Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3851–3855

TETRAHEDRON: *ASYMMETRY*

# Synthesis of an enantiopure 2-arylcyclohexanols from prochiral enol acetates by an enantioselective protonation/diastereoselective reduction sequence

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Received 15 August 2003; accepted 1 September 2003

**Abstract**—The enantioselective protonation with 2-sulfinyl alcohols of lithium enolates of 2-arylcyclohexanones with different substituents on the phenyl group takes place with excellent enantioselectivities (89–99%). Chiral 2-phenylcyclohexanone and 2-arylcyclohexanones carrying electron donor substituents on the aromatic ring are converted into the corresponding *trans*-2-arylcyclohexanols by diastereoselective reduction with sodium naphthalenide in the presence of acetamide. The stereochemical integrity of the tertiary stereocenter is fully preserved using this reduction procedure. Interestingly, the chiral proton source is not consumed in the synthesis.


## 1. Introduction

Chiral ketones are important building blocks in asymmetric synthesis. The preparation of chiral 2-alkyl ketones with a tertiary stereogenic center at the α position can be accomplished by enantioselective protonation (formation of a C–H bond)[1,2] or alkylation (formation of C–C bond)[3] of the corresponding lithium enolates. However, the preparation of 2-aryl ketones through the coupling of enolates with aryl halides catalyzed by palladium (C–C bond formation) is more difficult to conduct.[4] Although the asymmetric version of this reaction is known, it is restricted to the generation of a quaternary center.[5] Thus, the reported methods for arylation of carbonyl compounds (carbon–arene bond formation) do not allow homochiral carbonyl compounds with a tertiary stereogenic center at the α position to be obtained. Then the creation of a carbon-hydrogen bond by enantioselective protonation seems to be the simplest alternative methodology to achieve this kind of compound. Mikami[6] and Yamamoto[7] reported by this approach the preparation of 2-arylketones with similar good enantioselectivities (82–94% ee), by mixing samarium enolates/chiral diols and silyl enol eters/BINOL/$SnCl_4$ respectively.

Herein we report now the synthesis of chiral 2-arylcyclohexanones by enantioselective protonation of lithium enolates with chiral sulfinyl alcohols. Our procedure has the advantage of high enantioselectivity and the easy preparation and accessibility of the reagents if compared with those required for the synthesis of the same compounds by methods previously reported. In addition, we describe the efficient conversion of some chiral 2-arylketones to the corresponding chiral *trans*-2-arylcyclohexanols. Previously, we have reported an efficient new approach for the preparation of chiral *trans*-2-phenylcyclohexanol, based on the diastereoselective reduction of chiral 2-phenylcylohexanone with a sodium naphthalene/acetamide mixture.[8] Cyclohexanols occupy among the chiral auxiliaries a special position because of the versatility and high levels of stereocontrol they offer.[9] Owing to their importance, several different methods for the preparation of this kind of compounds, including resolution of racemic material (enzymatic[10] and nonenzymatic[11]) and asymmetric reactions, have been reported.[12,13] Resolution methods allow *trans*-2-arylcyclohexanols including the parent compound *trans*-2-phenylcyclohexanol to be obtained in practically enantiopure form. Concerning asymmetric synthesis methods, several procedures are suitable to obtain *trans*-2-phenylcyclohexanol with high stereoselectivity[12] but that is not the case for *trans*-2-arylcyclohexanols.[13] Thus development of new asym-

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doi:10.1016/j.tetasy.2003.09.002

metric reactions leading to these products remains as an interesting topic.

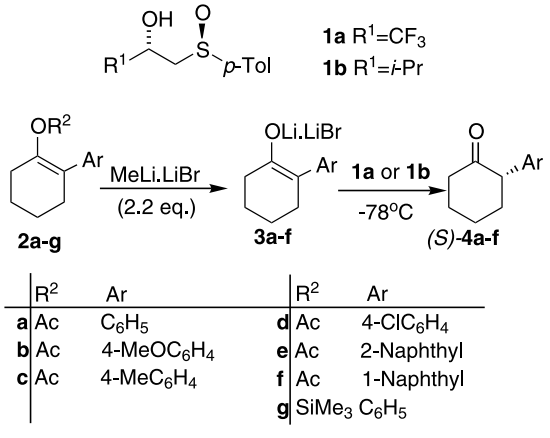
## 2. Results and discussion

In previous papers we have demonstrated that under defined reaction conditions 2-sulfinyl alcohols **1** ($R^1$: $CF_3$, $CHF_2$, $CH_2F$, Me, *i*-Pr, *t*-Bu) are efficient proton sources for the enantioselective protonation of lithium enolates. Sulfinyl alcohols **1a** ($R^1$: $CF_3$) and **1b** ($R^1$: *i*-Pr) provide the higher enantioselectivities.[14,15] Therefore we decided to explore the enantioselective protonation of enolates of 2-aryl ketones with sulfinyl alcohols **1a** and **1b** (Scheme 1).

Enol acetates **2a–f** were used as precursors of the corresponding lithium enolates **3a–f** because their advantages over the alternative silyl enol ether precursors such as **2g**. The main advantage is related with the facility to obtain the desired thermodynamic enol acetates **2a–f**[16,17] in practically regioisomerically pure form (98–99%) from the corresponding racemic ketones **4a–f**. On the contrary, in the preparation of silyl ethers as **2g**, a mixture of the kinetic and thermodynamic regioisomers is formed and an additional isomerization step is required to obtain the thermodynamic isomer in pure form.[7]

Racemic ketones **4a–f** were prepared in two steps by reaction of cyclohexene oxide with the corresponding aryl organometallic derivative according to procedures described in the literature[12,13] followed by oxidation of the resulting racemic *trans*-2-aryl cyclohexanols [(±)-**5**] to the corresponding ketone.[6]

Enolates **3a–f** were generated by treatment of enol acetates **2a–f** with 2.2 equiv. of methyllithium as its complex with lithium bromide. Subsequent enantioselective protonation with sulfinylacohols **1a** or **1b** afforded the corresponding non-racemic chiral ketones **4a–f** (Scheme 1).




**Scheme 1.**

The results of the enantioselective protonation of lithium enolates **3a–f** are collected in Table 1. In a first series of runs enolates **3a–c** (Table 1, entries 1–3) were submitted to protonation with sulfinyl alcohol **1a**. While ketone **4a** was obtained with excellent enantioselectivity, ketones **4b** and **4c** gave poor results. The differences observed can be interpreted by considering that the basicity of the three enolates is not the same since it is related to the type of substituent present in the phenyl group. The basicity is expected to increase in the order **3a**<**3c**<**3b** according to the electron donor ability of the substituents (H<Me<OMe) at the *para* position of the phenyl group. Then, in the protonation of enolates **3a–c** with sulfinyl alcohol **1a** the enantioselectivity decreases as the basicity of the enolate increases (Table 1, entries 1, 2 and 3).

**Table 1.** Enantioselective protonation of enolates **4a–f** with 2-sulfinylalcohols **1a** and **1b**

| Entry | 1 | 4 | Ar | Ee[a] | Yield | Ketone |
|---|---|---|---|---|---|---|
| 1 | **1a** | **4a** | Ph | **99** | 85 | (*S*)-**4a** |
| 2 | **1a** | **4b** | 4-$OCH_3$-$C_6H_4$ | 14 | 70 | (*S*)-**4b** |
| 3 | **1a** | **4c** | 4-$CH_3$-$C_6H_4$ | 43 | 81 | (*S*)-**4c** |
| 4 | **1b** | **4a** | Ph | **99** | 85 | (*S*)-**4a** |
| 5 | **1b** | **4b** | 4-$OCH_3$-$C_6H_4$ | **89** | 90 | (*S*)-**4b** |
| 6 | **1b** | **4c** | 4-$CH_3$-$C_6H_4$ | **99** | 81 | (*S*)-**4c** |
| 7 | **1b** | **4d** | 4-Cl-$C_6H_4$ | **99** | 75 | (*S*)-**4a** |
| 8 | **1b** | **4b** | 4-$OCH_3$-$C_6H_4$ | 85 | 91 | (*S*)-**4b** |
| 9 | **1b** | **4e** | 2-Naphthyl | 52 | 60 | (*S*)-**4f** |
| 10 | **1b** | **4e** | 2-Naphthyl | 80[b] | 62 | (*S*)-**4f** |
| 11 | **1a** | **4f** | 1-Naphthyl | 6 | 78 | (*S*)-**4e** |
| 12 | **1b** | **4f** | 1-Naphthyl | 43 | 72 | (*S*)-**4e** |
| 13 | **1b** | **4f** | 1-Naphthyl | 31[c] | 65 | (*S*)-**4e** |

[a] Reaction temperature −78°C otherwise noted.
[b] Reaction temperature −100°C.
[c] Reaction temperature −50°C.

Next we attempted the enantioselective protonation of **3** using a less acidic sulfinyl alcohol such as **1b**. In this way we were able to obtain ketone **4b** with a very good ee (89%) (Table 1, entry 5), and ketones **4a**, **4c** and **4d** with the maximum enantiomeric excess (99% ee) (Table 1, entries 4, 6 and 7). Since enolate **3b** is the most basic in the series, we attempted, unsuccessfully, to improve further the enantioselectivity in the case of ketone **4b** by conducting the protonation reaction at low temperature (−100°C) (Table 1, entry 8). On the contrary, the protonation of enolate **3e** with sulfinyl alcohol **1b** took place with moderate enantiomeric excess (52%, Table 1, entry 9) when the reaction was performed at −78°C but the enantioselectivity could be enhanced (80% ee, Table 1, entry 10) by increasing the protonation temperature to −50°C. These data along with that previously reported by our group[15] shows that sulfinyl alcohol **1b** is an efficient proton source for a wide range of lithium ketone enolates. Unfortunately, the protonation of the crowded enolate **3f** containing the 1-naphthyl group with sulfinyl alcohols **1a** and **1b** at different temperatures took place with lower enantioselectivity in all the cases most probably due to steric reasons (Table 1, entries 11–13). It seems reasonable that a planar conformation of the enolate in the proton transfer step would contribute to minimize the steric interactions

between the enolate and the sulfinyl alcohol moieties. Then, the presence of the bulky 1-naphthyl group in the enolate is expected to have a negative influence on the enantioselectivity of the protonation reaction. An examination of the geometry of the enolate **3f** reveals that this anion would suffer severe steric strain in the planar conformation, therefore a twist in the dihedral angle between the enolate double bond and the plane of the aryl ring decreases the steric hindrance in the molecule at the expense of the planarity. Thus the low enantioselectivity achieved in the preparation of ketone **4f** can be explained in these terms.

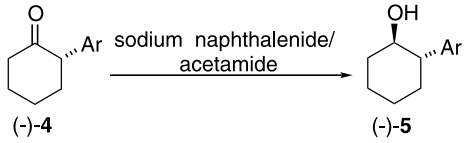
Once the ketones **4a–e** were prepared in practically homochiral form, we planned their conversion in the corresponding chiral *trans*-2-arylcyclohexanols. Usual methods for the reduction of α-substituted ketones with dialkylboranes or hydrides fail to afford stereoselectively the desired *trans*-cyclohexanols without the concomitant formation of the *cis*-isomer. So, common hydrides such as lithium aluminium hydride and sodium borohydride reduce α-substituted cycloalkanones to give predominantly (90%), but not exclusively, the more stable thermodynamically *trans*-cycloalkanol. Hindered dialkylboranes give preferentially the less stable *cis*-isomer.[18] On the other hand, the reduction of α-substituted ketones by dissolving metals is quite stereoselective leading to the formation of the corresponding *trans*-alcohols.[19] However, the strongly basic medium in which these reactions occur precludes the application of this simple methodology to the reduction of chiral ketones. Recently other procedures have been described in the literature to obtain the thermodynamic alcohols by reduction of cyclic ketones. However, higher temperatures (25°C or reflux) and prolonged reaction times (5 days) are required.[20] These methods are based on the reduction of the ketone to give in a first instance both isomeric alcohols and then, the less stable alcohol is converted under thermodynamic control in the most stable isomer by equilibration through a Meerwein–Pondorf–Verley type reduction. Obviously these procedures are not suitable to the streocontrolled reduction of enolizable chiral ketones. We have described previously[8] a selective reduction procedure that allows the conversion of chiral 2-phenyl cyclohexanone **4a** upon treatment with sodium naphthalenide in the presence of acetamide as proton source into the corresponding *trans*-alcohol **5a** without racemization. By our method, the diastereoselective reduction takes place quickly (1 h) at low temperature (−78°C), without racemization of the starting chiral ketone. Then, we tried the reduction of the chiral ketones above synthesized by this method.

Treatment of the cyclic chiral ketones **4a–c** with sodium naphthalenide/acetamide at −78°C, gave the thermodynamic reduction products *trans*-**5a–c** without contamination with the corresponding *cis* isomers and with total retention of the configuration at the adjacent tertiary stereogenic center (Scheme 2, Table 2, entries 1–3). However, this method could not be extended to the reduction of ketones **4d–f**. With these substrates, we obtained complex mixtures of products. Apparently, the electron transfer process is not selective in these ketones and it occurs at not only the carbonyl moiety but also involving the C–Cl bond (case of **4d**) and the aryl group. The coupling of the different radicals so formed would give rise to the complex mixture of products observed in the reduction of ketones **4d–f** (Table 2, entries 4–6, Scheme 2).[21]

**Table 2.** Reduction with sodium naphthalenide/acetamide of ketones **4**

| Run | (−)-**4** | (−)-**5** | Yield (%) | Ee (%) |
|---|---|---|---|---|
| 1 | **a** | **a** | 87 | 99 |
| 2 | **b** | **b** | 62 | 90 |
| 3 | **c** | **c** | 71 | 97 |
| 4 | **d** | **d** | 0[a] | – |
| 5 | **e** | **e** | 0[a] | – |
| 6 | **f** | **f** | 0[a] | – |

[a] Only formation of radical coupling products could be observed.




**Scheme 2.**

## 3. Conclusions

The protonation of lithium enolates of 2-arylcyclohexanones with 2-sulfinyl alcohol **1b** allows to obtain the corresponding ketones with excellent (enolates **3a–d**) to good (enolate **3e**) enantioselectivities. Thus, the enantioselective protonation reaction is among the reported procedures, the best method to obtain chiral 2-aryl ketones with a α-tertiary stereogenic center.

The chiral cyclohexanones can be reduced diastereoselectively with the mixture sodium naphthalenide/acetamide to afford exclusively the corresponding *trans*-arylcyclohexanols following the procedure previously described by us. The reduction procedure is restricted to aryl ketones in which the aryl group is phenyl or an activated aryl ring to avoid undesired radical side reactions.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC-300 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. CG analysis was done with a Fisons series 9000 using a capillary column BPX5 (0.25 μm×30 m). All experiments were carried out under an atmosphere of dry argon.

### 4.2. Materials

Methyllithium (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. Enol acetates **2a**–**f** were obtained following described procedures.[16,17] Racemic ketone **4a** was purchased by Aldrich Chemical Co. Ketones **4b**–**f**[6,7]were prepared following described procedures. Spectroscopic data for ketones **4b** and **4c** were coincident with literature data.[6] The absolute configuration of the chiral ketones **4a**–**f**[6,7] and the alcohols **5a**–**c**[10] were determined by comparison of specific rotations values with literature data. Enantiomeric excesses were determined by $^1$H NMR of the corresponding MTPA esters of the *trans*-cyclohexanols.

### 4.3. Generation of enolates 3a–f from enol acetates 2a–f

To a stirred solution of **2** (1.0 mmol) in diethyl ether (9 ml) at 0°C was added an ether solution of methyllithium as complex with lithium bromide 1.5 M (2.2 mmol). The mixture was stirred at room temperature for 30 min.

### 4.4. General procedure for enantioselective protonation

The corresponding lithium enolate solution (10 ml) cooled at −75°C was slowly added in 7 min to a solution of the appropriate sulfinyl alcohol (3mmol) in dichloromethane (30 ml) at −78°C. The mixture was stirred (1.5 h) at the same temperature and then gradually warmed up to −35°C (temperature increase approximately 1.2°C/min). The reaction mixture was quenched with $NH_4Cl$ and extracted with hexane. The residue was purified by column chromatography to give the corresponding chiral ketone (90–94% yield).

### 4.5. General procedure for diastereoselective reduction

Small pieces of sodium ($4.25\times10^{-3}$ atm-gr) were added to a solution of naphthalene (3.78 mmol) in THF (10 ml). After sonication for 3 h in an ice bath, the resulting dark green solution was diluted with THF (10 ml) and cooled to −78°C, and then acetamide (3.02 mmol) was added. A solution of (−)-**4a**–**c** (0.378 mmol) in THF (7 ml) was finally added dropwise over a period of 90 min. The reaction was quenched with methanol (5 ml) and poured into phosphate buffer. Usual workup gave *trans*-2-arylcyclohexanols **5**.

### 4.6. Enol acetate 2a

Yield 88%. Regioisomeric purity 98%. $^1$H NMR $\delta$ 1.77–1.88 (m, 7H), 2.21–2.32 (m, 2H), 2.34–2.44 (m, 2H), 7.15–7.73 (m, 5H). $^{13}$C NMR $\delta$ 20.4 (q), 23.1 (t), 23.2 (t), 27.3 (t), 30.5 (t), 125.7 (s), 127.5 (d), 128.2 (d), 128.5 (d), 139.8 (s), 143.4 (s), 169.5 (s).

### 4.7. Enol acetate 2b

Yield: 80%. Regioisomeric purity 99%.$^1$H NMR $\delta$ 1.69–1.91 (m, 4H), 1.94 (s, 3H), 2.21–2.32 (m, 2H), 2.34–2.47 (m, 2H), 3.80 (s, 3H), 6.84 (dd, 2H, $J_1=8.8$ Hz, $J_2=2.5$ Hz), 7.16 (dd, 2H, $J_1=8.8$ Hz, $J_2=2.5$ Hz). $^{13}$C NMR $\delta$ 20.9 (q), 22.6 (t), 22.8 (t), 27.5 (t), 30.1 (t), 55.1 (q), 113.4 (d), 124.7 (s), 128.5 (d), 129.7 (s), 143.0 (s), 158.2 (s), 169.5 (s).

### 4.8. Enol acetate 2c

Yield: 82%. Regioisomeric purity 98%. $^1$H NMR $\delta$ 1.69–1.91 (m, 4H), 1.95 (s, 3H), 2.21–2.33 (m, 2H), 2.34 (s, 3H), 2.37–2.48 (m, 2H), 7.12 (s, 4H). $^{13}$C NMR $\delta$ 21.3 (q), 21.6 (t), 23.2 (t), 27.9 (t), 30.5 (t), 125.5 (s), 127.7 (d), 128.5 (d), 129.2 (d), 136.7 (s), 143.5 (s), 169.9 (s).

### 4.9. Enol acetate 2d

Yield 86%. Regioisomeric purity 99%. $^1$H NMR $\delta$ 1.76–1.80 (m, 4H), 1.85 (s, 3H), 2.18–2.31 (m, 2H), 2.32–2.50 (m, 2H), 7.15 (d, 2H, $J=8.0$ Hz), 7.25 (d, 2H, $J=8.0$ Hz). $^{13}$C NMR $\delta$ 20.6 (q), 22.4 (t), 22.5 (t), 27.3 (t), 29.7 (t), 124.2 (s), 128.1 (d), 128.8 (d), 132.3 (s), 137.6 (s), 143.8 (s), 169.0 (s).

### 4.10. Enol acetate 2e

Yield 95%. Regioisomeric purity 99%. $^1$H NMR $\delta$ 1.60–1.80 (m, 4H), 1.85 (s, 3H), 2.40–2.50 (m, 4H), 7.20–7.40 (m, 3H), 7.55 (s, 1H), 7.65–7.80 (m, 3H); $^{13}$C NMR $\delta$ 21.3 (q), 23.1 (t), 23.2 (t), 28.0 (t), 30.5 (t), 125.8 (s), 126.1 (d), 126.3 (d), 126.5 (d), 126.6 (d), 127.9 (d), 128.0 (d), 128.3 (d) 132.7 (s), 133.7 (s), 137.3 (s),.144.2 (s), 169.9 (s).

### 4.11. Enol acetate 2f

Yield 95%. Regioisomeric purity 99% $^1$H NMR $\delta$ 1.61 (s, 3H), 1.84–1.95 (m, 4H), 2.36–2.50 (m, 4H), 7.23 (dd, 1H, $J_1=6.5$ Hz, $J_2=1.2$ Hz), 7.39 (dd, 1H, $J_1=6.5$ Hz, $J_2=1.2$ Hz), 7.44–7.48 (m, 2H), 7.73 (d, 1H, $J=8.1$ Hz), 7.82–7.90 (m, 2H). $^{13}$C NMR $\delta$ 20.3 (q), 22.6 (t), 22.9 (t), 27.2 (t), 31.0 (t), 124.6 (d), 125.0 (d), 125.3 (d), 125.5 (d), 125.6 (d), 127.0 (d), 128.1 (d), 130.8 (s), 133.5 (s), 137.4 (s), 144.6 (s), 169.0 (s).

### 4.12. Ketone (±)-4d

Yield 50%. Mp: 68–69°C. $^1$H NMR $\delta$ 1.66–2.53 (m, 8H), 3.60 (dd, 1H, $J_1=11.5$ Hz, $J_2=5$ Hz), 7.07 (d, 2H, $J=7$ Hz), 7.31 (d, 2H, $J=7$ Hz). $^{13}$C NMR $\delta$ 25.2 (t), 27.6 (t), 35.1 (t), 42.0 (t), 56.6 (t), 128.3 (d), 129.8 (d), 132.4 (s), 137.1 (s), 209.7 (s).

### 4.13. Ketone (±)-4f

Yield.: 72%. Mp: 86–87°C. $^1$H NMR $\delta$ 1.63–1.87 (m, 2H), 1.88–2.01 (m, 1H), 2.06–2.32 (m, 3H), 2.39–2.60 (m, 2H), 4.20 (dd, 1H, $J_1=12.2$ Hz, $J_2=5.25$ Hz), 7.22 (d, 1H, $J=7.2$ Hz), 7.31–7.34 (m, 3H), 7.59–7.62 (m,

1H), 7.65 (d, 1H, $J=8$ Hz), 7.72–7.75 (m, 1H).$^{13}$C NMR $\delta$ 25.7 (t), 27.8 (t), 34.1 (t), 42.5 (t), 53.2 (d), 123.2 (d), 125.1 (d), 125.2 (d), 125.3 (d), 125.7 (d), 127.5 (d), 128.9 (d), 131.7 (q), 133.7 (q), 135.2 (q), 209.9 (s).

## Acknowledgements

Financial support by the Spanish Dirección General de Investigación Científica y Técnica (BQU2000-1426) and the Generalitat Valenciana (GV CTIDIB 2002/239) is gratefully acknowledged. N.R. thanks the Spanish Ministerio de Educación y Ciencia and A.C. the Generalitat Valenciana for fellowships. We gratefully acknowledge the SCSIE (Universidad de Valencia) for the access to the instrumental facilities.

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