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Asymmetric aldol reactions of isatins catalyzed by phthalimido-prolinamide

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ABSTRACT

Enantioselective aldol reactions of isatins with acetone using phthalimido-prolinamide organocatalyst **1** are described. The protocol was effective under solvent free and additive free reaction conditions with 20 mol % of **1** leading to the desired aldol products in good yields and with good enantioselectivities.

1. Introduction

The aldol reaction is one of the most explored benchmark transformations using organocatalysts.[1] Specifically, it ranks at the top for testing and evaluating the efficacy of new catalyst designs.[2] The products of this reaction, β-hydroxy carbonyl compounds are important structural motifs, which are found in numerous bioactive natural products and drug molecules.[3] Among the various aldol substrates, isatins attract great attention as they lead to the formation of oxindole derivatives, which serve as valuable templates for further derivatization to hybrid and/or designed bioactives.[4] From a literature survey, isatins were found to be infrequent substrate partners for aldol reactions and thus drew our attention. Although a large number of organocatalysts such as proline derivatives, bifunctional thioureas, and others have been reported for various asymmetric reactions, only some of them have been evaluated for aldol reactions with isatin derivatives.[5] The first report on the enantioselective aldol reaction of isatin with acetone was presented by Tomasini et al. in 2005 using peptide based organocatalysts.[5b] Later on, Zhao et al. developed a thiourea catalyst,[5c] Chen et al. developed a carbohydrate derived catalyst,[5d] and several other catalysts were developed for this transformation with good levels of success.[5] In particular, several proline derived organocatalytic protocols were found to be effective.[6] Among the proline derivatives, prolinamides are prominent due to their functional characteristics such as graded NH acidity and tunable steric control.[7] An investigation into new catalytic approaches for aldol reaction of isatin substrates serves as valuable addition to the existing methods and extends the horizons of organocatalysis. Recently, we have reported on the design and development of phthalimido-prolinamide **1**[8] (Fig. 1) as an efficient organocatalyst for asymmetric direct aldol reactions with ketones and aldehydes under solvent free reaction conditions. Having been encouraged by this and in continuation of our research interests[8,9] on organocatalysis, we evaluated the catalytic performance of **1** for aldol reactions of isatins and acetone. Catalyst **1** worked well and resulted in the formation of the corresponding aldol adducts with good yields and selectivities under solvent free and additive free conditions when employing 20 mol % of **1**. Herein these studies are reported.

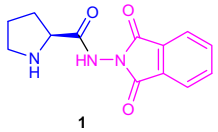

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Figure 1. Phthalimido-prolinamide.

2. Results and discussion

In order to explore the ability of **1** as an organocatalyst for aldol reactions of isatins and acetone, a series of screening studies were conducted to establish the optimal parameters by using isatin **2a** and acetone **3** as the model substrates (Scheme 1). Initially, experiments were conducted identically in various solvents at room temperature with 20 mol % of catalyst **1** and the results of these studies are shown in Table 1. The enantioselective aldol reaction between isatin **2a** and acetone **3** proceeded reasonably well in all solvents irrespective of their polar/non-polar nature resulting in products with moderate yields and enantioselectivities (Table 1, entries 1–12). However, when the reaction was performed under

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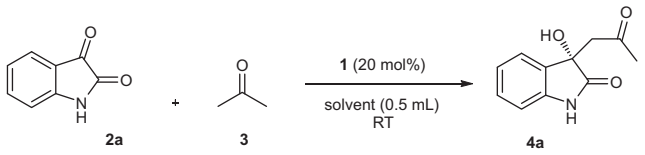


Scheme 1. Aldol reaction of isatin with acetone.

Table 1
Screening of solvents[a]

Entry	Solvent	Time (*d*)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	3	56	31
2	$CHCl_3$	3	59	34
3	Toluene	3	51	29
4	Hexane	3	46	42
5	THF	4	58	37
6	DMSO	4	61	25
7	MeOH	3	65	40
8	EtOH	3	62	38
9	Dioxan	4	52	30
10	CH_3CN	4	55	35
11	H_2O	4	41	33
12	Neat	3	71	53

[a] Reaction conditions: **1** (20 mol %), acetone (5 mmol), isatin (1 mmol).
[b] Isolated yields
[c] Determined by chiral stationary phase HPLC.

neat conditions, it was more impressive (71% yield, 53% ee, Table 1, entry 12) among the solvents screened and so selected for further optimization process.

In order to increase the catalytic efficiency, the reaction under solvent free conditions was tested for the effect of additives on the catalytic performance of **1**. It was evidenced by many reports that the presence of an additive enhances the efficiency of the catalytic cycle by accelerating enamine formation.[7] Various acid additives such as acetic acid, benzoic acid, formic acid, CSA, TFA, pTSA, phenol, 1-naphthol, and 2-naphthol were tested in the above transformation at room temperature (Table 2, entries 1–11), but none of them were found to be effective in promoting the reaction on comparison with additive free conditions. A series of additive screening experiments were then carried out at a lower temperature (−20 °C) without changing the other reaction parameters. With these studies, it was established that the aldol reaction of isatin **2a** with acetone **3** was effective under solvent free and additive free conditions when performed at −20 °C, employing 20 mol % of catalyst **1** (Table 2, entry 11). The values shown in parenthesis indicate the results for the screening experiments conducted at −20 °C.

Finally, screening experiments were conducted to determine further possibilities for improving catalytic performance and to set the optimal catalyst concentration for **1** to give the best efficiency possible. The results summarized in Table 3 show that the catalytic efficiency of **1** was at its maximum at −20 °C at a loading of 20 mol %. The efficiency of **1** decreases when changing any of the reaction parameters from the above optimum values.

After determining the optimal reaction parameters, the adaptability of organocatalyst **1** was assessed by conducting substrate-screening experiments. The aldol reaction was performed using different isatin derivatives with acetone and other ketones. As shown in Table 4, isatins **2a–g** reacted smoothly with ketones **3a–f** under the optimized reaction conditions and the corresponding aldol adducts **4a–n** were obtained in good yields and enantioselectivities regardless of the type of substitution on isatin (Table 4, entries 1–7). Overall, all substrate combinations were feasible for this protocol and the observed catalytic efficacy of **1** was in good agreement with those reported for a variety of organocatalysts known in the literature.[5,6]

Table 2
Screening of additives[a]

Entry	Additive	Time (*d*)	Yield[b] (%)	ee[c] (%)
1	Acetic acid	3 (5)	42 (51)	40 (44)
2	Benzoic acid	3 (5)	49 (57)	42 (51)
3	Formic acid	3 (5)	45 (54)	39 (42)
4	TFA	3 (5)	32 (35)	40 (49)
5	CSA	4 (5)	39 (35)	34 (31)
6	pTSA	4 (5)	43 (50)	31 (34)
7	HCl	3 (5)	46 (41)	29 (25)
8	1-naphthol	3 (5)	56 (61)	43 (49)
9	2-naphthol	4 (5)	60 (58)	45 (48)
10	Phenol	4 (5)	63 (65)	41 (50)
11	No additive	4 (5)	71 (78)	53 (67)

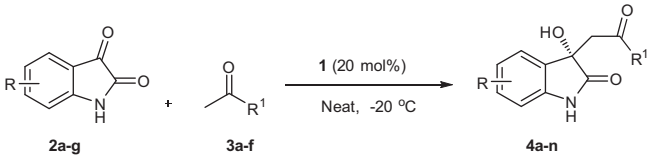
[a] Reaction conditions: **1** (20 mol %), acetone (5 mmol), isatin (1 mmol).
[b] Isolated yields.
[c] Determined by chiral stationary phase HPLC.

Table 3
Screening of catalyst loading and temperature[a]

Entry	1 (mol %)	Temp. (°C)	Time (*d*)	Yield[b] (%)	ee[c] (%)
1	10	0	3	46	31
2	10	−20	5	51	34
3	20	0	5	72	29
4	20	−10	3	73	42
5	30	RT	5	70	52
6	30	0	3	75	56
7	30	−10	5	79	69
8	40	RT	3	73	55
9	40	0	5	77	59
10	40	−20	5	81	70

[a] Reaction conditions: acetone (5 mmol), isatin (1 mmol), neat, no additive.
[b] Isolated yields.
[c] Determined by chiral stationary phase HPLC.

Table 4
Screening scope[a]



Entry	R	R^1	Time (*d*)	Product	Yield[b] (%)	ee[c] (%)
1	H	Me	5	**4a**	78	67
2	5-Br	Me	5	**4b**	83	72
3	5-Cl	Me	5	**4c**	76	65
4	5-F	Me	5	**4d**	81	69
5	6-Br	Me	5	**4e**	69	61
6	6-Cl	Me	5	**4f**	73	63
7	5-Me	Me	5	**4g**	75	71
8	H	Ph	5	**4h**	78	66
9	6-Br	Ph	5	**4i**	83	57
10	5-F	Ph	5	**4j**	76	62
11	H	4-BrC_6H_4	5	**4k**	81	53
12	H	4-MeC_6H_4	5	**4l**	69	56
13	H	2-Pyridyl	5	**4m**	73	54
14	H	1-Naphthyl	5	**4n**	75	51

[a] Reaction conditions: ketone (5 mmol), isatin (1 mmol), no additive.
[b] Isolated yields.
[c] Determined by chiral stationary phase HPLC.

The following transition state[5,6] model in Figure 2 is proposed to explain the stereochemical outcome of the above transformation. We believe that catalyst **1** acts by a dual activation mode wherein the pyrrolidine ring activates the ketone and the amide

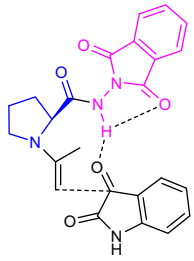


Figure 2. Possible transition state.

NH activates the isatin. The phthalimide ring of the catalyst further stabilizes the binding efficiency of the amide NH and contributes to effective steric control leading to a compact transition state resulting in products with high selectivities. Initially, catalyst **1** activates the ketone to form a reactive enamine and as the reaction progresses, the H-bonding interaction of the isatin C=O with the NH of catalyst **1** results in a compact transition state (Fig. 2), which facilitates the nucleophilic attack of the enamine onto the Re face of isatin C=O leading to the formation of (*S*)-**4a**–**n** as the major products. The absolute configuration of the major enantiomers was determined to be (*S*) by comparison of the specific rotation with the data reported in the literature.[10,6e]

3. Conclusions

In conclusion, we have described the application of phthalimido-prolinamide **1** as an organocatalyst for the enantioselective aldol reaction of isatins with ketones. The catalytic performance of **1** is effective under solvent free and additive free conditions with 20 mol % loading, giving rise to the corresponding aldol adducts in good yields and with good enantioselectivities. Further studies to extend the scope of this catalytic system to other substrates are currently in progress and will be reported accordingly.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Bruker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL. Chiral stationary phase HPLC analysis was carried out on chiral pak OD-H, IC, IA or AD-H columns using a mixture of isopropanol and hexanes (2:8) as the eluent, flow rate 1 mL/min, $\lambda = 254$ nm, retention times ranging between t_R (major) = 6.8–9.4 min, and t_R (minor) = 8.1–12.3 min, for the examples performed in the substrate screening experiments.

4.2. General procedure for the aldol reaction of isatins to ketones

To ketone (5 mmol) in a vial was added catalyst **1** (20 mol %) and stirred for 10 min at room temperature. Next, isatin (1 mmol) was added to the resulting mixture and stirred for the appropriate time (Table 3) at −20 °C. After completion of the reaction (monitored by TLC), the mixture was purified by silica-gel column chromatography to afford the desired product. The relative and absolute configurations of the products were determined by comparison of ^{1}H NMR, ^{13}C NMR, and specific rotation values with those reported in the literature.[6]

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10. *Specific rotation for compound* **4a**: $[\alpha]_D^{20} = -24.1$ (*c* 1, CH_3OH); literature[6e] $[\alpha]_D^{18} = -20.0$ (*c* 0.03, CH_3OH).