Stereoselection Parameters and Theoretical Model in the Enantioselective Protonation of Enolates with α-Sulfinyl Alcohols

Gregorio Asensio,* Pedro Aleman, Jesus Gil, Luis R. Domingo, and Mercedes Medio-Simon

Departamento de Quimica Organica, Campus de Burjassot, Avda. V. Andres Estelles s/n, 46100-Burjassot, Spain

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The effects of the solvent, temperature, presence of lithium salts in the medium, and acidity of the proton source on enantioselective protonation with α-sulfinyl alcohols **2a**−**e** were studied. Stereoselectivity was generally enhanced when lithium bromide was present in the medium during enolization and also with the use of methylene chloride solutions. Conversely, the optimal reaction temperature varied with the α-sulfinyl alcohol used as a proton source, and its effect appears to be related to both the acidity of the proton source and the enolate structure. α-Sulfinyl alcohols **2a** and **2b** gave the best results when the reactions were carried out at −100 °C, while the optimal temperature with **2c** was −78 °C. The same ee values were obtained with **2d** and **2e** at either −100 or −78 °C. In addition, an efficient synthesis of α-sulfinyl alcohols **2b** and **2c** is described.

Introduction

Enantioselective protonation of prochiral enolates or silyl enol ethers provides direct access to chiral carbonyl compounds that play an important role as synthons in the preparation of natural and other interesting products. Consequently, several procedures, including stoichiometric and catalytic versions of this reaction using a variety of chiral proton sources, have been reported in recent years,[1] although the stereoselectivity is not always satisfactory. Despite the empirical knowledge acquired, screening remains the only way to select an appropriate proton source for each particular enolate. The lack of a general predictive model may be due, in part, to the complexity of the reaction, as clearly reflected in the literature. Indeed, the stereochemical outcome of the reaction depends highly, although in an erratic manner, on several factors such as the solvents, presence of salts, temperature of the reaction, type of countercation in the enolate and/or acidity of the proton source. Thus, enantioselective protonation remains an attractive topic of research since additional empirical data are still required to clarify the keys to stereoselectivity before some general useful model can be proposed. Our interest in both the synthetic and mechanistic aspects of enantioselective protonation,[2] along with our current work with sulfoxides, prompted us to focus our attention on the behavior of chiral α-sulfinyl alcohols, a class of compounds that have been shown to be very effective enantioselective protonating reagents.[3] In a preliminary communication[2] we reported the dramatic effect on the enantioselection of the presence of lithium bromide in the reaction medium in the enolate generation step in protonations carried out with representative α-sulfinyl alcohols. Now we report our detailed experimental study of this reaction showing the effect of a series of parameters, some of them interrelated, such as the acidity of the alcohol, the temperature, the solvent, and the amount of lithium salt in solution and propose a new more accurate theoretical model to explain the salt effect on the enhancement of the enantioselectivity.

Results and Discussion

Synthesis of α-Sulfinyl Alcohols 2a−e. Following a simple approach, α-sulfinyl ketones **1a**−**e** were selected as starting compounds to obtain the corresponding secondary alcohols by reduction.[4] Stereospecific transformations of α-sulfinyl ketones to alcohols using hydride reagents have shown that the chirality of the alcohol is determined by the chirality of the sulfinyl group, the type of hydride reagent, and the reaction conditions. In this work, we focused on the preparation of the diastereomeric alcohols **2**, since Kosugi demonstrated a lower asymmetric induction of (*R*,*Rs*)-**3a** and (*R*,*Rs*)-**3e** compared to (*S*,*Rs*)-**2a** and (*S*,*Rs*)-**2e**.

The alcohols (*S*,*Rs*)-**2d**[4a] and (*S*,*Rs*)-**2e**[4b] can be obtained with high and moderate diastereoselectivity, respectively, by reduction of the corresponding ketones **1d** and **1e** with DIBALH. However, this procedure cannot be applied to fluoroketones **1a**−**c** because DIBALH only reduces ketones in the keto form and the fluoroketones **1a**−**c** exist mainly or exclusively in the hydrated form (*gem*-diol). Reduction with lithium borohydride in methanolic solution has been reported by Bravo[4a] to take

(1) (a) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566−2587 (Review). Recent examples: (b) Martin, J.; Lasne, M.-C.; Plaquevent, J.-P.; Duhamel, L. *Tetrahedron Lett.* **1997**, *38*, 7181−7182. (c) Riviere, P.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 7589−7592. (d) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka M.; Yoshida A.; Mikami K. *Tetrahedron Lett.* **1997**, *38*, 2709−2712. (e) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto H. *J. Am. Chem. Soc.* **1996**, *118*, 12854−12855. (f) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2366−2367. (g) Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3125−3130. (h) Yanagisawa, A.; Kikuchi, T.; Yamamoto, H. *Synlett* **1998**, 174−176. Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792−2793.

(2) Asensio, G.; Alemán, P. A.; Domingo, L. R.; Medio-Simón, M. *Tetrahedron Lett.* **1998**, *39*, 3277−3280.

(3) (a) Kosugi, H.; Hoshino, K.; Uda, H.*Phosphorous, Sulfur Silicon Relat. Elem.* **1994**, *95*−*96*, 401−402. (b) Kosugi, H.; Hoshino, K.; Uda, H. *Tetrahedron Lett.* **1997**, *38*, 6861−6864. (c) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1857−1858.

(4) (a) Bravo, P.; Frigerio, M.; Resnati, G. *Synthesis* **1988**, 955−960 and references therein. (b) Carreño, M. C.; García-Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120−2128 and references therein.

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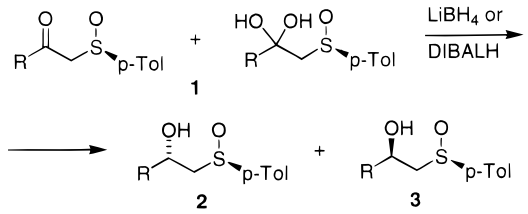
Scheme 1. Synthesis of α-Sulfinyl Alcohols 2 and 3



place with both the keto and hydrated forms of **1a** and **1b**, but the reaction proceeds with low diastereoselectivity and with predominance of the undesired diastereomers **3**. In addition, chromatographic separation of the mixtures **2a/3a** and **2b/3b** could be performed, although with some difficulty, whereas the mixture **2c**/**3c** could not be separated.

To prepare **2a**−**c** with high diastereoselectivity, we tried to transform the hydrated form of **1a**−**c** into the keto form by following a procedure similar to that described for related difluoroketones.[5]

Upon treatment with molecular sieves (4 Å), the hydrated ketones **1b** and **1c** are partially converted to their keto form. Subsequent reduction with DIBALH leads to (*R*,*Rs*)-**2b** and (*S*,*Rs*)-**2c** with high diastereoselectivity (90% and 95%) and moderate yields (40% and 60%).

Conversely, hydrated ketone **1a** could not be efficiently transformed into its anhydrous form, and consequently (*S*,*Rs*)-**2a** was obtained in only 20% yield.[6]

Enantioselective Protonations: Factors That Affect Stereocontrol. Recently, we reported the results of a preliminary study on the effect of several factors that modify enantioselectivity in the protonation with (*S*,*Rs*)-**2a**; i.e., the solvent, the temperature of protonation, the type of enol precursor, and the presence of lithium salts in the reaction medium. We extended our study of these factors to α-sulfinyl alcohols **2b**−**e**. In this series, along with the factors examined previously, we also tried to test the influence of the acidity of the proton source on the stereo-outcome of the protonation. We decided to study this factor because the high efficiency in the enantioselective protonation of enolates with (*S*,*Rs*)-**2a** regarding (*S*,*Rs*)-**2e** and other nonhalogenated α-sulfinyl alcohols **2** (R= *i*-Bu, Pr, CH_2Ph, Ph, CH_2-c-C_6H_{11}) has been suggested to be a consequence of the high acidity of (*S*,*Rs*)-**2a**.[3] In effect, high acidity may favor an efficient discriminating protonation because complete protonation can take place at a low temperature and hypothetical deprotonation of the chiral carbonyl compound by the corresponding lithium alkoxide can be excluded. These arguments have also been used to explain the better results obtained when phenol derivatives instead of aliphatic alcohols are used as chiral proton sources. It is problematic to associate pK_a values with the efficiency of proton sources, since these values are determined under conditions that differ from those in enolate protonation. Indeed, proton donors that are seemingly too weak can protonate an enolate to completion with high stereoselectivity under kinetically controlled conditions if deprotonation of the resulting carbonyl compound is prohibited.

To clarify whether enantioselectivity in the protonation with (*S*,*Rs*)-**2a** arises from its intrinsic acidity, we planned a set of enantioselective protonations with α-sulfinyl alcohols **2**. If acidity is the key factor in the success of the enantioselective protonation, it seems reasonable to expect that the ee values achieved with the different α-sulfinyl alcohols **2** should progressively decrease on standing from the more to the less acidic proton source. The acidity of alcohols **2a**−**e** is modulated by variation of the number of halogen atoms bound to the C-1 carbon. The acidity in the α-sulfinyl alcohols **2a**−**e** can be related to that of the corresponding haloethanols and ethanol[7] provided that the sulfinyl group is common to all of the alcohols **2a**−**e**.

Compounds **4a**,**b**[8] were used as precursors of enolate **5**, which by protonation using α-sulfinyl alcohols **2** afforded ketone (*R*)-**6**. Since commercially available diethyl ether solutions of methyllithium were used in all cases, protonations were always carried out in ethereal solutions. The reactions were performed by chilling the solution containing the chiral alcohol **2** at −100 or −78 °C and then adding a precooled solution of the enolate at −75 °C.

Solvent Effect. To test the effect of the solvent, halogenated alcohol (*S*,*Rs*)-**2a** and nonhalogenated (*S*,*Rs*)-**2e** were selected. When the reaction was carried out with alcohol (*S*,*Rs*)-**2e** in a very weakly polar solvent such as toluene, which has virtually no ability to solvate cations or anions, poor diastereoselectivity was achieved (entry 30). Conversely, when methylene chloride was used as a solvent, which has similar properties as toluene except that the proton source is soluble, stereoselectivity was enhanced (entry 28). Thus, the low stereoselectivity found in toluene can be ascribed to the poor solubility of the alcohol and not to the nonpolar character of the solvent. On the other hand, the use of a mixture (1:1) of a nonpolar solvent (methylene chloride) and a weakly polar solvent which can solvate cations (diethyl ether) produces only a slight decrease in stereoselectivity (entry 29). Comparable results (entries 4, 5) were obtained for trifluoro alcohol (*S*,*Rs*)-**2a**. Therefore, methylene chloride was selected as an appropriate solvent for use in the protonation reactions.

Lithium Salt Effect. The presence of lithium salts as well as the choice of the enolate precursor play a crucial role in the stereochemical outcome of the reaction. To determine the effect of the type of enol precursor on enantioselectivity, enolates **5a** and **5c** were obtained upon treatmet of silyl enol ether **4a** and enol acetate **4b** with 1 or 2 equiv of methyllithium (1.6 M solution in diethyl ether, $d = 0.701$; 0.09 M in LiCl), respectively, and then were protonated at −100 °C with (*S*,*Rs*)-**2a**. Under these conditions[2] ketone (*R*)-**6**[9] was obtained in only 59% and 58% ee in each case (entries 1, 6), proving that the presence of Bu^{t}OLi in the medium does not affect the protonation of 2-methyl-1-tetralone enolate (**5**), as has

(5) Bravo, P.; Pregnaloto, M.; Resnati, G. *J. Org. Chem.* **1992**, *57*, 2726−2731.

(6) Kosugi reported the preparation of (*S*,*Rs*)-**2a** by reduction of the keto form of the ketone **1a**[3a,b] with DIBALH, but the method used for dehydration was not described.

(7) Haszeldine, R. N. *J. Chem. Soc.* **1953**, 1757.

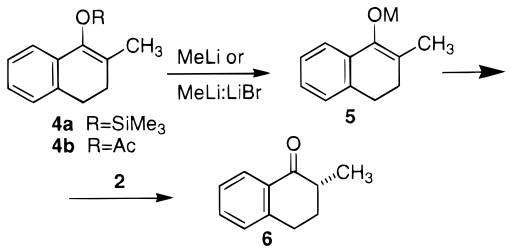
(8) (a) Cazeau, F.; Duboudin, F.; Moulines, F.; Babot, O.; Donouges, J. *Tetrahedron* **1987**, *43*, 2075−2088. (b) Fuji, K.; Tanaka, K.; Miyamoto, M. *Tetrahedron: Asymmetry* **1993**, *4*, 247−259.

(9) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Drueling, M. *J. Am. Chem. Soc.* **1981**, 103, 3081−3087.

been described for cyclohexanone enolates.[10] In another series of runs, enolates were generated upon treatment of enol **4a** or **4b** with 1 or 2 equiv of methyllithium (1.5 M solution in diethyl ether, $d = 0.852$; 1.0 M in LiBr), respectively. Under these conditions, a remarkable enhancement of the selectivity was achieved in the protonation of enolates **5b** and **5d**, giving ee values of 80% and 92%,[11] respectively (entries 2, 7, 8). An identical trend was observed when protonations were performed with α-sulfinyl alcohols **2b**−**e**. Since the protonation of enolate **5a** (entries 1, 17), enolate **5b** (entries 2, 3, 12, 18, 28) and enolate **5c** (entries 6, 22, 31) always gave a lower enantiomeric excess than that of enolate **5d** (entries 8, 10, 13, 23, 32), we attributed this result to the lower amount of LiBr in the first three instances. The effect of the presence of larger amounts of lithium bromide during the enolate generation step could not be determined due to the lack of solubility of this salt in ether. In an attempt to solve this difficulty, a greater dilution was used, but the conversion to enolate was not quantitative under these conditions even with longer reaction times. Alternatively, a saturated ether solution containing an additional 1 equiv of lithium bromide was added to an ether solution of the enolates **5b** or **5d**, and the resulting solution was stirred for 2 h prior to protonation with (*S*,*Rs*)-**2d**, but no improvement in the enantioselectivity was attained (entries 19, 27). Then, it seems to be clear that LiBr must already be present during enolate generation in agreement with other observations concerning enantioselective protonation with tartaric acid derivatives as a chiral proton source.[12] Due to the difficulties found upon adding lithium bromide, we decided to generate enolate **5f** using silyl enol ether **4a** as a precursor and 2 equiv of MeLi−LiBr, so that 1.46 equiv of lithium bromide was present in the reaction medium. The stereoselectivity using α-sulfinyl alcohol (*S*,*Rs*)-**2d** as a proton source (entry 20) was similar to that obtained with the same proton donor in the reaction with enolate **5d** (entry 23), i.e., when enolate was prepared from enol acetate **4b** and 2 equiv of MeLi−LiBr. The ee was not improved by generating enolate **5g** from **4a** and 3 equiv of MeLi−LiBr (in this case, four equivalents of alcohol **2c** were used in the protonation step), showing that addition of further amounts of lithium salt does not lead to any improvement of the selectivity (entry 21).

The role played by lithium bromide may be related to a change in the enolate structure, such as the conversion of pure aggregates to mixed aggregates or monomeric contact ion pairs.[13] In addition, the presence of a common cation salt should prevent the existence of free enolate ion, thus decreasing the possibility of O-protonation. Nevertheless, the effect of lithium halides on enantioselective protonation has received little attention. Only a few examples of improved enantiodifferentation are known, most of them associated with protonations in the presence of amines.[1b,c,h,12]

Scheme 2. Enantioselective Protonation of Enolate 5 with α-Sulfinyl Alcohols



Effects of the Temperature and the Acidity of the Proton Source. In marked contrast to the general trends found for the α-sulfinyl alcohols **2** regarding the need for lithium bromide and the type of solvent, the reaction temperature affected the enantioselectivity differently depending on the α-sulfinyl alcohol used in the protonation. For alcohols (*S*,*Rs*)-**2a** and (*R*,*Rs*)-**2b**, the enantioselectivity was strongly observed at low temperatures (entries 2, 3, 9, 10). Conversely, the temperature of quenching[14] (−50 or 0 °C) appeared to have no effect even in the presence of lithium *tert*-butoxide (entries 5, 6 and 7, 8). The lower temperature of quenching was examined to prevent any possible epimerization of the resulting ketone (*R*)-**6** in the basic medium. In any case, the usual workup was followed once the selected temperature was reached.

The alcohol (*S*,*Rs*)-**2c** showed a unique behavior. Enantioselective protonation at −78 °C over 1.5 h gave the highest ee (entry 13). However, an unexpected result was obtained when the reaction was performed below −78 °C. The ee decreased when the reaction was conducted at −100 °C for 1.5 h (entry 14). On the basis of these results in the protonation with α-sulfinyl alcohols **2a**, **2b**, and **2c** at −78 and −100 °C, there appears to be a relation between the acidity and the optimal reaction temperature, since the more acidic alcohols (*S*,*Rs*)-**2a** and (R,R)-**2b** had an optimal temperature of −100 °C, whereas the less acidic alcohol (*S*,*Rs*)-**2c** had an optimal temperature of −78 °C. These results strongly suggest that the decrease in the ee observed at −100 °C with (*S*,*Rs*)-**2c** is related to a slower rate constant for proton transfer. However, further experiments to support this postulate gave contradictory results. Indeed, the decrease in the ee increased when the reaction time was doubled (3 h) (entry 15), although the opposite would be expected if a slow rate of proton transfer is related to a decrease in stereoselectivity. In addition, stereoselectivity was not improved by changing the temperature profile up to the aqueous quenching step (entry 16), which shows that protonation occurs at a low temperature. Furthermore, α-sulfinyl alcohols (*S*,*Rs*)-**2d** and (*S*,*Rs*)-**2e** gave similar ee values at both temperatures (entries 24, 25, 32, 33), and no improvement was attained when the reaction was performed at −60 °C using (*S*,*Rs*)-**2d** (entry 26). In addition, for a fixed temperature and reaction time, the ee values for alcohols **2b**−**e** are within a narrow range, despite their difference in acidity. To account for these facts, it is worth considering that *temperature, in addition to the rate of proton transfer, can strongly affect other aspects of the reaction*. Thus, the enolates occur in solution as *monomeric ion pairs and their pure or mixed*

(10) Matsumoto, K.; Otha, H. *Tetrahedron Lett.* **1991**, *32*, 4729−4732

(11) We obtained the same ee value as reported elsewhere[3a,b] *only* when the enolate was generated from **4b** and *methyllithium complexed with LiBr*.

(12) Gerlach, U.; Hanbereich, T.; Hünig, S. *Chem. Ber.* **1994**, *127*, 1981−1988.

(13) (a) Seebach, D.; Beck, A. K.; Studer, A. In *Modern Synthetic Methods*; Ernst, B., Leumann, C., Ed.; VCH: Weinheim, 1995; Vol. 7, pp 1−78. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.

(14) In contrast with previous reports[3a,b] we obtained similar optical yields when the reactions were quenched at −50 or at 0 °C.

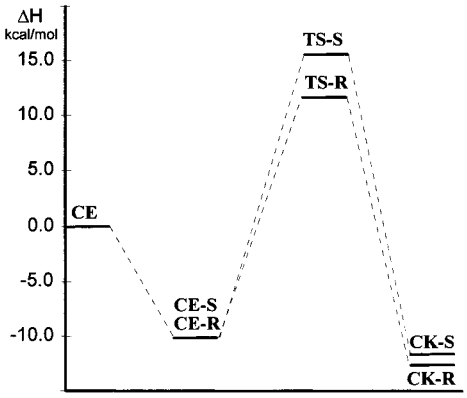


Figure 1. Energy profiles for the intramolecular proton-transfer process between **2** and **5** in the presence of LiBr.

Table 1. Synthesis of α-Sulfinyl Alcohols 2 and 3

1	R	[H]	**2** (%yield)	**3** (%yield)
a	CF_3	$LiBH_4$[a]	(*S*,*Rs*)-**2a** (27)	(*R*,*Rs*)-**3a** (63)
a	CF_3	DIBALH[b]	(*S*,*Rs*)-**2a** (20)	–
b	$CClF_2$	$LiBH_4$[a]	(*R*,*Rs*)-**2b** (29)	(*S*,*Rs*)-**3b** (62)
b	$CClF_2$	DIBALH[b]	(*R*,*Rs*)-**2b** (40)	–
c	CHF_2	$LiBH_4$	(*S*,*Rs*)-**2c** (25)[c]	(*R*,*Rs*)-**3c** (64)[c]
c	CHF_2	DIBALH[b]	(*S*,*Rs*)-**2c** (60)	–
d	CH_2F	DIBALH[a]	(*S*,*Rs*)-**2d** (85)	–
e	CH_3	DIBALH	(*S*,*Rs*)-**2e** (73)[d]	(*R*,*Rs*)-**3e** (18)

[a] See reference 4a. [b] Reduction effected previous treatment of ketone with molecular sieves. [c] Unseparable diastereomer mixture. [d] Pure diastereomer obtained by several crystallizations (see Experimental Section).

aggregates, which equilibrate slowly depending on the *temperature* and solvent. Therefore, the protonation reaction may result in different stereoselectivities from each of the aggregates. In addition, α-sulfinyl alcohols **2** are weak proton donors, and the direct protonation of the enolate by (solvated) protons is unlikely. In this case, the proton source and substrate should assemble before the proton and the enolate metal are exchanged (more or less simultaneously) between the two reactants. Thus, for a given temperature and proton source, stereoselectivity is the complex result of several factors that might reflect the composition of the mixture formed by the enolate as an ion pair, pure-aggregate or mixed-aggregate, and the rate of the assembly of each type of enolate with the proton source.

Steric factors also seem to play a significant role. For example, within the size range of the CHF_2 (entry 13) and CF_3 (entry 8) groups, up to 90% ee was attained. However, with a larger (α-sulfinyl alcohol **2b**) (entry 11) or smaller (α-sulfinyl alcohols **2d** and **2e**) (entries 23, 32) substituent, the stereoselectivity dropped below 90%, although in these latter cases the lower acidity of the alcohol could be the determining factor.

The increase in enantioselectivity with an increase in the temperature of protonations with alcohol (*S*,*Rs*)-**2c** is not common in the field of enantioselective protonation. In fact, there is only one precedent in the literature concerning the protonation of a silyl enol ether by mandelic acid bound to a polymeric resin.[15] The authors of that report explained their result on the basis of a two-step mechanism involving the preliminary formation of rapidly interconverting diastereomeric complexes. However, the ee values obtained at different temperatures do not fit the Eyring plot. Therefore, these results cannot be explained solely by a change in the dominance of enthalpy and entropy in intermediate steps. Due to the complex structure of the enolate, we suppose that although an isoselective temperature may exist, it might be difficult to demonstrate using realistic kinetic data.

(15) Cavelier, F.; Gomez, S.; Jacquier, R.; Verducci, J. *Tetrahedron Lett.* **1994**, *35*, 2891–2894.

Table 2. Enantioselective Protonation of Enolate 5 with α-Sulfinyl Alcohols 2 under Different Conditions

run	**2**	**4**	**5**	lithium salts[a]	solvent[b] (*T*, °C)[c] (time)[d]	% ee[e]
1	**a**	**a**	**a**	LiCl[f]	A (−100)	59
2	**a**	**a**	**b**	LiBr[g]	A (−100)	80
3	**a**	**a**	**b**	LiBr[g]	A (−78)	57
4	**a**	**b**	**c**	LiCl[h]·Bu^{t}OLi[i]	B (−100)[j]	58
5	**a**	**b**	**c**	LiCl[h]·Bu^{t}OLi[i]	A (−100)[j]	59
6	**a**	**b**	**c**	LiCl[h]·Bu^{t}OLi[i]	A (−100)	58
7	**a**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100)[j]	92
8	**a**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100)	92
9	**b**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−78)	71
10	**b**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100)	87
11	**b**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100) (3 h)	85
12	**c**	**a**	**b**	LiBr[g]	A (−78)	83
13	**c**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−78)	93
14	**c**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100)	87
15	**c**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100) (3 h)	40
16	**c**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100)[l]	46
17	**d**	**a**	**a**	LiCl[f]	A (−78)	22
18	**d**	**a**	**b**	LiBr[g]	A (−78)	66
19	**d**	**a**	**e**	LiBr[g,m]	A (−78)	67
20	**d**	**a**	**f**	LiBr[k]·**2d**Li[i]	A (−78)	80
21	**d**	**a**	**g**	LiBr[n]·**2d**Li[o]	A (−78)	81
22	**d**	**b**	**c**	LiCl[h]·Bu^{t}OLi[i]	A (−78)	22
23	**d**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−78)	83
24	**d**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−78) (3 h)	81
25	**d**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100)	82
26	**d**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−60)	80
27	**d**	**b**	**h**	LiBr[k,m]·Bu^{t}OLi[i]	A (−78)	82
28	**e**	**a**	**b**	LiBr[g]	A (−78)	58
29	**e**	**a**	**b**	LiBr[g]	B (−78)	55
30	**e**	**a**	**b**	LiBr[g]	C (−78)	36
31	**e**	**b**	**c**	LiBr[h]·Bu^{t}OLi[i]	A (−78)	53
32	**e**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−78)	80
33	**e**	**b**	**d**	LiBr[k]·Bu^{t}OLi[i]	A (−100)	85

[a] Equivalents of lithium salt/equivalents of enolate **5**. [b] A: CH_2Cl_2; B: CH_2Cl_2/Et_2O (1:1); C: toluene. [c] Reaction was quenched at 0 °C unless otherwise specified. [d] 1.5 h, if otherwise not specified. [e] Determined by [α][9] and ^{1}H-NMR (Eu(hfc)). [f] 0.073. [g] 0.73. [h] 0.146. [i] 1.0. [j] Reaction was quenched at −50 °C. [k] 1.46. [l] Then −78 (1.5 h). [m] LiBr (1.2 equiv) added to enolate **5b** or **5d**. [n] 2.19. [o] 2.0.

Study of the Molecular Mechanism for the Proton-Transfer Process. To understand the mechanism of these enantioselective protonations, and the role of lithium bromide along the reaction pathway, the molecular process associated with the proton transfer has been studied using quantum mechanical procedures at PM3 semiempirical level (see computing methods in Experimental Section). The energy profiles for the two pathways, considering the proton transfer as an intramolecular process, are sketched in Figure 1. The geometries of the transition structures (TS) including selected geometrical parameters are shown in Figure 2. The heats of formation for the stationary points are presented in Table 3.

In a preliminary approach[2] to understand the enantioselectivity found in the proton transfer by α-sulfinyl alcohols to lithium enolates we postulated two transition structures leading, respectively, to each one of the enantiomeric ketones in which both the chiral alcohol and the enolate were linked together by coordination to one

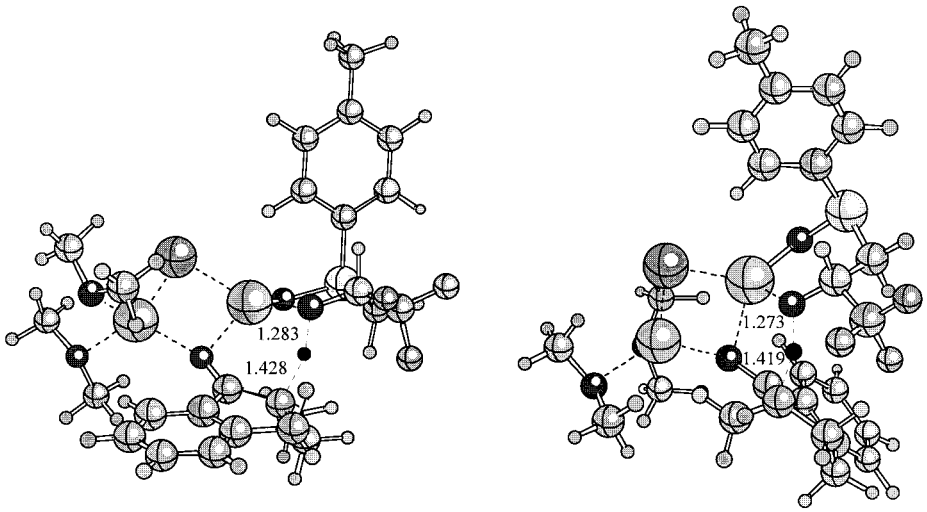


Figure 2. PM3 geometries and selected geometrical parameters (in angstroms) for the transition structures **TS-R** and **TS-S**.

Table 3. Heat of Formation (kcal/mol) of the Stationary Points along the Intramolecular Proton Transfer Process for the Reaction between 2 and 5 in Presence of LiBr

CE-R	CE-S	TS-R	TS-S	CK-R	CK-S
−442.44	−442.37	−420.59	−416.68	−444.87	−443.29

lithium atom. This situation leads to a favorable intramolecular proton-transfer reaction. However, the model suffers from two major drawbacks: (i) the enhancement of the selectivity by lithium bromide is not explained, and (ii) quantitatively, the difference in energy calculated for the transition structures does not account for the selectivity found. These facts prompted us to search for a more accurate model.

First, we have considered the existence of a mixed dimer arising from lithium enolate and lithium bromide. On the basis of literature data,[13] we have defined the structure of the mixed dimer as a four-membered ring where the bromide anion and the oxygen atom of the enolate are connected by two lithium cations. These bridging cations are in an approximately tetrahedral environment provided by two pairs of oxygen atoms corresponding to two molecules of dimethyl ether. The solvent employed for the empirical generation of the enolate was diethyl ether. However, the ethyl groups were replaced by methyl to simplify the calculations. Subsequent substitution of the solvent molecules of one lithium atom for the chiral alcohol **2** affords two enolate complexes, **CE-R** and **CE-S**, which may be considered precursors to the corresponding transition structures. These species are minima in the corresponding reaction pathways as shown in Figure 1. Finally, **CE-R** and **CE-S** can be converted to two chiral complexed ketones **CK-R** and **CK-S**, via the transition structures **TS-R** and **TS-S**, respectively.

The dilithium transition structures **TS-R** and **TS-S** can be described as six-membered rings in which the proton-transfer process takes place via a favorable intramolecular pathway. In constrast with the very similar energy values calculated for the monolithium TS2, the transition structure **TS-R** is 3.9 kcal/mol less energetic than **TS-S** in good agreement with the experimental results. The lengths of the breaking O−Ht and forming C−Ht bonds in **TS-R** are 1.283 and 1.428 Å, respectively, whereas in **TS-S** they are shorter, at 1.273 and 1.419 Å, respectively. These geometrical values are close to those in monolithium TSs, illustrating the invariance of the geometry relative to the lithium aggregate state. The normal-mode analysis of these TSs gave only one imaginary frequency in each case (1950.2i and 1931.1i cm^{-1} for **TS-R** and **TS-S**, respectively). The relatively high value of these imaginary frecuencies reflect the fact that the migrating proton is not coupled with the heavy atoms motion.[16] These imaginary frequencies are higher than those calculated for monolithium TSs,[2] (1753.0i and 1556.8i cm^{-1}, respectively), showing a lower freedom of movement of the heavy atoms in the two-lithium aggregates. Consequently, the lower activation energy for **TS-R**, if compared with **TS-S**, is responsible of the preferential protonation via **TS-R**.

Despite the difficulty in studying these chemical processes in solution, where different aggregates are assumed to exist simultaneously, the present work provides new insights on the general mechanism of the enantioselective protonation and furthermore underlines the role played by the lithium bromide in the formation of mixed dimers.

Conclusions

The present results obtained in the protonation of enolate **5** with α-sulfinyl alcohols **2** suggest that (i) the presence of lithium bromide in the enolization step is essential for achieving good stereoselectivity due to the influence of the presence of excess lithium cation on the structure of the enolate affording a mixed aggregate, (ii) PM3 calculations performed with a simple mixed dimer model found that it can coordinate with the chiral alcohol favoring the subsequent intramolecular proton transfer; the process takes place along a favorable six-membered transition structure, which is geometrically invariant with the lithium aggregate state, and less energetic for the R pathway, (iii) the acidity of the proton source is not the only factor that determines the success of the stereoselection; conformational steric factors may also play a significant role, and (iv) the temperature plays a critical role not only in controlling the proton-transfer

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rate but also in determining the enolate structure when proton transfer takes place.

From a practical viewpoint, alcohol (*S*,*Rs*)-**2c** is the proton source of choice in this series since it gives a high enantiomeric excess in the protonation and is also easy to prepare in moderate yield and with a high degree of diastereoselectivity.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument using $CDCl_3$ as a solvent. Melting points were determined with a Cambridge Instruments apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Fisons VG Autospec instrument.

Materials. Methyllithium (1.6 M solution in diethyl ether, $d = 0.701$; 0.09 M in LiCl) and methyllithium (1.5 M solution in diethyl ether, $d = 0.852$; 1.0 M in LiBr) were purchase from Aldrich. All solvents were dried before use. Toluene was distilled under argon from sodium, diethyl ether from sodium−benzophenone, and dichloromethane from calcium hydride. Compounds **4a**[8a] and **4b**,[8b] ketones **1a**−**d**[4a] and **1e**,[17] and α-sulfinyl alcohols **2a**−**d**[4a] and **2e**[4b] were prepared as described in the literature. Compound **2e** was obtained in enantiomerically pure form after several crystallizations.[18]

Computational Details. The computational study has been carried out using the PM3 semiempirical method[19] implemented in the MOPAC program.[20] This method renders reliable parameter set[21] for Li element and it has been applied to study different organic compounds.[22−24] The molecular geometries of the transition structures (TS) were optimized using optimization routine TS.[25] Stationary points on the potential energy surface (PES) were located by minimizing the gradients of energy to 0.1 kcal/mol/Å-radian. Examination of the TSs has been achieved by the evaluation of the Hessian matrix; the nature of these stationary points was established by analytical calculations and diagonalization of the matrix of energy second derivatives, to determine the unique imaginary frequency.

(2*S*)-1,1-Difluoro-3(*R*)-[(4-methylphenyl)sulfinyl]propan-2-ol (2c): mp 124−126 °C; $[\alpha]^D_{22} = +278°$ (2, chloroform); ^{1}H NMR: δ 2.43 (s, 3H), 2.91 (dd, ^2J = 12.5 Hz, ^3J = 2 Hz, 1H), 3.06 (dd, ^2J = 12.5 Hz, ^3J = 10 Hz, 1H), 4.33−4.45 (m, 1H), 5.62 (bb, 1H), 5.79 (ddd, $^2J_{HF}$ = 56 and 55 Hz, ^3J = 2.5 Hz, 1H), 7.37 (d, ^3J = 7.5 Hz, 2H), 7.56 (d, ^3J = 7.5 Hz, 2H); ^{13}C NMR δ 21.4, 56.6, 65.6 (dd, $^2J_{CF}$ = 26 and 24 Hz), 115.2 (t, $^1J_{CF}$ = 244 Hz), 124.0, 130.2, 138.7, 142.2; ^{19}F NMR δ −132.3 (ddd, $^2J_{FF}$ = 286 Hz, $^2J_{HF}$ = 56 Hz, $^3J_{HF}$ = 15 Hz, 1F), −127.2 (ddd, $^2J_{FF}$ = 286 Hz, $^2J_{HF}$ = 55 Hz, $^3J_{HF}$ = 8 Hz, 1F); HRMS: calcd for $C_{10}H_{12}F_2O_2S$ 234.0526, found 234.0519.

Generation of Enolates 5a and 5b. A diethyl ether solution of methyllithium 1.6 M or methyllithium as a complex with lithium bromide 1.5 M (1.1 mmol) was added to neat **4a** (1.0 mmol) at room temperature. The mixture was stirred for 1 h, and then diethyl ether was added (9 mL).

Generation of Enolates 5c and 5d. To a stirred solution of **4b** (1.0 mmol) in diethyl ether (9 mL) at 0 °C was added an ether solution of methyllithium 1.6 M or methyllithium as complex with lithium bromide 1.5 M (2.2 mmol). The mixture was stirred at room temperature for 30 min.

General Procedure for Protonation. The lithium enolate solution (10 mL) at −75 °C was slowly added in 7 min to a solution of **2a**−**e** (3.0 mmol) in the appropriate solvent (30 mL) and at the appropriate temperature. The mixture was stirred (1.5 h) at the same temperature and then gradually warmed to the quenching temperature (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 (*R*)-**6** (90−94% yield).

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