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# Highly Enantioselective Organocatalyzed Construction of Quaternary Carbon Centers *via* Cross-Aldol Reaction of Ketones in Water

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**Abstract:** The asymmetric construction of quaternary carbon centers *via* cross-aldol reactions of ketones with β,γ-unsaturated keto esters catalyzed by 4-(*tert*-butyldiphenylsilyloxy)-pyrrolidine-2-carboxylic acid in water is described. The adducts bearing two adjacent chiral centers were obtained in high yields, mostly up to 99% *ee*, and with high diastereoselectivities. The corresponding polyfunctional products could also be easily transformed to useful lactones with three chiral centers.

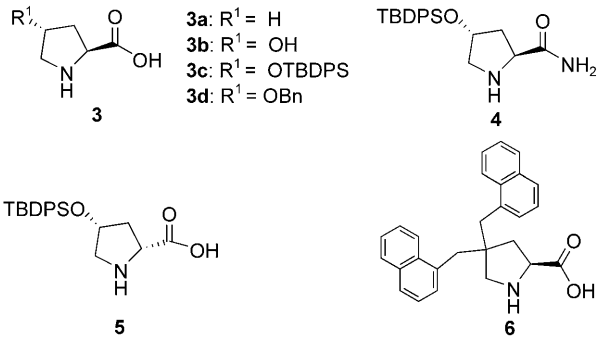
**Keywords:** aldols; ketones; organocatalysis; quaternary stereocenters; water

The development of new carbon-carbon bond formation reactions has been one of the most challenging problems in organic synthesis,[1] especially in the context of creating new quaternary carbon centers with high enantio- and diastereoselectivity involving a catalyzed asymmetric reaction. Quaternary carbon centers are prevalent throughout most classes of natural products and pharmaceutical agents;[2] hence, there are numerous ingenious methods that have been developed to selectively access this structural motif.[3] Despite these advances, the solution to this far-reaching problem has not been completely attained. On the other hand, asymmetric organocatalysis is a rapidly growing and important field of organic chemistry.[4] Especially, the proline-catalyzed aldol reaction plays an important role in carbon-carbon bond formation reactions.[5] The intermolecular aldol reactions of the ketone-aldehyde type and aldehyde-aldehyde type with mostly high stereoselectivities have been reported by List,[6] Barbas[7] and Hayashi[8] et al. In contrast, catalytic asymmetric intermolecular aldol reactions of the ketone-ketone type are less well developed.[9]

α-Keto esters behaving as activated ketones have been used in a great deal of reactions.[10] The addition to the α-carbonyl group of these compounds creates a quaternary center. Just recently, the asymmetric direct aldol reactions between cyclohexanone and phenylglyoxylates have been reported by Maruoka,[9a] Córdova[9b] and Zhao.[9c] Other intermolecular aldol reactions of ketones using acetone as the nucleophile and trifluromethylated ketones as the electrophile[11] have also been reported by Gong,[11a] Zhao[11b] and Liu[12] et al. However, most of the reactions of cyclohexanone reported above, especially those using the α-keto esters as the electrophile, suffered from several drawbacks such as high catalyst loading, a large excess of nucleophilic ketones and long reaction time.[9a,b] Herein, we would like to report a highly stereoselective cross-aldol reaction of ketones to *β,γ*-unsaturated keto esters catalyzed by proline derivatives in water.

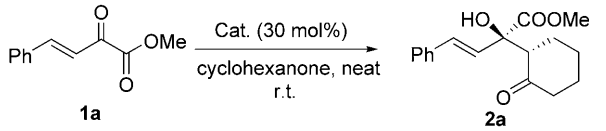
Initially, the reaction of α-keto ester **1a** with cyclohexanone was examined in the presence of L-proline **3a** and other proline-derived catalysts shown in Scheme 1. The results are compiled in Table 1. The addition of cyclohexanone to **1a** catalyzed by **3a** in neat cyclohexanone gave the tertiary alcohol **2a** in moderate yield and enantioselectivity at room temperature (entry 1 in Table 1). A similar result was obtained when the catalyst *cis*-siloxy-D-proline **5** was used (entry 6 in Table 1). Gratifyingly, a change of the configuration of **5** led to an improved result, the *trans*-siloxy-L-proline **3c** was capable of furnishing **2a** in good yield and advanced selectivity after 48 h. (entry 3 in Table 1). This improvement can be explained by referring to the transition state, the *cis*-TBDPS substitution in the catalyst **5** disturbs the H-bonding interaction of the carboxyl group with the




**Scheme 1.** Organocatalysts tested in this study.

**Table 1.** The effect of catalysts on the reaction yield and selectivity.[a]




| Entry | Catalyst | *t* [h] | Yield [%][b] | *ee* [%][c] | *dr*[d] |
|---|---|---|---|---|---|
| 1 | **3a** | 48 | 72 | 55 | 19:1 |
| 2 | **3b** | 72 | <5 | – | – |
| 3 | **3c** | 48 | 86 | 82 | 24:1 |
| 4 | **3d** | 72 | <10 | – | – |
| 5 | **4** | 72 | <10 | – | – |
| 6 | **5** | 48 | 62 | −50 | 19:1 |
| 7 | **6** | 72 | <5 | – | – |

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.1 mmol) in cyclohexanone (0.5 mL) in the presence of catalysts (30 mol%) at room temperature.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.
[d] Determined by $^1$H NMR spectroscopy of the crude products and HPLC analysis.

substrate and therefore is inferior to **3c**. Other catalysts potentially suitable for aldol reactions seemed to be inactive to this ketone-to-ketone reactions. The same reaction catalyzed by other substituted prolines or prolinamide afforded only trace of the adduct **2a** (entries 2, 4, 5 and 7, in Table 1). The effect of the siloxyproline catalysts compared to proline and hydroxyproline can be attributed to the solubility of the catalysts. Introduction of the hydrophobic siloxy moiety into the catalyst creates a hydrophobic organic phase in the presence of water, which is most probably the key to the excellent reactivity and stereoselectivity[8f].

Next, the effects of solvents on the yield and selectivity of this reaction were also investigated. The results were summarized in Table 2. Protonic solvents seemed to be advantageous for this reaction. When isopropyl alcohol, as well as ethanol and methanol, was employed as the solvent, the reaction could be

**Table 2.** The effect of solvents and catalyst loadings on the yield and selectivity.[a]

| Entry | Solvent | *t* [h] | Yield [%][b] | *ee* [%][c] | *dr*[d] |
|---|---|---|---|---|---|
| 1 | DMF | 48 | 55 | 78 | 24:1 |
| 2 | $CHCl_3$ | 48 | 52 | 84 | 1:1 |
| 3 | Toluene | 48 | 62 | 96 | >19:1 |
| 4 | *i*-PrOH | 24 | 55 | 88 | 7:3 |
| 5 | EtOH | 24 | 45 | 77 | 19:1 |
| 6 | MeOH | 24 | 64 | 85 | 19:1 |
| 7[e] | $H_2O$ | 24 | 83 | 98 | >19:1 |
| 8[e,f] | $H_2O$ | 24 | 83 | 97 | >19:1 |
| 9[e,g] | $H_2O$ | 24 | 76 | 99 | >19:1 |
| 10[e,h] | $H_2O$ | 24 | 69 | 98 | >19:1 |
| 11[e,g,i] | $H_2O$ | 24 | 52 | 99 | >19:1 |

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) and cyclohexanone (0.5 mmol) in the solvent (0.5 mL) in the presence of catalysts **3c** (30 mol%) at room temperature.
[b] Yields of isolated products.
[c] Determined by chiral HPLC.
[d] Determined by $^1$H NMR spectroscopy of the crude products or HPLC.
[e] 1.0 mL of water was used.
[f] 20 mol% of the catalyst was loaded.
[g] 15 mol% of the catalyst was loaded.
[h] 10 mol% of the catalyst was loaded.
[i] 0.3 mmol of cyclohexanone was employed

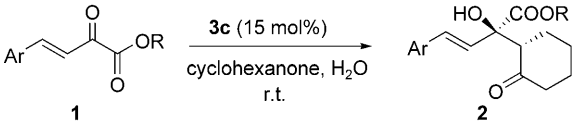
completed in a short time although with some decline in yield and diastereoselectivity compared to that in neat cyclohexanone (entries 4–6 in Table 2). Water as the solvent was also investigated. When the reaction was carried out in water, good yield and nearly a single isomer were obtained[13](entry 7 in Table 2). In comparison, the reaction proceeded in non-protonic solvents to give **2a** with a low yield and moderate diastereoselectivity, except for toluene as the solvent (entries 1–3 in Table 2).

A further study was carried out with different catalyst loadings and amounts of cyclohexanone in water. Decreasing the amount of the catalyst **3c** from 30% to 10% led to a slight change in yield and enantioselectivity (entries 7–10 in Table 2). But a great loss of yield was observed when cychexanone was reduced from 5 equivalents to 3 equivalents (entry 11 in Table 2). Hence, with the optimal conditions achieved above, the compatibility of **3c** with $\alpha$-keto esters having various steric and electronic characteristics was then investigated in water. The results are shown in Table 3.

Generally, excellent enantio- and diastereoselectivities could be achieved with β,γ-unsaturated α-keto esters bearing various segments of esters or $\gamma$-aryl substituents in 24 h. All of the reactions gave the aldol adducts in up to 99% *ee* and the values of the diastereoselectivities were also up to 19:1. The yields of the products ranged from moderate to high de-

**Table 3.** Scope of the cross-aldol reaction of **1** to yield the tertiary alcohol **2**.[a]



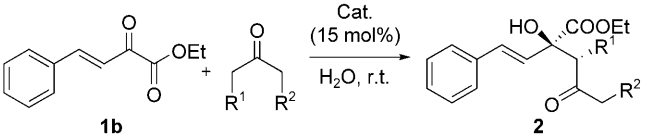

| Entry | Ar, R | *t* [h] | Product | Yield [%][b] | *ee* [%][c] | *dr*[d] |
|---|---|---|---|---|---|---|
| 1 | Ph, Me | 24 | **2a** | 76 | 99 | >19:1 |
| 2 | Ph, Et | 18 | **2b** | 99 | >99 | >19:1 |
| 3 | Ph, Allyl | 18 | **2c** | 99 | >99 | >19:1 |
| 4 | Ph, *i*-Pr | 18 | **2d** | 98 | >99 | >19:1 |
| 5 | Ph, Benzyl | 24 | **2e** | 77 | >99 | >19:1 |
| 6 | Ph, *t*-Bu | 18 | **2f** | 85 | >99 | >19:1 |
| 7 | *p*-$FC_6H_4$, Me | 18 | **2g** | 99 | >99 | >19:1 |
| 8[f] | *p*-$ClC_6H_4$, Me | 24 | **2h** | 74 | >99 | >19:1 |
| 9 | *p*-$BrC_6H_4$, Me | 24 | **2i** | 77 | >99 | >19:1 |
| 10[e] | *p*-$BrC_6H_4$, Me | 24 | **2i** | 67 | 98 | >19:1 |
| 11[f] | *m*-$ClC_6H_4$, Me | 24 | **2j** | 74 | >99 | 19:1 |
| 12 | *o*-$BrC_6H_4$, Me | 24 | **2k** | 92 | >99 | >19:1 |
| 13[f] | *p*-$MeC_6H_4$, Me | 24 | **2m** | 80 | >99 | >19:1 |
| 14 | 2-Furyl, Me | 24 | **2n** | 72 | >99 | >24:1 |

[a] Unless otherwise specified, the reaction of **1** (0.1 mmol) with cyclohexanone (5 equiv.) in water (1.0 mL) was carried out in the presence of catalysts **3c** (15 mol%) at room temperature.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.
[d] Determined by $^1$H NMR spectroscopy of the crude products and HPLC analysis.
[e] The reaction was carried out on 1.0 mmol scale.
[f] 10 equivalents of cyclohexanone were used.

pending on the solubility of the substrates in the two-phase system. Substrates with good solubility afforded the desired products with yields from 85% to 99% in short times (entries 2–4, 6, 7 and 12 in Table 3). Those with lower solubility gave the products in moderate yields (entries 1 and 5 in Table 3). Additionally, more cyclohexanone was needed to obtain high yields in short times when the substrates had a poor solubility in the system (entries 8, 11 and 13 in Table 3). Nonetheless, the product **2i** may be obtained with almost no loss of stereoselectivity even when the reaction was scaled up 10 times (entry 10 in Table 3).

Changing cyclohexanone to acetone or other relatively inactive ketones resulted in a decrease in yields and selectivities. The addition of acetone to **1b** afforded the adduct **3o** with 45% *ee* in good yield (entry 1 in Table 4), while cyclopentanone and other heterocyclic ketones gave the corresponding products only in moderate yields ranging from 41% to 56%, which was attributed to their low reaction activities. The *ee* values of the products **3p**–**3s** ranged from 81% to 93%, accompanied by a slight decrease in diastereoselectivities (entries 2–5 in Table 4). Other acyclic aliphatic ketones such as 2-butanone, 3-methyl-2-butanone, hydroxyacetone, dihydroxyacetone and 1-(*tert*-butyldimethylsilyloxy)propan-2-one were also studied, but no desired products were obtained with the starting materials being recovered. It should also be noted that no Michael products or hemiketals were detected in the reactions through $^1$H NMR analysis of the crude products.

**Table 4.** Cross-aldol reaction of **1b** with acetone and other cyclic ketones.[a]

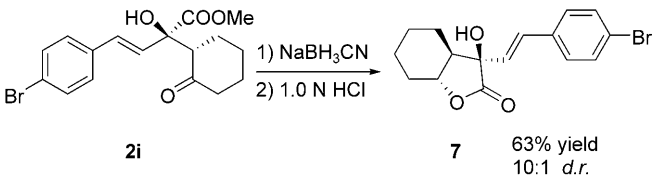



| Entry | $R^1$, $R^2$ | Product | Yield [%][b] | *ee* [%][c] | *dr*[d] |
|---|---|---|---|---|---|
| 1[e] | H, H | **2o** | 85 | 45 | - |
| 2 | -$CH_2CH_2$- | **2p** | 41 | 93 | 19:1 |
| 3 | -$CH_2OCH_2$- | **2q** | 53 | 93 | 19:1 |
| 4 | -$CH_2SCH_2$- | **2r** | 50 | 86 | 24:1 |
| 5 | -$CH_2$N-(Boc)$CH_2$- | **2s** | 56 | 81 | 19:1 |

[a] Unless otherwise specified, the reaction of **1b** (0.1 mmol) with acetone or other cyclic ketones (10 equiv.) in water (1.0 mL) was carried out in the presence of catalysts **3c** (15 mol%) at room temperature for 48 h.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.
[d] Determined by $^1$H NMR spectroscopy of the crude products and HPLC analysis.
[e] 5 equivalents of cyclohexanone were used and the reaction was stirred for 24 h.

The adduct of the aldol reaction **2i** may be easily converted to a bicyclic lactone **7** through a simple reduction and subsequent acid treatment.[11a] The product containing two adjacent chiral centers and a quaternary carbon was obtained with a 10:1 diastereoselectivity[14] (Sheme 2).

The absolute configuration of the tertiary alcohol **2** was assigned by X-ray structural analysis of **2i** to be 2*S*,3*R*.[15] The absolute configuration observed may be explained by an intermolecular version of a hydrogen-bond activation and then attack of the carbonyl group from back as shown in Figure 1. Hindrance between the *tert*-butyldiphenylsilyloxy group and the




**Scheme 2.** Conversion of **2i** to **7**

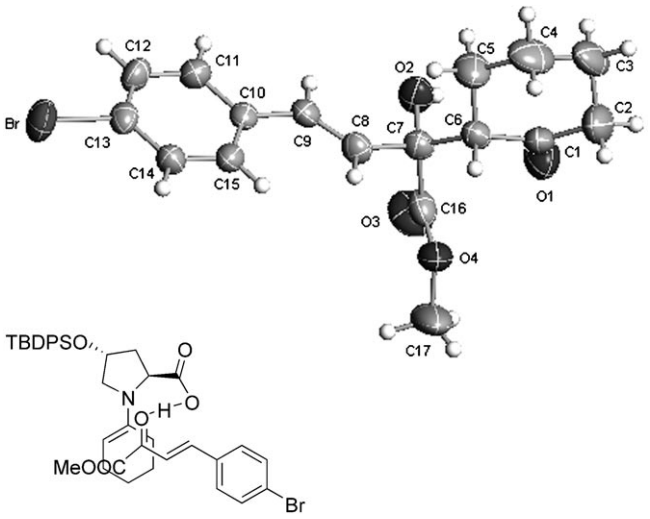



**Figure 1.** X-ray structure of adduct **2i** and the proposed transition state.

aryl section of the keto esters may be responsible for the excellent enatioselectivities and diastereoselectivities.

In conclusion, the present report reveals a highly efficient organocatalyzed cross-aldol reaction of ketones with β,γ-unsaturated α-keto esters in the presence of water that provides a simple and direct access to the corresponding tertiary aldol products in excellent enantioselectivities and high diastereoselectivities. The protocol is practical and quite efficient. Further applications of these reactions are currently under investigation.

## Experimental Section

### Typical Procedure for the Cross-Aldol Reaction using Catalyst 3c in Water

The following procedure for the reaction of methyl 2-oxo-4-phenylbut-(*E*)-3-enoate (**1a**) with cyclohexanone in water using catalyst **3c** is representative. To a mixture of catalyst **3c** (6.0 mg, 0.015 mmol), and methyl 2-oxo-4-phenylbut-(*E*)-3-enoate (**1a**) (19 mg, 0.1 mmol) in water (1.0 mL), cyclohexanone (52 μL, 0.5 mmol) was added at room temperature. The reaction mixture was vigorously stirred for the time indicated in the tables, then extracted with ethyl acetate (3×3 mL), and dried over $Na_2SO_4$. Purification by flash chromatography (hexane/EtOAc, 10:1–5:1) afforded product **2a** as a yellow oil; yield: 76%; $[\alpha]_D^{24.3}$: −110.9 (*c* 1.15, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 5H), 6.90 (d, *J* = 15.8 Hz, 1H), 6.04 (d, *J* = 15.9 Hz, 1H), 3.77 (s, 3H), 3.63 (s, 1H), 3.13 (m, 1H), 2.04 (m, 2H), 2.11 (m, 2H), 1.94 (m, 1H), 1.68 (m, 3H); IR (neat): ν = 3519, 2948, 1737, 1708, 1245, 1147, 976 $cm^{-1}$; HPLC separation conditions: Chiralcel AS-H, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 1.0 mL $min^{-1}$; $t_{major}$ = 26.1 min, $t_{minor}$ = 16.4 min.

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