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Preparation and Reactions of Enantiomerically Pure α-Functionalized Grignard Reagents

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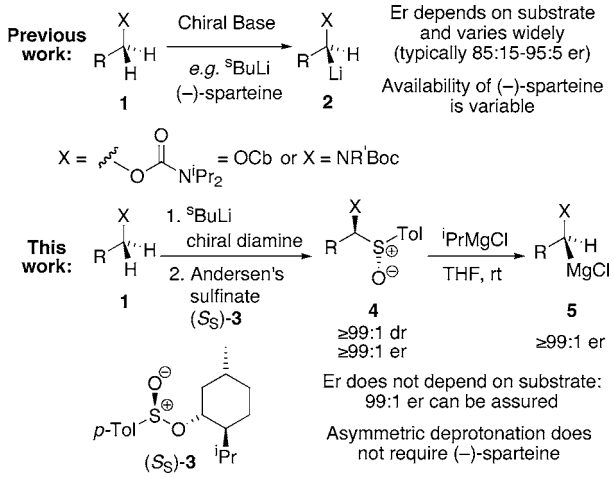
Supporting Information

ABSTRACT: A strategy for the generation of enantiomerically pure α-functionalized 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 min) 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 min.

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-functionalized 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.

Scheme 1. Comparison of Asymmetric Deprotonation with Asymmetric Deprotonation-Chiral Sulfinate Trapping



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-functionalized sulfoxides **4** would then generate chiral α-functionalized 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.

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

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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-functionalized 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-functionalized Grignard reagents have a higher degree of configurational stability than their organolithium counterparts.[11] While there are some related sulfoxide → Li exchanges[12] (especially in the area of chiral ferrocene synthesis),[12a,c] we know of only two specific cases where enantioenriched α-functionalized 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 summarized 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-functionalized Grignard reagents derived from sulfoxides *anti*-**6** and *syn*-**7** (Figure 1), the synthesis of which does not require (−)-sparteine.

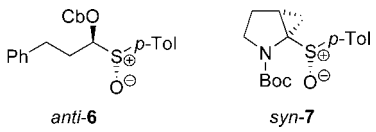
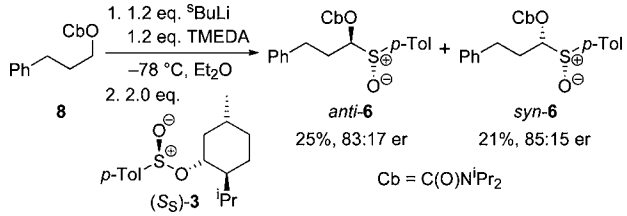


Figure 1. α-Substituted sulfoxides *anti*-**6** and *syn*-**7**.

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 recognized 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 equiv of *s*-BuLi/TMEDA in Et_2O at −78 °C and addition of 2.0 equiv 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

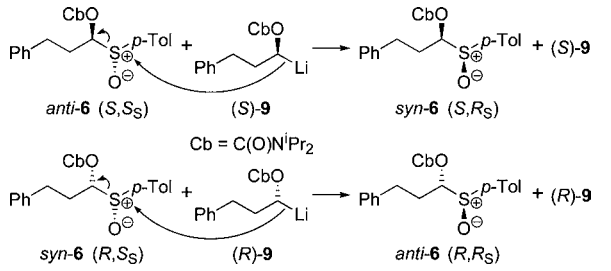
Scheme 2. Racemic Deprotonation of *O*-Alkyl Carbamate 8 and Trapping with Andersen's Sulfinate (S_S)-3



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 epimerization of Andersen's sulfinate (S_S)-**3** during the reaction as the excess (S_S)-**3** was recovered unchanged.

Our proposed mechanism to account for the lack of stereospecificity in the trapping step is shown in Scheme 3.

Scheme 3. Proposed Mechanism to Account for Lack of Stereospecificity in Trapping with Sulfinate (S_S)-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**.

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 equiv of *s*-BuLi/TMEDA in Et_2O at −78 °C, and then 1.0 equiv 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 synthesized and characterized, see Supporting Information) indicating that

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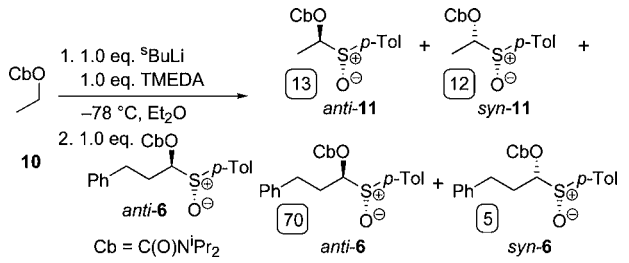
Scheme 4. Crossover-Type Experiment to Establish the Viability of the Proposed Sulfoxide → Li Exchange Process



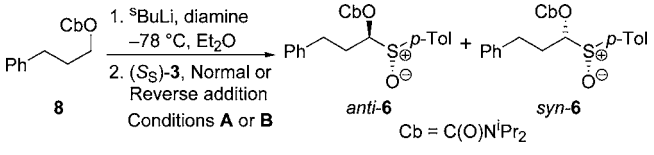
the proposed sulfoxide → Li exchange was occurring, even at −78 °C. It is also notable that some *syn*-**6** was also present. This suggests that lithiated carbamates (*S*)-**9** and (*R*)-**9** are formed in the solution, as necessitated by the sulfoxide → Li exchange.

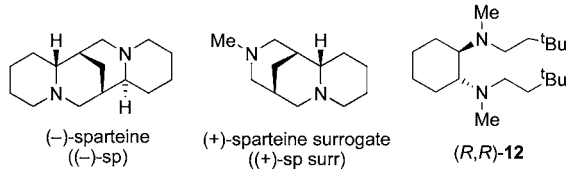
With a mechanism for the lack of stereospecifity at sulfur established, we then attempted to minimize the loss of er in the trapping with Andersen's sulfinate (S_S)-**3**. The reaction time was reduced from warming to room temperature over 18 h (conditions A) to 5 min at −78 °C (MeOH quench, conditions 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 summarized 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).

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 center 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. Optimization was carried out using racemic *anti*-**6** which was treated with 1.3−2.5 equiv of *i*-PrMgCl in THF at room temperature before trapping with MeO_2CCl. This gave ester **13** together with the sulfoxide **14**, the byproduct of the sulfoxide exchange process. In addition, some of *O*-alkyl carbamate **8** and starting material, *anti*-**6**, were also isolated (Table 2).

Table 1. Synthesis of α-Alkoxy Sulfoxides *anti*-6 and *syn*-6

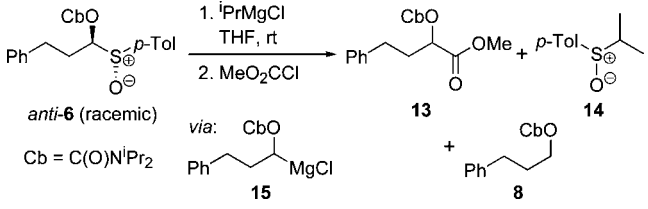




entry	diamine[a]	trapping conditions[b]	*anti*-**6** %,[c] er[d]	*syn*-**6** %,[c] er[d]
1	TMEDA	normal, A	25, 83:17	21, 85:15
2	TMEDA	normal, B	23, 88:12	32, 91:9
3	TMEDA	reverse, B	25, 87:13	29, 90:10
4	(−)-sp	normal, A	53, 99:1	0.2, nd
5	(+)-sp surr	normal, A	7, 87:13	45, 99:1
6	(*R*,*R*)-**12**	reverse,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

[a]1.2 equiv *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.

Table 2. Optimisation of Sulfoxide → Mg Exchange with *anti*-6



entry	equiv 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 equiv 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 or 2.5 equiv 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 equiv of *i*-PrMgCl in THF at room

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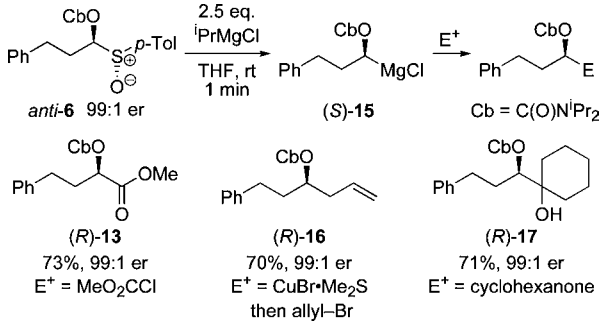
temperature for 1 min; after trapping, ester **13** was isolated in 75% yield (entry 5). This 75% yield of **13** is similar to the 84% yield of sulfoxide exchange byproduct **14** indicating that any side reactions of Grignard reagent **15** can be minimized with a 1 min reaction time.

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

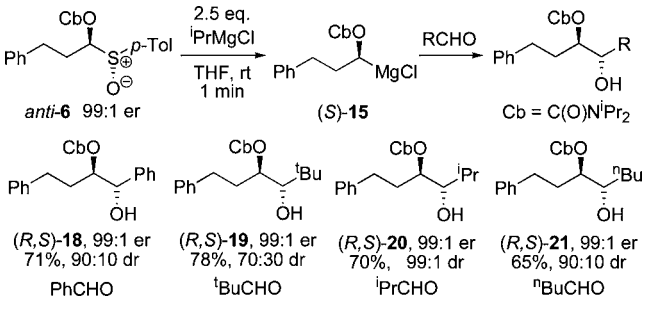
Scheme 5. Synthesis of Trapped Products in 99:1 er via Sulfoxide → Mg Exchange with *anti*-6



i-PrMgCl in THF at room temperature for 1 min (to give Grignard reagent (*S*)-**15**) and then reacted with MeO_2CCl, $CuBr{\cdot}SMe_2$/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**, e.g., sulfoxide → Mg exchange on *syn*-**6**, and trapping gave (*S*)-**17** in 74% yield and 99:1 er.

Reaction of the Grignard reagent (*S*)-**15** derived from *anti*-**6** with aldehydes was also explored (Scheme 6). These reactions

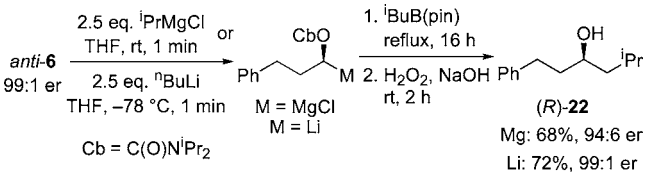
Scheme 6. Synthesis of Monoprotected Diols in 99:1 er via Sulfoxide → Mg Exchange with *anti*-6



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 synthesized in two steps (Wittig reaction and asymmetric dihydroxylation).

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

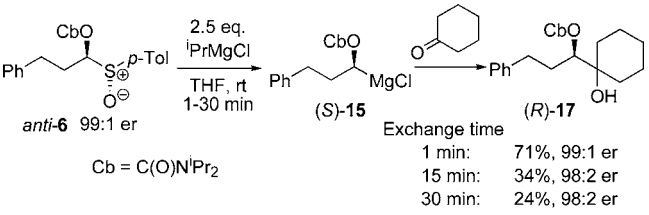
Scheme 7. Use of Sulfoxide *anti*-6 in Boronate Rearrangement Chemistry to Give Alcohol (*R*)-22 in 99:1 er



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).

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

Scheme 8. Investigation of the Configurational Stability of α-Functionalized Grignard Reagent (*S*)-15



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-functionalized 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-functionalized organometallic reagents.

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 deproto-

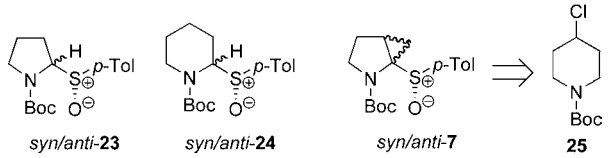


Figure 2. α-Amino sulfoxides *syn*/*anti*-**23**, *syn*/*anti*-**24** and *syn*/*anti*-7.

nation (*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

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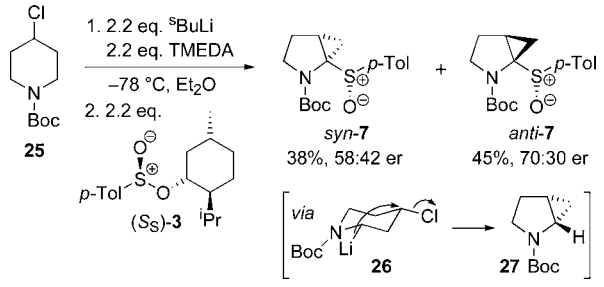
the nitrogen lone pair. Our attention thus focused on α-amino sulfoxides *syn*/*anti*-**7** (derived from *N*-Boc chloropiperidine **25** as reported by Beak,[25] Figure 2) since α-elimination should be disfavored by the [3.1.0] bicyclic system. Furthermore, the highest enantioselectivity reported for the *s*-BuLi/(−)-sparteine-mediated desymmetrisation of 4-chloro and 4-tosyl *N*-Boc piperidines was only 78:22 er.[25b,c] Our sulfoxide methodology could thus provide a significant improvement by generating products in 99:1 er.

To start with, racemic deprotonation of 4-chloro *N*-Boc piperidine **25** was carried out using 2.2 equiv of *s*-BuLi/TMEDA (Scheme 9). Mechanistically, the reaction proceeds

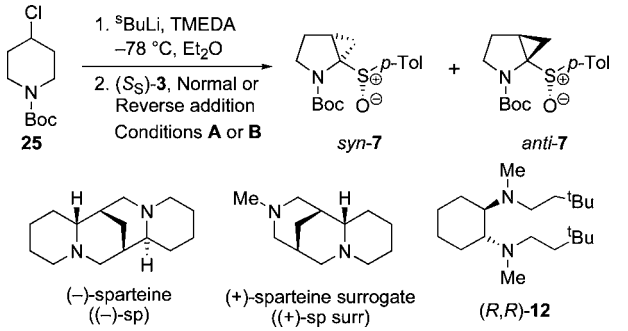
Scheme 9. Racemic Deprotonation of *N*-Boc Chloropiperidine 25 and Trapping with Andersen's Sulfinate (S_S)-3



via cyclization of α-lithiated piperidine **26** to cyclopropane **27**, which undergoes a second α-lithiation before electrophilic trapping. In this case, addition of 2.2 equiv 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*).

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−cyclization−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

Table 3. Synthesis of α-Amino Sulfoxides *syn*-7 and *anti*-7



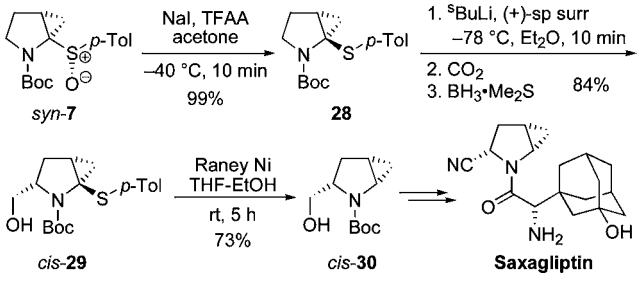
entry	diamine[a]	trapping conditions[b]	*syn*-7 %,[c] er[d]	*anti*-7 %,[c] er[d]
1	TMEDA	normal, A	38, 58:42	45, 70:30
2	TMEDA	normal, B	36, 80:20	47, 78:22
3	TMEDA	reverse, B	39, 89:11	44, 88:12
4	(−)-sp	reverse, B	27, 96:4	24, 89:11
5	(+)-sp surr	reverse, B	26, 99:1	27, 93:7
6	(*R*,*R*)-**12**	reverse,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

[a]2.2 equiv *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.

(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**.

The configuration of sulfoxide *syn*-**7** was assigned based on the known[25c] deprotonation−cyclization 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

Scheme 10. Synthesis of Known Amino Alcohol *cis*-30 from Sulfoxide *syn*-7 and Formal Synthesis of Saxagliptin



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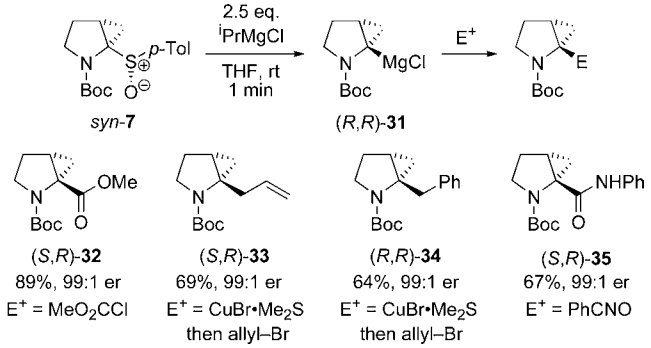
reduction gave alcohol *cis*-**29** as a single diastereomer. Use of *s*-BuLi/TMEDA gave *cis*-**29** in only 68:32 dr. Finally, reductive cleavage of the sulfide gave amino alcohol *cis*-**30**. The relative and absolute configuration was established by comparison of spectroscopic and optical rotation 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]

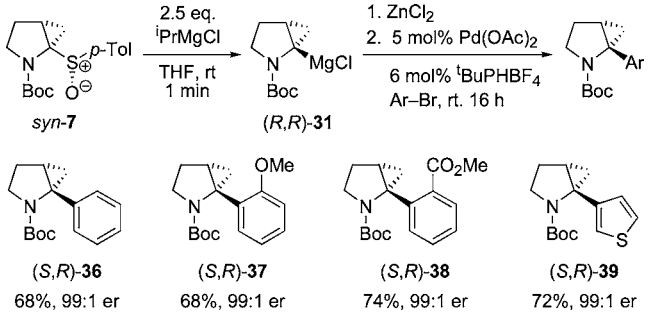
With ready access to α-amino sulfoxide *syn*-**7** in 99:1 er, sulfoxide → Mg exchange and subsequent trapping of α-functionalized Grignard reagent (*R*,*R*)-**31** with electrophiles were explored. The sulfoxide → Mg exchange on sulfoxide *syn*-**7** (99:1 er) worked well using 2.5 equiv of *i*-PrMgCl 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-functionalized Grignard reagent (*R*,*R*)-**31** derived from *syn*-**7** could be coupled with aryl bromides (via transmetalation to Zn and Pd-mediated Negishi coupling).[18,30] 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 is 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-functionalized 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 min. Finally, extension of this approach to access chiral α-functionalized 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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