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Phthalimido-prolinamide: a new chiral catalyst for solvent free enantioselective aldol reactions

Togapur Pavan Kumar *, Namdevrao Chethan Vavle, Vidyavathi Patro, Kothapalli Haribabu

Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A new prolinamide derivative phthalimido-prolinamide **1** was developed for organocatalytic enantioselective direct aldol reactions of various aldehydes with ketones. The catalytic protocol is effective with 15 mol % of catalyst under solvent free and additive free reaction conditions. By employing a catalytic amount of water, the efficiency of the reaction increased further and the desired products β-hydroxy carbonyl compounds were obtained in high yields and stereoselectivities.

1. Introduction

The aldol reaction is one of the most explored fundamental carbon–carbon bond forming reactions in organocatalytic asymmetric synthesis.[1] This reaction offers the formation of chiral products with one or more stereogenic centers with the possibility of stereo regulation. The products of this reaction, β-hydroxy carbonyl compounds, constitute as an important structural motif and can be found in numerous bio-active natural products and drug molecules.[2] Since the pioneering work of List and Barbas III on proline catalysis,[3] a large variety of organocatalysts with diverse functional features have been designed and explored for stereocontrol in aldol reactions and others.[4,5] Prolinamides were found to be more significant in promoting enamine catalysis compared to proline itself. Since most of the proline remains in the zwitterionic form, the carboxylic group is scarcely accessible for catalysis.[6] Several prolinamide derivatives with graded NH acidity and varying levels of steric control were employed as organocatalysts for direct aldol reactions between aldehydes and ketones and found to be competent with various levels of success.[7] There are several reports on green organocatalysis such as reactions under solvent free conditions or ball-milling.[8] However, we noticed that most of the organocatalytic protocols involve the use of organic solvents as the reaction medium, high reaction times or long synthetic routes to obtain the catalyst. Therefore, investigation of facile catalytic methods for this transformation is still challenging. With our continued interest in organocatalysis,[9] we developed a new prolinamide derivate phthalimido-prolinamide **1** (Fig. 1) from L-proline and *N*-aminophthalimide under peptide coupling reaction conditions.

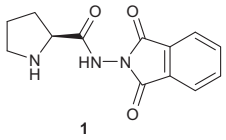

Figure 1. Phthalimido-prolinamide.

The pyrrolidine ring of catalyst **1** acts as active site and amide NH participates in hydrogen bonding while the bulky phthalimide ring facilitates in providing steric control and additional hydrogen bonding interactions in the transition state as the reaction progress. Herein we report the synthesis and application of phthalimido-prolinamide **1** as a new catalytic system for direct asymmetric aldol reactions of aldehydes with ketones.

2. Results and discussion

The prolinamide catalyst **1** was synthesized in two steps from *N*-Boc-proline and *N*-aminophthalimide using standard peptide coupling conditions followed by deprotection using TFA as shown in Scheme 1. In order to investigate the ability of phthalimido-prolinamide **1** as an organocatalyst, we initially attempted solvent screening studies for direct asymmetric aldol reactions by taking cyclohexanone **4a** and *p*-nitrobenzaldehyde **5a** as the model substrates (Scheme 2). The experiments were uniformly conducted in various solvents at two different temperatures (one series at

* Corresponding author. Tel.: +91 40 27191727; fax: +91 40 27160512.
E-mail address: pavantogapur@gmail.com (T.P. Kumar).

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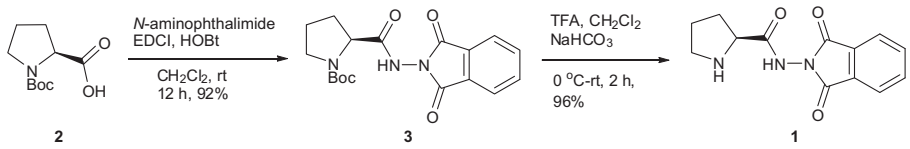
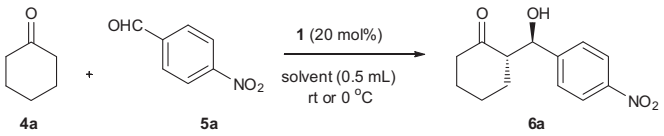


Scheme 1. Synthesis of phthalimido-prolinamide **1**.



Scheme 2. Aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde.

room temperature and another at 0 °C) using 20 mol % of the catalyst loading (Table 1). As apparent from the survey, the reaction proceeded well in all solvents irrespective of their polar/non-polar nature except for the time taken for completion. The reactions performed at 0 °C took long reaction times for completion compared to their counterparts at room temperature (Table 1, entries 1–11, depicted in parenthesis).

Table 1
Screening of solvents[a]

Entry	Solvent	Time (d)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	$CHCl_3$	24 (48)	77 (73)	8:2 (8:2)	73 (76)
2	Hexane	24 (48)	69 (70)	7:3 (8:2)	78 (84)
3	DMF	24 (36)	83 (85)	93:7 (93:7)	75 (80)
4	DMSO	24 (36)	84 (80)	92:7 (9:1)	80 (81)
5	THF	20 (42)	85 (81)	85:15 (9:1)	80 (76)
6	CH_3CN	24 (48)	82 (79)	91:9 (92:8)	81 (77)
7	MeOH	20 (42)	89 (85)	94:6 (94:6)	85 (81)
8	**Neat**	**20 (36)**	**95 (90)**	**95:5 (96:4)**	**90 (91)**
9	Dioxan	24 (42)	76 (71)	7:3 (7:3)	82 (82)
10	CH_2Cl_2	20 (40)	86 (80)	8:2 (9:1)	71 (75)
11	H_2O	24 (48)	88 (83)	6:4 (8:2)	81 (80)

[a] Reaction conditions: **1** (20 mol %), cyclohexanone (4 mmol), aldehyde (1 mmol).
[b] Isolated yields.
[c] Determined by the ^1H NMR of the crude product.
[d] Determined by chiral HPLC.

However, both the protocols appeared to give almost similar results, affording product **4a** in good yield and stereoselectivities (Table 1, entries 1–11). The reaction performed under neat conditions was more productive (95% yield, 95:5 *anti*/*syn*, and 90% ee, Table 1, entry 8) among the conditions tested and laid the basis for further optimization experiments.

We then explored the effect of various acid additives in the above transformation at room temperature and the results of this are summarized in Table 2.

Table 2
Screening of additives[a]

Entry	Additive	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	A cetic acid	18	71	84:16	89
2	F ormic acid	18	69	8:2	80
3	Benzoic acid	18	83	92:8	82
4	Citric acid	20	76	9:1	85
5	TFA	18	85	93:7	89
6	pTSA	24	61	74:26	77
7	CSA	24	63	7:3	71
8	MeOH	15	86	93:7	90
9	DMSO	15	84	91:9	87
10	**H_2O**	**15**	**96**	**96:4**	**95**

[a] Reaction conditions: **1** (20 mol %), cyclohexanone (4 mmol), aldehyde (1 mmol), additive (5 mol %).
[b] Isolated yields.
[c] Determined by the ^1H NMR of the crude product.
[d] Determined by chiral HPLC.

The reaction was feasible in the presence of acid additives, although it was found to be inferior in productivity as compared to additive free transformations (Table 2, entries 1–7).

Based on a literature survey we realized the role of water in accelerating the catalytic process in Nature and in organic synthesis.[10] We then tested the effect of a small molecule in the organocatalytic direct aldol reaction (Table 2, entries 8–10). The addition of 5 mol % of water to the reaction medium gave the best results among the conditions tested (96% yield, 96:4 *anti*/*syn*, and 95% ee, Table 2, entry 10). Finally, screening experiments were conducted to establish the optimal catalyst concentration required for the above transformation. As shown in Table 3, the use of 15 mol % of catalyst and 5 mol % of water under neat reaction conditions at room temperature (95% yield, 96:4 *anti*/*syn*, and 95% ee, Table 3, entry 3) were set as the optimal conditions to evaluate the substrate generality of this protocol.

The versatility of organocatalyst **1** was examined against several substrate combinations in which a variety of aldehydes **5b**–**m** were employed as aldol acceptors, while the cyclohexanone **4a** (Table 4) and other ketones **4b**–**f** (Table 5) were taken as the donors. As shown in Table 4, aldehydes **5b**–**m** reacted smoothly with cyclohexanone **4a** under the optimized reaction conditions and the corresponding aldol adducts **6b**–**m** were obtained in good yields with high levels of stereoselectivities regardless of the nature of the substitution pattern in the aldehydes (Table 4, entries 1–12). However, reactions with other ketones **2b**–**f** were less compatible, and the products **6n**–**v** were obtained with moderate to good yield and selectivities (Table 5, entries 1–9). The major adducts formed were *anti*-diastereomers in all cases, except for the reaction of cyclopentanone, which gave the *syn*-diastereomer as the major product (Table 5, entry 9). Overall, the observed efficacy of this new catalytic system is in good agreement with those reported for a variety of organocatalysts known in the literature.[7,11]

Table 3
Screening of catalyst loading[a]

Entry	1 (mol %)	H_2O (mol %)	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	20	5	15	96	96:4	95
2	20	10	15	96	96:4	94
3	**15**	**5**	**15**	**95**	**96:4**	**95**
4	15	10	15	94	94:6	95
5	10	5	20	91	92:8	92
6	10	10	20	92	93:7	91
7	5	5	24	84	91:9	90
8	1	5	48	58	91:9	87

[a] Reaction conditions: cyclohexanone (4 mmol), aldehyde (1 mmol).
[b] Isolated yields.
[c] Determined by the ^1H NMR of the crude product.
[d] Determined by chiral HPLC.

The stereochemical outcome of the reaction is in agreement with a simplified transition state[12] as shown in Figure 2. We believe that the phthalimide moiety in the catalyst may be involved in transition state by way of providing steric control and also contributing toward additional H-bonding interactions with the intermediacy of the water molecule, which creates a more compact transition state and leads to the formation of the desired products with high stereoselectivities.