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Reversal of enantioselectivity on protonation of enol(ate)s derived from 2-methyl-1-tetralone using C_2-symmetric sulfonamides

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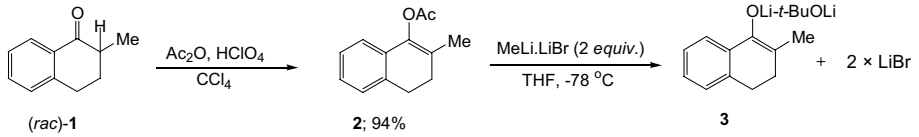
Abstract—The synthesis of enantiomerically enriched (*R*)-2-methyl-1-tetralone **1** (64% e.e.) was achieved through protonation of its lithium enolate **3** using a C_2-symmetrical bis-sulfonamide **5d** as an internal proton source. Access to the complementary (*S*)-enantiomer **1** (45% e.e.) can be achieved using an external quench strategy involving acetic acid as the external proton source.

1. Introduction

The synthesis of optical active α-substituted carbonyl compounds by enantioselective protonation of enolic and enolate species, derived from racemic carbonyl compounds is well documented.[1] However, there are a limited number of reports into the use of chiral proton donors that exhibit good levels of enantiocontrol for a wide range of structurally related ketones.[2] Within this area, there are two general approaches; the more common has focussed on the use of an internal chiral proton source, such as enantiomerically pure chiral acids,[3] whereas, the use of an external achiral proton source in the presence of a chiral ligand has attracted much less attention.[4] Reports into the comparison between these two strategies are rare.[5]

We now report our study into the use of C_2-symmetrical bis-sulfonamides as potential chiral proton donors for the enantioselective protonation of enol(ate)s derived from 2-methyl tetralone **1** and compare the use of these bis-sulfonamides as chiral scaffolds for internal and external enantioselective protonation. We were interested in the use of chiral bis-sulfonamides as proton donors due to their mild acidity.[6] For this study, we focussed on the use of chiral bis-sulfonamides[7] derived from the conformationally rigid C_2-symmetric 1,2-diaminocyclohexane (*R*,*R*)-**4** as this chiral scaffold has shown to lead to good levels of facial selectivity for a variety of enantioselective processes.[8]

We decided to use (±)-2-methyl-1-tetralone **1** as our parent ketone due to its predictable enolate stereochemistry and known enantiomeric separability,[9] and the corresponding enol acetate **2**[10] as our pro-enolate precursor due to improved thermal stability over other related enol derivatives (Scheme 1).[11] This enol acetate **2** was efficiently synthesised by addition of acetic anhydride and $HClO_4$ to a solution of (±)-2-methyl-1-tetralone **1** and CCl_4 at room temperature (Scheme 1).[10] The required



(*rac*)-**1** **2**; 94% **3**

Scheme 1. Synthesis of enol acetate **2** and conversion to the lithium enolate **3**.

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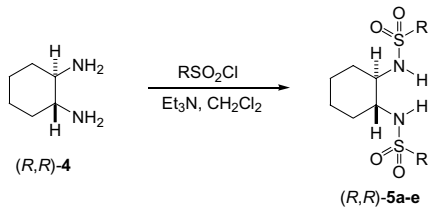


Entry	Aryl sulfonyl chloride	Bis-sulfonamide	% Yield
1	R = C_6H_5-	(*R*,*R*)-**5a**[7a]	71
2	R = 4-Me-C_6H_4-	(*R*,*R*)-**5b**[7b]	79
3	R = 1-naphthyl-	(*R*,*R*)-**5c**[7c]	72
4	R = 2-naphthyl-	(*R*,*R*)-**5d**[7d]	84
5	R = 2,4,6-(*i*-Pr)$_3$-C_6H_2-	(*R*,*R*)-**5e**[7e]	94

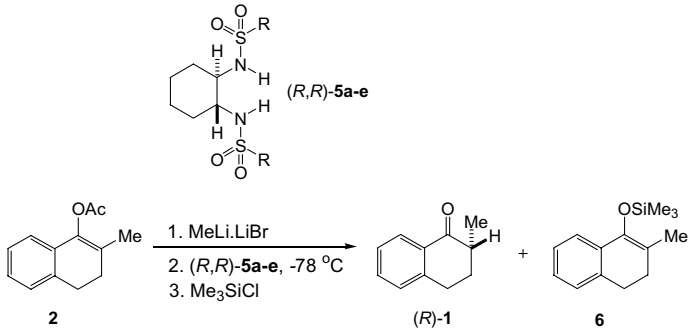
Scheme 2. Synthesis of C_2-symmetric sulfonamides (*R*,*R*)-**5a**–**e**.

lithium enolate complex **3** was liberated from the enol acetate **2** using House and Trost's approach,[12] by simple addition of MeLi·LiBr (2 equiv).[13]

We initially screened a series of structurally related C_2-symmetric bis-sulfonamides **5a**–**e**[7] as potential chiral Brønsted acids against the lithium enolate complex **3** to determine their relative facial protonation preference. The required bis-sulfonamides **5a**–**e**[7] were efficiently synthesised by addition of a variety of substituted aryl sulfonyl chlorides to a solution of (*R*,*R*)-1,2-diaminocyclohexane **4** and Et_3N in CH_2Cl_2 (Scheme 2). Addition of these sulfonamides in THF to a stirred solution of the prostereogenic lithium enolate **3** in THF at −78 °C gave, after quenching the resulting solution after 1 h with Me_3SiCl (to remove any unreacted lithium enolate **3** as its silyl enol ether **6** in order to prevent in situ racemisation), the enantiomerically enriched 2-methyl-tetralone **1** in moderate yield (Scheme 3). The overall levels of enantioselectivity varied considerably and was evidently dependent on the structural nature of the bis-sulfonamide used.

The highest enantioselectivity was obtained using the bis-2-naphthyl sulfonamide **5d**, which gave the (*R*)-enantiomer of 2-methyl tetralone **1** with 64% enantiomeric excess (Scheme 3: entry 4). It appears that the structural nature of the sulfonamide was very important on the facial outcome of protonation and the overall level of enantioselectivity. For the simplest unsubstituted bis-aryl sulfonamide **5a** and the bis-toluyl-sulfonamide **5b** formation of the other complementary (*S*)-enantiomer **1** was preferred although with low enantiomeric excess (Scheme 3: entries 1 and 2). Whereas, the constitutional isomer, bis-1-naphthyl sulfonamide **5c** surprisingly gave no enantioselectivity presumably due to equally favoured facial protonation pathways (Scheme 3: entry 3). By comparison, the sterically demanding 2,4,6-tri-isopropylphenyl bis-sulfonamide **5e** favoured formation of the (*R*)-2-methyl tetralone **1** with 24% enantiomeric excess. From these facial selectivities it appears that the aryl substituents present within the bis-sulfonamides **5a**–**e** influence the facial protonation more than the (*R*,*R*)-1,2-diaminocyclohexane sub-structure itself. This may be a consequence of differing aggregates present within each lithium enolate sub-structure and the associated lithium enolate complex in solution.

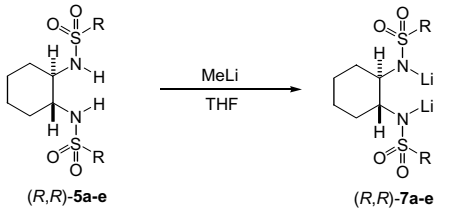
Our attention next turned to probing the use of these bis-sulfonamides **5a**–**e** as potential chiral scaffolds for the enantioselective protonation of enol(ate)s derived from 2-methyl-1-tetralone **1** using acetic acid[14] as an external proton source. We chose to deprotonate these bis-sulfonamides **5a**–**e** using MeLi to form the required bis-lithium-sulfonamides **7a**–**e** (Scheme 4). Construction of the chiral enolate complex was achieved by simple



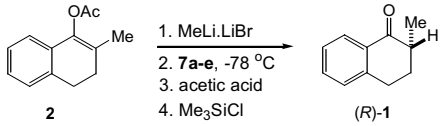
Entry	Bis-sulfonamides		Ketone	% *e.e.*	% Yield
1	R = C_6H_5-	(*R*,*R*)-**5a**	(*S*)-**1**	12	36
2	R = 4-Me-C_6H_4-	(*R*,*R*)-**5b**	(*S*)-**1**	22	69
3	R = 1-naphthyl-	(*R*,*R*)-**5c**	(*rac*)-**1**	0	49
4	R = 2-naphthyl-	(*R*,*R*)-**5d**	(*R*)-**1**	64	57
5	R = 2,4,6-(*i*-Pr)$_3$-C_6H_2-	(*R*,*R*)-**5e**	(*R*)-**1**	24	51

Scheme 3. Enantioselective protonation of enol acetate **2** using proton sources (*R*,*R*)-**5a**–**e**.

addition of a solution of bis-lithium-sulfonamides **7a–e** in THF at −78 °C to a solution of lithium enolate complex **3** in THF at −78 °C (derived from addition of MeLi to the enol acetate **2**) (Scheme 5). The resulting solution was allowed to stir for 30 min at −78 °C, before being quenched by the addition of acetic acid. Using this approach, the highest level of enantioselectivity achieved was 63% e.e. favouring formation of the (*R*)-enantiomer of 2-methyl tetralone **1** using the bis-toluyl sulfonamide **7b**. From this study, it is very interesting to note that relative levels of facial protonation in all these examples have been reversed, most notably for bis-2-toluyl sulfonamide **5b** and bis-2-naphthyl sulfonamide **5d** from (*S*)-**1**; 22% *e.e.* → (*R*)-**1**; 63% *e.e.* and (*R*)-**1**; 64% *e.e.* → (*S*)-**1**; 45% *e.e.*, respectively (Scheme 3: entries 2 and 4 vs Scheme 5: entries 2 and 4). This is presumably a consequence of internal proton delivery (from the bis-sulfonamide) for internal quench versus competitive external protonation on the other face of the enolate away from the bis-sulfonamide ligand. This type of complementary stereocontrol has previously been documented;[4,15] Koga has elegantly shown that internal enantioselective protonation of a related lithium enolate (derived from 2-methyl tetralone **1**) can lead to one relative enantiomer, whereas, external alkylation of the same enolate with benzyl bromide leads to the other relative enantiomer.[4,15] However, it appears to our knowledge that this is the first report of moderate reversal of facial control through the use of two complementary enantioselective protonation strategies. Evidently both internal and external proton transfer processes are different since they lead to reversed facial selectivity. This fine balance between these processes is particularly important when considering the generation of lithium enolates derived from enol equivalents [e.g., silyl enol ethers (e.g., **6**) and enol acetates (e.g., **2**)] and organolithium reagents (e.g., MeLi and MeLi·LiBr). The use of an excess of MeLi to maximise lithium enolate **1** formation, can potentially lower the enantiomeric excess for internal enantioselective protonation due to competing external protonation (through direct deprotonation of the chiral proton donor with the remaining MeLi·LiBr complex, and subsequent external protonation on aqueous work-up). This competitive protonation pathway can lead to the other unwanted enantiomeric product and will consequently lower the overall enantiomeric excess.



Scheme 4. Synthesis of C_2-symmetric bis-lithium sulfonamides (*R*,*R*)-**7a–e**.



Entry	Bis-sulfonamides		Ketone	% *e.e.*	% Yield
1	R = C_6H_5-	(*R*,*R*)-**7a**	(*S*)-**1**	4	63
2	R = 4-Me-C_6H_4-	(*R*,*R*)-**7b**	(*R*)-**1**	63	50
3	R = 1-naphthyl-	(*R*,*R*)-**7c**	(*R*)-**1**	12	47
4	R = 2-naphthyl-	(*R*,*R*)-**7d**	(*S*)-**1**	45	54
5	R = 2,4,6-(*i*-Pr)$_3$-C_6H_2-	(*R*,*R*)-**7e**	(*rac*)-**1**	0	53

Scheme 5. Enantioselective protonation of enol acetate **2** using acetic acid as an external proton sources.

In conclusion, we have reported two complementary protonation processes, which allow access to both enantiomers of 2-methyl tetralone **1** via an internal and external enantioselective protonation strategy using substituted bis-sulfonamides as the chiral proton mediator. Both these protonation pathways lead to opposite facial control. Previous reports into the enantioselective protonation of 2-methyl-1-tetralone have mostly relied on the use of internal chiral proton donors (e.g., chiral alcohols,[3a,b,d] ammonium salts,[10c] and amides).[3e] However, there are a few reports which have given excellent enantiocontrol for a chiral ligand and external achiral proton donor combination.[16] The associated levels of stereocontrol have been shown to be good to excellent (up to 94% *e.e.*,[3a,b,d] 40% *e.e.*,[10c] and 64% *e.e.*,[3e] respectively) for a wide range of acids.

2. Representative experimental procedures

2.1. (*R*)-2-methyl tetralone 1

Typical procedure for an internal quench: A solution of MeLi·LiBr (0.20 mL, 1.50 M in ether, 0.30 mmol) was added dropwise to the enol acetate **2** (32 mg, 0.15 mmol) at room temperature. The resulting solution was stirred for 30 min and then cooled to −78 °C. A pre-cooled solution of bis-sulfonamide **5d** (74 mg, 0.15 mmol) in THF (1 mL) at −78 °C was slowly added, and the resulting solution was stirred for 1 h before being quenched with Me_3SiCl (0.1 mL). A saturated solution of $NaHCO_3$was added and the resulting solution was extracted with ether (3 × 10 mL). The organic phase was washed again with a saturated solution of $NaHCO_3$ and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum/ether (19:1) to give (*R*)-2-methyl-1-tetralone **1**[5] (14 mg, 57%) as a colourless oil with 64% enantiomeric excess (determined by chiral HPLC using a Chiralcel OD column[9] solvent hexane/isopropyl alcohol (98:2): flow rate: 0.7 mL/min; retention time (*S*)-enantiomer 10.8 min, (*R*)-enantiomer 11.6 min); R_F [light petroleum (40–60 °C)/ether (9:1)] 0.5; υ_{max}(film)/cm^{-1}1686 (CO); δ_H (250 MHz, $CDCl_3$) 8.00 (1H, d, ^3J = 7.7, CH; Ar), 7.47 (1H, dd, ^3J = 7.7 and 7.6, CH; Ar), 7.25 (1H, t, ^3J = 7.7, CH; Ar), 7.22 (1H, d, ^3J = 7.6, CH; Ar), 3.00 (2H, m, $CH_2C{=}C$), 2.60 (1H, m, CHMe), 2.20 (1H, dt, ^3J = 13.2 and 4.4, CH_AH_B), 1.87 (1H, m, CH_AH_B) and 1.28 (3H, d, ^3J = 7.3, MeCH); δ_C

(62.5 MHz, $CDCl_3$) 200.8, 144.2, 133.1, 132.4, 128.7, 127.4, 126.6, 42.0, 31.3, 28.8 and 15.3 (Found M^+, 160.0882. $C_{11}H_{12}O$ requires M^+, 160.0882); *m/z* 160.1 (100%, M). The purity was >99% determined by HPLC.

Typical procedure for an external quench: A solution of MeLi·LiBr (0.20 mL, 1.50 M in ether, 0.30 mmol) was added dropwise to the enol acetate **2** (32 mg, 0.15 mmol) at room temperature. A solution of pre-formed lithium sulfonamide **7b** [sulfonamide **5b** 74 mg, 0.15 mmol and MeLi (0.20 mL, 1.50 M in ether, 0.30 mmol)] in THF (1 mL) was added. The resulting solution was stirred for 30 min at −78 °C. The reaction was quenched, by the dropwise addition of glacial acetic acid (0.2 mL), followed by Me_3SiCl (0.2 mL). A saturated solution of $NaHCO_3$ was added and this solution was extracted with ether (3 × 10 mL). The organic phase was washed again with a saturated solution of $NaHCO_3$ and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum/ether (9:1) to give (*R*)-2-methyl-1-tetralone **1**[5](12 mg, 50%) as a colourless oil with 63% enantiomeric excess (determined by chiral HPLC using a Chiralcel OD column[9] solvent hexane/isopropyl alcohol (98:2): flow rate: 0.7 mL/min; retention time (*S*)-enantiomer 10.8 min, (*R*)-enantiomer 11.6 min). The purity was >99% determined by HPLC.

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