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trans-4-Hydroxy-L-prolinamide as an efficient catalyst for direct asymmetric aldol reaction of acetone with isatins

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ABSTRACT

Prolinamide (2*S*,4*R*)-4-hydroxy-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide was found to be an efficient organocatalyst (10 mol %) for the direct asymmetric aldol reactions of isatins with acetone at −35 °C in THF and afforded the product in 79% yield with 74% *ee*. We have generalised the methodology for the direct asymmetric aldol reaction between isatin derivatives and acetone, and the corresponding aldol products were obtained in high yields (up to 99%) and with moderate enantioselectivities (up to 80%). This method has been applied to the enantioselective synthesis of (*S*)-convolutamydine.

1. Introduction

Enantioselective β-hydroxy ketones can be efficiently synthesised by asymmetric aldol reactions via the formation of enantioselective carbon–carbon bonds.[1] Since the exploration of the proline catalysed cross-aldol reaction of ketones and aldehydes by List and Barbas,[2] many amine derivatives have been applied to asymmetric cross-aldol reactions.[3] Chiral amines such as pyrrolidine and primary amine based organocatalysts can often complement each other in their ability to activate different substrates[4] and expand their application to a wide range of carbonyl compounds via enamine catalysis.[5] The first asymmetric aldol reaction of isatin with acetone catalysed by dipeptide-based organocatalysts was reported by Tomasini et al. in 2005.[6] 3-Substituted-3-hydroxyindolin-2-ones have received much attention from organic and medicinal chemists because it exist as a key skeleton in natural products and drug candidates. The aldol addition of ketones to isatin and substituted isatins would appear to be a simple and suitable route towards important biological compounds.[7,8] Proline,[9] prolinamides,[10–14] sulfonamides,[15] chiral amines,[16] quinidine thiourea,[17] vicinal amino alcohol,[18] enzymatic,[19] 4-hydroxydiarylprolinol[20] and amino acid salts are used as organocatalysts for this reaction.[21]

We recently reported 4-hydroxy-(*S*)-prolinamide as a catalyst for asymmetric aldol reaction of ketones and aldehydes;[22] *N*-aryl-L-prolinamides were used as catalysts for enantioselective aldol reactions of isatin and acetone.[23] Herein, we extend the catalytic activity of 4-hydroxy-(*S*)-prolinamide (Fig. 1) in enantioselective aldol reactions of isatin and acetone.

2. Results and discussion

Prolinamides **1**–**6** were synthesised according to our previously reported procedure.[22] These prolinamides were evaluated as organocatalysts for direct asymmetric aldol reactions of acetone and isatin. In our initial investigations, the catalytic activity of prolinamide **2** for aldol reactions of isatin **7a** and acetone in different solvents was studied at 25 °C (Table 1). Polar solvents, such as H_2O, DMF, EtOH and THF, gave excellent yields of the product **8a** with 23–52% *ee* (Table 1, entries 1–4). We also used dichloromethane and chloroform as solvents which gave 92–94% yield but the *ee* was poor. The neat reaction also afforded product **8a** with 84% yield but the *ee* was found to be at its lowest. Solvent THF was found to be the optimal choice which afforded the product in 99% yield with 52% *ee* after 36 h (Table 1, entry 4). The effect of the amount of acetone on the aldol reaction was investigated, and it was found that high amounts of acetone led to better yields and *ee* of the product **8a** (Table 1, entries 4, 8 and 9).

An additive can enhance the efficiency of the catalytic cycles by accelerating enamine formaton.[24] We screened various acid additives, such as benzoic acid, *p*-nitrobenzoic acid, *p*-methoxybenzoic acid, *p*-nitrophenol, acetic acid, trifluoroacetic acid and trifluoromethanesulfonic acid (TfOH) for the reaction between acetone and isatin using a catalyst **2** at 25 °C in THF (Table 2, entries 1–7). We observed that none of them were found to be very effective in promoting the reaction in comparison to additive free conditions. Similar results have also been reported in the literature with phthalimido-prolinamide and *N*-arylprolinamide.[13,23] The

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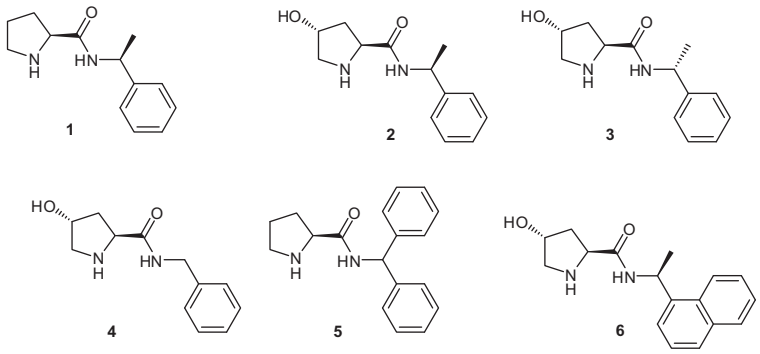
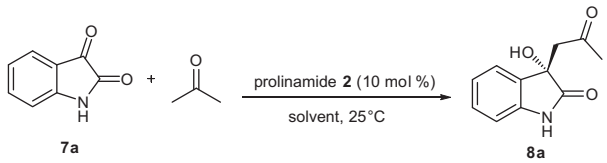


Figure 1. Prolinamides **1**–**6** as organocatalysts for aldol reactions between isatin and acetone.

Table 1
Screening of the solvents and amount of acetone[a]



Entry	Solvent	Time (h)	Yield[b] (%)	*ee*[c] (%)
1	H_2O	3	99	44
2	EtOH	36	94	26
3	DMF	24	92	23
4	THF	36	99	52
5	DCM	24	92	30
6	$CHCl_3$	24	94	34
7	Neat	6	84	12
8	THF	36	48	44[d]
9	THF	36	47	40[e]

[a] Prolinamide **2** (10 mol %), isatin (0.3 mmol) and acetone (1 mL, 45.4 equiv) in a specified solvent (2 mL) stirred at 25 °C for the specified time.
[b] Isolated yield after purification by column chromatography.
[c] The *ee* was determined by HPLC using Chiralpak AD-H column and the absolute configuration of the product was found to be (*S*).[6,21,23]
[d] Acetone (0.5 mL, 22.7 equiv) was used.
[e] Acetone (0.125 mL, 5.7 equiv) was used.

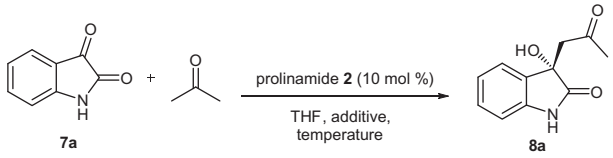
effect of temperature on the reaction was investigated by varying the temperature from reflux to −35 °C. Decreasing the temperature improved the *ee* of product **8a**, but the reaction time increased (Table 2, entries 8–10). We also varied the catalyst loading in the range of 2–20 mol % and the optimum catalyst loading was found to be 10 mol %, which is comparatively less than our previously reported *N*-arylprolinamide catalyst.[23]

Finally, we evaluated a variety of L-prolinamides **1**–**6** for aldol reactions between isatin **7a** and acetone in THF at −35 °C. We believe that a small variation in the structural motif of the catalyst can greatly affect the enantioselectivity of the aldol product. We observed that the absolute configuration of product **8a** (*S*) is governed by the (*S*)-proline while the additional enhancement in *ee* of the product is induced by the appropriate bulkiness and absolute configuration of the amine part of the prolinamide (Table 3, entries 1–6). The phenyl group of (2*S*,4*R*)-4-hydroxy-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide **2** was replaced by a more bulky naphthyl group, which decreased the *ee* and yield of product **8a** (Table 3, entries 2 and 6). Prolinamide **4** derived from the less bulky amine (benzyl amine) gave the lowest *ee* for product **8a** (Table 3, entry 4). Prolinamide **5** derived from a more bulky amine (diphenyl methyl amine) afforded the lowest yield of product **8a** with 38% *ee* (Table 3, entry 5).

N-Phenyl-(*S*)-prolinamide **1** afforded product **8a** in 43% yield and with 74% *ee* after 48 h while introduction of a hydroxyl group at the 4-poistion of prolidine ring of prolinamide **1**, increased the yield up to 79% of the catalytic product **8a** (Table 3, entries 1 and 2). The hydroxyl group enhanced the yield of the product with the appropriate bulkiness and absolute configuration of the amine may be due to intermolecular hydrogen bonding between molecules of *trans*-4-hydroxy-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide **2** and similar effect we have proposed for these catalyst in direct asymmetric aldol reaction between cyclohexanone and benzaldehydes in our earlier report.[22]

In order to determine the scope and limitations of this methodology, we tested prolinamide **2** for aldol reaction of a variety isatin derivatives and acetone in THF at −35 °C. The absolute configuration for all of the products was found to be (*S*).[6,21,23] Substitution on the *N*-atom of the isatin molecule such as *N*-methyl, *N*-allyl and *N*-benzyl gave the corresponding aldol product in 72–91% yields and with lower *ee* than aldol product **8a**. The halogen substituted on isatin at the 5-position also afforded the corresponding products in excellent yields; increasing the size of the halogens atom increased the *ee* (Table 4, entries 5–7). Electron withdrawing

Table 2
Effects of additive, temperature and catalyst loading on the direct aldol reaction of isatin **7a** with acetone[a]



Entry	Additive	Temperature (°C)	Time (h)	Yield[b] (%)	*ee*[c] (%)
1	PhCOOH	25	9	99	29
2	*p*-OMePhCOOH	25	9	99	37
3	*p*-NO_2PhCOOH	25	9	75	19
4	*p*-NO_2-Phenol	25	6	86	40
5	CH_3COOH	25	6	89	34
6	CF_3COOH	25	4	89	40
7	TfOH	25	4	99	31
8	No additive	Reflux	12	99	36
9	No additive	25	36	99	52
10	No additive	−35	48	79	74
11	No additive	−35	48	78	50[d]
12	No additive	−35	36	99	41[e]

[a] Prolinamide **2** (10 mol %), additive (10 mol %), isatin (0.3 mmol) and acetone (1 mL) in THF (2 mL) stirred at specified temp for specified time.
[b] Isolated yield after purification by column chromatography.
[c] The *ee* was determined by HPLC using chiralpak AD-H Column and the absolute configuration of the product was found to be (*S*).
[d] Catalyst 2 mol % was used.
[e] Catalyst 20 mol % was used.