

Enantioselective Protonation of a Lithium Enolate Derived from 2-Methyl-1-tetralone Using Chiral Sulfonamides

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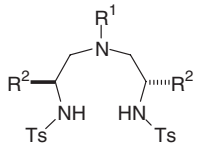
The synthesis of enantiomerically enriched (*R*)-2-methyl-1-tetralone (**1**) with 77% e.e. was achieved through protonation of its lithium enolate (**3**) using a C_2-symmetric tris-sulfonamide (**6**) as an internal chiral proton source. Access to the complementary (*S*)-enantiomer **1** with 33% e.e. was achieved using a related C_2-symmetric bis-sulfonamide (**9**) as the chiral proton source.

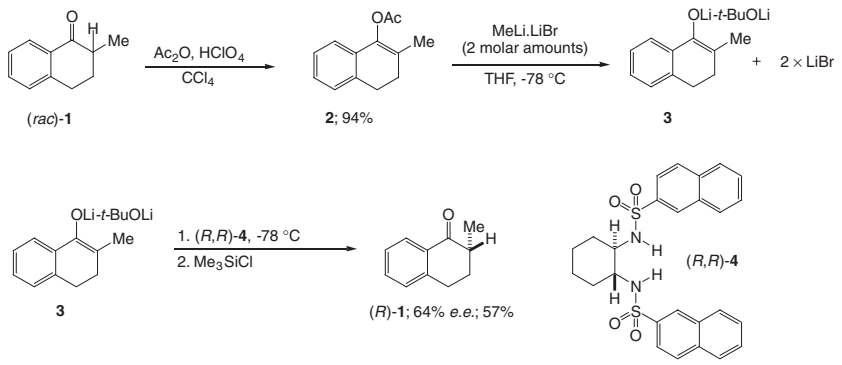
The synthesis of optically active α-substituted carbonyl compounds by the enantioselective protonation of enolic and enolate species, derived from racemic carbonyl compounds, is very well documented.[1] The majority of these studies have focussed on the use of chelating chiral proton donors. These chiral proton donors have generally contained an heteroatomic acid, such as *O*-based carboxylic acids,[2] phenols,[3] alcohols,[4] and water,[5] *N*-based amides,[6] anilines,[7] oxazolidinones,[8] sulfonamides,[9] succinimides,[10] ammonium salts,[11] amines,[12] and *S*-based thiols.[13] The success of these types of proton donors is largely due to their mild acidity[14] and efficient proton transfer.[15]

We have recently become interested in the use of chiral C_2-symmetric bis-sulfonamides,[16] such as (*R*,*R*)-(**4**), as potential chiral proton donors, since they have been shown to lead to moderate-to-good levels of enantioselectivity for the protonation of lithium enolate (**3**) [derived from the enol acetate (**2**) of racemic 2-methyltetralone (**1**)] to give the corresponding enantiomerically enriched 2-methyltetralone (*R*)-(**1**) with 64% enantiomeric excess (Scheme 1). We now wish to report our study on the use of a related class of conformationally flexible C_2-symmetric sulfonamides as potential chiral proton donors for the enantioselective protonation of enol(ate)s derived from racemic 2-methyltetralone (**1**). For this study, we focussed on the use of chiral bis-sulfonamides (**5**), (**7**), and (**8**–**10**) and tris-sulfonamide (**6**), derived from the corresponding *N*-tosyl aziridine[17] as our chiral proton source (Scheme 2). We have always preferred to use (±)-2-methyl-1-tetralone (**1**) as our parent compound due to its UV activity, predictable enolate stereochemistry and known enantiomeric separability.[18] We chose to use enol acetate (**2**)[19] as our pro-enolate precursor due to its improved thermal stability over other related enol derivatives (Scheme 1). This enol acetate (**2**) was efficiently synthesized in 94% yield by the addition of acetic anhydride and $HClO_4$ to a solution of (±)-2-methyl-1-tetralone (**1**) in CCl_4 at room temperature.[20] The required lithium enolate complex (**3**) was liberated from enol acetate (**2**) using House and Trost's ap-



	5	6	7	8	9	10
R^1	Ac	Ts	Bn	H	Bn	H
R^2	*i*-Pr	*i*-Pr	*i*-Pr	*i*-Pr	*i*-Bu	Bn

Scheme 2.



Scheme 1.

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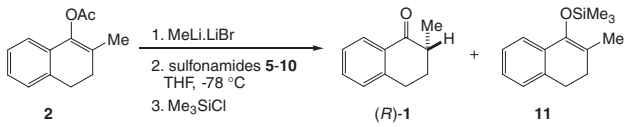


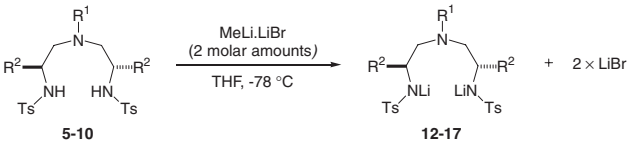
Entry	Sulfonamides	Ketone	% e.e.	% Yield	Silyl Enol Ether	% Yield
1	**5**	(*R*)-**1**	4	40	**11**	25
2	**6**	(*R*)-**1**	77	58	**11**	26
3	**7**	(*R*)-**1**	5	70	**11**	5
4	**8**	(*R*)-**1**	5	60	**11**	11
5	**9**	(*S*)-**1**	33	52	**11**	7
6	**10**	(*R*)-**1**	2	60	**11**	18

Scheme 3.

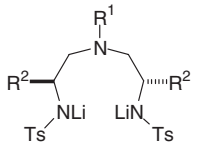
proach,[21] by the simple addition of MeLi·LiBr complex in THF (2 molar amounts) (Scheme 1).[22]

We initially screened a series of structurally related C_2-symmetric bis-sulfonamides (**5**), (**7**), and (**8–10**), and tris-sulfonamide (**6**) as potential chiral Brønsted acids against the lithium enolate complex (**3**) to determine their relative facial protonation preference (Scheme 3). The addition of these sulfonamides to a stirred solution of enolate (**3**) in THF at −78 °C, gave after quenching the resulting solution after 1 h with Me_3SiCl [to remove any unreacted enolate (**3**) in the form of the corresponding silyl enol ether **11**] the required enantiomerically enriched 2-methyl-1-tetralone (**1**) in moderate yield (Scheme 3). The facial preference and levels of enantioselectivity were found to vary considerably depending on the structural nature of the sulfonamide used. The highest level of enantioselectivity was obtained using the tris-sulfonamide (**6**), which gave the 2-methyltetralone (**1**) enriched in its (*R*)-enantiomer with 77% e.e. (Scheme 3, Entry 2). In the majority of these cases, protonation occurred on the same face, leading to the (*R*)-enantiomer. This was presumably due to the same relative configuration being present in all of these substituted sulfonamides (Scheme 3). However, a notable exception to this was bis-sulfonamide (**9**), which preferred to protonate on the opposite face, leading to the complementary (*S*)-enantiomer (**1**) with 33% e.e. (Scheme 3).

Our attention next turned to probing the use of these substituted lithium sulfonamides (**12–17**) as potential chiral scaffolds for the enantioselective protonation of enolate (**3**) using acetic acid as an external mild achiral proton source (Schemes 4 and 5). The formation of the required chiral lithium enolate complex, such as (**18**), was achieved by deprotonation of the chiral sulfonamides (**5–10**) with a solution of MeLi·LiBr complex in THF, followed by the addition of a solution of pre-formed lithium enolate (**3**) [derived from the corresponding enol acetate (**2**) and MeLi·LiBr complex] (Schemes 6 and 7). The treatment of the enol acetate (**2**) with MeLi·LiBr in THF (2 molar amounts), followed by a slow addition of the lithium sulfonamides (**12–17**) and quenching the resulting chiral ensemble (**18**) after 1 h with acetic acid, interestingly gave no level of enantiocontrol (Schemes 5 and 6). However, simple protonation of the resulting achiral lithium enolate of 2-methyltetralone may have occurred to give racemic 2-methyltetralone (**1**).

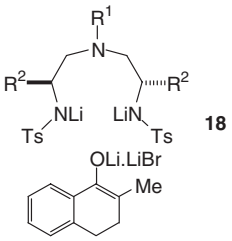


Scheme 4.

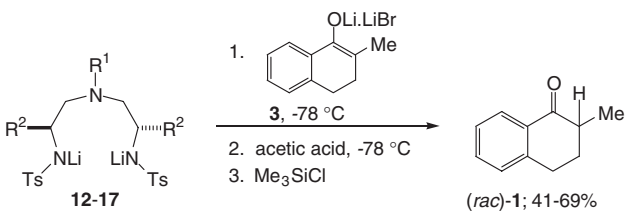


	12	**13**	**14**	**15**	**16**	**17**
R^1	Ac	Ts	Bn	H	Bn	H
R^2	*i*-Pr	*i*-Pr	*i*-Pr	*i*-Pr	*i*-Bu	Bn

Scheme 5.



Scheme 6.



Lithium sulfonamide	Ketone	Yield
12	(*rac*)-**1**	53%
13	(*rac*)-**1**	69%
14	(*rac*)-**1**	66%
15	(*rac*)-**1**	52%
16	(*rac*)-**1**	41%
17	(*rac*)-**1**	47%

Scheme 7.

From this study it is evident that a co-ordinating chiral acid, like a chiral sulfonamide, gives far superior enantiocontrol than using a combination of chiral sulfonamide and an external acid (acetic acid). The reasons for this are not clear; however, there appear to be subtle effects within these chiral proton sources that have a dramatic effect on the level and facial preference of protonation. Whilst the effect of changing the alkyl substituent R^2 appears to be slight, the stereoelectronic nature of the substituent R^1 has a dominant affect (e.g., Scheme 3,

Entries 2 and 5). However, altering the Lewis basicity of the amine donor (NR^1) does not appear to influence the facial protonation. The sulfonamide donor (**6**) gave better levels of stereoselectivity than an amine donor in (**7**) and (**8**) (Scheme 3, Entry 2 versus Entries 3 and 4). Recently, there have been some reports[1] into the de-racemisation of 2-methyl-1-tetralone (**1**) using other chiral Brønsted acids, such as chiral alcohols,[23] ammonium salts,[11] and amides.[6b] The associated levels of stereocontrol were shown to be good to excellent (up to 94% e.e.,[23] 40% e.e.,[11] and 64% e.e.[6b]) for a wide range of structurally different chiral acids. The results reported therein further serve to substantiate the efficacy of chiral Brønsted acids in the enantioselective protonation of lithium enolates derived from 2-methyl-1-tetralone; however, as yet there is no clear rationale between the levels of enentioselectivity, structure of acids and their relative acidity. Investigations along these lines are currently underway within our laboratories.

Experimental

Typical Procedure for a Co-ordinating Acid. A solution of MeLi·LiBr (0.21 mL, 1.54 M in ether, 0.32 mmol) was added dropwise to a stirred solution of enol acetate (**2**) (32 mg, 0.16 mmol) in THF (2 mL) at −78 °C temperature. The resulting solution was stirred for 1 h. A pre-cooled solution of sulfonamide (**6**) (0.13 g, 0.21 mmol) in THF (2 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 (2 × 20 mL). The organic phase was washed again with a saturated solution of $NaHCO_3$ (5 mL) and the solvent was removed under a 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 (*R*)-(**1**)[18] (15 mg, 58%) as a colorless oil with 77% enantiomeric excess (determined by chiral HPLC using a Chiralcel OD column[18]—solvent hexane:isopropyl alcohol (98:2); flow rate: 0.70 mL/min; retention time (*S*)-enantiomer 10.95 min, (*R*)-enantiomer 11.89 min); R_f [light petroleum (40–60 °C):ether (9:1)] 0.5; ν_{max} (film)/cm^{-1} 1686 (CO); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.00 (1H, d, $^3J = 7.7$ Hz, CH; Ar), 7.47 (1H, dd, $^3J = 7.7$, 7.6 Hz, CH; Ar), 7.25 (1H, t, $^3J = 7.7$ Hz, CH; Ar), 7.22 (1H, d, $^3J = 7.6$ Hz, CH; Ar), 3.00 (2H, m, CH_2C=C), 2.60 (1H, m, CHMe), 2.20 (1H, dt, $^3J = 13.2$, 4.4 Hz, CH_AH$_B$), 1.87 (1H, m, CH$_A$H$_B$), 1.28 (3H, d, $^3J = 7.3$ Hz, MeCH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 200.8, 144.2, 133.1, 132.4, 128.7, 127.4, 126.6, 42.0, 31.3, 28.8, 15.3; (Found M^+, 160.0882. $C_{11}H_{12}O$ requires M^+, 160.0882); *m*/*z* 160.1 (100%, M) and silyl enol ether (**11**) (10 mg, 26%) as an oil; R_f [light petroleum (40–60 °C):ether (9:1)] 0.85; ν_{max} (film)/cm^{-1} 1657 (C=C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.54–7.43 (1H, m, CH; Ar), 7.14–7.05 (3H, m, 3 × CH; Ar), 2.78–2.60 (2H, t, $J =$ 7.8 Hz, CH_2), 2.24 (2H, t, $J = 7.9$ Hz, CH_2), 1.80 (3H, s, CH_3), 0.20 (9H, s, 3 × CH_3; $(CH_3)_3$Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8 (C=*C*–O), 135.3 (*i*-C; Ar), 133.7 (*i*-C; Ar), 126.4, 125.5, 125.0 and 120.9 (4 × CH; Ar), 116.3 (*C*=C–O), 29.8 and 27.6 (2 × CH_2), 16.7 (CH_3), 0.3 (3 × CH_3; $(CH_3)_3$Si); (Found M^+, 232.1274. $C_{14}H_{20}OSi$ requires M, 232.1283).

Typical Procedure for the Use of a Conjugate Base and External Achiral Acid. A solution of MeLi·LiBr (0.28 mL, 1.54 M in ether, 0.43 mmol) was added dropwise to the enol acetate (**2**) (43 mg, 0.21 mmol) in THF (2 mL) at −78 °C. A solution of pre-formed lithium sulfonamide (**13**) [sulfonamide (**6**) (0.13 g, 0.21 mmol) and MeLi·LiBr (0.28 mL, 1.54 M in ether, 0.43 mmol)] in THF (2 mL) was added. The resulting solution was stirred for 1 h. The reaction was quenched by the dropwise addition of acetic acid (1 mL). After a saturated solution of $NaHCO_3$ (10 mL) was added, this solution was extracted with ether (2 × 20 mL). The organic phase was washed again with a saturated solution of $NaHCO_3$ (10 mL) and the solvent was removed under a vacuum. The residue was purified by flash chromatography on silica gel, eluting with light petroleum:ether (9:1) to give 2-methyl-1-tetralone (*rac*)-(**1**)[18] (22 mg, 70%) as a colorless oil with 0% enantiomeric excess (determined by chiral HPLC using a Chiralcel OD column[18]—solvent hexane:isopropyl alcohol (98:2); flow rate: 0.70 mL/min; retention time (*S*)-enantiomer 10.95 min, (*R*)-enantiomer 11.89 min).

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