* asymmetric deprotonation using *s*-BuLi/diamine (*R*,*R*)-**12**, trapping with sulfinate (S_S)-**3** and subsequent sulfoxide → Mg exchange and electrophilic trapping.

Scheme 12. Sulfoxide → Mg exchange and Negishi coupling to give arylated products in 99:1 er from *syn*-7.



Conclusion

In conclusion, we present a new strategy for the generation of enantiopure α-functionalised chiral Grignard reagents *via* asymmetric deprotonation, trapping with Andersen's sulfinate (S_S)-**3** and sulfoxide → Mg exchange. Using α-alkoxy- and α-amino sulfoxides *anti*-**6** and *syn*-**7** in ≥99:1 dr and ≥99:1 er, access to a range of enantiopure α-substituted products (*via* sulfoxide → Mg exchange at room temperature for 1 min and trapping) is possible. Our methodology does not rely on the use of (–)-sparteine for the asymmetric deprotonation step and delivers a wide range of previously inaccessible α-substituted products in 99:1 er. In the course of our studies, we have identified two important aspects. First, in the deprotonation and trapping with Andersen's sulfinate (S_S)-**3**, there is a lack of stereospecificity at sulfur due to attack of a lithiated intermediate onto the sulfur in the α-alkoxy- and α-amino sulfoxides as they form. Second, the α-alkoxy-substituted Grignard reagent (*S*)-**15** is configurationally stable at room temperature for 30 minutes. Finally, extension of this approach to ac-

cess chiral α-functionalised Grignard reagents from a wide range of asymmetric deprotonation reactions without the need for (–)-sparteine can be envisaged.

ASSOCIATED CONTENT

Supporting Information. Full experimental procedures and spectroscopic data, copies of NMR spectra and CSP-HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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