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REMARKABLE EFFECT OF LITHIUM BROMIDE IN THE ENANTIOSELECTIVE PROTONATION WITH α–SULFINYL ALCOHOLS

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Summary: The favourable effect of lithium bromide enhancing the facial enantioselectivity in the protonation of methyl tetralone enolate with α-sulfinyl alcohols is described. Theoretical calculations allow to propose a model to explain the stereochemical course of the protonation reaction.

Enantioselective protonation has become a field of intense research in recent years. Consequently several procedures have been reported allowing direct access to chiral carbonyl compounds.[1] However, a general understanding of the factors governing the enantioselectivity of the proton transfer is still an open question. Our interest in both synthetic and mechanistic aspects of this kind of reaction, along with our current work in the sulfoxide area prompted us to focus our attention to the behaviour of chiral α-sulfinylalcohols, a class of compounds that have been found very effective enantioselective protonating reagents.[2]

We wish now to report our preliminary study on the effect of several factors that modify the enantioselectivity in the protonation with α-sulfinyl alcohols[3] (**1a-c**) and the result of theoretical calculations which allow to propose a model to explain the stereochemical course of the reaction.

Compounds **2a-b**[4] were used as precursors of enolate **3** which by protonation using **1** afforded ketone (R)-**4** with variable stereochemical outcome that highly depends on the structure of **1** and the reaction conditions employed (see Scheme). The effect of several factors on the enantioselectivity have been analyzed; namely the temperature of protonation, the type of enol precursor and finally, the presence of lithium salts in the reaction medium. Based on previous reports by Kosugi *et al.*[2] sulfinylalcohol (S,Rs)-**1a** was used as reference chiral proton source in this study, provided that the corresponding (R,Rs)-**1a** diastereomer and compounds **1b** and **1c** lead to a lower level of asymmetric induction.[2a,b] Commercially available diethyl ether solutions of methyllithium were employed in all cases. For this reason protonations were also carried out in ethereal solutions adding the chiral alcohol (S,Rs)-**1a** in a mixture (1 :1) of diethyl ether : methylene chloride or in pure methylene chloride as stated in the Scheme. Comparable results were obtained in both cases (entries 4, 5). In contrast the temperature plays a remarkable effect. Protonations were performed by chilling the solution containing the chiral alcohol (S,Rs)-**1a** at −100 or -78 °C, then adding over a precooled solution of the enolate at -75°C. An important enhancement of the enantioselectivity was observed at lower temperatures (entries 2, 3). Conversely, no influence of the temperature of quenching[5] (-50 or 0 °C) could be determined even when lithium *tert*-butoxide was present (entries 5, 6 and 7, 8). The lower temperature was assayed to prevent the possible epimerization of the resulting ketone (R)-**4** in the basic medium. In any case, the usual work up was followed once the temperature reached 0 °C.

Silyl enol ether **2a** and enol acetate **2b** were transformed into enolates **3a** and **3c** by treatment with one or two eq. of methyllithium (1.6 M solution in diethyl ether, d = 0.701; 0.09 M in LiCl) respectively and then submitted to protonation at -100 °C with (S,Rs)-**1a** to determine the effect of the type of enol precursor on the enantioselectivity. *Surprisingly, in contrast with previous reports* [2a,b] *ketone* (R)-**4**[6] *was obtained with only*

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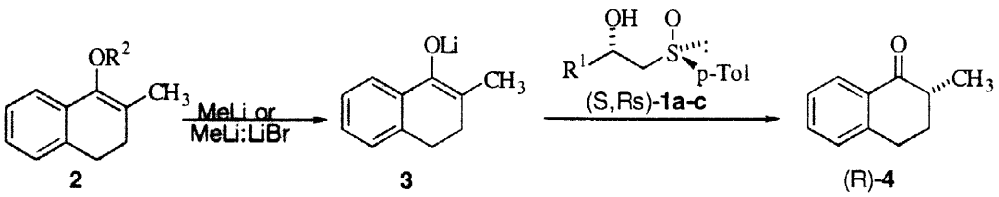


2 3 (R)-4

entry	1	R^1	2	R^2	3	lithium salts[a]	solvent[b] (T^o C)	% ee [c]
1	**a**	CF_3	**a**	$SiMe_3$	**a**	LiCl[d]	A (-100→ 0)	59
2	**a**	CF_3	**a**	$SiMe_3$	**b**	LiBr[e]	A (-100 →0)	80
3	**a**	CF_3	**a**	$SiMe_3$	**b**	LiBr[e]	A (-78→ 0)	57
4	**a**	CF_3	**b**	Ac	**c**	LiCl[f].Bu^{t}OLi[g]	B (-100 →-50)	58
5	**a**	CF_3	**b**	Ac	**c**	LiCl[f].Bu^{t}OLi[g]	A (-100→ -50)	59
6	**a**	CF_3	**b**	Ac	**c**	LiCl[f].Bu^{t}OLi[g]	A (-100 →0)	58
7	**a**	CF_3	**b**	Ac	**d**	LiBr[h].Bu^{t}OLi[g]	A (-100→ -50)	92
8	**a**	CF_3	**b**	Ac	**d**	LiBr[h].Bu^{t}OLi[g]	A (-100→0)	92
9	**b**	CH_3	**b**	Ac	**c**	LiCl[f].Bu^{t}OLi[g]	A (-78→0)	53
10	**b**	CH_3	**b**	Ac	**d**	LiBr[h].Bu^{t}OLi[g]	A (-78→0)	80
11	**c**	Bu^i	**b**	Ac	**c**	LiCl[f].Bu^{t}OLi[g]	A (-78→0)	41
12	**c**	Bu^i	**b**	Ac	**d**	LiBr[h].Bu^{t}OLi[g]	A (-78→0)	76

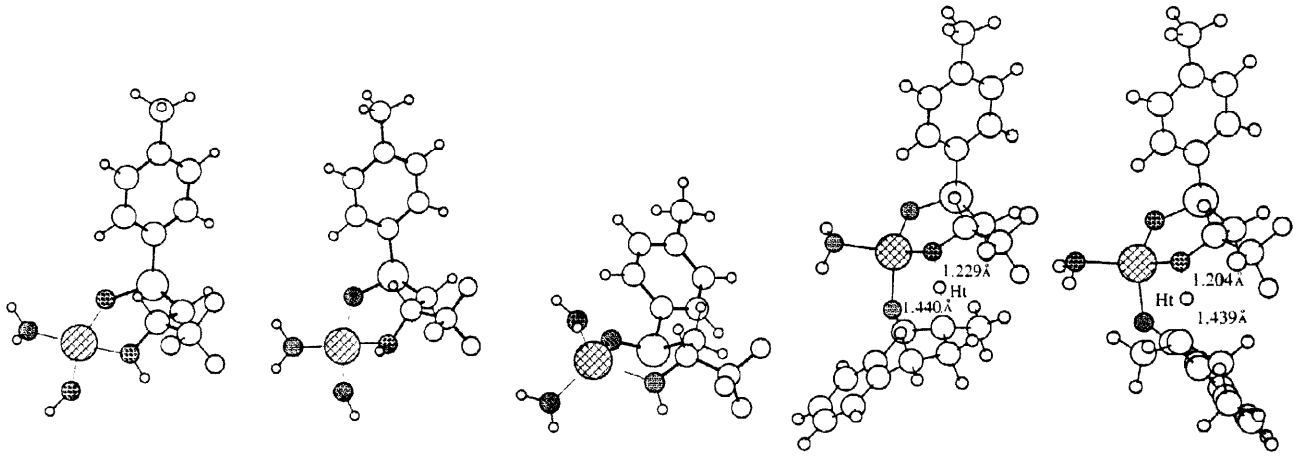
a) equiv. of lithium salt /equiv. of enolate 3 ; b) A:CH_2Cl_2 ; B:CH_2Cl_2 :Et_2O (1:1) ; c) Determined by $[\alpha]^6$ and ^{1}H-NMR [Eu(hfc)]; d) 0.073 ; e) 0.73 ; f) 0.146 ; g) 1.0 ; h) 1.46.

Scheme

59% and 58% e.e in each case (entries 1, 6), also proving that the presence of Bu^{t}OLi in the medium does not affect the course of protonation of tetralone enolate (**3**), in the same way as described for cyclohexanone enolates.[7] In other series of runs, enolates were generated upon treatment of enol **2a** or **2b** with one or two eq. of methyllithium (1.5 M solution in diethyl ether, d = 0.852; 1.0 M in LiBr) respectively. *Under these conditions, a very remarkable enhancement of the selectivity was observed* increasing the e.e. to 80% and 92%[8] respectively for the protonation of **3b** and **3d** (entries 2, 7 and 8). Since the protonation of **3b** gave a lower enantiomeric excess we related this fact to its lower content in LiBr. Subsequently we attempted to generate the enolate from **2a** in the presence of one additional eq. of anhydrous lithium bromide in the reaction medium. However, due to the low solubility of LiBr in ether a greater dilution had to be used in this case and the conversion to enolate was not achieved quantitatively even under the influence of longer reaction times. On the other hand, when a saturated ether solution containing one additional eq. of lithium bromide was added to an ether solution of **3b** previously formed and the resulting solution was stirred for 2 h prior to protonation with (S,Rs)-**1a**, no improvement in the enantioselectivity was achieved suggesting that LiBr must be already present during the enolate generation step. This is in agreement with other observations reported related to the enantioselective protonation with tartaric acid derivatives as the chiral proton source.[9] The role played by lithium bromide should be related to a change in the enolate structure.[10] A similar salt effect was observed in the prototonation with α-sulfinyl alcohols (S,Rs)-**1b** and (S,Rs)-**1c** (entries 9-12). Nevertheless the effect of lithium halides in the enantioselective protonation has been scarcely explored and only a few examples of enantiodifferentation improvement are known, always associated with protonations in the presence of amines.[1b,1c,9]

The molecular mechanism associated with the proton transfer process has been studied by PM3 semiempirical methods.[11,12] It has been assumed that both enolate and sulfinyl alcohol are coordinated to a

lithium atom, favouring the intramolecular proton transfer process.[2b] Due to the flexibility of the cyclic structures which result of chelation of the lithium atom to the sulfinyl alcohol, we have firstly carried out a conformational analysis of the cyclic chelates obtained by coordination of a lithium atom to (S,Rs)-**1a** and to two water molecules simulating the solvent.[13] This study gave two cyclic conformers **5a** and **5b** with a twisted chair arrangement, which differ in the relative disposal of the alcohol hydrogen. The most stable conformer **5a** bears this hydrogen at the less hindered face of the chelate molecule with an axial orientation. Optimization of the boat conformation **5c** which has been proposed previously as a model to explain the enantioselective protonation of enolates with sulfinyl alcohols,[2b] leads to the aforementioned conformer **5a**.



ΔH_f	-91.18	-90.09	-85.22	-305.68	-305.92
	5a	**5b**	**5c**	**TS-R**	**TS-S**

Figure. PM3 geometries and heats of formation (in kcal/mol) for the comformers **5a**, **5b** and **5c**, and the transition structures **TS-R** and **TS-S**.

Substitution of the water molecule located out of the molecular plane of the more stable chelate **5a** for the enolate anion affords two diastereomeric complex precursors for the enantioselective protonation. The weak bond Li-O (enolate) in these complexes allows closer approach of the enolate carbon atom to the hydroxy group, facilitating the proton transfer process. The same model was obtained by calculation for the protonation of **3** with alcohols **1b** and **1c**.

Finally, the transition structures (TSs) associated with the two stereoisomeric proton transfer pathways, **TS-R** and **TS-S** have been located. The PM3 calculations gave similar energies for these TSs, (see Figure), showing that both diastereomeric paths can be competitive. These TSs are described as six membered rings in which the proton transfer processes take place via a favourable intramolecular pathway. In the case of **1a**, the lengths of breaking O-Ht and forming C-Ht bonds in **TS-R** are 1.229 and 1.440 Å, while in **TS-S** these values are 1.204 and 1.439Å respectively. The normal mode analysis for these TSs gives only one high imaginary frequency in each case (1753.0i and 1556.8i cm^{-1}, for **TS-R** and **TS-S** respectively) showing that these processes are mainly associated with the hydrogen motion. From this theoretical study we can conclude that the coordination of a lithium atom to both enolate and sulfinyl alcohol favours the intramolecular proton transfer process. The experimental results indicate that the enantioselectivity is sensitive to experimental environments as the lithium concentration, showing the difficulty for a correct modelization of these processes.

However, despite the approximations used, this study allows us to characterise the reaction pathways that take place during the enantioselective protonation.

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