# Enantioselective desymmetrization of prochiral cyclohexanone derivatives *via* the organocatalytic direct Aldol reaction†

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**Asymmetric desymmetrization of 4-substituted cyclohexanones using proline amide-catalyzed direct aldol reaction afforded β-hydroxyketones with three stereogenic centers in high enantioselectivities of up to >99% ee.**

Desymmetrizations and kinetic resolutions of meso-, prochiral and racemic substances represent a class of powerful asymmetric catalytic transformations for the manufacture of chiral non-racemic organic molecules. Recently, an increasing number of efforts have been invested on enantioselective desymmetrization and kinetic resolutions by using well-established asymmetric transformations,[1] most of which are particularly focused on meso- or/and racemic anhydrides, epoxides and diols.[2]

Prochiral and meso-ketones are plentiful and the asymmetric desymmetrization of these compounds principally leads to the formation of chiral products with the creation of multiple stereogenic centers. The asymmetric desymmetrization of ketones by enzymatic and transition metal-catalytic methods has been reported.[3] Recently, organocatalytic asymmetric reactions have received increasing attention.[4] Even though many organocatalytic reactions involve a ketone as a reaction component,[4] they have been rarely employed for the asymmetric desymmetrization of meso- and prochiral ketones. Very recently, Ramachary and Barbas reported an enantioselective desymmetrization of meso-cyclohexanone derivatives *via* proline-catalyzed aminooxylation.[5] Hayashi *et al*. developed an intramolecular Michael reaction used for removing the symmetry of cyclohexadienones with high enantioselectivity.[6] Rovis and Liu discovered another desymmetrization of cyclohexadienones *via* asymmetric intramolecular Stetter reaction.[7] Surprisingly, there has been, to date, no report of using organocatalytic asymmetric aldol reactions to break the symmetry of prochiral and meso-ketones[8p] although many efficient and highly enantioselective variants have appeared[8–15] after the discovery of the proline-catalyzed direct aldol reaction.[16] The desymmetrization of prochiral cyclic ketones such as **1** through their aldolization with aldehydes **2** is a great challenge as the prochiral center (C4) is remote to the carbon (C2) of cyclic ketones **1** where the aldolization takes place (eqn (1), Fig. 1). The chiral catalyst must have strong ability to control the diastereo- and enantioselectivities, and more importantly, to distinguish the stereogenicity of the carbon (C4) remote to the reactive site (C2). We have recently developed a family of proline amides capable of catalyzing highly enantioselective direct aldol reactions.[11] As part of our continuous effort to explore new organocatalytic processes, we considered the possibility to remove the symmetry of prochial ketones using the asymmetric direct aldol reaction catalyzed by proline amides. Herein, we report an enantioselective desymmetrization of prochiral cyclic ketones *via* asymmetric organocatalytic direct aldol reactions, simultaneously generating three stereogenic centres in high ee (>99%).

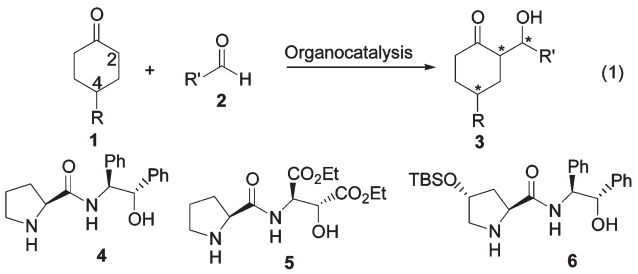


**Fig. 1** Organocatalysts evaluated for the desymmetrization of prochiral cyclohexanone derivatives.

Proline amides **4** and **5** have proven to be efficient and highly enantioselective organocatalysts for direct aldol reactions of both aromatic and aliphatic aldehydes with acetone.[11] Thus, proline amides **4** and **5** were first tested to catalyze the aldol reaction of 4-methylcyclohexanone (**1a**) with 4-nitrobenzaldehyde (**2a**) in dichloromethane at 0 °C, indeed leading to an enantioselective desymmetrization and yielding **3aa** as a major product with moderate enantioselectivity (79 and 74% ee, respectively). The minor products that were identified to be isomers of **3aa** were observed in less than 10% total yields (entries 1 and 2). We were pleased to observe that organocatalyst **6**, derived from 3-hydroxyproline and (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol, turned out to be the best catalyst, giving an excellent enantioselectivity (93% ee) and a high yield (87%) for the major product **3aa** (entry 3).[18] A survey of solvents revealed that dichloromethane is the solvent of choice, in which the highest level of enantioselectivity was observed (entries 3–5). The enantioselectivity was improved to >99% ee and the formation of isomers of **3aa** was inhibited to less than 1% yield by conducting the reaction at −40 °C (entry 6).

The desymmetrization of 4-methylcyclohexanone (**1a**) with a range of aromatic aldehydes in the presence of 5 mol% **6** was then investigated under the optimal conditions (Table 2). The catalyst **6** showed strong ability to control the diastereo- and enantioselectivities (ratios of **3aa–al** : **3aa′–al′** range from 92 : 8 to >99 : 1, and

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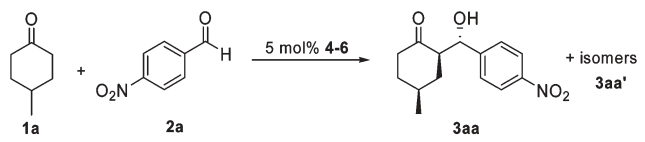
**Table 1** Optimization of reaction conditions and catalyst screening[a]



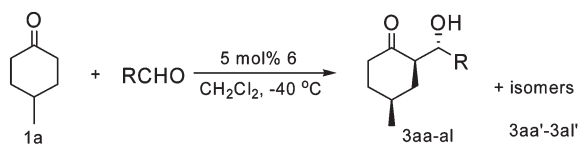

| Entry | Cat. | Solvent | $T$/°C | Yield[b] of **3aa** (%) | Ee[c] (%) | Yield[d] of **3aa′** (%) |
|---|---|---|---|---|---|---|
| 1 | **4** | $CH_2Cl_2$ | 0 | 90 | 79 | 9 |
| 2 | **5** | $CH_2Cl_2$ | 0 | 46 | 74 | 7 |
| 3 | **6** | $CH_2Cl_2$ | 0 | 87 | 93 | 6 |
| 4 | **6** | THF | 0 | 60 | 81 | 5 |
| 5 | **6** | Toluene | 0 | 76 | 91 | 7 |
| 6 | **6** | $CH_2Cl_2$ | −40 | 90 | >99 | <1[e] |

[a] The reaction was performed in 0.5 mmol scale and the reaction time is 2 days. [b] Isolated yields based on the aldehyde and analytically pure product. [c] Determined by chiral HPLC. The configuration of the major product was assigned by comparison of the optical rotation with the literature value.[17] [d] Total yield of all isomers of **3aa**. [e] The reaction time is 4 days.

ee values range from 94 to >99%). Both reactivity and enantioselectivity are to some degree dependent on the electronic and steric feature of the substituent of the aldehyde. For monosubstituted benzaldehydes, those bearing a nitro, fluoro or trifluoromethyl substituent were suitable for removing the symmetry of **1a**, affording high yields and high enantioselectivities (Table 1, entry 6 and Table 2, entries 1–4, up to 90% yield and >99% ee). The desymmetrization of **1a** with the other *para*-substituted benzaldehydes resulted in comparably lower, but still excellent enantioselectivities (entries 5–7, up to 96% ee). Among disubsituted benzaldehydes, 2,6-dichlorobenzaldehyde is the best substrate for removing the symmetry of **1a** with high enantiomeric outcome (entry 10). Benzaldehyde is considerably less reactive toward **1a**, leading to the formation of **3al** in a low yield (46%) albeit with excellent enantioselectivity (Table 2, entry 11, 94% ee).

The desymmetrization of various 4-substituted cyclohexanones with 4-nitrobenzaldehyde was then investigated for further probing

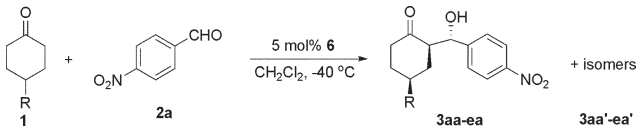
**Table 2** Asymmetric desymmetrizations of 4-methylcyclohexanone (**1a**) with various aldehydes[a]




| Entry | R | $t$/day | Product | Yield[b] (%) | Ee[c] (%) |
|---|---|---|---|---|---|
| 1 | 2-$FC_6H_4$ | 3 | **3ab** | 90 | >99 |
| 2 | 4-$FC_6H_4$ | 4 | **3ac** | 76 | >99 |
| 3 | 2-$NO_2C_6H_4$ | 4 | **3ad** | 84 | >99 |
| 4 | 4-$CF_3C_6H_4$ | 4 | **3ae** | 70 | 99 |
| 5 | 4-$CNC_6H_4$ | 4 | **3af** | 80 | 96 |
| 6 | 4-$BrC_6H_4$ | 5 | **3aj** | 61 | 96 |
| 7 | 4-$ClC_6H_4$ | 5 | **3ah** | 70 | 96 |
| 8 | 3,5-$Br_2C_6H_4$ | 5 | **3ai** | 82 | 96 |
| 9 | 3,5-$(CF_3)_2C_6H_4$ | 5 | **3aj** | 55 | 98 |
| 10 | 2,6-$Cl_2C_6H_4$ | 3 | **3ak** | 95 | >99 |
| 11 | $C_6H_5$ | 5 | **3al** | 46 | 94 |

[a] The reaction was performed in 0.5 mmol scale. [b] Isolated yields based on the aldehyde and analytically pure product. [c] Determined by chiral HPLC

**Table 3** Desymmetrizations of 4-substituted cyclohexanones with 4-nitrobenzaldehyde[a]



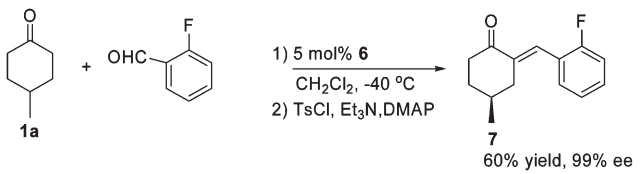

| Entry | R | $t$/day | Product | Yield[b] (%) | Ee[c] (%) |
|---|---|---|---|---|---|
| 1 | Me | 4 | **3aa** | 90 | >99 |
| 2 | Et | 3 | **3ba** | 90 | 99 |
| 3 | $Pr^n$ | 1.5 | **3ca** | 90 | 98 |
| 4 | $Bu^t$ | 5 | **3da** | 52 | 93 |
| 5 | Ph | 5 | **3ea** | 74 | 94 |

[a] The reaction was performed in 0.5 mmol scale. [b] Isolated yields based on the aldehyde and analytically pure product. [c] Determined by chiral HPLC.

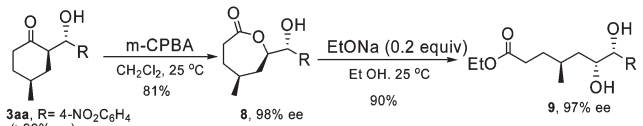
the substrate scope (Table 3). Hindered substituents at the ketone played a deleterious effect on both the reactivity and enantioselectivity. Excellent enantioselectivities ranging from 98 to >99% ee were observed for 4-methyl-, 4-ethyl- and 4-propylcyclohexenones (Table 3, entries 1–3). However, similar reactions of 4-*tert*-butylcyclohexanone and 4-phenylcyclohexanone afforded 93 and 94% ee, respectively (entries 4 and 5), which are slightly lower than those observed with less hindered cyclohexanones (entries 1–3). In all these cases, excellent diastereoselectivities (ratios of **3aa–ea** : **3aa′–ea′** range from 94 : 6 to >99 : 1) were obtained.

This desymmetrization can be applied to the synthesis of enantioenriched 2-arylidene-4-methylcyclohexanones such as **7**, a type of important synthetic intermediate for building up complex natural products.[19] After the reaction of 4-methylcyclohexanone (**1a**) with aldehydes was complete, removal of the excess 4-methylcyclohexanone, followed by exposure of the crude product to 4-toluenesulfonyl choride, triethylamine and DMAP smoothly led to elimination which readily provided **7** with high enantioselectivities (Scheme 1).

Synthetic application of the desymmetrization process was further illustrated by the convenient preparation of some chiral substances with multiple stereogenic centres (Scheme 2). The enantiomerically pure compound **3aa** obtained from the desymmetrization was subjected to a Baeyer–Villiger reaction with *m*-chloroperbenzoic acid as an oxidant, giving lactone **8** in 81%




**Scheme 1** Synthesis of (*S*)-2-(2-fluorobenzylidene-4-methylcyclohexanone.




**Scheme 2** Synthetic application of the desymmetrization.

yield with 98% ee. Exposure of compound **8** to 20 mol% sodium ethoxide in ethanol afforded **9** in 90% yield with a maintained enantiomeric excess (97% ee).

In summary, we have developed an efficient enantioselective desymmetrization of 4-substituted cyclohexanones using a proline amide-catalyzed direct aldol reaction. The resulting products with three newly generated stereogenic centres were obtained in high yields and with excellent diastereoselectivities and enantioselectivities. The application to preparing some chiral intermediates revealed the high potential in organic synthesis of the enantioselective desymmetrization.

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18 The use of proline **10** and pyrrolidine-2-carboxamide **11** as catalyst gave less than 10% yield of product **3aa**. Diphenyl(pyrrolidin-2-yl)methanol **12** provided 46% yield with 73 : 27 dr and 66% ee.

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