



An improved method for the asymmetric protonation of enolates with chiral α -sulfinyl alcohols/trifluoroethanol

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Abstract—Enantioselective protonation of 2-methyl tetralone enolate using a stoichiometric amount of 2-sulfinyl alcohol (S,R_s)-**1** as a chiral proton donor yields the corresponding chiral ketone with a high level of enantioselectivity, provided that the chiral proton donor (CPD) is regenerated with an achiral proton source (APS). In contrast, stereoselectivity was only moderate if catalytic CPD (0.2 equiv.) and an APS are used. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

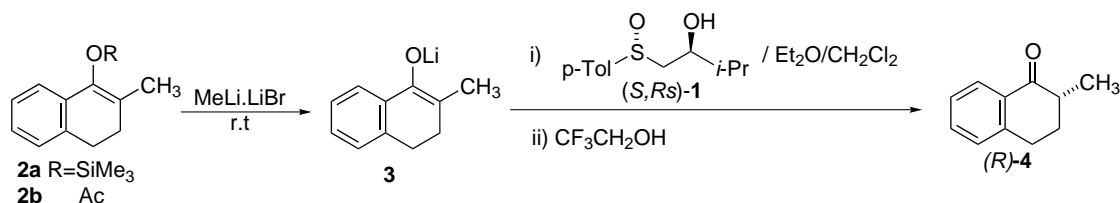
The asymmetric protonation of enolates is an efficient route to obtain optically active carbonyl compounds with a tertiary stereogenic carbon at the α -position.¹ Although this reaction formally requires 1 equiv. of the chiral proton source, in most cases simple aqueous work-up allows efficient recovery of the chiral reagent, which can then be re-used. Nevertheless, processes which use sub-stoichiometric quantities of the chiral proton source would provide clear advantages. Although several examples of catalytic enantioselective protonation reactions have been published recently,^{2–5} either a stoichiometric amount¹ or even an excess^{6,7} of the chiral proton source are usually required to achieve optimal stereoselectivity.

We have previously reported the asymmetric protonation of enolates of 2-alkylcycloalkanones with excellent levels of enantioselectivity using sulfinyl alcohol (S,R_s)-**1** as a chiral proton donor in the presence of lithium bromide.⁸ In these reactions optimal stereoselectivity was reached when the sulfinyl alcohol/enolate ratio was 3:1. Although in this case the chiral sulfinyl alcohol (S,R_s)-**1** was fully recovered in the work-up, we were interested in determining the degree of enantioselectivity that could be achieved using stoichiometric and sub-stoichiometric amounts of the chiral alcohol (S,R_s)-**1**.

2. Results and discussion

In general, either silyl enol ether **2a** or enol acetate **2b** can be used as precursors of the enolate **3** (Table 1), but for our purposes **2a** was preferable since no additional base is formed in the medium during the enolate generation step while 1 equiv. of lithium *tert*-butoxide is generated when **2b** is converted into enolate **3**; therefore, proton exchange will occur between the alkoxide and the chiral proton source and consequently a higher concentration of the chiral proton donor could be needed to keep the **3**/(S,R_s)-**1** ratio constant. When enolate **3** which had been generated by treating **2a**⁹ with MeLi·LiBr (1.1 equiv.) was reacted with 3 equiv. of the chiral sulfinyl alcohol (S,R_s)-**1** at -50°C , ketone (R)-**4**¹⁰ was obtained with high enantioselectivity (19:1). In a parallel experiment, the same amount of alcohol (S,R_s)-**1** (3 equiv.) was added in two portions. First, 1.2 equiv. of (S,R_s)-**1** was added at -50°C and after 1.5 h, the remaining 1.8 equiv. were added also at -50°C and then the temperature was allowed to rise to 0°C . By adding (S,R_s)-**1** in two portions we hoped to avoid the deprotonation of the chiral ketone (R)-**4** by the alkoxide (S,R_s)-**1**-Li. However, this procedure actually lowered the enantioselectivity to 89:11. This result indicates that more than 1.2 equiv. of protons are required during the protonation step to achieve optimum enantioselectivity, which, in turn, may be a consequence of several factors: (i) a low equilibrium constant for complexes **1**–**3**, (ii) the formation of complexes of type (**1**)_{*n*}–**3** (*n*>1), and/or (iii) a decrease of available sulfinyl alcohol (S,R_s)-**1** by complexation with the LiBr present in the reaction medium. Thus, in order to improve the enantioselectiv-

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Table 1. Asymmetric protonation of enolate **3** with stoichiometric and sub-stoichiometric amounts of the sulfinyl alcohol (*S,R_s*)-**1**

Entry	(<i>S,R_s</i>)- 1 (equiv.)	TFE (equiv.)	Time (h) ^a	E.r.
1	1.2	1.3	1.5	93:7
2	1.2	1.3	1.5	91:9
3	1.2	1.3	2.0	9:1
4	1.2	1.3	1.0	91:9
5	1.0	1.3	1.5	92:8
6	0.8	1.3	2.0	87:13
7	0.8	1.3	3.0	88:12
8	0.4	1.3	4.0	81:19
9	0.2	1.3	4.0	77:23
10	0.4	1.7	5.0	82:18
11	0.4	1.9	5.7	4:1
12	0.4	2.1	6.5	85:15
13	3.0	3.0	1.5	64:36

^a Addition time was adjusted to keep the CPS/APS ratio constant in each run.

ity using the stoichiometric chiral sulfinyl alcohol, we tried to regenerate the chiral proton donor by adding an achiral proton source (APS).

Selection of the appropriate APS was based on its *pK_a* value. Vedejs et al. reported that the optimal *pK_a* value for the APS should be near that of the chiral proton donor.² High enantioselectivity can actually be observed over a broad *pK_a* range (ΔpK_a ca. 8). As a first approach we chose 2,2,2-trifluoroethanol (TFE) as the APS since it falls in the required *pK_a* range and can be removed easily by means of evaporation, facilitating the recovery of the chiral ketone (*R*)-**4**. Thus, when enolate **3** generated from **2a** underwent protonation with (*S,R_s*)-**1** (1.2 equiv.) and TFE (1.3 equiv.) was added to the solution over a period of 1.5 h (Table 1, entry 1), ketone (*R*)-**4** could be isolated with a very high level of enantioselectivity (93:7). In this run a further equivalent of TFE was added at -50°C before the temperature was allowed to rise to 0°C in order to minimize deprotonation (with eventual racemization) of the chiral ketone by the basic species in the medium (*S,R_s*)-**1**-Li and CF₃CH₂OLi. Enolate **3** generated from **2b** yielded, under similar conditions, ketone (*R*)-**4** with decreased enantioselectivity (91:9; Table 1, entry 2) probably due to the presence in the medium of lithium *tert*-butoxide. Thus, **2a** was used as the enolate precursor in all the following runs. Changes in the TFE addition time (Table 1, entries 3 and 4) affected the observed enantioselectivity only slightly. Since the chiral proton source was regenerated during the reaction upon reprotonation by an achiral reagent, ketones could be prepared in optimal yield and stereoselectivity in a stoichiometric process.

As a follow up, the reaction was performed using sub-stoichiometric amounts of the chiral sulfinyl alcohol (*S,R_s*)-**1** and TFE. The results are summarized in Table 2.

The stereoselection is influenced by the value of the (*S,R_s*)-**1**/TFE ratio and also by the concentration proton donors (CPS+APS) at the end of the protonation process. Decreasing the amount of the chiral alcohol (*S,R_s*)-**1** resulted in a progressive decrease in the observed enantioselectivity, regardless of the addition time of the APS (Table 1, entries 5–9). On the other hand, the best enantioselectivity results were achieved using an alcohol (CPS+APS)/enolate **3** ratio of 2.5 (Table 1, entries 10–12). These data strongly suggest

Table 2. Catalytic enantioselective protonation of enolate **3** with 20% of sulfinyl alcohol (*S,R_s*)-**1**

Entry	APS (1.3 equiv.)	Time (h)	<i>pK_a</i> ^a	E.r.
1	2,6-DTF	4	16.85	3:1
2	PhCH ₂ CN	4	21.9	7:3
3	CF ₃ CH ₂ OH	4	23.45	77:23
4	CH ₃ CONH ₂	4	25.5	67:33
5	CH ₃ CH ₂ OH	4	29.0	71:29
6	CF ₃ CH ₂ OH	2	23.45	66:34
7	CH ₃ CONH ₂	2	25.5	68:32
8	ClCH ₂ CH ₂ OH	2		57:43
9	<i>tert</i> -BuOH	2	32.2	7:3
10	CF ₃ CH ₂ OH	6	23.45	74:26
11	CH ₃ CONH ₂	6	25.5	74:26
12	CF ₃ CH ₂ OH	14	23.45	73:27

^a *pK_a* values from Ref. 11.

that enolate **3** and ketone (*R*)-**4** exist in a proton-transfer equilibrium under the experimental conditions in such a way that an excess of alcohol must be present to shift the keto–enol tautomerism to the keto side. The alcohol excess required can be evaluated to be at least 2.5 equiv. to obtain good enantioselectivity. Otherwise, a significant amount of enol **3** seems to exist during the work-up leading to decreased enantioselectivities.

Further reactions were performed in the search for an APS better than TFE to achieve the catalytic enantioselective protonation of enolate **3** with (*S*,*R*_s)-**1**. As pointed out by Fehr,¹¹ the key to success in a catalytic cycle is to find an achiral proton source with a higher reactivity toward the conjugate base of the chiral proton donor than to the enolate. For this purpose, pK_a matching between the achiral proton source and the enolate, along with the control of the concentration of the achiral proton donor are important variables to be considered. With this in mind, we carried out a series of experiments with different achiral proton donors, modulating their concentration in the reaction medium by changing the addition times. The results are summarized in Table 2.

In this series of runs we used 20 mol% of the chiral proton donor and a stoichiometric amount of the achiral proton source. APSs were selected in the pK_a range¹² 16.85–29. However, despite the wide pK_a range studied, the various types of atoms used to deliver the proton, and the different concentrations utilized, in all cases the product enantiomer ratios obtained for the ketone (*R*)-**4** were quite similar. These findings suggest that while sulfinyl alcohol (*S*,*R*_s)-**1** is indeed recycled, the rate of protonation of the enolate is not sufficiently enhanced upon aggregation with the chiral alcohol (*S*,*R*_s)-**1** to yield a genuinely effective catalytic cycle. Consequently, reprotonation of catalyst (*S*,*R*_s)-**1** and protonation of enolate **3** by the APS compete to a certain extent. This hypothesis was ascertained by running a competitive protonation experiment in which (*S*,*R*_s)-**1** (3.0 equiv.) were mixed with **3** (1 equiv.) and then TFE (3 equiv.) were added over a period of 1.5 h. These experimental conditions led to a substantial decrease in the enantioselectivity (Table 1, entry 13)

3. Conclusions

In summary, chiral ketones such as (*R*)-2-methyl tetralone **4** can be prepared with a high level of enantioselectivity by means of enantioselective protonation of the corresponding lithium enolate with the stoichiometric amount of sulfinyl alcohol (*S*,*R*_s)-**1** when the chiral proton donor is regenerated in the reaction medium by addition of an achiral proton source such as trifluoroethanol using an alcohol (CPS+APS)/enolate **3** ratio of 2.5. These seem to be the optimal conditions for the enantioselective protonation of enolates with sulfinyl alcohols, but only moderate stereoselectivities are achieved in protonations with catalytic amounts of sulfinyl alcohol (*S*,*R*_s)-**1**.

4. Experimental

4.1. General procedures and materials

Methylolithium (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 from calcium hydride. Compounds (*S*,*R*_s)-**1**¹³ and **2a**⁹ were prepared as described in the literature. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. Enantiomeric ratios were determined by ¹H NMR [Eu(hfc)].

4.2. General experimental procedure when sub-stoichiometric amounts of (*S*,*R*_s)-**1** are employed

Neat **2a**⁹ (1.0 mmol) was treated with MeLi–LiBr 1.5 M (1.2 mmol) at rt. After stirring for 2 h, Et₂O (9 mL) was added and the resulting solution was cooled to -75°C . The solution was then added slowly (over a period of 7 min) to a solution of the appropriate amount of (*S*,*R*_s)-**1** in dichloromethane (30 mL) at -50°C . This solution was then stirred at -50°C for 30 min, after which the achiral proton source (the amount required to satisfy the equation **1**+APS=1.5 mmol) was slowly added with a syringe pump over the period indicated in each run. A further amount of APS (1.5 mmol) was added in one portion and the solution was allowed to reach the quenching temperature (the temperature increase was approximately $1.2^{\circ}\text{C}/\text{min}$). The reaction mixture was treated with phosphate buffer (pH 7.2) and extracted with hexane. The residue was purified by means of column chromatography to give (*R*)-**4**¹⁰ (90–94% yield).

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