Enantioselective Protonation of the Lithium Transient Enolate of 2-Methyltetralone with 2-Sulfinyl Alcohols

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A new catalytic cycle for the enantioselective protonation of cyclic ketone enolates with sulfinyl alcohols has been developed. An enol trifluoroacetate that can be easily obtained from the corresponding ketone is used for the first time as an enolate precursor of a cyclic ketone enolate. In this method, the achiral alcohol plays two roles: it is involved, as is usual in catalytic asymmetric protonation reactions, in the turnover of the chiral proton source and also in the generation of a transient enolate through the reaction of its corresponding alkoxide with the enol trifluoroacetate precursor. Stereoselectivity is highly dependent on the structure of the achiral alcohol. High levels of stereoselectivity can be achieved with the use of cyclohexanol.

Introduction

Enantioselective protonation represents a useful method for the desymmetrization of prochiral enolates, which enables the preparation of optically active carbonyl compounds with a stereogenic carbon at the α position.[1] Although the catalytic version of the enantioselective protonation reaction was initially classified in the field of organocatalysis[2a] a more restrictive use of the term has now been proposed.[2b] By means of the enantioselective protonation reaction, the synthesis of some important chemicals such as anti-inflammatory agents,[3] fragrances,[4] and pheromones[5] has been reported. The methods used for enantioselective protonation developed to date can be classified into two categories: a) *internal quench*,[6] where the protonating reagent is a chiral protic compound, and b) *external quench*,[7] where the proton source is an achiral protic compound coupled with a chiral additive/ligand. In both categories there have been several described examples in which the use of a stoichiometric amount or even an excess of the chiral compound makes it possible to obtain the corresponding chiral carbonyl derivatives with high *ee*.[8] Most of these reports have been on the preparation of optically active ketones, and have demonstrated the utility of this approach for the preparation of these useful synthetic intermediates. If the asymmetric protonation of ketone enolates can be shown to be an attractive alternative to asymmetric alkylation for the preparation of chiral alkyl ketones, this procedure may be the most reliable method for the synthesis of optically active aryl ketones with tertiary stereogenic centers at the α positions.[8e] Although the preparation of chiral aryl ketones by palladium-catalyzed arylation has been described, it is restricted to the generation of a nonracemizable quaternary center because the basic medium required in this reaction[9] is not compatible with the enantioselective creation of an easily racemizable tertiary center α to a carbonyl group. An alternative to the enantioselective protonation of ketone enolates for the preparation of optically active ketones has been described by Yamamoto[10] and consists of the asymmetric protonation of silyl enol ethers by use of a chiral Brønsted acid, the acidity of which is enhanced by combining it with a Lewis acid (LBA method).

Recently, the development of catalytic versions of the enantioselective protonation reaction has been a challenging target. Despite the possibility of complete recovery of the chiral compound, in most cases by simple aqueous workup, the option of performing the reaction with a reduced amount of chiral compounds is very attractive and justifies the constant work in this field. There are some literature examples of both internal[11] and external quench[6b,12] catalytic enantioselective protonation. Among the methods described for the internal quench catalytic enantioselective protonation of lithium enolates, two protocols can be distinguished by the concentration of the enolate in the reaction medium. The first and more frequently described protocol involves a preformed enolate[11d–11m,12c–12d] (i.e., all of the enolate is generated in the initial stage of the reaction; Protocol A, Scheme 1). The second variant involves a transient enolate (i.e., the enolate[11a–11c,12a–12b] is slowly and progressively generated during the reaction; Protocol B, Scheme 2). In both variants, only a substoichiometric (or catalytic) amount of a chiral protic compound (HX*) is used to protonate the enolate, and subsequent regeneration

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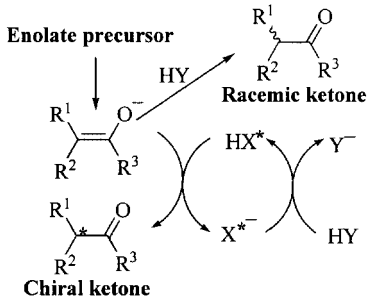
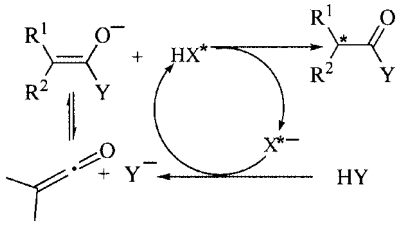
of this chiral proton source (CPS) by the addition of a stoichiometric amount of an achiral proton source (APS) is required to bring the reaction to completion.



Scheme 1. Catalytic enantioselective protonation (Protocol A).



Scheme 2. Catalytic enantioselective protonation (Protocol B).

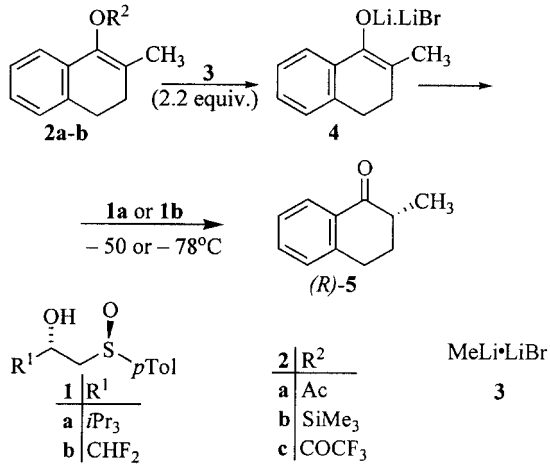
General requirements for the catalytic cycle. The catalytic cycle can be efficient when the two following conditions are preserved.[11d]

i) The proportion of protonation of enolate by the CPS is large compared with that of the protonation of the enolate by the APS. Thus, the concentration of the APS (HY) must be kept lower than that of the chiral reagent (HX*). This condition can be achieved by two alternative procedures: slow addition of the APS or the application of a biphasic system in which enolate and the APS exist in separate phases (both solid–liquid[12b,12e] and liquid–liquid[11m] systems have been described).

ii) Catalytic turnover of the CPS (HX*) requires that the APS (HY) react more rapidly with the conjugated base of the former (LiX*) than with enolate. A high selectivity for the desired process is especially required when enantiocatalytic protonation is conducted with a preformed enolate, since in this case the relative concentrations of the basic species ([enolate] > [LiX*]) disfavor the expected process.

The above requirements can be attained if the pK_a values of the reactive species and the relative rates of the different equations of the catalytic cycle are properly matched.[11e,13] As a consequence, high enantiomeric selectivity in the catalytic enantioselective protonation can be achieved only under precise control of all of these variables, which highlights the complexity of the process.

Recently, we have examined both stoichiometric[14] and catalytic[15] versions of the enantioselective protonation reaction by using sulfinyl alcohols **1** in the asymmetric protonation of enolates **4** generated by treatment of the corresponding precursors **2a–b** with complexed methyllithium **3** (Scheme 3). Sulfinyl alcohols **1** have been shown to be efficient chiral proton sources, giving the corresponding ketones with high enantioselectivity, but more than 1.2 equiv. of the chiral alcohols **1** were needed during the protonation step to achieve the optimum stereoselection. Despite the total recovery of the CPS, we thought that it would be interesting to search for conditions that would make it possible to reduce the amount of the chiral protic compound while maintaining the stereoselectivity, and our recent work on the enantioselective protonation reaction has been mainly addressed toward this end. We report here a new methodology for the efficient protonation of cyclic ketone enolates with sulfinyl alcohols **1** under substoichiometric and catalytic conditions.



Scheme 3. Enantioselective protonation of cyclic ketone lithium enolates with sulfinyl alcohols **1**.

Results and Discussion

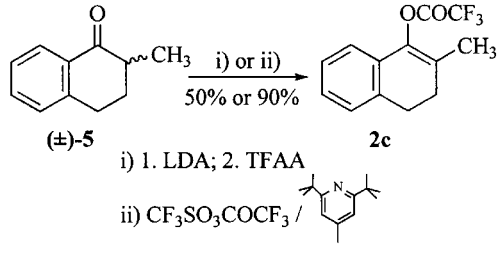
Rational Design of the Catalytic Cycle

This catalytic cycle is based on the application of the general concepts described above to our previous work on the enantiocatalytic protonation of the enolate **4** with the chiral alcohol **1a**. With our previous methodology, based on the protonation of preformed enolates (protocol A), only moderate stereoselectivity (75% *ee*) was attained.[15] One important drawback was that since the protonation reaction is reversible, a 2.5-fold excess of protic compounds (chiral + achiral) relative to the enolate is needed to take the reaction to completion. In fact, a decrease in enantiomeric selectivity was observed when the amount of protic compounds was lowered. Since only 0.4 equiv. of sulfinyl alcohol **1a** were used in our previous work, it is evident that it would have been impossible to maintain a low concentration of achiral protic compound with respect to the chiral one, which is crucial for achieving good stereoselection (vide supra). Therefore, under these conditions the catalytic cycle cannot compete with the unwanted protonation of the enolate by the APS, and only moderate stereoselection can be achieved. Additionally, when the preformed enolate protocol is followed, at least in the initial stages of the reaction, the concentration of enolate exceeds that of the sulfinyl

alcohol conjugate base (**1a**-Li), which may lead to undesired deprotonation of the APS by the enolate. It should be possible to control these two unfavorable aspects if the enolate is slowly generated in the reaction medium (the transient enolate protocol). We proposed a working hypothesis that, following this second alternative, the amount of enolate could be maintained at a concentration low enough to allow irreversible protonation by a substoichiometric or catalytic amount of the chiral alcohol. A point further along in the cycle could also be more favorable in this regard. To achieve a high turnover and enantioselectivity, the achiral alcohol must be deprotonated by the sulfinyl alkoxide but not the enolate. The low concentration of enolate in the medium disfavors its unwanted competitive protonation by the achiral proton source. With these ideas in mind, we devised a catalytic cycle for the enantioselective protonation of cyclic ketone enolates by slow generation of the enolate in which an achiral alcohol plays two roles: regenerating the chiral proton source by proton transfer and generating the enolate through reaction of its conjugate base (alkoxide) with the appropriate enolate precursor. This method for the generation of enolates offers an additional advantage, since the alkoxide of the achiral proton source is transformed into a neutral compound, thus avoiding base accumulation in the medium and precluding the eventual racemization of the resulting chiral ketone.

Synthesis of Enolate Precursor

We initially focused on finding an adequate precursor that could provide a cyclic ketone enolate by reaction with an alkoxide. The methods described in the literature for the generation of transient ketone enolates in catalytic enantioselective protonations are restricted to the preparation of open-chain ketone enolates by treatment of a ketene with a nucleophile.[11a–11c] With regard to the generation of cyclic ketone enolates, neither of the usual enolate precursors, such as enol acetate **2a** or silyl enol ether **2b**, which produce enolates by reacting with organolithium compounds[16] or alkoxides[17] at room temperature, reacted with alkoxides at the low temperature required to carry out enantioselective protonation reactions. However, we found that the more reactive enol trifluoroacetate **2c** could react under the conditions required. Enol trifluoroacetate **2c** was prepared by two procedures (Scheme 4). In the first, the lithium enolate was treated with an excess of TFAA (2.25 equiv.). The desired *O*-acylated product was obtained in 50% yield. An alternative and more efficient procedure consisted of treatment of the parent ketone with trifluoroacetyl triflate.[18] By this method, the expected *O*-acylated derivative was obtained in 90% yield.



Scheme 4. Preparation of precursor **2c**.

Enantiocatalytic Protonations

Initial experiments were carried out with methanol as an achiral proton source. We performed the reaction by a three-step procedure.

1) Firstly, a small portion of the enolate **4** (0.2 equiv.) was generated by treatment of enol trifluoroacetate **2c** (0.2 equiv.) with complexed methyllithium **3** (0.4 equiv.). Compound **3** was selected to initiate the enolate generation on the basis of the positive effect of lithium bromide on enantioselectivity in the protonation of lithium enolates with sulfinyl alcohols **1**.[14a]

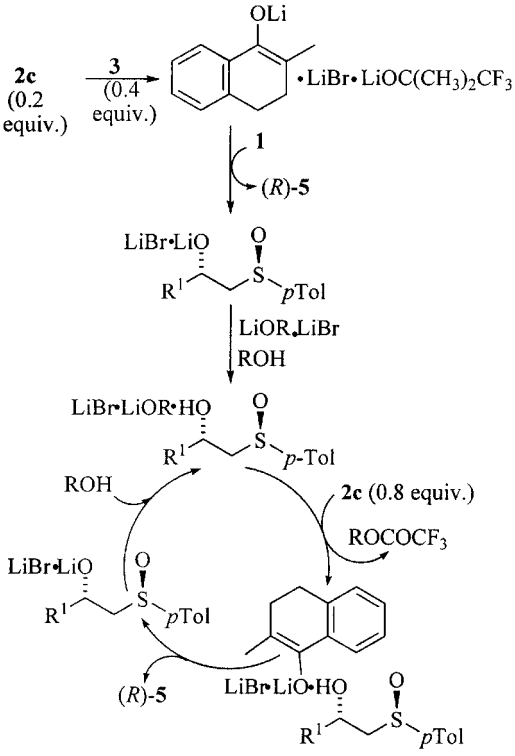
2) Secondly, a solution of **1a** (0.4 equiv.) in dry DEE was added. A portion of MeOLi·LiBr (generated by reaction of methyllithium **3** and anhydrous methanol) was then also added to the mixture.

3) Finally, enol trifluoroacetate **2c** (0.8 equiv.) and methanol were added slowly at –50 °C over 24 h.

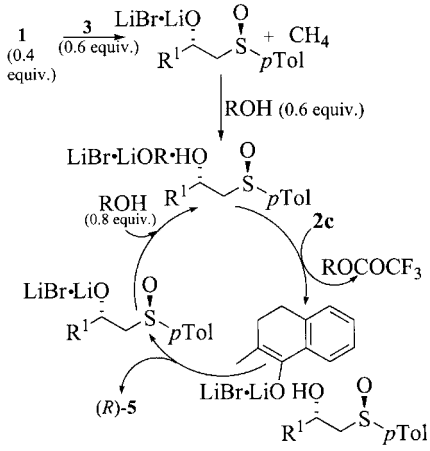
With this sequence, a catalytic cycle runs as depicted in Scheme 5. The enolate generated in the first step will react with the sulfinyl alcohol **1a**, leading to a chiral ketone and sulfinyl alkoxide **1a**–Li. The MeOLi·LiBr complex added in the second step will serve to generate further enolate by reacting with trifluoroacetate **2c** added in the third step. The methoxide is consumed in the reaction with **2c** but is then regenerated by the reaction of methanol (added in the third step) with sulfinyl alkoxide **1a**–Li. In addition, proton exchange between methanol and **1a**–Li allows the turnover of the chiral proton source to complete the catalytic cycle.

With this protocol, chiral ketone was obtained with 35% *ee*. We ascribed the low stereoselectivity to the presence of different types of aggregates, since two different procedures were used to generate the enolate.[2b] Accordingly, in the next set of experiments the first step was suppressed and the enolate was generated exclusively by treating MeOLi·LiBr with enol trifluoroacetate **2c** (see Scheme 6 and typical experiment in Experimental Section). In this way, the stereoselectivity was increased to 62% *ee* (Table 1, entry1), which shows that the method used to generate the enolate affects the stereoselectivity of the process. Next, we examined the effect of the presence of lithium bromide on stereoselectivity and, in sharp contrast with our previous results,[14a–14b] we found in this case a small effect of LiBr in the course of the protonation (Table 1, entries 1 and 2).

Variations in the MeOLi/MeOH concentration ratio did not significantly affect the stereoselectivity, although the reaction time was shortened when the concentration of methoxide was increased (Table 1, entries 1 and 3). The order in which **1a** and methanol were allowed to react with MeLi·LiBr in the first step of the catalytic cycle did not affect the stereoselectivity (Table 1, entries 1 and 4). Conversely, the choice of solvent significantly affected the



Scheme 5. Catalytic cycle for the enantioselective protonation with slow generation of the enolate – first approach.



Scheme 6. Catalytic cycle of the enantioselective protonation with slow generation of the enolate – second approach.

stereoselectivity. Thus, the use of a solvent that strongly coordinates to lithium, such as THF, decreases the stereoselectivity (Table 1, entry 5). An opposite effect was also observed when a smaller amount (0.1 equiv.) of the chiral alcohol **1a** was used (Table 1, entry 6,). Finally, we also performed the protonation with use of an excess of **1a** to determine the highest stereoselectivity attainable with this model. In this run, the chiral ketone was obtained with 83% *ee* (Table 1, entry 7) suggesting that the catalytic cycle could be improved.

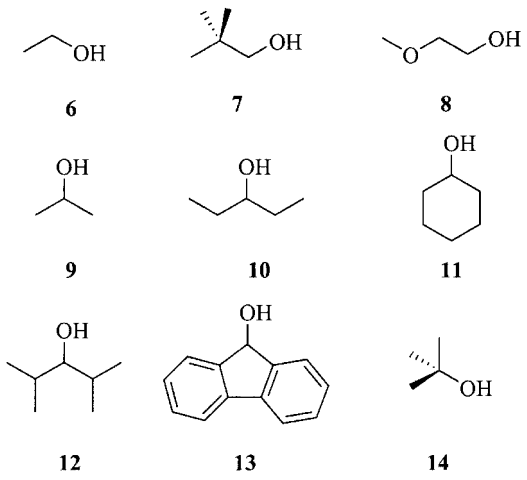
Table 1. Catalytic enantioselective protonation with sulfinyl alcohols **1** with slow generation of enolate.[a]

Run	**1a** equiv.	**3** equiv.	ROH (equiv.)[b]	**2c**/ROH[c] ratio	*ee*
1	0.4	0.6	**6** (0.6)	1:0.8	62
2	0.4	0.6[d]	**6** (0.6)	1:0.8	51
3	0.4	0.15	**6** (0.1)	1:0.8	54
4	0.4	0.3	**6** (0.3)	1:0.8	65
5[e]	0.4	0.3	**6** (0.3)	1:0.8	25
6	0.1	0.3	**6** (0.3)	1:1.1	17
7	3	1	**6** (1)	1:0	83
8	0.4	0.6	**7** (0.)6	1:0.8	75
9	0.4	0.3	**8** (0.3)	1:0.8	5
10	0.4	0.3	**9** (0.3)	1:0.8	73
11	0.4	0.6	**9** (0.6)	1:0.8	82
12	0.4	0.6	**10** (0.6)	1:0.8	81
13	0.4	0.6	**11** (0.6)	1:0.8	84
14	0.4	0.6	**12** (0.6)	1:0.8	61
15	0.4	0.6	**13** (0.6)	1:0.8	59
16	0.4	0.6	**14** (0.6)	1:0.8	67
17	3	1	**11** (1)	1:0	86
18	0.5	0.75	**11** (0.75)	1:1	84
19	0.2	0.4	**11** (0.4)	1:0.6	65
20[f]	0.2	0.4	**11** (0.6)	1:0.6	63
21[g]	0.4	0.6	**11** (0.6)	1:0.8	70
22	0.4[h]	0.6	**11** (0.6)	1:0.8	58

[a] Reaction conditions: DEE/CH_2Cl_2, 24 h, –50 °C unless otherwise specified. [b] Added in the first step. [c] Added slowly with **2c**. [d] Without LiBr. [e] Reaction conditions: THF, 24 h, –50 °C. [f] Reaction time 50 h. [g] Temperature of reaction –78 °C. [h] Reaction performed with **1b**.

Modification of the Achiral Alcohol Structure

Further experiments were designed to determine the influence of the structure of the achiral alcohol on the stereochemical outcome of the reaction. We tested different types of simple alcohols (see Scheme 7) and other compounds that contained additional chelating groups. The results show that the success of the asymmetric protonation is highly dependent on the structure of the achiral alcohol (Table 1, entries 8–16). The best results, with regard to the easy generation of the enolate from the precursor enol trifluoroacetate **2c**, the time required to complete the reaction, and the stereoselectivity attained in the protonation, were obtained with unbranched secondary alcohols **9**–**11** (Table 1, entries 11–13). The use of cyclohexanol gave a slightly better *ee* than the use of its acyclic equivalent isopropyl alcohol (Table 1, entries 11 and 13). Branched secondary alcohols and tertiary alcohols (Table 1, entries 14–16) gave similar results. On the other hand, the presence of a second coordinating group in the achiral alcohol decreased the stereoselectivity of the protonation reaction (Table 1, entry 9). It is difficult to provide a simple explanation to account for the influence of the structure of the achiral alcohol on the stereoselection, since it might influence different key features of the reaction, such as: i) the inclusion of the alkoxide in the structure of the enolate, which would modify the nature of the reactive species,[19] ii) the rate of reprotonation of the sulfinyl alcohol, and/or iii) the rate of protonation of the enolate itself.



Scheme 7. Alcohols used as achiral proton sources.

Variations in the Reaction Conditions and the Chiral Alcohol Structure

Once cyclohexanol had been identified as the most efficient achiral counterpart, the next series of experiments was designed to determine the minimum amount of chiral alcohol **1** necessary to achieve good stereoselection. The results obtained with an excess of sulfinyl alcohol **1a** (3 equiv.) (i.e., under noncatalytic conditions; Table 1, entry 17), were almost the same as those obtained with the use of 0.5 equiv. of **1a** (Table 1, entry 18) and comparable (Table 1, entry 13) to those obtained with 0.4 equiv. of sulfinyl alcohol. Conversely, when the amount of sulfinyl alcohol **1a** was further reduced to 0.2 equiv., the *ee* dropped to 65% (Table 1, entry 19), probably because in this case the sulfinyl alcohol/enolate molar ratio is not large enough to allow for the fast proton transfer required. This result did not improve with a longer reaction time (Table 1, entry 20). Although the *ee* values achieved were already close to the maximum, we also tested the influence of the temperature to optimize the efficiency of the catalytic cycle. However, the enantioselectivity decreased when reactions were carried out at lower temperature (Table 1, entry 21). Although the enantioselective protonation of enolates occurs under kinetic control, it appears that there is a temperature threshold (around –50 °C) above which efficient proton transfer takes place. This apparent paradoxical effect of temperature in enantioselective protonation has been reported previously by us[14c] and by others.[20] Finally, a different sulfinyl alcohol **1b** was tested, but the *ee* could not be improved (Table 1, entry 22) because of its low solubility under our reaction conditions.

Conclusions

Enol trifluoroacetate **2c** is a suitable substrate for the generation of cyclic enolates by reaction with alkoxides. This compound is readily available in high yields from the reaction of the racemic ketone with trifluoroacetyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as a base. The new catalytic method described here allows for the generation of a transient cyclic ketone enolate and its asymmetric protonation with a substoichiometric amount of sulfinyl alcohol **1a**, leading to the corresponding chiral ketone. Significantly, the *ee* values observed under these conditions were only slightly lower than those obtained with use of an excess of the sulfinyl alcohol **1a**. Conversely, the enantioselectivity decreases in proportion to the amount of CPS used when catalytic enantioselective protonation with sulfinyl alcohol **1a** is carried out following the preformed enolate protocol. Thus, the method involving a transient enolate reported here is an important improvement in approaches to the catalytic enantioselective protonation of enolates with sulfinyl alcohols. In addition, this method could be extended, and could offer new perspectives in enolate chemistry.

Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 300 instrument with tetramethylsilane as an internal reference and $CDCl_3$ as a solvent. Optical rotation measurements were determined on a Perkin–Elmer 241 polarimeter at room temperature. High Resolution Mass Spectra were determined on a Fisons VG Autospec instrument. Reactions were monitored by analytical thin-layer chromatography with commercial aluminium sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Product purification by flash chromatography was performed with E. Merck Silica Gel (230–400 mesh). The *ee* values were determined by HPLC (Chiralcel OD). All experiments were carried out under dry argon.

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 purchased from Aldrich. All solvents were dried before use. Diethyl ether was distilled under argon from sodium/benzophenone and dichloromethane from calcium hydride. Sulfinyl alcohols (*S*,*Rs*)-**1a**[14c] and (*S*,*Rs*)-**1b**,[14b] silyl enol ether **2a**,[21] and enol acetate **2b**[16b] were prepared by previously described procedures.

Synthesis of 2-Methyl-1-trifluoroacetoxy-3,4-dihydronaphthalene (2c). Procedure 1: 2-Methyl-1-tetralone (13.2 mmol) in dry THF (15 mL) was added at –20 °C and under an inert atmosphere to a solution of freshly prepared LDA (16.5 mmol). After 1 h of stirring at the same temperature, the solution was added by cannula to a solution of TFAA (30 mmol) in dry THF (10 mL) cooled to –78 °C. After 30 min the temperature was raised to –20 °C and the solution was kept at this temperature for 1 h. The solvent and the excess TFAA were evaporated in vacuo. The reaction mixture was diluted in ethyl acetate (40 mL) and washed with $NaHCO_3$ (2×15 mL) and brine (2×15 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated, and the residue was purified by flash chromatography with hexane/ethyl acetate (50:1) to give **2c** (50% yield). ^{1}H NMR: δ = 1.73 s (3 H), 2.38 (t, J = 7.5 Hz, 2 H), 2.82 (t, J = 7.5 Hz, 2 H), 6.91–6.93 (m, 1 H), 7.08–7.19 (m, 3 H) ppm. ^{13}C NMR: δ = 16.4 (q), 27.2 (t), 28.8 (t), 114.8 (q, $J_{F,C}$ = 284 Hz), 119.5 (d), 125.4 (s), 126.5 (d), 127.5 (d), 127.6 (d), 129.2 (s), 135.2 (s), 139.4 (s), 155.3 (q, $J_{F,C}$ = 42 Hz) ppm. ^{19}F NMR: δ = –74.93 (s) ppm. HRMS: *m*/*z* calcd. for $C_{13}H_{11}F_3O_2$ 256.0711; found 256.0717.

Synthesis of 2-Methyl-1-trifluoroacetoxy-3,4-dihydronaphthalene (2c). Procedure 2: A solution of 2-methyl-1-tetralone (10 mmol) in dichloromethane (15 mL) was added at 0 °C and under an inert atmosphere to a solution of 2,6-di-*tert*-butyl-4-methylpyridine (10 mmol) and trifluoroacetyl triflate (20 mmol) in dichloromethane (15 mL) . After stirring for 16 h at the same temperature, the mixture was concentrated in vacuo and the residue was diluted in diethyl ether. The resulting precipitate was filtered off and the filtrate was washed with water. The organic phase was dried over sodium sulfate, filtered, and concentrated to give **2c** in 90% yield.

Catalytic Enantioselective Protonation. Typical General Experimental Procedure: MeLi·LiBr **3** (0.6 mmol) was added at –20 °C under an inert atmosphere to a solution of the chiral alcohol (*S*,*R*s)-**1** (0.4 mmol) in diethyl ether (15 mL), and the solution was stirred for 30 min. A solution of the achiral alcohol (0.6 mmol) in diethyl ether (5 mL) was then added and the mixture was stirred for an additional 30 min at the same temperature. Dichloromethane (10 mL) was added and the reaction mixture was cooled to –50 °C. A solution of enol trifluoroacetate **2c** (1 mmol) and achiral alcohol (0.8 mmol) in dichloromethane (10 mL) was added by syringe pump over 24 h. Next, trifluoroethanol (0.4 mmol) was added in one portion and the solution was allowed to reach the quenching temperature (temperature increased at approximately 1.2 ° min^{-1}). 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 chiral ketone (*R*)-**5** (90–94% yield).

Acknowledgments

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