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COMMUNICATION

Addition of Highly Polarized Organometallic Compounds to *N-tert*-Butanesulfinyl Imines in Deep Eutectic Solvents under Air: Preparation of Chiral Amines of Pharmaceutical Interest

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In memory of Professor Hans J. Reich, a pioneer of organolithium chemistry, who has left an indelible mark in this field.

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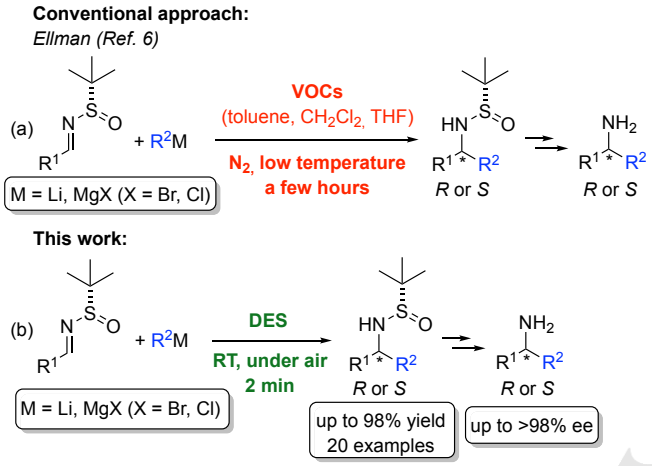
Abstract: We first report that highly polarized organometallic compounds of s-block elements add smoothly to chiral *N-tert*-butanesulfinyl imines in the biodegradable D-sorbitol/choline chloride eutectic mixture, thereby granting access to enantioenriched primary amines after quantitatively deblocking the sulfinyl group. The practicability of the methodology was further highlighted by (a) working at ambient temperature and under air, (b) very short reaction times (2 min), (c) the preparation of diastereomeric sulfinamides in very good yields (74–98%) and with a broad substrate scope, (d) the possibility of scaling up the process, and (e) the asymmetric synthesis of both the chiral amine side-chain of (*R*,*R*)-Formoterol (96% ee) and the pharmaceutically relevant (*R*)-Cinacalcet (98% ee).

Chiral nonracemic primary amines are well-established and flexible building blocks for the synthesis of valuable active pharmaceutical ingredients (APIs) and intermediates thereof, agrochemicals, fragrances, and are also key players in organocatalysis and in catalytic asymmetric synthesis.[1] The asymmetric reduction of a prochiral precursor containing the C=N moiety represents among one of the most pursued approaches to synthesize chiral amines. Enantioselective methodologies include transition metal-catalyzed amination reactions in the presence of amine sources and reductants,[2] organocatalyzed strategies,[3] and biotechnological processes.[4] Diastereoselective methodologies usually encompass reduction of Schiff bases derived from carbonyl compounds containing removable chiral amine auxiliaries (e.g., phenylethylamine).[5] Within this context, the nucleophilic addition of highly polarized organometallic reagents to chiral *N-tert*-butanesulfinyl imines, pioneered by Ellman and co-workers, followed by the removal of the *N-tert*-butanesulfinyl auxiliary group, represents a versatile approach to forge new C-C bonds *en route* to chiral α-branched amines.[6] These reactions, however, are typically carried out in toxic, anhydrous and aprotic volatile organic compounds (VOCs) (e.g., THF, CH_2Cl_2, toluene), at low temperature (up to -78 °C), under inert atmospheres, and for reaction times of a few hours (Scheme 1a).

Recent, independent ground-breaking studies by Hevia, García-Álvarez and our group has led to a profound paradigm shift in the way s-block organometallic compounds can be used in organic synthesis.[7] It was indeed shown that these commodity reagents are truly compatible with environmentally responsible, bio-inspired protic solvents like the so-called deep eutectic solvents (DESs).[8] As a consequence, they have been successfully employed as nucleophilic partners either to promote addition reactions to unsaturated functional groups such as carbonyl derivatives,[9] imines,[10] styrene derivatives,[11] amides,[12] and nitriles[10b,13] in DESs, glycerol and even water or to trigger fast, direct Pd-catalyzed cross-coupling reactions under "on water" conditions.[14] Building upon these findings, we were eager to investigate the usefulness of sustainable, unconventional reaction media to prepare enantiomerically enriched primary amines. Here we first show that the nucleophilic

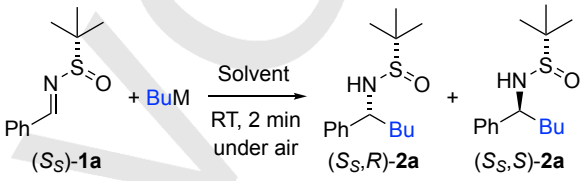
addition of both organolithium and Grignard reagents to *N-tert*-butanesulfinyl imines are feasible in DESs, working at room temperature (RT, 25 °C) and under air, thereby granting access to both enantiomers of chiral α,α-disubstituted primary amines in overall yields up to 98% and within 2 min reaction time (Scheme 1b). Comparison of DESs with water and other solvents as reaction media have been provided and discussed. The application and the utility of the described protocol was additionally demonstrated by the whole synthesis of (*R*)-Cinacalcet and of the chiral amine side chain of (*R,R*)-Formoterol in a choline chloride (ChCl)-based eutectic mixture.



Scheme 1. Organometallic nucleophilic addition to sulfinyl imines using (a) VOCs under inert atmospheres and at low temperature (up to -78 °C) or (b) DES at room temperature (RT, 25 °C) and under air (ee = enantiomeric excess).

We elected to study the reaction between S_S-sulfinyl imine **1a** (0.5 mmol) and commercially available *n*-BuLi as a model system for the preparation of sulfinamide **2a** in various protic solvents and mixtures. We first investigated the reaction in water. When 1.4 equiv of *n*-BuLi (2.0 M in cyclohexane) were quickly spread over a suspension of **2a** in water (1 mL), at RT and under air and vigorous stirring to generate an emulsion, followed after 2 min reaction time by dilution with the environmentally friendly cyclopentyl methyl ether (CPME)[15] (5 mL), adduct **2a** was isolated in 87% yield as a separable mixture of two diastereomers [diastereomeric ratio (dr) 65:35 in favor of (S_S,*R*)-**2a**]. The absolute configuration of the two diastereomers was secured by comparing their NMR spectroscopic data with those reported in the literature (Table 1, entry 1) (ESI). By carrying out the reaction in the absence of any solvent, the yield of **2a** was 72% only (dr: 65:35), whereas by changing water to pure glycerol (Gly) the yield of **2a** dropped down to 17% (dr: 58:42) (Table 1, entries 2,3). We then screened this transformation in some prototypical choline chloride (ChCl)-based eutectic mixtures, namely ChCl/Gly (1:2 mol mol^{-1}), ChCl/urea (1:2 mol mol^{-1}), ChCl/L-lactic acid (LA) (1:2 mol mol^{-1}), ChCl/H_2O (1:2 mol mol^{-1}), ChCl/ethylene glycol (EG) (1:2 mol mol^{-1}), D-isosorbide/ChCl (2:1 mol mol^{-1}), ChCl/D-fructose (1:2 mol mol^{-1}) and D-sorbitol/ChCl (1:1 mol mol^{-1}) (Table 1, entries 4–11). Sugar-based eutectic mixtures emerged among as optimal regarding the yield of **2a**, and in D-sorbitol/ChCl adduct **2a** formed in 98% yield as the sole product (dr: 65:35) (Table 1, entry 11). A lower yield (66%) was instead achieved by decreasing the number of equiv of *n*-BuLi from 1.4 to 1.1 (Table 1, entry 12). The effectiveness of this transformation was still maintained when *n*-BuMgCl was alternatively used (**2a**: 91% yield), but no reaction occurred when *n*-BuMgCl was reacted with **2a** in water (Table 1, entries 13,14). The addition of *n*-BuLi or *n*-BuMgCl in the presence of a Lewis acid additive like LiCl (2 equiv) gave no improvement on the yield and stereoselectivity of the transformation (Table 1, entries 15,16). Scaling up the process was also successful. Indeed, the reaction of (S_S)-**1a** (5 mmol, 1.05 g) with *n*-BuLi (1.4 equiv) in 5.0 g of D-sorbitol/ChCl resulted In the formation of (S_S,*R*)-**2a** in 96% (1.28 g) isolated yield (Table 1, entry 11).

Table 1. Synthesis of sulfinamide **2a** from *n*-BuLi or *n*-BuMgCl and sulfinyl imine **1a** in different solvents: reaction condition optimization.[a]

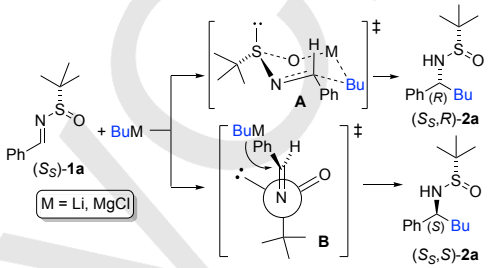


Entry	BuM	Solvent	**2a** yield (%)	dr[b]
1	*n*-BuLi	H_2O[c]	87[d]	65:35
2	*n*-BuLi	–	72[d]	65:35
3	*n*-BuLi	Gly[c]	17[b]	58:42
4	*n*-BuLi	ChCl/Gly[c]	31[b]	61:39
5	*n*-BuLi	ChCl/urea[c]	28[b]	50:50
6	*n*-BuLi	ChCl/LA[e]	NR[f]	–
7	*n*-BuLi	ChCl/H_2O[c]	32[b]	58:42
8	*n*-BuLi	ChCl/EG[e]	48[b]	60:40
9	*n*-BuLi	D-isosorbide/ChCl[e]	49[b]	64:36
10	*n*-BuLi	D-fructose/ChCl[c]	85[d]	65:35
11	***n*-BuLi**	**D-sorbitol/ChCl[e]**	**98[d,g]**	**65:35**
12	*n*-BuLi[h]	D-sorbitol/ChCl[e]	66[d]	65:35
13	*n*-BuMgCl	D-sorbitol/ChCl[e]	91[d]	53:47
14	*n*-BuMgCl[i]	H_2O[c]	NR[f]	–
15	*n*-BuLi[j]	D-sorbitol/ChCl	93[d]	62:38
16	*n*-BuMgCl[j]	D-sorbitol/ChCl	90[d]	52:50

[a] Reaction conditions: 1.0 g DES or 1 mL H_2O or 1 mL Gly per 0.5 mmol of (S_S)-**1a** and 1.4 equiv BuM; DES: ChCl/Gly (1:2 mol mol^{-1}); ChCl/urea (1:2 mol mol^{-1}); ChCl/L-lactic acid (LA) (1:2 mol mol^{-1}); ChCl/H_2O (1:2 mol mol^{-1}); ChCl/ethylene glycol (EG) (1:2 mol mol^{-1}); D-isosorbide/ChCl (2:1 mol mol^{-1}); ChCl/D-fructose (1:2 mol mol^{-1}); D-sorbitol/ChCl (1:1 mol mol^{-1}). [b] Calculated by ^{1}H-NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: CH_2Br_2). [c] Heterogeneous conditions: suspension of **1a** in water, in Gly or in DES. [d] The yields reported are for products isolated and purified by column chromatography. [e] Homogeneous conditions: solution of **1a** in DES. [f] NR = no reaction; substrate **1a** was quantitatively recovered. [g] 96% isolated yield by carrying out the reaction between (S_S)-**1a** (5 mmol) and *n*-BuLi (1.4 equiv) in 5.0 g DES. [h] 1.1 equiv of *n*-BuLi. [i] 3.0 equiv of *n*-BuMgCl. [j] In the presence of 2.0 equiv of LiCl.

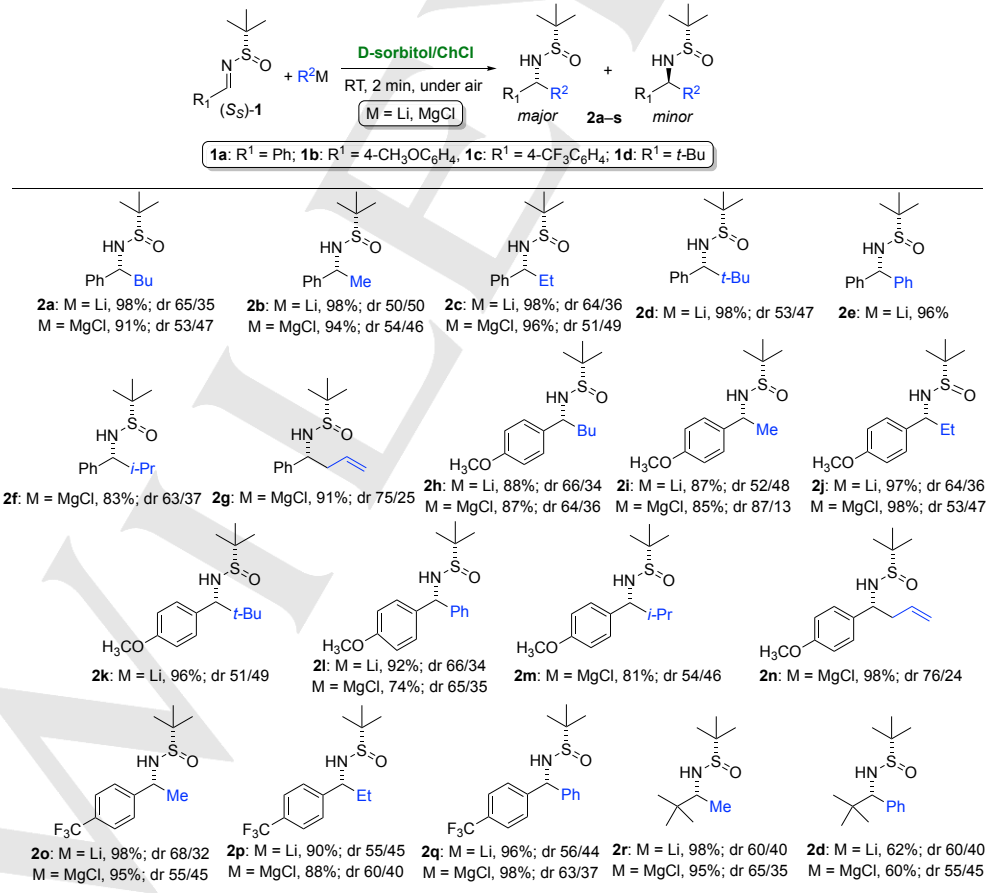
The formation of the S_S,*R*-diastereomer as the major stereoisomer is consistent with the intervention of a chelated transition state (**A**, Scheme 2), which is known to be typically favored in conventional non-coordinating reaction solvents such as toluene or CH_2Cl_2, where steric hindrance factors are mainly responsible for the selectivity. Water and DESs, however, are both characterized by strong and extended H-bond networks, where (i) protonolysis processes are disfavored compared to organolithium-promoted nucleophilic additions, and (ii) alkali metal ion-chelated supramolecular heteroaggregates are highly privileged.[7b] Overall, the poor-to-moderate diastereoselectivity observed with Grignard and organolithium reagents may likely be due to a competition between the proposed chelated and open (**B**, Scheme 2) transition states for such nucleophilic additions, the latter being favored in conventional coordinating solvents (e.g., THF).[16] It is also particularly interesting to note that despite S–N bonds have been recognized to be quite polar in nature by the topological analysis of the experimental electron density,[17] the integrity of *N*-*tert*-butanesulfinyl imine (S_S)-**1a** remains well preserved in the aforementioned DES media in the presence of organolithium/Grignard reagents.

We then evaluated the scope of the reaction by reacting several α-functionalized *N*-*tert*-butanesulfinyl imines (S_S)-**1** with representative, commercially available Grignard and organolithium reagents in a D-sorbitol/ChCl mixture at RT and under air (Table 2). The reaction is amenable to both electron-withdrawing and electron-donating groups. Indeed, either the unsubstituted arylsulfinyl imine **1a** or aryl-substituted sulfinyl imines **1b**,**c** effectively participated as electrophilic partners, thereby providing in the reaction with both aliphatic and aromatic organomagnesium chlorides (*n*-BuMgCl, MeMgCl, EtMgCl, *i*-PrMgCl, allylMgCl) and organolithiums (*n*-BuLi, MeLi, EtLi, *t*-BuLi, PhLi) the expected adducts **2a**–**q** in very good yields (RLi: 87–98%; RMgCl: 74–98%).‡



Scheme 2. Competition between chelating six-membered (**A**) and open (**B**) transition states in the nucleophilic addition of Grignard and organolithium reagents to *N*-*tert*-butanesulfinyl imines in nonconventional solvents (water and DES).

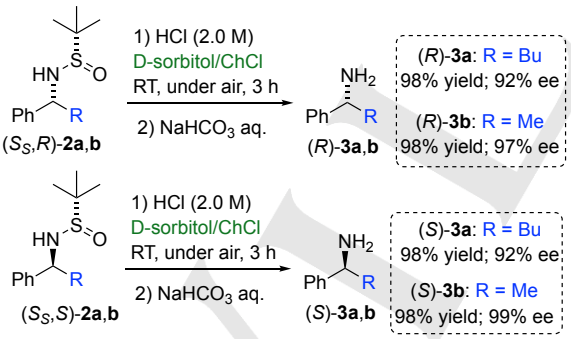
Table 2. Synthesis of sulfinamides **2a**–**r** by addition of organolithium and Grignard reagents to sulfinyl imines **1a**–**d**.[a]



[a] Reaction conditions: 1.0 g DES per 0.5 mmol of (S_S)-**1** and 1.4 equiv RM. The yields reported are for products isolated and purified by column chromatography.

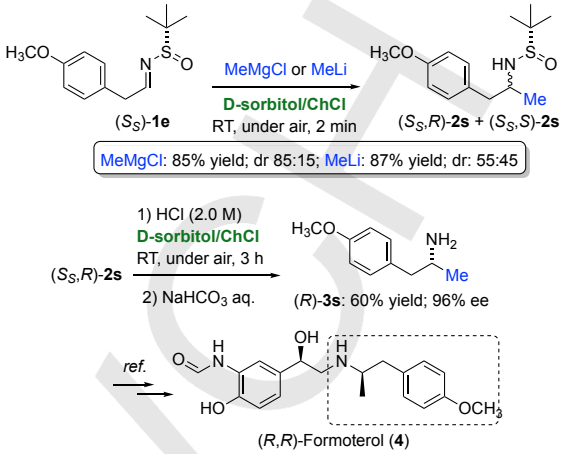
Notably, the presence of a considerably sterically hindered *t*-butyl group at the iminic carbon atom (**1d**) was equally tolerated, and the nucleophilic addition promoted by MeLi and PhLi or MeMgCl and PhMgCl delivered adducts **2r** and **2d** in overall 60–98% yield (Table 2). A secondary organolithium like *s*-BuLi, because of the presence of an additional stereogenic center, gave complex mixtures of three diastereomers, and thus its reactions were not further investigated. In all cases studied, sulfinamides **2** formed with poor-to-moderate (up to 87:13) diastereoselectivity, as assessed by ^{1}H NMR analysis of the crude reaction mixture. It is worth noting, however, that, under the best conditions, each reaction proceeded fast (2 min) at RT and under air, with high yield and high chemoselectivity. When using conventional VOCs, a higher stereoselectivity is usually offset by a low reactivity and longer reaction times (a few hours) at low temperature (up to –78 °C). Competitive imine reduction has also been observed.[6] The two diastereomers obtained using DES as solvent could always be easily separated by column chromatography on silica gel. The absolute configuration of each sulfinamide at the newly formed stereogenic center was established either by matching its ^{1}H NMR data with those of known compounds (adducts **2a**–**g**, **2i**–**o**, **2q**,**r**) or, in the case of unknown adducts (**2h** and **2p**), by DFT computations (ESI). It was also ascertained that the major stereoisomer isolated in each reaction was always the one formed via the chelating six-membered transition state (**A**, Scheme 2).

Cleavage of the sulfinyl group was easily achieved under acidic conditions (HCl 2 M) directly in a D-sorbitol/ChCl eutectic mixture at RT and under air, followed by extraction with CPME and basification with $NaHCO_3$ (ESI). The practicability of this procedure was demonstrated by the preparation of chiral nonracemic primary amines (*R*)- and (*S*)-**3a**,**b** (98% yield, up to 99% ee) from the corresponding sulfinamides (S_SR)- and (S_SS)-**2a**,**b** (Scheme 3), and of (*R*)-**3s** (60% yield, 96% ee) from sulfinamide (S_SR)-**2s**. The latter, in turn, was obtained by reacting sulfinyl imine (S_S)-**1e** with MeMgCl (85% yield; dr 85/15) or with MeLi (87% yield; dr 55/45) in D-sorbitol/ChCl and separating the two diastereomers via column chromatography (Scheme 4) (ESI).



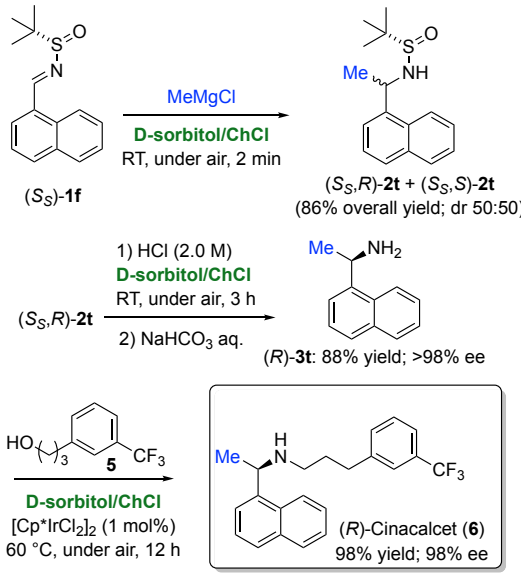
Scheme 3. Synthesis of enantioenriched amines (*R*)- and (*S*)-**3a** and (*R*)- and (*S*)-**3b** (ee: enantiomeric excess).

Enantioenriched amine (*R*)-**3s** is an important chiral intermediate for the synthesis of (*R*,*R*)-Formoterol (**4**), which is known to be a long-acting β_2-agonist used as a bronchodilator in the management of asthma and chronic obstructive pulmonary disease. Formoterol is commercialized in its racemic form, but the (*R*,*R*)-isomer was found to be 1000-fold more potent than the (*S*,*S*)-isomer.[18] The preparation of eutomer **4** has been realized so far via chemoenzymatic[19] or transition-metal-catalyzed[20] approaches using either free or protected amine (*R*)-**3s**.



Scheme 4. Synthesis of enantioenriched amine side-chain (*R*)-**3s** of (*R*,*R*)-Formoterol (**4**) (ee: enantiomeric excess).

Finally, we embarked on the asymmetric synthesis of (*R*)-Cinacalcet (**6**) (Scheme 5), which is a blockbuster drug acting as calcimimetic, and used to treat secondary hyperparathyroidism. It is sold under the brand name Sensipar in USA and Australia, as Mimpara in Europe, and as Regpara in Asia.[21] (*R*)-(+)-1-(1-Naphthyl)ethylamine (**3t**) is the key intermediate towards the preparation of this drug. Synthetic methodologies to access this enantiopure amine include (a) classical or enzymatic resolution of the racemic amine,[22] and (b) transition-metal-catalyzed asymmetric hydrogenation or hydrogen-transfer reductive amination of the corresponding sulfinyl imine or ketone, respectively.[23] Several strategies have then been developed to couple (*R*)-**3t** to the remaining skeleton of the molecule. Among these, for example, are amide reduction and reductive amination or substitution reactions.[24] All the described procedures, however, typically rely on several steps using toxic VOCs. Recent chemoenzymatic routes employing transaminases and ketoreductases as effective biocatalysts have also been explored.[25] Following the aforementioned approach, we succeeded in synthesising (*R*)-**6** in only three steps making use of D-sorbitol/ChCl as a sustainable reaction mixture. As depicted in Scheme 5, first, sulfinyl imine (S_S)-**1f** was treated with MeMgCl (1.4 equiv), at RT and under air, thereby providing sulfinamide **2t** in overall 86% yield as a mixture of two diastereomers (dr 1:1), which were separated by column chromatography. Diastereoisomer (S_S,*R*)-**2t** was then dissolved in the above eutectic mixture and treated with a solution of HCl (2.0 M) to afford free amine (*R*)-**3t** (88% yield; >98% ee). Finally, (*R*)-**3t** was directly *N*-alkylated in DES with alcohol **5** in a process mediated by the Iridum catalyst $[Cp^*IrCl_2]_2$ (1 mol%)[26] to give the desired target drug (*R*)-**6** in 98% yield and 98% ee (HPLC analysis) after 12 h reaction time at 60 °C, and working under air (Scheme 5). It is worth noting that by performing this same alkylation in toluene, at 110 °C for 17 h in a sealed reactor and under an Argon atmosphere, enantiopure (*R*)-**6** could be isolated in an overall yield of only 50%.[25]



Scheme 5. Asymmetric synthesis of (*R*)-Cinacalcet (**6**) in a D-sorbitol/ChCl eutectic mixture.

In summary, we have developed the first asymmetric synthesis of chiral primary amines in DESs using D-sorbitol/ChCl as a sustainable and biodegradable unconventional reaction mixture. The nucleophilic addition promoted by both Grignard and organolithium reagents to chiral nonracemic aromatic and aliphatic sulfinyl imines proceeded smoothly and very quicky (2 min reaction time) in the above eutectic mixture, at RT and under air, and provided the desired sulfinamides in very good yields (74–98%) regardless the presence of electron-donating or electron-withdrawing groups in the aromatic ring, though with poor-to-moderate diastereoselectivity. The two diastereomers, however, could always and easily be separated by column chromatography on silica gel and deblocked to the corresponding enantioenriched free amines in high yield (98%). Further, we have applied this methodology to synthesize in D-sorbitol/ChCl (a) the chiral amine side-chain of (*R*,*R*)-Formoterol (96% ee) and (b) the enantiopure API (*R*)-Cinacalcet (98% ee) in three steps. The described proof-of-concept protocol enables scientists to use highly polarized organometallic reagents of s-block elements directly in protic eutectic mixtures and under aerobic conditions not only to synthesize libraries of chiral nonracemic primary amines, which are prevalent structural units in pharmaceutical drug molecules and several commodity chemicals, but also to set up other sustainable metal-mediated asymmetric organic transformations.

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Keywords: deep eutectic solvents • organolithiums • Grignard reagents • imines • amines

‡ SAFETY NOTE: No particular problems were experienced during these additions. *t*-BuLi, however, is known to be prone to ignition in air and caution should be exercised in adopting the recommended procedure, especially on a larger scale.

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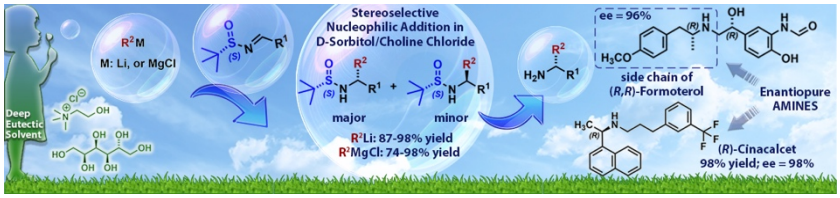

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