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

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ABSTRACT

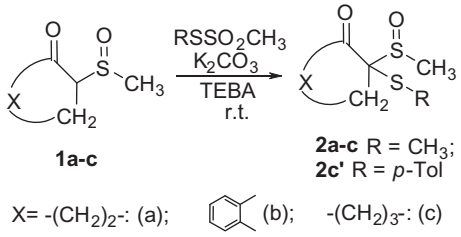
Increased diastereoisomeric excesses are obtained for the sulfanylation reactions of some 2-methylsulfinyl cyclanones under phase-transfer catalysis using the chiral catalyst QUIBEC instead of TEBA. The optically pure (*SS*,2*S*)-2-methylsulfinyl-2-methylsulfanylcyclohexanone thus prepared reacts with 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 CH_3SO and CH_3S 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.[1] Only two examples of such reactions using electrophiles bearing the sulfinyl moiety are reported in the literature.[2] Ruano et al.[2a] 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*-tolylsulfinylcyclohexanones, due to the instability of such *p*-tolylsulfinyl derivatives.[2b]

2. Results and discussion

In a previous communication from this laboratory,[3] we reported the sulfanylation of some 2-methylsulfinyl cyclanones by the PTC method, employing as catalyst triethylbenzylammonium chloride (TEBA) (Scheme 1). In the case of 2-methylsulfinylcyclohexanone (**1c**), the methylsulfanylated product (**2c**) proved to be a stable compound, in contrast to the *p*-tolylsulfinyl derivative, allowing



Scheme 1. PTC sulfanylation of (±)-2-methylsulfinyl cyclanones **1a–c**.

the determination of its (*SS**,2*S**) 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 aldolic 1,2-asymmetric induction process.

The sulfanylation of (±)-2-methylsulfinylcyclanones **1a** and **1b** by the previously reported PTC procedure[3] 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[4,5] 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-methylsulfinyl-cyclanones **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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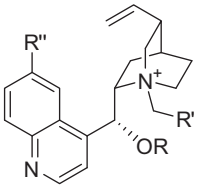


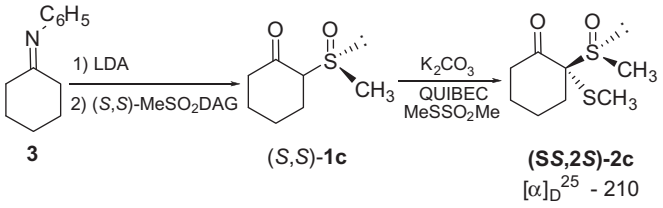
A: (QUIBEC): R= H; R'= Ph; R"= OMe
B: R=H; R'= 9-Anthracenyl; R"= H
C: R=Bn; R'= 9-Anthracenyl; R"= H

Figure 1. Chiral phase-transfer catalysts.

Table 1
PTC sulfanylation of some (±)-2-methylsulfinyl cyclanones **1a–c**

Compound	Sulfanylated product	Catalyst	
		TEBA de (yield; %)	A de (yield; %)
1a	**2a**	100 (80)	100 (75)
1b	**2b**	70 (85)	80 (84)
1c	**2c**	20 (75)	70 (93)[a,b]
1c	**2c'**	40 (93)	74 (84)

[a] For catalyst B: de = 70% (yield 89%).
[b] For catalyst C: de = 30% (yield 65%).



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

when catalyst **B** was employed. In contrast, a lower de was observed 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 sulfanylation reaction, we turned our attention to the enantiomerically pure 2-methylsulfinylcyclohexanone (**1c**) which, after sulfanylation, would provide the new stereogenic center of known absolute configuration. Compound **1c**, of *SS* configuration was obtained in 75% yield as a mixture of epimers (7:3), starting from cyclohexylideneimine (**3**)[6,7] and employing 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl (−)-(*SS*)-methane-sulfinate ((*SS*)-MeSO$_2$-DAG)[8,9] as chiral sulfinylating agent. The sulfanylation of *SS*-**1c** by the PTC method, employing as the catalyst QUIBEC, afforded (−)-(*SS*,2*S*)-**2c** as the major diastereoisomer, isolated in 56% yield and (+)-(*SS*,2*R*)-**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-tolylsulfinylcyclohexanones, 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 CH_2CO_2Et 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/equatorial equilibrium of disubstituted cyclohexanone (−)-**2c** (Scheme 4), and the influence of steric and electronic effects on the conformational flexibility properties are essential to rationalize the stereocontrol 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 resolved carbonyl bands of compound (−)-**2c**. In all cases a doublet of ca. 80:20 relative intensity in favor of the higher frequency component was observed.

Aiming to attribute each component of the observed doublet to the representative conformations of (−)-**2c**, a density functional theory (DFT) calculation was performed. Thorough geometry optimization and frequency calculations resulted in the three more stable conformations **I–III** which present ΔE_{gas} values lower than 2.0 kcal/mol. (Fig. 3). The sulfinyl group adopted geometry, as well

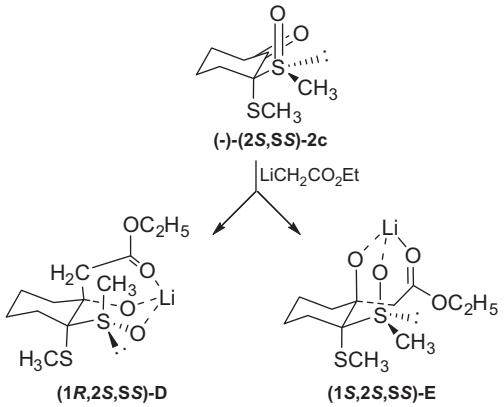
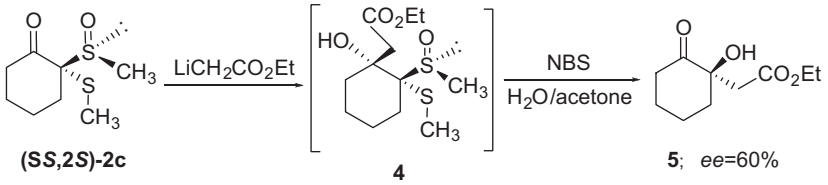
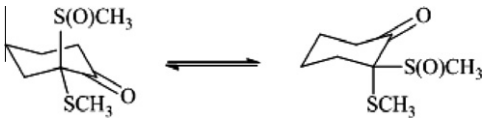


Figure 2. Possible chelates formed by attack of lithium ethyl acetate enolate at the two faces of the carbonyl group of (−)-**2c**.



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



Scheme 4. Axial/equatorial equilibrium of (*SS*,2*S*)-2-methylsulfinyl-2-methylsulfanylcyclohexanone ((−)-**2c**).

Table 2
Frequencies (ν_{co}; cm^{-1}) and intensities (P; in % of absorbance) for the carbonyl stretching bands in the IR spectra of (−)-**2c**

n-Hexane		CCl_4		$CHCl_3$		CH_2Cl_2		CH_3CN	
ν_{CO}	*P*	ν_{CO}	*P*	ν_{CO}	*P*	ν_{CO}	*P*	ν_{CO}	*P*
1713	81	1710	85	1706	84	1705	80	1705	77
1697	19	1689	15	1682	16	1679	20	1679	23

as the relative energy (ΔE_{gas}), and free energy (ΔG_{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 $O^{\delta-}_{(co)}\cdots S^{\delta+}_{(so)}$ 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 β-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 $O^{\delta-}_{(so)}\cdots S^{\delta+}_{(co)}$ 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 β-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.[2a] 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

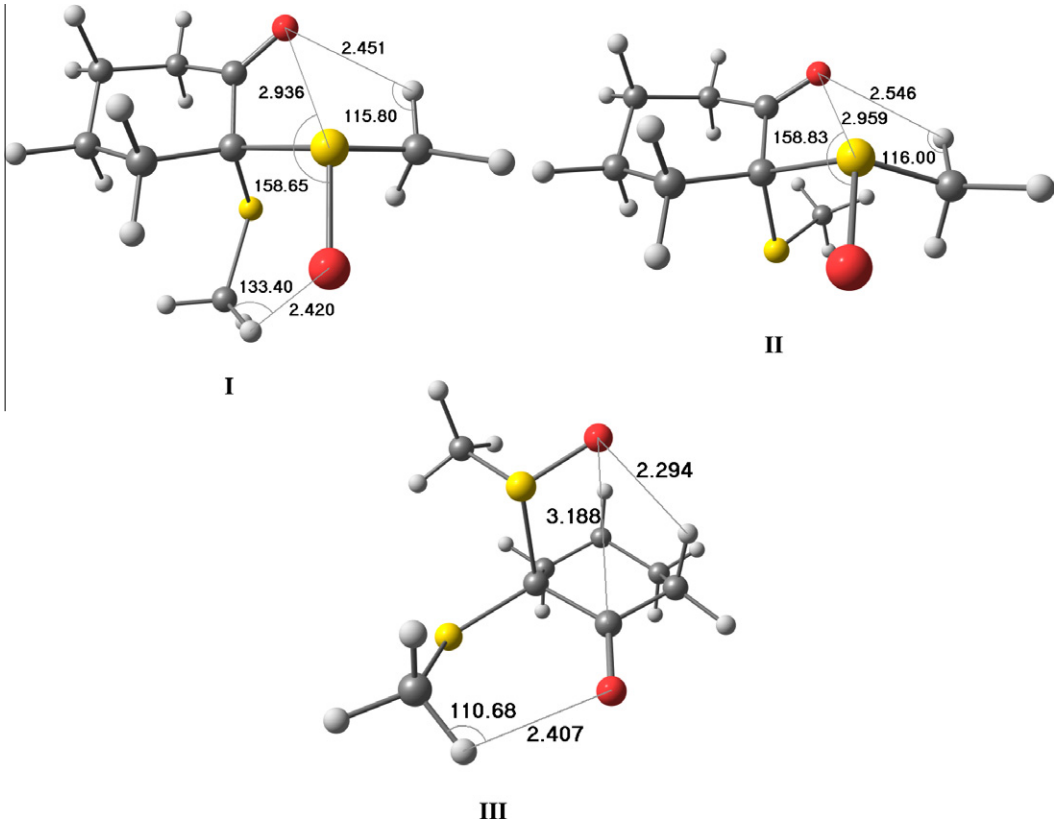
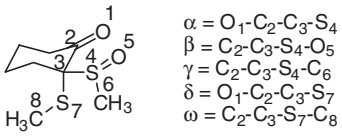


Figure 3. Selected minimum energy conformations for (−)-**2c** at the B3LYP/6-311++G(d,p) level.

Table 3
Dihedral angles,[a] relative energy (ΔE_{gp}),[b] relative free energy (ΔG_{gp})[b] and populations (P)[c] for the most stable conformers of (−)-**2c**, as characterized at the B3LYP/6-311++G(d,p) level



Conformer	$SOCH_3$ position	α	β	γ	δ	ω	ΔE_{gp}	ΔG_{gp}	P
I	*eq*	16.6	178.1	−71.7	−106.3	−164.0	0	0	87.4
II	*eq*	27.8	170.9	−79.1	−98.7	29.6	1.5	1.5	7.1
III	*ax*	102.9	52.7	163.2	−13.2	52.2	1.8	1.6	5.5

[a] In degrees.
[b] In kcal/mol, in the gas phase.
[c] In %.

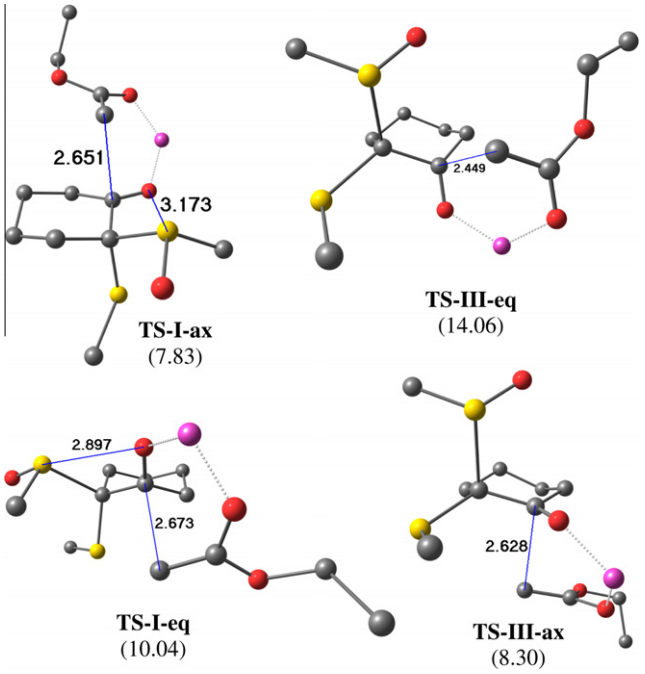


Figure 4. Optimized TSs geometries for the reaction of ethyl acetate lithium enolate to (−)-**2c**. Selected distances are in Å. Free energies relative to reactants in the gas phase (in parentheses) are in kcal/mol. The hydrogen atoms were omitted for clarity.

(**TS-I-eq**), 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 ϕ_1 is −176.7° for the axial addition to **I**, and 173.1° 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_3S group, and is able to delocalize the nucleophile electron density into the antibonding σ^*_{C-S} 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 °C), which is in very good

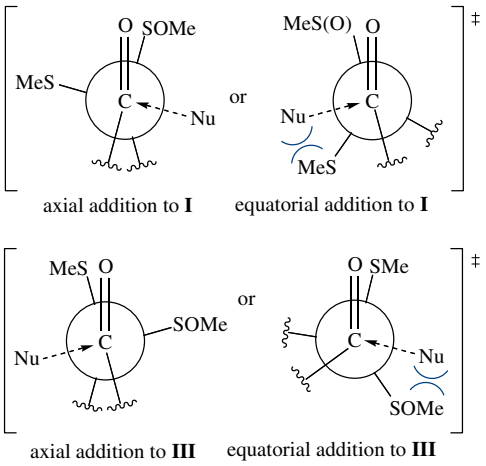


Figure 5. Staggered transition-state representations for nucleophilic attack on to conformers **I** and **III**.

agreement with the obtained enantiomeric ratio for compound **5** (80:20 in THF; −78 °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*,2*S*)-**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

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Supplementary data

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

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