Asymmetric phase-transfer catalytic sulfanylation of some 2-methylsulfinyl cyclanones. Modeling of the stereochemical course of the aldol reaction of (SS,2S)-2-methylsulfinyl-2-methylsulfanylcyclohexanone

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Article info
Article history:
Received 5 July 2010
Accepted 4 August 2010
Available online 9 August 2010

Keywords:
Asymmetric phase-transfer catalysis
Aldol reaction
Density functional theory calculations

Abstract
Increased diastereoisomeric excesses are obtained for the sulfanylation reactions of some 2-methylsulfinyl cyclanones under phase-transfer catalysis using the chiral catalyst QUIBEC instead of TEBA. The optically pure (SS,2S)-2-methylsulfinyl-2-methylsulfanylcyclohexanone thus prepared reacts with ethyl acetate lithium enolate affording, after hydrolysis, (R)-2-[(ethoxycarbonyl)methyl]-2-hydroxycyclohexanone in 60% ee. Density functional theory calculations (at the B3LYP/6-311++G(d,p) level) can successfully explain the origin of this result as the kinetically favored axial attack of the nucleophile to the carbonyl group of the most stable conformer of the cyclanone, in which the CH₃SO and CH₃S groups are at the equatorial and axial positions, respectively.

1. Introduction
Although the sulfinyl group has been used as chiral auxiliary in aldol reactions, most examples are confined to the presence of this group in the nucleophilic species. Only two examples of such reactions using electrophiles bearing the sulfinyl moiety are reported in the literature. Ruano et al. studied the addition of lithium ester enolates to 2-tolylsulfinylcyclohexanones and concluded that the observed 1,2-asymmetric induction resulted from nucleophilic attack at the carbonyl group via an equatorial approach, forming a stable tricoordinated lithium species, with the sulfinyl moiety lying in an equatorial position. However, no rationalization was presented to explain the stereochemical course of the addition of ethyl acetate lithium enolate to the 2-alkylsulfanyl- or 2-p-tolylsulfanyl-2-p-tolylsulfanylcyclohexanones, due to the instability of such p-tolylsulfanyl derivatives.

2. Results and discussion
In a previous communication from this laboratory, we reported the sulfanylation of some 2-methylsulfanyl cyclanones by the PTC method, employing as catalyst triethylbenzylammonium chloride (TEBA) (Scheme 1). In the case of 2-methylsulfanylcyclohexanone (1c), the methylsulfanylated product (2c) proved to be a stable compound, in contrast to the p-tolylsulfanyl derivative, allowing the determination of its (SS,2S) relative configuration. This compound, in its optically pure form, would be of great importance for the elucidation of the role of the thioketal S-oxide carbon in the mentioned aldol 1,2-asymmetric induction process.

The sulfanylation of (±)-2-methylsulfinylcyclohexanones 1a–c by the previously reported PTC procedure furnished compounds (±)-2a and (±)-2b in 100% and 70% de, respectively. However, in the case of sulfanylation of 1c, the obtained de (20%) for 2c made this method unsuitable for the preparation of the corresponding optically pure compound. Previous results from this laboratory concerning the PTC sulfanylation of open chain β-ketosulfoxides indicated that de could be obtained by using QUIBEC instead of TEBA. This fact prompted us to perform the sulfanylation of (±)-2-methylsulfanyl-cyclohexanones 1a-c using chiral catalysts.

When the chiral catalyst A (QUIBEC; see Fig. 1) was substituted for TEBA, 2b,c and 2c were obtained in increased de (see Table 1). However, no improvements in yield or in de for 2c were observed.

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configuration. Compound would provide the new stereogenic center of known absolute con-

When catalyst B was employed. In contrast, a lower de was ob-

served for the reaction performed in the presence of catalyst C
bearing an alkylated oxygen. This result reinforces the importance
of hydrogen-bond formation between the OH group of the catalyst
and both enolate and sulfinyl oxygens.5

Having improved the diastereoselectivity of the sulfinylation
reaction, we turned our attention to the enantiomerically pure
2-methylsulfinylcyclohexanone (1c) which, after sulfinylation,
would provide the new stereogenic center of known absolute con-

The sulfinylation of SS-1c by the PTC method, employing as the catalyst QUIBEC, afforded (−)-(SS,2S)-

2c as the major diastereoisomer, isolated in 56% yield and

(+)-(SS,2R)-2c in 14% yield (Scheme 2).

With (−)-2c in hand, this compound was submitted to the reaction with ethyl acetate lithium enolate. The crude product 4

was subsequently hydrolyzed, yielding (−)-2-[((ethoxycarbonyl)-
methyl]-2-hydroxycyclohexanone (−)-5 in 76% overall yield

(ee = 60% by chiral GC) (Scheme 3). The R absolute configuration for the major enantiomer of this product could be assigned by comparison of the optical rotation value with the previously reported one.2b

Assuming the chelation model proposed by Ruano et al.,2a

for the addition of ester enolates to 2-tolysulfinylcyclohexanones,

the nucleophilic axial and equatorial attacks on (−)-2c would lead
to chelates D and E, respectively (Fig. 2).

This rationalization seems to be unsuitable for explaining our
results, because: (i) chelate D should be more difficult to form
due to steric destabilizing 1,3-interactions between the CH2CO2Et
and methylsulfinyl groups; (ii) the more stable chelate E, once
formed, would lead to (+)-5 of S configuration at the newly formed
stereogenic center, which is contrary to our observation.

In our opinion, conformational investigations on the axial/equa-
torial equilibrium of disubstituted cyclohexanone (−)-2c (Scheme
4), and the influence of steric and electronic effects on the confor-
mational flexibility properties are essential to rationalize the ste-
erocontrol of the aldol addition reaction. Thus, an experimental
and theoretical conformational analysis of (−)-2c was performed.
Carbonyl compounds are excellent targets for conformational
analysis purposes by means of infrared spectroscopy as the key tool.10

Therefore, IR spectra for compound (−)-2c were registered in a
range of different polarity solvents. Table 2 presents the stretching
frequencies and the absorbance percentage of the analytically re-

presentative conformations of (−)-2c which present Δνgas values lower than 2.0 kcal/mol. (Fig. 3). The sulfinyl group adopted geometry, as well

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sulfanylated product</th>
<th>Catalyst</th>
<th>TEBA de (yield; %) A de (yield; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2a</td>
<td></td>
<td>100 (80) 100 (75)</td>
</tr>
<tr>
<td>1b</td>
<td>2b</td>
<td></td>
<td>70 (85)  80 (84)</td>
</tr>
<tr>
<td>1c</td>
<td>2c</td>
<td></td>
<td>20 (75)  70 (93)b</td>
</tr>
<tr>
<td>1c</td>
<td>2c</td>
<td></td>
<td>40 (53)  74 (84)</td>
</tr>
</tbody>
</table>

* For catalyst B: de = 70% (yield 89%).
* For catalyst C: de = 30% (yield 65%).

Scheme 2. Synthesis of enantiomerically pure (SS,2S)-2-methylsulfinyl-2-
methylsulfinylcyclohexanone.

Scheme 3. Aldol reaction of (−)-2c followed by hydrolysis.

Figure 1. Chiral phase-transfer catalysts.

Figure 2. Possible chelates formed by attack of lithium ethyl acetate enolate at the
two faces of the carbonyl group of (−)-2c.
as the relative energy ($\Delta E_{\text{gas}}$), and free energy ($\Delta G_{\text{gas}}$) calculated at the B3LYP/6-311++G(d,p) level, and population ($P$) for each conformer are presented in Table 3.

Conformers $I$ and $II$ bearing the sulfinyl group in equatorial, and the sulfanyl group in the axial positions are stabilized by a very short intramolecular contact (ca. 2.947 Å) between the negative carbonyl oxygen and the positively charged sulfur atom of sulfinyl group, resulting in strong $O_{(\text{co})}^{{\text{d}_1}}\cdots S_{(\text{so})}^{\text{d}_1}$ electrostatic and charge transfer interactions as depicted in Figure 3. These intramolecular attractive interactions have been considered as the key behavior governing the relative stability of conformers of $\beta$-ketosulfoxide and related compounds.$^{11}$

As for conformer $III$ the sulfinyl group lies in the axial position and the sulfanyl in the equatorial one. In this geometry an $O_{(\text{co})}^{{\text{d}_1}}\cdots S_{(\text{so})}^{\text{d}_1}$ electrostatic interaction (3.188 Å, as depicted in Fig. 3) arises in lieu of the attractive interaction observed in conformers $I$ and $II$. In brief, it is quite reasonable to associate conformers $I$ and $II$ to the more intense component of the carbonyl doublet, and the less intense one to conformer $III$. The computed carbonyl frequencies for conformers $I$–$III$ are practically coincident within ca. 3 cm$^{-1}$. However, from previous$^{11}$ results on $\beta$-ketosulfoxide, it is well established that the higher carbonyl frequency component, in solution, should correspond to the more-populated equatorial conformers $I$ and $II$, while the lower frequency component to the less-populated axial conformer $III$.

Once having established the most important conformations for compound (−)-2c, we decided to investigate the origins of the asymmetric induction on the aldol reaction using DFT method and to propose a mechanistic model that would account for our results. Having in mind that the aldol addition to $I$ and $II$ would lead to the same stereochemical result, we considered only conformers $I$ and $III$. The B3LYP/6-311++G(d,p) transition-state structures were obtained by full optimization without constraints, and are presented along with their relative energies in Figure 4. The first step for the attack of lithium enolate to the carbonyl group of cyclohexanone (−)-2c is the formation of a reactant-like complex precursor followed by the positioning of the lithium cation from the enolate next to the oxygen atom of the carbonyl group of the cyclohexanone, resulting in distorted half-chair six-member ring-transition states. In all cases, the lithium cation plays a fundamental role by forming a bis-coordinate transition-state complex, as previously proposed.$^{24}$ Calculations for the aldol reaction involving the addition to both faces of conformers $I$ and $III$ resulted in four TS potential structures (Fig. 4). As for conformer $I$, the computed free energies relative to reactants were 7.83 for the axial attack (TS-$I$-ax) and 10.04 kcal/mol for the equatorial attack.
respectively, indicating the preference of axial addition as compared to the equatorial pathway. In the case of conformer III, axial attack (TS-III-ax) is also predominant (8.30 kcal/mol versus 14.03 kcal/mol for TS-III-eq). Therefore, it may be concluded that the best direction for the nucleophilic addition to the carbonyl carbon atom is anti to the axial substituent in both conformers I and III (see Fig. 5). The lowest energy structures for the formation of diastereomers 4 are those in which $\phi_1$ is $-176.7^\circ$ for the axial addition to I, and $173.1^\circ$ for the axial addition to III, respectively. This diastereofacial selectivity can also be predicted by the Felkin–Anh model for which, in this particular case, the TS is stabilized by the presence of the antiperiplanar CH$_3$S group, and is able to delocalize the nucleophile electron density into the anti-bonding $\sigma^*_C$ orbital.$^{12}$

The computed free activation energy barriers for the addition reaction suggests that re addition to (-)-2c should be favored, giving 4 in a 76:24 diastereomeric ratio, according to the calculated Boltzmann distribution (gas phase; $-78^\circ$C), which is in very good agreement with the obtained enantiomeric ratio for compound 5 (80:20 in THF; $-78^\circ$C).

3. Conclusion

The use of chiral catalysts A and B instead of TEBA increased the diastereoselectivity of the sulfanylation reaction of 1b,c. DFT calculations at the B3LYP/6-311++G(d,p) level suggest that the kinetically favored axial attack to the most stable conformer I of (SS,SS)-2c is responsible for the observed enantiomeric excess of (-)-5. Further studies on the full scope of these reactions are in progress and will be reported in due course.

Acknowledgments

We acknowledge CNPq (for Grants B.W. and P.R.O.) and FAPESP for the financial support. We also thank Professor F. H. Quina for revising the manuscript and Dr. L. H. de Andrade for ee determinations. The LCCA-Laboratory of Advanced Scientific Computation of the University of São Paulo is acknowledged for access to resources.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.010.
References and notes


