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Novel efficient bifunctional calixarene thiourea organocatalysts: synthesis and application in the direct enantioselective aldol reactions

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ABSTRACT

Novel efficient bifunctional calixarene thiourea organocatalysts have been designed as efficient organocatalysts for direct asymmetric aldol reactions between acetone and aromatic aldehydes. The reactions generated the corresponding products in satisfactory isolated yields (up to 96%) and with excellent enantiomeric excesses (up to 99%) in the presence of catalyst (10 mol %).

1. Introduction

The concept of using organic catalysts to encourage asymmetric transformations is definitely not a new one, however it has quickly gained common currency among organic chemists over the course of the last decade.[1] In particular, bifunctional organocatalysts have been developed for the simultaneous activation of both electrophilic and nucleophilic components of different organic reactions.[2]

One of the most accomplished classes of organocatalysts improved to date, bifunctional thiourea catalysts, have been successfully applied in many reactions,[3] such as Henry or aza-Henry,[4] Mannich,[5] Strecker,[6] and Friedel–Crafts[7] reactions or Michael[8] and nitro-Michael[9] additions. However, the design and progress of new, influential, and easily obtainable bifunctional chiral organic catalysts continues to be a major challenge, therefore synthesizing bifunctional catalysts remains important.[10]

The asymmetric aldol reaction, which is a basic C—C bond-forming method, provides a great incentive in synthetic chemistry. Among the different types of catalysts used, organocatalysis has contributed to one of the most exciting advances in recent years.[11] In general, asymmetric catalytic aldol reactions are classified into two main categories. The first type of aldol reaction needs the preconversion of a ketone or ester to a more effective aldol donor, such as an enol ether or a ketene acetal by the use of a chiral Lewis acid or Lewis base as the catalyst. The other type is a direct aldol reaction, which is very atom economic.[12] Low catalyst loading and high chiral induction are the aims of synthetic chemists and excessive effort has been dedicated to this point.[13] Chiral amines, such as cinchona and 1,2-cyclohexanediamine or their derivatives have received great attention for their incomparable activation modes and high performances.[14]

Calixarenes constitute an important category of macrocyclic compounds due to their potential for forming host–guest complexes with several classes of compounds in supramolecular chemistry.[15] The sites accessible on these macrocyclic compounds can be simply modified to tailor them for many applications, such as phase-transfer catalysts, ionophores in catalysis, carriers in liquid membrane technology, heavy metal adsorption agents, alkali metal complexation agents, extractants for anions and cations, and chemical sensors.[16] Chirality can be introduced into the calixarene platform either by attaching chiral units at one of the calixarene rims, or by synthesizing 'inherently' chiral derivatives, in which the non-planarity of the molecule is exploited.[17] Therefore, chiral calix[4]arene derivatives acquired in this way not only supply a controlled means for studying the fundamentals of non-covalent interactions in Nature, but also provide new directions for expanding upon novel enantioselective sensors, asymmetric catalysts,[18] selectors, and other molecular devices.[19]

We have previously reported the synthesis of novel chiral calix[4]arenes containing various functionalities as organocatalysts and their catalytic activities in asymmetric Michael additions of aldehydes to nitroalkenes and maleimides.[20] Herein we report the design and synthesis of a novel class of calix[4]arene-based thioureas in both enantiomeric forms, which are the first effective bifunctional organocatalysts (up to 99% ee) for highly enantioselective aldol reactions of aldehydes to acetone.

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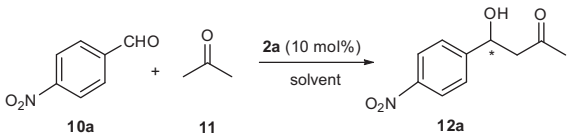
2. Results and discussion

The chiral calix[4]arene derivatives **2a**–**b**, **3a**–**b** chosen for the asymmetric aldol reaction were synthesized in five steps starting from *p*-*tert*-butylcalix[4]arene. Thus, following the literature chiral calix[4]arene derivatives **2a**–**b**, **3a**–**b** were readily prepared from **1a**–**b** which were synthesized in two steps in good overall yields.[20a] The chiral calix[4]arene derivatives **1a** and **1b** were obtained in 84% and 82% yields by the reaction of *p*-*tert*-butylcalix[4]arene diamine[21] with chiral subunits in two steps. Chiral calix[4]arene derivatives bearing two primary amine thiourea units were directly reacted with acetaldehyde or benzyl bromide in CH_3CN to give catalysts **2a** and **3a**. Repeating the same procedures, catalysts **2b** and **3b** could be prepared in good yields (Scheme 1).

For the evaluation of the catalytic properties of chiral calix[4]arene thiourea catalysts and the optimization of the aldol reaction conditions, the reaction between *p*-nitrobenzaldehyde and acetone served as a model. We examined the effect of the solvent on the catalysis of the aldol reaction using **2a**. To check the effect of various solvents for better yields and selectivities, the same reaction was tested in different solvents and the results are summarized in Table 1. When *p*-nitrobenzaldehyde **10a** was treated with acetone **11** with a catalyst loading of 10 mol % **2a** at room temperature for five days, the desired aldol condensation product was obtained in 90% yield and with 97% ee (Table 1, entry 2). When polar solvents were used, the reactions were fast but the selectivities were low (Table 1, entries 4, 7, and 10). This was, of course, not

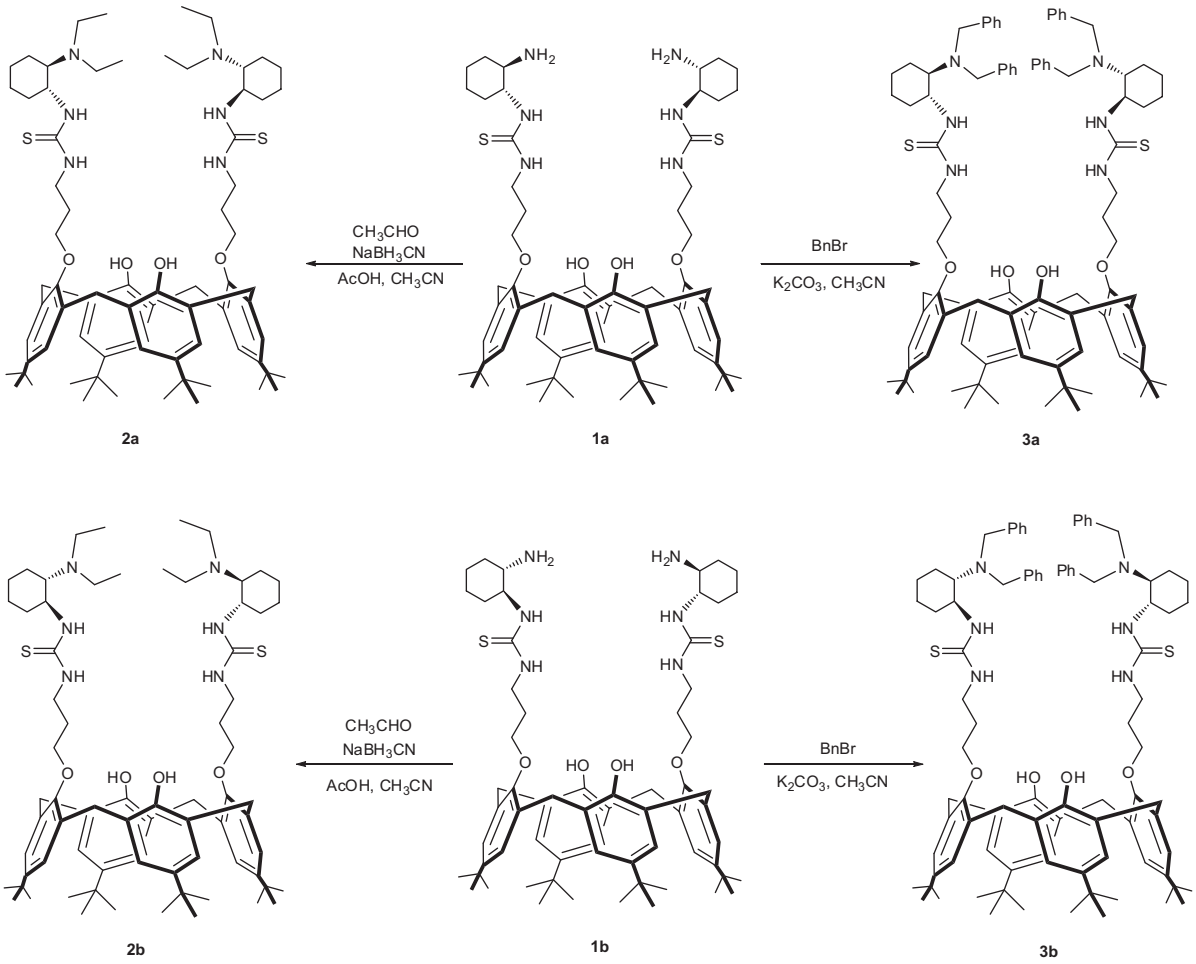
Table 1
Optimization of the asymmetric Aldol reaction of *p*-nitrobenzaldehyde **10a** to acetone **11** catalyzed by **2a**



10a **11** **12a**

Entry[a]	Catalyst	Solvent	Time (d)	Yield[b] (%)	ee[c,d] (%)
1	**2a**	CH_2Cl_2	5	87	90 (*R*)
2	**2a**	Toluene	5	90	97 (*R*)
3	**2a**	$CHCl_3$	4	85	84 (*R*)
4	**2a**	$ClCH_2CH_2Cl$	5	84	91 (*R*)
5	**2a**	EtOAc	4	82	85 (*R*)
6	**2a**	CCl_4	5	88	93 (*R*)
7	**2a**	CH_3CN	3	81	72 (*R*)
8	**2a**	THF	4	84	90 (*R*)
9	**2a**	MeOH	3	82	88 (*R*)
10	**2a**	DMF	3	80	87 (*R*)
11[e]	**2a**	Toluene	4	89	96 (*R*)
12[f]	**2a**	Toluene	3	81	87 (*R*)

[a] All reactions were carried out with *p*-nitrobenzaldehyde (0.07 mmol), acetone (0.007 mmol) and the catalyst indicated (10 mol %) in solvents (0.5 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralcel AS-H).
[d] The absolute configuration was determined by comparison with literature data.
[e] 15 mol % catalyst was used.
[f] Reaction was carried out at 0 °C.



Scheme 1. Synthesis of chiral calix[4]arene thiourea catalysts **2a**/**2b** and **3a**/**3b**.