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Highly Enantio- and Diastereoselective Organocatalytic Desymmetrization of Prochiral Cyclohexanones by Simple Direct Aldol Reaction Catalyzed by Proline

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The use of desymmetrization reactions in organic chemistry is one of the most common and powerful methods for the stereocontrolled preparation of chiral molecules.

Enzymatic transformation strategies are, to the best of our knowledge, the most usual type of desymmetrization. For example, Reetz and co-workers developed a new cyclohexanone monooxygenase by directed evolution that showed high levels of enantioselectivity in Baeyer–Villiger reactions of prochiral cyclohexanones.[1] However, there are few examples of desymmetrizations using well established chemical organic transformations. In 2005, Shibasaki and co-workers described an elegant desymmetrization of *meso*-*N*-acylaziridines with TMSCN, achieving high levels of enantioselectivity.[2] In the realm of organocatalysis, there are few examples of desymmetrization reactions. In 2008, Song and Connon almost simultaneously reported a very efficient desymmetrization of anhydrides.[3] In 2005, Barbas et al. reported an elegant desymmetrization of *meso* compounds by a direct amino acid-catalyzed aminoxylation.[4]

Since the rediscovery of proline-catalyzed intermolecular enantioselective direct aldol reactions between ketones and aldehydes reported by List, Barbas and Lerner in 2000,[5] the organocatalytic aldol reaction has become one of the cornerstones of organocatalysis. A huge effort has been devoted to the optimization of conditions, catalysts and additives that allow us to achieve high levels of enantio- and diastereoselectivities. Surprisingly, although the aldol reaction of simple cyclohexanones has received much attention, the use of aldol reaction in the desymmetrization of 4-substituted cyclohexanones remains almost unexplored.[6] Only in 2007, Gong and co-workers described a nice desymmetrization of 4-substituted cyclohexanones catalyzed by 4-hydroxyprolinamide derivatives (Scheme 1), providing the resulting compounds in good diastereo- and enantioselectivities and with moderate to good yields.[7] However, the use of 4-hydroxyprolinamides derived from β-aminoalcohols (which are much more precious than proline) and the use of low temperatures in order to achieve high enantioselectivities make this method not very useful from a practical point of view. Soon after, Bolm and co-workers reported a few examples of desymmetrization of ketones using proline in ball mills as catalyst.[8]

Based in our previous work, we thought that proline could be a suitable catalyst for the desymmetrization of prochiral ketones.[9] However, proline itself presents some potential drawbacks, such as poor performance in aldol reactions with aromatic aldehydes, poor solubility in non-polar organic solvents, and potential parasitic reactions that make

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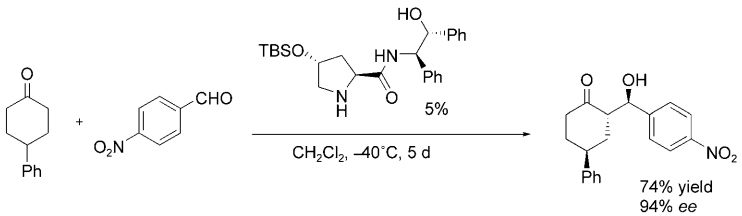


Scheme 1. Reaction reported by Gong and co-workers.[7]

necessary the use of high catalyst loadings to achieve good conversions.

In the area of organocatalytic aldol reaction, several research groups have been working in order to overcome these drawbacks. For example, Pericàs and co-workers reported recently an interesting polymer-bound 4-hydroxyproline catalyst with excellent results.[10] On the other hand, several groups described the use of additives such as acids or hydrogen-bond donors in order to enhance the catalytic properties of proline. For example, Shan and co-workers showed that the use of chiral diols as additives in aldol reactions improved the enantioselectivity of proline, probably by hydrogen-bonding interaction in the transition state.[11] In 2009, Demir et al. described the use of Schreiner thiourea as suitable additive to enhance the catalytic activity of proline in the direct aldol reaction.[12]

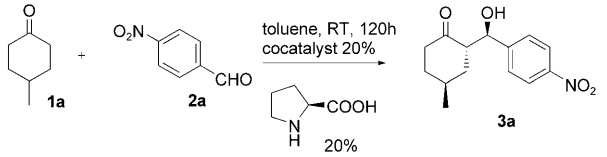
Clearly inspired by the original work of Demir et al. and based on those previous reports, we envisioned an easy entry for the desymmetrization of 4-substituted-cyclohexanones catalyzed by proline, using as cocatalyst different hydrogen-bonding donors. As proper additives,[13] we chose thioureas,[14] squaramides[15] and different diamines as hydrogen bond donors.

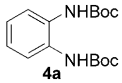
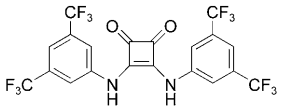
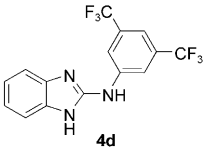
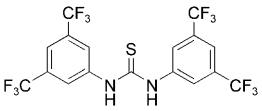
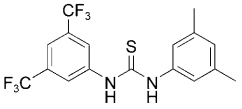
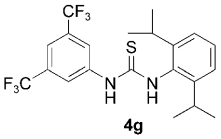
To our delight, when a toluene solution of 4-methyl-cyclohexanone was reacted with 4-nitrobenzaldehyde using proline as organocatalyst in the presence of **4a**, the reaction took place in moderate conversion after 120 h, and with good enantioselectivity and with excellent diastereoselectivity (entry 2, Table 1). In contrast, when only proline was used as organocatalyst no reaction was observed (entry 1). Surprisingly, when BINOL (**4b**) or squaramides (**4c**) were used as cocatalysts no reaction was observed after 120 h. Next, we studied the aldol reaction using as cocatalyst the 2-aminobenzoimidazole (**4d**). We were pleased to observe that the enantioselectivity of the reaction rose to 94% (entry 5). When different thioureas were used as additives the enhancement of the diastereo- and enantioselectivity was evident (entries 6, 7 and 8; Table 1). We obtained the best results when 3,5-dimethylphenyl 3,5-bistrifluoromethylphenyl thiourea (**4f**) was used, affording aldol adduct in 99% *ee* and 10:1:0:0 diastereomeric ratio (entry 7). It should be noticed that Schreiner thiourea **4e** showed also a very good enantio- and diastereoselectivity, but lower conversions than previously reported (entry 6). This result can be easily explained by parasitic reactions of proline catalyzed by thioureas (Scheme 2).

When 1 equiv of proline and 2 equiv of 4-nitrobenzaldehyde in toluene were added to a catalytic amount of thioureas **4e**–**g** (10 mol%), the parasitic reaction[16] took place. Schreiner thiourea **4e** catalyzed this reaction faster than 3,5-dimethylphenyl-3,5-bistrifluoromethylphenyl thiourea (**4f**) or 2,6-diisopropylphenyl-3,4-bistrifluoromethylphenyl thiourea (**4g**), as shown in Scheme 2.

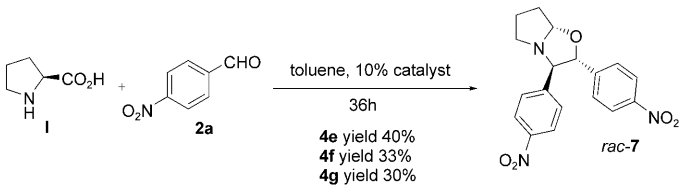
Once we obtained a suitable catalyst system for the desymmetrization of 4-methylcyclohexanone (**1a**) by aldol addition, we studied the reaction of different 4-substituted cyclohexanones with 4-nitrobenzaldehyde (Table 2). To our

Table 1. Screening of cocatalysts.[a]



Entry	Cocatalyst	Conversion [%][b]	d.r.[c]	*ee*[d]
1	–	0	–	–
2	 **4a**	50	14:1:0:0	87
3	(+)-BINOL (**4b**)	traces	–	–
4	 **4c**	traces	–	57
5	 **4d**	70	4:1:0:0	94
6	 **4e**	75	7:1:0:0	99
7	 **4f**	90	10:1:0:0	99
8	 **4g**	53	5:1:0:0	99

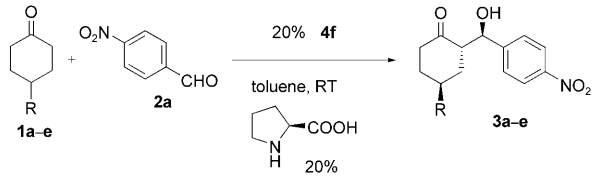
[a] See Supporting Information for conditions. [b] Determined by NMR spectroscopy. [c] Determined by NMR spectroscopy. [d] Determined by chiral HPLC analysis.

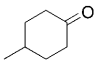
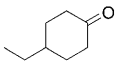
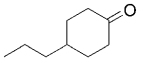
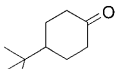
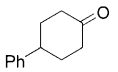


Scheme 2. Parasitic reaction of proline.

delight, in all the entries we obtained the final aldol adduct in excellent enantioselectivities and in good to excellent yields and diastereoselectivities. For example, 4-phenylcyclohexanone (**3e**) reacted with 4-nitrobenzaldehyde (**2a**) to furnish the diastereopure aldol adduct in 83% yield, isolated from a 11:2:0:0 diastereomeric mixture and with 97% enantiomeric excess (entry 5; Table 2).

Table 2. Ketone scope.[a]



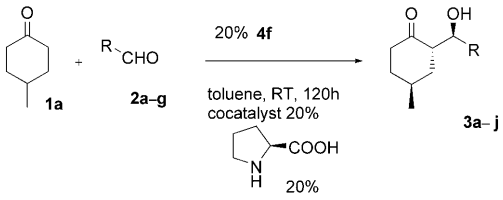
Entry	Ketone	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	 1a	**3a**	85	10:1:0:0	99
2	 1b	**3b**	65	11:2:0:0	94
3	 1c	**3c**	80	4:1:0:0	96
4	 1d	**3d**	69	7:2:1:0	97
5	 1e	**3e**	83	11:2:0:0	97

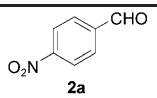
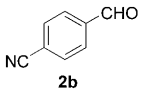
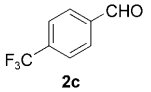
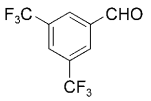
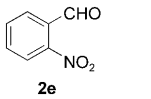
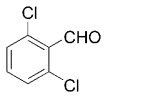
[a] See Supporting Information for conditions. [b] Isolated yield of diastereopure aldol adduct. [c] Determined by NMR spectroscopy. [d] Determined by chiral HPLC analysis.

Next, we decided to study the scope of the reaction using different benzaldehydes with 4-methylcyclohexanone **1a** (Table 3). When electron-withdrawing groups such as nitro or cyano were present in the benzaldehyde, the reaction took place in reasonable reaction times and gave excellent enantio- and diastereoselectivities. It is noteworthy that when 2,6-dichlorobenzaldehyde was used, only one diastereomer was observed by NMR spectroscopy, with good enantioselectivities (entry 6).

To investigate the stoichiometry between additives and proline in $CHCl_3$, we recorded both the UV and fluorescence spectra of the additive **4f** with different amounts of proline. As shown in Figure 1 (top), the UV spectrum of compound **4f** showed a slight blue-shift to 360 nm, an absorbance increase at 360 nm and an isosbestic point around 310 nm with increasing concentration of proline. These spectral features suggest a ground-state complex between thiourea and proline. Since the UV spectra did not show large enough differences to calculate the stoichiometry of the complex, fluorescence spectroscopy was used to evaluate this interaction. Addition of increasing amounts of proline to a solution of **4f** led to a decrease of the fluorescence signal at 360 nm and to an increase at 445 nm (Figure 1, middle). A Job plot[17] with these two λ indicated the formation of a stable 1:1 complex between proline and compound **4f** (Figure 1, bottom). On the other hand, when BINOL was used the ratio between proline and BINOL in the complex was 1.4:1 (see the Supporting Information).

Table 3. Aldehyde scope.[a]



Entry	Aldehyde	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	 2a	**3a**	85	10:1:0:0	99
2	 2b	**3f**	68	7:2:0:0	99
3	 2c	**3g**	86	24:3:1:0	99
4	 2d	**3h**	74	5:1:0:0	95
5	 2e	**3i**	86	12:1:0:0	97
6	 2f	**3j**	87	[e]	96

[a] See Supporting Information for conditions. [b] Isolated yield of diastereopure aldol adduct. [c] Determined by NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] Only one diastereomer detected by NMR spectroscopy.

The absolute configuration of the products was ascertained from comparison with data reported by Gong and co-workers[7] and Bolm and co-workers,[8] and by conversion of product **3a** to dihydroxyester **6a** (Scheme 3), which shows spectral data identical with those reported in the literature.[7]

The general stereochemical outcome of the reaction can be explained by the following mechanism: As shown by Houk et al.[18] and the original work by Demir et al.,[12] the proline mediated aldol reaction takes place through a Zimmerman–Traxler transition state. Since the spectroscopic studies described above show the formation of a stable 1:1 complex between thiourea and proline, we propose a hydrogen bond between the NH hydrogens of the thiourea and the carboxyl moiety of proline. This interaction will increase the acidity of the carboxylic hydrogen of proline and at the same time stabilize the "chair" transition state. Accordingly, we can draw two possible transition states with the prochiral ketones (Scheme 4). In **TS I**, the interactions between 4-substituent of the ketone and the aldehyde will make this transition state more unstable than **TS II**. This is in accordance with the stereoselectivity observed in the reaction.

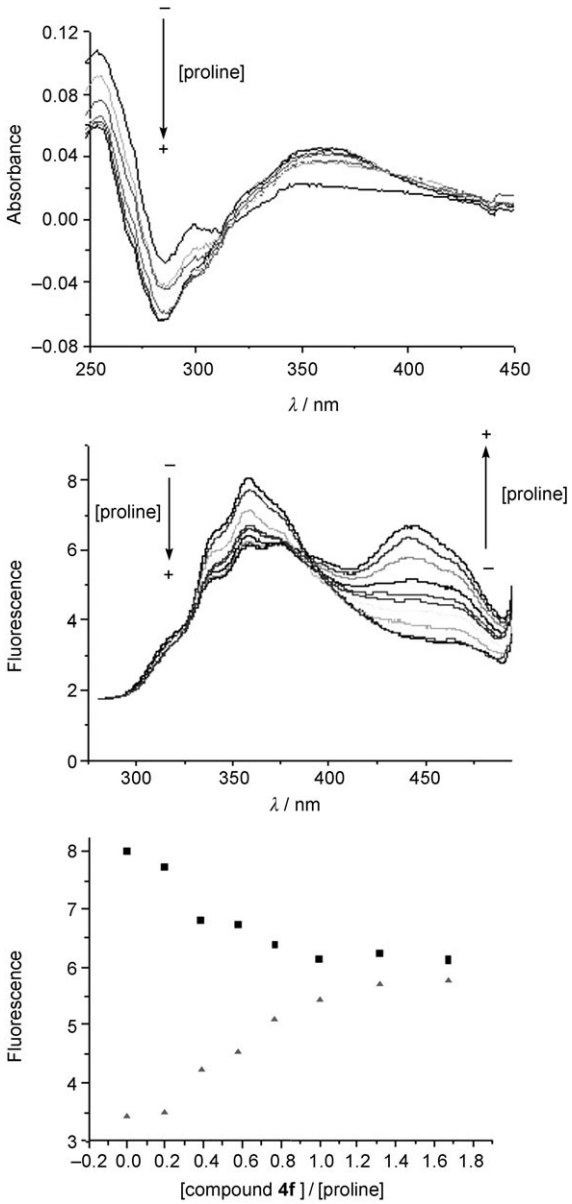
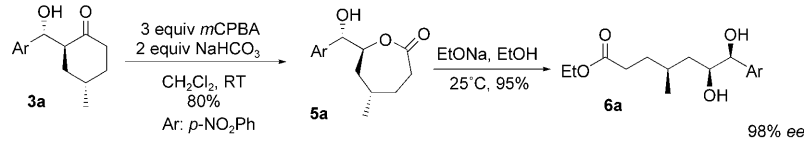
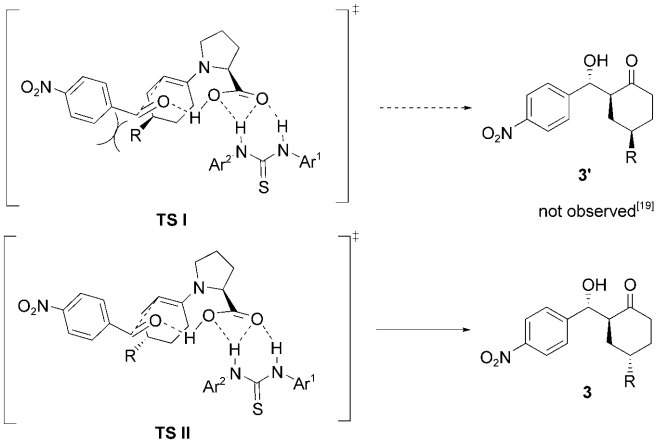


Figure 1. Top: UV spectra; middle: fluorescence spectra for proline/**4f** mixtures; bottom: Job plot at $\lambda = 360$ nm (■) and 445 nm (▲).



Scheme 3. Synthesis of compound **6a**.

In summary, we have developed a straightforward, efficient and highly enantio- and diastereoselective desymmetrization of 4-substituted cyclohexanones using proline as catalyst. We have shown that the use of simple hydrogen-bond donors as additives increases dramatically the efficiency of the process. Mechanistic studies and synthetic applications



Scheme 4. Transition states proposed.

of this transformation, as well as the development of enantioselective reactions based on this new concept are ongoing in our laboratories and will be reported in due course.

Experimental Section

To a stirred solution of proline (11.5 mg, 0.10 mmol, 20 mol%, 0.2 equiv) in toluene (2.0 mL), cocatalyst **4f** (40 mg, 0.10 mmol, 20 mol%, 0.2 equiv) and 4-methylcyclohexanone **1a** (560.0 mg, 5 mmol, 10 equiv) were added. The reaction was stirred at room temperature for 30 min, and then 4-nitrobenzaldehyde **2a** (75.5 mg, 0.50 mmol, 1 equiv) was added. The reaction was vigorously stirred at room temperature for 120 h. Next, the crude product was purified by silica gel chromatography (hexane/EtOAc mixtures) to give the corresponding diastereopure aldol product **3a** (111.8 mg, 85% yield). The NMR data matched with the previously reported in the literature.[7] ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): $\delta = 1.05$ (d, $J = 6.9$ Hz, 3H), 1.31–1.35 (m, 1H), 1.54–1.60 (m, 1H), 1.78–1.81 (m, 1H), 1.89–1.93 (m, 1H), 2.07–2.09 (m, 1H), 2.38–2.43 (m, 1H), 2.48–2.50 (m, 1H), 2.72–2.78 (m, 1H), 3.82–3.89 (br s, 1H), 4.92 (d, $J =$ 8.6 Hz, 1H), 7.47–7.52 (m, 2H), 8.18–8.23 ppm (m, 2H).

Acknowledgements

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Keywords: aldol reaction · desymmetrization · hydrogen bonds · organocatalysis · proline

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