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Efficient asymmetric protonation of enolates with readily accessible chiral α-sulfinyl alcohols

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Abstract

The efficient asymmetric protonation of lithium enolates of 2-alkylcycloalkanones (87–96% ee) with readily accessible chiral α-sulfinyl alcohols is described. Optimal stereoselection is achieved for each lithium enolate at a different reaction temperature in the range −40 to −100°C. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Over the past few years, enantioselective protonation of enolates or silyl enol ethers has been recognized as an efficient approach to chiral α-carbonyl compounds.[1] Although some efficient chiral proton sources have been described by others[1–4] and by us,[5] it is generally difficult to obtain these compounds. It seems reasonable that when a chiral proton source requires a complex synthesis, organic chemists are reticent to apply enantioselective protonation to a given sequence, and this is even more so when the outcome of this type of reaction is not yet predictable and a difficult synthesis might be followed by low stereoselective asymmetric protonation. Thus, highly effective and readily accessible chiral protonating reagents are needed.

We report here our results in the asymmetric protonation of enolates of 2-alkylcycloalkanones using α-sulfinyl alcohol (*S*,*Rs*)-**1a**, which has been shown to be an efficient proton donor under the conditions that are commonly used in this type of reaction. In addition, the α-sulfinyl alcohol (*S*,*Rs*)-**1a** can be obtained in a homochiral form with good yield in two steps from the commercially available (*R*)-*p*-tolylmethylsulfoxide by following procedures described in the literature.[6,7]

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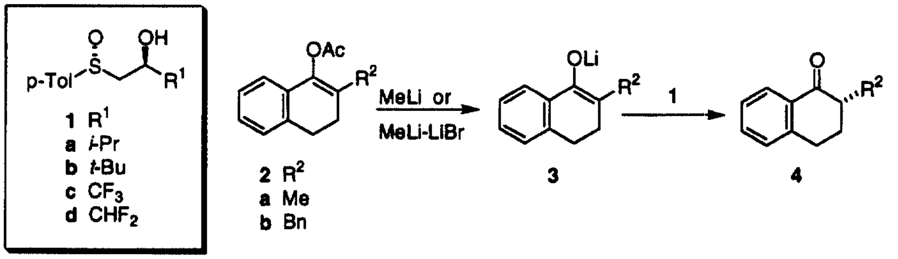
2. Results and discussion

In previous work,[5] we reported that α-sulfinyl alcohols (*S*,*Rs*)-**1c** and (*S*,*Rs*)-**1d**, bearing a trifluoromethyl and a difluoromethyl group, respectively, attached to the carbinol moiety, gave high ee values in the enantioselective protonation of the lithium enolate **3a** in reactions at −100°C (92% ee) and −78°C (93% ee), respectively, in the presence of lithium bromide. The final stereochemical outcome of the asymmetric protonation depends on both the reaction temperature and steric hindrance resulting from the presence of the R group in the environment of the proton to be transferred (Scheme 1).



Scheme 1. Generation of enolates **3** and enantioselective protonation with **1**

From the steric perspective, the trifluoromethyl group is considered to be as bulky as an isopropyl group and similar to the *tert*-butyl group in terms of its enantiocontrolling capacity.[8] Therefore, to assay the enantioselective protonation of enolates, we chose the α-sulfinyl alcohols (*S*,*Rs*)-**1a** and (*S*,*Rs*)-**1b**, which have, with the exception of their lower acidity, characteristics similar to those of (*S*,*Rs*)-**1c**, and offer the advantage of being easy to prepare. While α-sulfinyl alcohols (*S*,*Rs*)-**1a** and (*S*,*Rs*)-**1b** can be easily obtained with high diastereoselection by reduction with DIBALH[6] of the corresponding ketones,[7] difluoro and trifluoro α-sulfinyl ketones exist mainly as hydrates which are unreactive towards DIBALH.[9]

Initially, we assayed the enantioselective protonation of lithium 2-methyl-1-tetralone enolate **3a** generated from enol acetate **2a**. The protonation with (*S*,*Rs*)-**1a** was first carried out under the same optimal reaction conditions which we had found previously;[5,10] i.e. in dichloromethane solution and in the presence of lithium bromide in the reaction medium. Lithium bromide was incorporated in the reaction by using a solution of commercially available MeLi–LiBr (2.1 equiv.) to generate the enolate **3a** from the enol acetate **2a**. At −78°C, ketone (*R*)-**4a** was obtained with 85% ee (Table 1, entry 2). The enantioselectivity was not improved by lowering the protonation temperature to −100°C (Table 1, entry 1). In contrast, an optimal ee value (90%) was found by raising the reaction temperature to −50°C, (Table 1, entry 4). Small changes in temperature around this optimal point negatively affected the stereoselection (Table 1, entries 3 and 5).

To ascertain the influence of lithium bromide on the stereochemical outcome of the protonation of **3a** with (*S*,*Rs*)-**1a**, the reaction was repeated at the optimal temperature (−50°C) but in the absence of the lithium salt. Under these conditions, ketone (*R*)-**4** was obtained with only 54% ee (Table 1, entry 6).

Since lithium bromide has a positive influence on the asymmetric induction, we tested whether the presence of chiral lithium alkoxide (*S*,*Rs*)-**1a**–Li in the medium would eventually lead to better enantioselectivity. Since the effects of lithium salts may be related to the enolate structure,[11,12] they must be present in the reaction medium prior to enolate generation.[13] Indeed, we prepared a solution containing alkoxide (*S*,*Rs*)-**1a**–Li and enolate **3a** by mixing 1 equivalent of alcohol (*S*,*Rs*)-**1a** with 3 equivalents of MeLi and then adding the enolate precursor **2a**. Disappointingly, the ketone (*R*)-**4** was obtained in only moderate ee (55%) (Table 1, entry 7). Conversely, when the same experiment was performed using MeLi–LiBr instead of MeLi, the ketone (*R*)-**4** was isolated with 87% ee (Table 1,

Table 1
Asymmetric protonation of lithium enolates of 2-cycloalkanones with α-sulfinyl alcohols (*S*,*Rs*)-**1**

Entry	(*S*,*Rs*)-**1**	Enolate[a]	Temperature	Ketone	(%ee)[b]
1	**1a**	**3a**	-100	(*R*)-**4a**	83
2	**1a**	**3a**	-78	(*R*)-**4a**	85
3	**1a**	**3a**	-65	(*R*)-**4a**	83
4	**1a**	**3a**	-50	(*R*)-**4a**	90
5	**1a**	**3a**	-40	(*R*)-**4a**	82
6	**1a**	**3a**[c]	-50	(*R*)-**4a**	54
7	**1a**	**3a**[d]	-50	(*R*)-**4a**	55
8	**1a**	**3a**[e]	-50	(*R*)-**4a**	87
9	**1b**	**3a**	-100	(*R*)-**4a**	82
10	**1b**	**3a**	-78	(*R*)-**4a**	81
11	**1b**	**3a**	-65	(*R*)-**4a**	68
12	**1b**	**3a**	-50	(*R*)-**4a**	65
13	**1a**	**3b**	-100	(*S*)-**4b**	76
14	**1a**	**3b**	-78	(*S*)-**4b**	76
15	**1a**	**3b**	-50	(*S*)-**4b**	84
16	**1a**	**3b**	-40	(*S*)-**4b**	87
17	**1a**	**3b**	-25	(*S*)-**4b**	3
18	**1a**	**6**	-100	(*S*)-**7**	85 (89)[f]
19	**1a**	**6**	-78	(*S*)-**7**	75 (79)[f]
20	**1a**	**6**	-65	(*S*)-**7**	84 (88)[f]
21	**1a**	**6**	-50	(*S*)-**7**	72 (76)[f]
22	**1a**	**9**	-100	(*S*)-**10**	88 (95)[f]
23	**1a**	**9**	-78	(*S*)-**10**	89 (96)[f]
24	**1a**	**9**	-65	(*S*)-**10**	83 (90)[f]
25	**1a**	**9**	-50	(*S*)-**10**	80 (87)[f]

[a] 1 eq. of enolate contains 1.46 eq. of lithium bromide otherwise noted

[b] ee determined by [α] (see experimental section)

[c] 1 eq. of enolate contains 0.146 eq. of lithium chloride

[d] 1eq. of enolate contains 1 eq. of (*S*,*Rs*)-**1a**Li

[e] 1eq. of enolate contains 1 eq. of (*S*,*Rs*)-**1a**Li and 1.46 eq. of lithium bromide

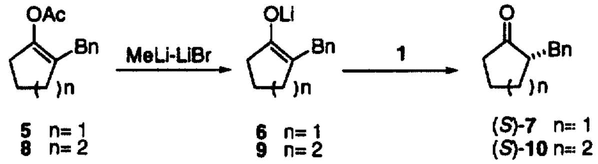
[f] values corrected for the regioisomeric purity of enol acetate **5** or **8** (see experimental section)

entry 8), showing that the presence of lithium alkoxide does not affect the enantioselectivity, whereas lithium bromide has a clear positive effect. Consequently, enolates were generated using MeLi–LiBr in the following experiments.

The asymmetric protonation of enolate **3a** in the temperature range −50 to −100°C showed that alcohol (*S*,*Rs*)-**1b** was less efficient than (*S*,*Rs*)-**1a**. In the latter case, the best enantioselection was achieved at lower temperatures (−78 or −100°C) (Table 1, entries 9–12).

The good results obtained in the enantioselective protonation of enolate **3a** with (*S*,*Rs*)-**1a** prompted us to explore the use of this chiral proton source with other ketone enolates such as **3b**, **6** and **9** (Scheme 2). With enolate **3b**, lower temperatures (−78 or −100°C) again did not produce the best stereoselection (76% ee) (Table 1, entries 13 and 14). When the reaction was performed at −40°C, the ee increased to 87% (Table 1, entry 16), but no further increase in the degree of asymmetric induction was attained by minor changes around this temperature (Table 1, entries 15 and 16). A sharp decrease in enantioselectivity was observed at −25°C (Table 1, entry 17).

In another series of runs, the lithium enolates **6** and **9** were subjected to protonation with alcohol (*S*,*Rs*)-**1a**. With **6**, the effect of temperature on the stereochemical outcome of the reaction was unusual,



Scheme 2. Generation of enolates **6** and **9** and enantioselective protonation with **1**

since optimal stereoselection was achieved at both −65 and −100°C (Table 1, entries 18 and 20), while the ee values decreased at −50 and −78°C (Table 1, entries 19 and 21). Conversely, enolate **9** showed normal behavior, with the greatest enantioselection at lower temperatures (−100 and −78°C) (Table 1, entries 22–25).

3. Conclusions

We can conclude that α-sulfinyl alcohol (*S*,*Rs*)-**1a** is an efficient chiral proton source for the enantioselective protonation of lithium enolates of 2-alkylcycloalkanones. In the case of tetralone enolates **3a** and **3b**, the use of low temperatures (−78 or −100°C) has a negative effect on the induction. This peculiar trend is difficult to explain with a reaction in which proton transfer occurs under kinetic control. However, the temperature not only affects proton transfer, but may also produce variations in the enolate structure and probably modifies the rate of assembly (which has been postulated to be the preceding step in the protonation of enolates by weak proton sources) of the α-sulfinyl alcohol to each type of enolate present in the reaction medium. Thus, enantioselection depends on the temperature in a complex way which makes it difficult to draw general conclusions about the optimal conditions to effect a given asymmetric protonation. Until now, −78 and −100°C have been standard temperatures for enantioselective protonation reactions with proton sources in solution. Although low (−78°C) or very low temperatures (−100°C) may often be the best choice for such reactions, in some cases moderately low temperatures (−40 or −50°C) provide the best enantioselection. In these latter cases, the ability to avoid very low temperatures offers several practical advantages. In conclusion, temperature is an important parameter to be considered in enantioselective protonation reactions, and this type of reaction should be carefully examined over a range of temperatures to determine the optimal stereoselection in each case.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 with tetramethylsilane as an internal reference and $CDCl_3$ as a solvent. Melting points were determined with a Cambridge Instruments apparatus and are uncorrected. Optical rotation measurements were determined on a Perkin–Elmer 241 polarimeter at room temperature. High resolution mass spectra (HRMS) were recorded on a Fisons VG Autospec instrument. Analytical gas chromatography was performed on a Fisons Series 9000 instrument equipped with a flame ionization detector and a capillary column of BPX5 (0.22×30000 mm) (d_f 0.25 μm).

4.2. Materials

Methyllithium (1.6 M solution in diethyl ether, d=0.701; 0.09 M in LiCl; 1.5 M solution in diethyl ether, d=0.852; 1.0 M in LiBr) was purchased from Aldrich. All solvents were dried before use. Diethyl ether was distilled under argon from sodium benzophenone and dichloromethane was distilled from calcium hydride. Enol acetates **2a**, **2b**, **5** and **8** were prepared from the corresponding racemic ketones as described previously.[14] The thermodynamic enol acetates **5** and **8** were obtained as (95:5) and (92:8) inseparable mixtures, respectively, with the corresponding less-substituted regioisomers. The mixture composition was analyzed by GC. The ee values for chiral ketones **4a**,[15] **4b**,[16] **7**[17] and **10**[15] were assigned by comparison with the literature.

4.3. (R)-(+)-3-Methyl-1-(4-methylphenylsulfinyl)-2-butanone

This was obtained according to a literature procedure;[7] m.p. and $[\alpha]_D$ agreed with the literature; ^{1}H-NMR δ 1.02 (d, 3H, J=7.5 Hz), 1.09 (d, 3H, J=7.5 Hz), 2.42 (s, 3H), 2.53–2.64 (m, 1H), 3.81 (d, 1H, J=12.5), 4.01 (d, 1H, J=12.5 Hz), 7.34 (d, 2H, J=7.5 Hz), 7.56 (d, 2H, J=7.5 Hz); ^{13}C-NMR δ 17.2 (c), 17.4 (c), 21.4 (c), 42.2 (d), 66.9 (t), 124.1 (d), 130.0 (d), 140.0 (s), 142.1 (s), 205.5 (s).

4.4. (R)-(+)-3,3-Dimethyl-1-(4-methylphenylsulfinyl)-2-butanone

This was obtained according to a literature procedure;[6] m.p, $[\alpha]_D$ and ^{1}H-NMR agreed with the literature; ^{13}C-NMR δ 21.2 (c), 25.4 (c), 44.4 (s), 65.2 (t), 124.2 (d), 129.8 (d), 140.4 (s), 141.9 (s), 207.2 (s).

4.5. (S,Rs)-(+)-3-Methyl-1-(4-methylphenylsulfinyl)-2-butanol (1a)

This was prepared from the corresponding ketone following the general procedure described in the literature;[6] yield 90%; m.p.: 83–84°C (from hexane); $[\alpha]_D$ +304.0 (c=2, $CHCl_3$); ^{1}H-NMR δ 0.91 (d, 6H, J=7.5 Hz), 1.70–1.78 (m, 1H), 2.42 (s, 3H), 2.73 (dd, 1H, J_1=15 Hz, J_2=1.8 Hz), 2.95 (dd, 1H, J_1=15 Hz, J_2=10 Hz), 3.88–4.06 (m, 1H), 4.39 (d, 1H, J=5 Hz), 7.34 (d, 2H, J=7.5 Hz), 7.54 (d, 2H, J=7.5 Hz); ^{13}C-NMR δ 17.3 (c), 18.2 (c), 21.3 (c), 33.6 (d), 60.6 (t), 70.3 (d), 123.9 (d), 129.9 (d), 139.8 (s), 141.3 (s); HRMS calculated for $C_{12}H_{18}O_2S$: 226.1027, found 226.1105.

4.6. (S,Rs)-(+)-3,3-Dimethyl-1-(4-methylphenylsulfinyl)-2-butanol (1b)

This was prepared according to a literature procedure;[6] m.p. and ^{1}H-NMR agreed with the literature; $[\alpha]_D$ +297.5 (c=2, $CHCl_3$); ^{13}C-NMR δ 21.4 (c), 25.4 (c), 34.8 (s), 58.0 (t), 73.5 (d), 124.0 (d), 130.0 (d), 139.7 (s), 141.3 (s).

4.7. General procedure for generation of enolates

To a stirred solution of the corresponding enol acetate (1.0 mmol) in diethyl ether (9 ml) at 0°C was added an ether solution of methyllithium as a complex with lithium bromide 1.5 M or methyllithium 1.6 M (2.1 mmol). The mixture was stirred at room temperature for 30 min.

4.8. General procedure for protonation

The appropriate lithium enolate solution (10 ml) at −75°C was slowly added over 7 min to a solution of α-sulfinyl alcohol (3.0 mmol) in dichloromethane (30 ml) at the temperature specified in each case (see Table 1). The mixture was stirred (1.5 h) at the same temperature and then gradually warmed up to 0°C (temperature increase approximately 1.2°C/min). The reaction mixture was treated with phosphate buffer (pH: 7.2) and extracted with hexane. The residue was purified by column chromatography to give the corresponding ketone (90–94% yield).

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