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# L-Proline-Catalyzed Direct Intermolecular Asymmetric Aldol Reactions of 1-Phenylthiocycloalkyl Carboxaldehydes with Ketones. Easy Access to Spiro- and Fused-Cyclobutyl Tetrahydrofurans and Cyclopentanones

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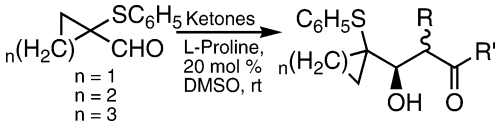
## ABSTRACT




**Acid-catalyzed ring expansion of chiral cyclopropyl and cyclobutyl derivatives for the synthesis of carbo- and heterocyclic compounds is reported. The starting materials have been successfully prepared by L-proline-catalyzed direct asymmetric aldol reactions of 1-phenylthiocycloalkyl carboxaldehydes with ketones.**

The proline-catalyzed direct enantioselective aldol reaction between aldehydes and ketones is one of the most important catalytic approaches to asymmetric synthesis of new C−C bonds.[1] A major limitation of the proline-promoted aldol reactions is the rather narrow substrate scope. As a matter of fact, organic catalysts that initiate asymmetric aldol reactions of thio-substituted aldehydes have scarcely been investigated,[2] notwithstanding the great number of biologically relevant compounds that feature sulfur-containing groups and the wide range of synthetic opportunities offered by their manipulation.[3] Furthermore, the synthesis of sulfur-carrying cyclopropyl- and cyclobutylcarbinols is a useful target as they are known to be efficient precursors of cyclobutanones[4] and cyclopentanones[5] and of new carbo- and heterocyclic cyclobutyl derivatives.[6] For the above reasons, we planned the study of the proline-catalyzed asymmetric

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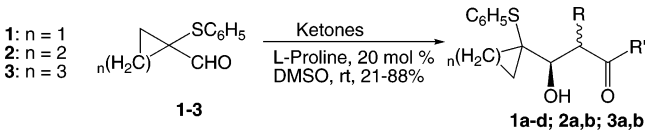
direct aldol reactions of the α-phenylsulfanyl aldehydes **1**−**3** with ketones as donors under the List−Barbas conditions[1a] (Scheme 1). Moreover, following our current research interest

**Scheme 1**




in the preparation of carbocyclic[7] and heterocyclic[8] compounds using cyclopropyl or cyclobutyl derivatives, we were also interested in the study of the acid-catalyzed ring expansion of the corresponding cyclopropyl and cyclobutyl aldols, obtainable from **1** and **2**, hopefully in an enantioenriched form.

The reaction of **1**−**3** with different ketones in the presence of proline led to the corresponding aldol products **1a**−**d**, **2a**,**b**, and **3a**,**b** in moderate to good yields and with ee values in the range of 95−99% (Scheme 1).

The chiral discrimination increased with the increasing bulkiness of the ring sizes (Table 1, entries 1−6), while a very small amount of condensation product was isolated only in the case of entry 1. The preferential formation of the aldol rather than the condensation products was very likely dictated from the steric hindrance of the phenylsulfanyl group that could render more difficult the Mannich-elimination sequence.[9] In fact, the same reaction with acetone and the corresponding cycloalkyl carboxaldehydes, lacking the α-phenylsulfanyl group, led exclusively or mainly to the condensation products (see the Supporting Information). For the study of the acid-catalyzed ring expansion of **1a**−**d** and **2a**,**b**, we used as a model compound the aldols **1a** and **2a** whose absolute configuration (*R*) was known by X-ray analysis (see the Supporting Information). A preliminary attempt, in different acid conditions, led only to the corresponding dehydration products by an elimination reaction. For this reason, we reduced **1a** and **2a** to the corresponding optically pure *syn*- and *anti*-diols **4** and **9** using either the Prasad's reduction protocol[10] or $NaBH_4$ without chelating Lewis acid and then separating the two diastereoisomers by column chromatography.

**Table 1.** Direct Asymmetric Aldol Reactions Catalyzed by L-proline.

| entry | aldol | *n* | R | R′ | time (h) | yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | 1 | H | Me | 16 | 80 | 95 |
| 2 | **2a** | 2 | H | Me | 16 | 88 | 98 |
| 3 | **3a** | 3 | H | Me | 24 | 56[c] | >99 |
| 4 | **1b** | 1 | H | Et | 24 | 51[c] | 96 |
| 5 | **2b** | 2 | H | Et | 24 | 44[c] | 99 |
| 6 | **3b** | 3 | H | Et | 48 | 21[c] | >99 |
| 7 | **1c** | 1 | H | Pr | 48 | 21[c] | 96 |
| 8 | **1d** | 1 | $-(CH_2)_3-$ | | 16 | syn: 29 | >99 |
| | | | | | | anti: 51 | 89 |

[a] Isolated yields after column chromatography. [b] The ee was determined by chiral-phase HPLC analysis. [c] Moderate yield due to low conversion.

After screening different acids, we treated the cyclopropyl diols **4** with $SnCl_4$ in $CH_2Cl_2$ at rt, and unexpectedly, we did not isolate the corresponding cyclobutanones. As a matter of fact, (1*R*,3*S*)-*anti*-**4** gave a mixture of two cis-fused (see Supporting Information) cyclobutyl tetrahydrofuran diastereoisomers (1*R*,3*S*,5*S*)-**6** and (1*S*,3*S*,5*R*)-**6** in a 14:86 ratio, while the (1*R*,3*R*)-*syn*-**4** led to the corresponding enantiomers (1*S*,3*R*,5*R*)-**8** and (1*R*,3*R*,5*S*)-**8** in a 60:40 ratio.

We suppose that the ring expansion could occur through two concurrent paths: (a) formation of an episulfonium ion (path "a") that allows preservation of the stereochemical integrity[11] of the migrating terminus through two consecutive inversions during the ring expansion to the cyclobutylthionium ion **5** or **7**, that are finally captured by the oxygen atom of the 3-hydroxyl group; (b) intermediacy of a carbocation (path "b") that causes a loss of stereochemical integrity of the migrating terminus and consequent formation of both **5** and **5′** or **7** and **7′** (Scheme 2).

If we make the reasonable hypothesis that the stereochemistry of the carbon carrying the 3-hydroxy group in both the diols **4** is preserved, it is evident that a different amount of epimerization of the migrating terminus is occurring in the two isomers, during the ring expansion. This fact should be a consequence of the different importance of the two possible reaction paths for the two diols **4**.

In Scheme 2, it appears that the reactions following path "a" with the *anti*-diol **4** should lead to the corresponding tetrahydrofuran (1*S*,3*S*,5*R*)-**6** with the two large group in a trans position, while the *syn*-diol **4** should lead to the tetrahydrofuran (1*S*,3*R*,5*R*)-**8** with the two large substituents in a less stable cis position. This fact could imply that path "a" will be more important in the reaction of the *anti*-diol **4** rather than in the *syn*-diol **4**, with a consequent high level of preservation of the stereochemistry of the migrating terminus. Therefore, the reaction of the *syn*-diol **4** will have a higher percentage of the ionic mechanism (path "b") with major erosion of the stereochemical integrity of the migrating terminus.

Interestingly, when we treated the diols (1*R*,3*R*)-*syn*-**9** and (1*R*,3*S*)-*anti*-**9** with $SnCl_4$ we did not obtain the corresponding cyclopentanones[5] but the spiro-cyclobutyl tetrahydrofurans (6*R*,8*S*)-*syn*-**10** and (6*S*,8*S*)-*trans*-**10**, diastereoisomerically pure by stereospecific [1,2]-PhS migration.

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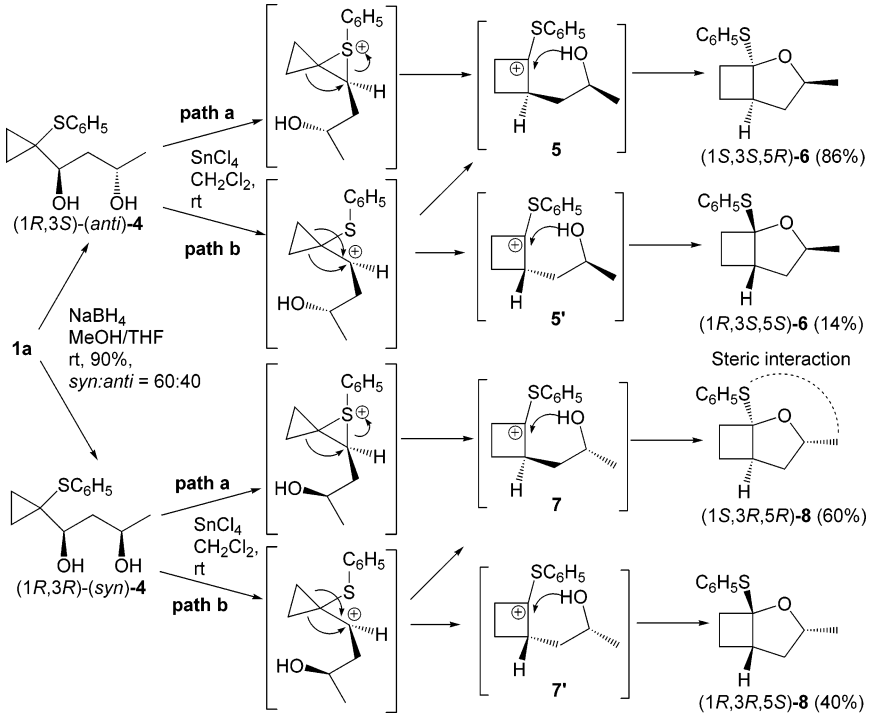
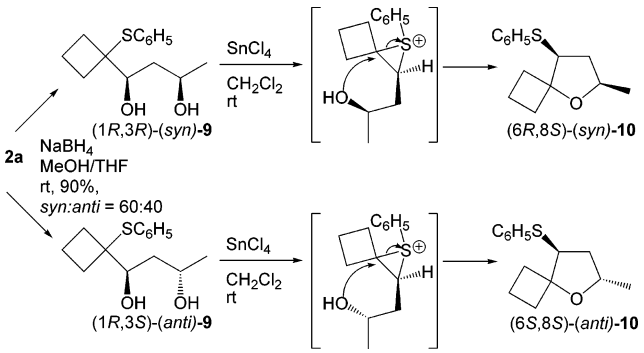
**Scheme 2.** Synthesis of Cis-Fused Cyclobutyl Tetrahydrofurans




Stereochemistry as reported by Warren for analogous systemswas presumably inverted at the migrating terminus[12] (Scheme 3).

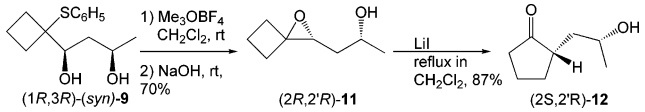
**Scheme 3.** Synthesis of Spirocyclic Tetrahydrofurans




Depending upon the size of the carbocyclic ring of the starting diols, the reaction with $SnCl_4$ can give either the cis-fused or the spirocyclic tetrahydrofurans. This remarkably different behavior represents a further evidence that, despite the almost equal strain energies, dissimilar effects are at work in cyclopropanes and cyclobutanes in determining the chemical reactivity and the outcome of chemical transformations.[13]

Finally we have investigated an alternative approach to cyclopentanones. Thus, the diol (1*R*,3*R*)-*syn*-**9** was transformed[14] into the oxaspirohexane **11** that by reaction with lithium iodide gave the cyclopentanone **12**. This transformation[15] is here reported for the first time with a chiral nonracemic oxaspirohexane to obtain **12** diastereoisomerically pure with no loss of stereochemical integrity through inversion[16] of configuration at the migrating terminus (Scheme 4).

**Scheme 4.** Synthesis of Cyclopentanones




In conclusion, we have presented the first successful proline-catalyzed direct asymmetric aldol reactions of 1-phenylthiocycloalkyl carboxaldehydes with ketones. Some of the obtained cycloalkyl carbinols are useful substrates for subsequent acid-catalyzed transformation into the corresponding cis-fused or spirocyclic tetrahydrofurans and cyclopentanones.

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organique et de Méthodologie, UMR 8122, ICMMO, Paris-Sud, XI) for the crystallization of samples for the X-ray analysis.

**Supporting Information Available:** Experimental procedures, stereochemical proofs, representative $^{1}H$ NMR and $^{13}C$ NMR spectra, and CIF files of **1a**, **2a**, and the corresponding sulfones of (1*S**,3*R**,5*R**)-**8** and (1*R**,3*R**,5*S**)-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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