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Asymmetric direct aldol reaction of 1,2-diketones and ketones mediated by proline derivatives

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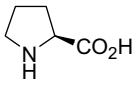
Abstract—The direct aldol reaction of 1,2-diketones and ketones mediated by proline derivatives yields the corresponding 2-hydroxy 1,4-diketones in high regioselectivity, diastereoselectivity and good enantioselectivity. This reaction provides an easy access to optically active tertiary alcohols, which are flanked by two carbonyl groups for further elaborations.

The aldol reaction is one of the most important carbon–carbon bond formation methods in organic synthesis.[1] Due to the importance of optically active compounds in organic synthesis, medicinal chemistry and pharmaceutical industry, to achieve high asymmetric inductions in the aldol reaction has been the goal of organic chemists for decades. Great progress has been achieved in the transition-metal-catalyzed asymmetric aldol reactions.[2] Due to potential environmental concerns of the metal catalysts in general, organocatalysis has become the current research focus.[3] In this regard, proline and its derivatives have risen to prominence since the early discovery of List and Barbas III that proline can catalyze the cross aldol reaction of ketone and aldehyde in good enantioselectivities.[4] Many new proline derivatives have been synthesized in an effort to improve asymmetric inductions and the reactivity of the original catalyst.[5] So far, catalyst loading as low as 2 mol % and enantioselectivity up to >99% ee may be achieved with some of the most recent catalysts.[6] However, even with these great advances, a successful cross aldol reaction is usually only possible with aldehydes as the enamine acceptors. Although the proline-catalyzed intramolecular reaction of two ketone carbonyls is known from the very beginning of this chemistry,[7] examples of cross aldol reaction using ketone as enamine acceptor have been rare. To the best of our knowledge, only four isolated examples are known in the literature, all were reported most recently: Namely the proline derivative-catalyzed cross aldol reaction of *N*-alkylated isatins (α-keto lactames) with acetone reported by Tomasini and co-workers;[8] the proline-catalyzed synthesis of 1,3-diketones via acyl cyanides[9] and the proline-catalyzed aldol reaction of ethyl phenylglyoxylate (an α-keto ester) with cyclohexanone,[10] and self-aldol of 2,2-dimethyl-1,3-dioxan-5-one.[11] The reason is probably due to the low reactivity of the ketone carbonyl as an enamine acceptor.

Compared with normal ketone, the carbonyl groups in a 1,2-diketone are more electrophilic since the two carbonyl groups are activating each other through electron withdrawal. We speculated that this type of carbonyl is active enough as an enamine acceptor. Such a cross aldol reaction of 1,2-diketone and ketone should produce an optically active 2-hydroxy 1,4-diketone, a very useful building block with multiple functional groups for further elaborations. The cross aldol reactions of 1,2-diketones and ketones have been studied sporadically in the literature with alumina or inorganic bases as the catalysts;[12] however, no asymmetric method has ever been developed for this reaction. Herein, we wish to report the first asymmetric synthesis of these compounds via organocatalysis.



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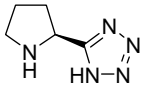

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Figure 1. L-Proline (**1**) and L-proline tetrazole (**2**).

Keywords: Ketone; Diketone; Aldol reaction; Asymmetric; Proline.
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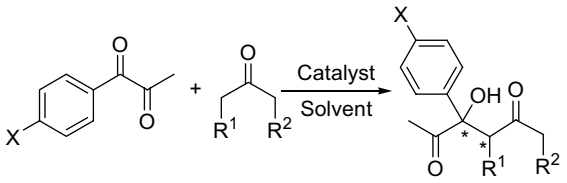
Table 1. Cross aldol reaction of 1-aryl-1,2-propanedione and ketones[a]



Entry	X	R^1	R^2	Solvent	T (°C)	t (h)	Yield (%)[b]	ee (%)[c,d]
1[e]		H	H	DMSO	rt	24	89	59
2[e]		H	H	Acetone	−15	72	61	64
3[e]		H	H	DMF	−15	96	51	80
4[f]		H	H	DMSO	rt	24	91	50
5[f]	H	H	H	DMF	−15	72	63	77
6[f]		H	H	DMF	−35	96	83	83
7[e]		H	Me	DMSO	rt	42	53[g]	58
8[e]		–$(CH_2)_3$–		DMSO	rt	96	43[h]	80
9[e]		–$(CH_2)_2$–		DMSO	rt	72	27[i]	99
10[e]	NO_2	H	H	DMF	−15	24	75	84
11[e]	CF_3	H	H	DMF	−15	48	59	85

[a] All the reactions were conducted with 1-aryl-1,2-propanedione (0.5 mmol), ketone (0.5 mL) and the catalyst in the specified solvent (2.0 mL), unless otherwise specified.
[b] Yield of isolated product after column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis; absolute configuration of the major enantiomer was tentatively assigned as *R* based on the reaction mechanism. Determination of the absolute configuration is currently under way.
[d] All major isomers are levorotary.
[e] L-Proline (**1**) as the catalyst [0.25 mmol (50 mol %)].
[f] L-Proline tetrazole (**2**) as the catalyst [0.15 mmol (30 mol %)].
[g] Only the regioisomer as shown was obtained.
[h] Only one diastereomer was obtained according to ^{1}H NMR of the crude product.
[i] dr ⩾ 95:5.

We first studied the cross aldol reaction of 1-phenyl-1,2-propanedione and acetone, catalyzed by L-proline (**1**) and L-proline tetrazole (**2**) (Fig. 1),[5i,13] and the results are summarized in Table 1.

The cross aldol reaction of 1-phenyl-1,2-propanedione with acetone in DMSO at room temperature gives a regioselective product with an ee value of 59% when **1** was used as the catalyst (entry 1). Probably due to steric hindrance, the reaction is pretty slow and, therefore, large loading (50 mol %) of the catalyst was necessary to achieve good yields. The ee value may be further improved by carrying out the reaction at sub-ambient temperature (entries 2 and 3). Catalyst **2** leads to similar results (entries 4 and 5). The highest ee value of 83% was achieved when the reaction was conducted at −35 °C in DMF (entry 6). A similar reaction with 2-butanone produced only one regioisomer (out of four possible regioisomers), with ee value comparable to that of acetone (entries 1 and 7). Cyclohexanone yielded only one diastereomer in this aldol reaction, with an ee value of 80% for the product (entry 8). The best enantioselectivity (99% ee) was obtained for the aldol product of cyclopentanone (entry 9). 1-(4-Nitrophenyl)-1,2-propanedione is a more reactive substrate; it also generates slightly better ee value (84%) than its phenyl counterpart (80%, entries 10 and 3). Similarly, 1-(4-trifluoromethylphenyl)-1,2-propanedione also gives excellent ee value (85%) of the aldol product (entry 11).

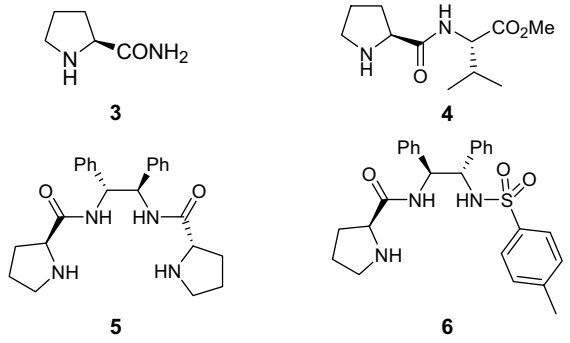
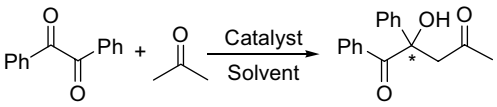


Figure 2. Structures of L-proline derivatives used in this study.

Symmetric benzil is a poorer substrate for this reaction. In an effort to improve the enantioselectivity, besides **1** and **2**, we also screened several proline derivatives (Fig. 2), and the results are collected in Table 2. An ee value of 18% was obtained for the cross aldol of benzil and acetone when **1** was used as the catalyst (entry 1). A slightly better (23%) enantioselectivity could be obtained when the reaction was carried out in DMSO instead of in acetone (entry 2). L-Prolinamide (**3**) is a more reactive catalyst for this reaction, yet its asymmetric induction power was poorer (entry 3). Catalyst **2** gave yields comparable to **3** and enantioselectivity slightly better than **1** (entries 4 and 5). Dipeptide ester catalyst **4**[6b] led to poor enantioselectivity (entry 6). The diamine-derived catalysts **5** and **6**, which are very

Table 2. Cross aldol reaction of benzil and acetone[a]



Entry	Catalyst	Loading (mol %)	Solvent	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**1**	50	—	24	20	18[e]
2	**1**[d]	50	DMSO	48	42	23[e]
3	**2**	20	—	24	69	10[e]
4	**3**	20	—	24	33	23[e]
5	**3**[d]	20	DMSO	24	36	27[e]
6	**4**	30	—	24	21	4[f]
7	**5**	10	—	24	16	26[f]
8	**6**	10	—	24	24	33[f]

[a] All the reactions were conducted with benzil (0.25 mmol) and the catalyst in anhydrous acetone (0.5 mL) at room temperature, unless otherwise specified.
[b] Yield of isolated product after column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis; absolute configuration of the major enantiomer was not determined.
[d] Carried out in DMSO (1.0 mL) with 5.0 mmol acetone.
[e] The major isomer is levorotary.
[f] The major isomer is dextrorotary.

efficient catalysts for the cross aldol reaction of ketone and aldehyde,[6f,g] produced the best ee values for the product (entries 7 and 8), yet they are still low. It is interesting to note that the major enantiomer formed in the last three cases is dextrorotary, which is opposite to that of the previous catalysts.

If this reaction also follows the normal aldol mechanism,[14] benzil giving poor enantioselectivity is not surprising, since the energy difference between the two diastereomeric transition states, which leads to the two enantiomers, is not that much (axial phenyl vs axial benzoyl, Fig. 3). We speculated that the remote hydrogen bonding[6] formed in the cases of catalysts **5** and **6** can overturn the steric preference so that the opposite sense of enantioselectivity is observed (entries 5 and 6), which is worth further study.

The cross aldol reaction of some cyclic 1,2-diones and acetone was also studied, and the results are collected in Table 3.

L-Proline (**1**) catalyzes the reaction of 1,2-cyclohexanedione (**7**) and acetone and gave the product in 61% yield and 48% ee (entry 1). A similar reaction with **2** as the catalyst produced an ee value of 66% (entry 2). L-Proline-catalyzed reaction of 9,10-phenanthrenequinone (**8**) and acetone generated a dialdolized product, which

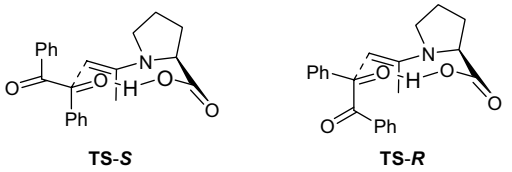
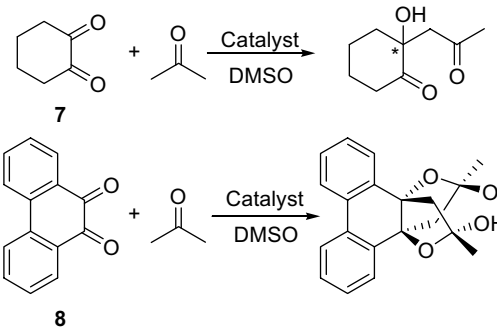


Figure 3. Plausible transition states (TS) of the cross aldol of benzil and acetone.

Table 3. Cross aldol reaction of cyclic diones and acetone[a]



Entry	Dione	Catalyst	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**7**	**1**	96	61	48[d]
2	**7**	**3**	96	48	66[d]
3	**8**[e]	**1**	96	55	86[d]
4	**8**[e]	**3**	96	57	64[d]
5	**8**[e,f]	**3**	72	38	56[d]

[a] All the reactions were conducted with the cyclic 1,2-diketone (0.25 mmol), acetone (0.25 mL) and the catalyst (0.125 mmol, 50 mol %) in DMSO (1.0 mL).
[b] Yield of isolated product after column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis; absolute configuration of the major enantiomer was not determined.
[d] The major isomer is levorotary.
[e] The reaction product was dissolved in $CHCl_3$ for 24 h to give a single diastereomer (relative configuration is shown in Table 3).
[f] DMF was used as the solvent.

forms dihemiacetal in situ (Table 3). A mixture of diastereomers was obtained initially; however, after treating the product with $CHCl_3$ for 24 h, all the minor diastereomers disappeared and a single diastereomer was obtained (relative configuration is shown in Scheme 1, which is identical to the racemic form reported by Linko and co-workers[12g]). The ee value of this diastereomer was determined to be 86% (entry 3). This result indicates that the dialdolization process is totally diastereoselective and the additional diastereomers were due to the hemiacetal formation, during which two new chiral centers were generated. Catalyst **2** catalyzes the same reaction, albeit with lower enantioselectivity (entries 4 and 5).

In summary, we have developed the first organocatalytic method for the asymmetric synthesis of 2-hydroxy-1,4-diketone compounds. Although their catalytic efficiency is low at the moment, L-proline and L-proline tetrazole have been identified to be good catalysts for the cross aldol reaction of 1,2-diketones and ketones, which yields the corresponding 2-hydroxy-1,4-diketones in a highly regioselective and diastereoselective manner with mediocre to excellent enantioselectivities depending on substrate structures. Extending this reaction to other 1,2-dicarbonyl compounds is currently under way.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.085.

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