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Enantioselective organocatalytic aldol reaction of unactivated ketones with isatins

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This paper is dedicated respectfully to Professor Yashwant D. Vankar on the occasion of his 60th birthday

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ABSTRACT

Enantioselective organocatalytic direct aldol reaction of unactivated ketones with various isatin derivatives was developed using cinchonine based urea ligand employing a noncovalent catalysis mechanism. Using this protocol we can access functionalized 3-alkyl-3-hydroxyindolin-2-ones in high yields with good to excellent enantioselectivities.

Organocatalytic direct aldol reactions of activated carbonyl compounds via preformed enamine pathway are currently one of the most promising areas of research.[1] This method provides a useful route to access chiral β-hydroxy carbonyl compounds which are versatile synthetic motifs for biologically and pharmaceutically important intermediates.[2] The efficiency of these processes relies mainly on the formation of a highly reactive enamine intermediate which is derived from activated ketones. Enamines, obtained from unactivated ketones such as aromatic ones, are less reactive due to the low orbital overlap between the enamine double bond and the nitrogen lone pair[3] which, inturn, results in very slow and incomplete reaction. To the best of our knowledge, there are very few organocatalysts reported so far based on enolization-driven mechanism using base catalysis for the effective aldol reaction of unactivated ketones[3,4] and while our work was in progress, a report has recently been disclosed by Zhao et al.[5] using isatin as an acceptor.[6]

Intensive efforts have been devoted to the development of asymmetric transformations using isatin as an electrophile[7] as they provide powerful tools for the rapid and efficient construction of 2-oxindole containing chiral quaternary carbon center at its 3-position.[8] The product, 3-alkyl-3-hydroxyindolin-2-one[9] constitutes a key structural feature of vast majority of important and complex natural products[10] as well as pharmaceutically active compounds.[11] Hence, the synthesis of enantiomerically pure 3-alkyl-3-hydroxyindolin-2-ones via catalytic enantioselective process has emerged as an area of active research.[10,12]

Chiral bifunctional compounds have become powerful catalysts for inducing asymmetric induction in various reactions.[13] During the last few years, several enantioselective processes have been reported using these catalysts for asymmetric C–C bond-forming reactions.[14] Isatins are relatively stronger and directional H-bond acceptors in comparison to normal ketones-a property which makes them one of the best substrates for H-bond catalysis.[15] We envisioned that the tertiary amine part of a chiral bifunctional catalyst **1** (Fig. 1) would assist in the formation of an enolate and thus effectively catalyze aldol reaction of isatins with unactivated carbonyls. Further, we anticipated that the aldol reaction of aromatic ketones with isatin would work better via a soft enolate[16] mechanism in the presence of bifunctional catalysts. Based on this idea, we herein report cinchonine based urea catalyst for direct aldol reaction of unactivated ketones as well as activated ones with a variety of isatins. In addition, we have also shown that the reversal of enantioselectivity was observed using chinchonidine based primary amine catalysts.

At the outset, the reaction of acetophenone with isatin was initially examined under enamine catalysis using 10 mol % of diamines **1a**–**1e**[17] in combination with equimolar acid additives.

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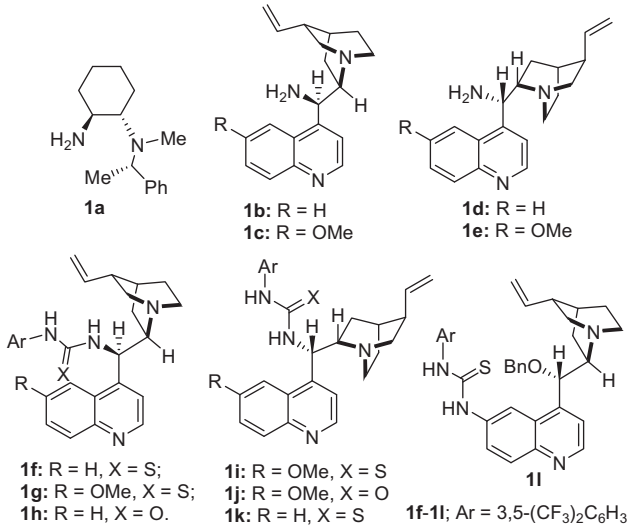
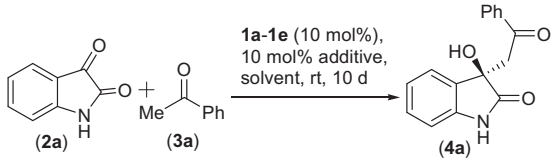


Figure 1. Vicinal diamines based chiral catalysts.

Table 1
Optimization of aldol reaction using **1a–1e**[a]



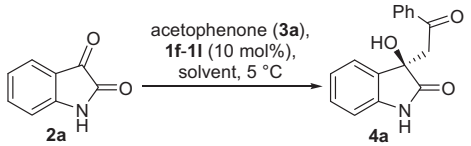
Entry	Diamine	Additive	Solvent	Yield (%)	ee[b] (%)
1	**1a**	CF_3COOH	Water	51	74
2	**1a**	CH_3COOH	Water	40	26
3	**1a**	CF_3SO_3H	Water	53	67
4	**1a**	HCOOH	Water	48	63
5	**1a**	PhCOOH	Water	35	45
6	**1a**	*P*-TSA	Water	38	10
7	**1a**	CF_3COOH	THF	42	52
8	**1a**	CF_3COOH	DMF	58	63
9	**1a**	CF_3COOH	DCM	42	49
10	**1a**	CF_3COOH	Brine	58	81
11	**1b**	CF_3COOH	Brine	58	−80[c]
12	**1c**	CF_3COOH	Brine	55	−75[c]
13	**1d**	CF_3COOH	Brine	59	90
14	**1e**	CF_3COOH	Brine	60	89

[a] Unless otherwise stated, all the reactions were carried out on 0.25 mmol scale using 5.0 mmol of acetophenone in 250 μL of solvent.
[b] Determined by HPLC using chiral column.
[c] Opposite enantiomers were obtained.

Under optimized conditions, in the presence of 10 mol % of TFA, a maximum of 81% ee was observed with a moderate yield of 58% when **1a–1c** were used (Table 1, entries 10–12). Increased enantioselectivities were observed (up to 90% ee) using **1d** and **1e** in the presence of 10 mol % of TFA (entries 13 and 14) in brine.[18] As it is obvious, the ligands **1b** and **1c** provided aldol products with opposite stereochemistry. In these cases, the reaction proceeded through an enamine mechanism. The longer reaction time (10 days) is a limitation.

In contrast, the bifunctional thiourea **1f** catalyzed the aldol reaction of isatin with acetophneone more efficiently but in poor ee (Table 2, entry 1). To our delight, a remarkable increase in the enantioselectivity on decreasing the reaction temperature to 5 °C was observed (entry 2). Further decrease in the temperature to

Table 2
Optimization of aldol reaction using **1f–1l**[a]



Entry	Catalyst	Solvent	Time (d)	Yield (%)	ee[b] (%)
1	**1f**	THF	2	85	46[c]
2	**1f**	THF	5	82	82
3	**1f**	Dioxane	4	93	83
4	**1f**	Et_2O	4	70	68
5	**1f**	$CHCl_3$	5	86	56
6	**1f**	DCM	5	79	66
7	**1f**	Toluene	5	85	66
8	**1f**	CH_3CN	3	60	45
9	**1f**	Water	3	65	62
10	**1g**	Dioxane	4	91	81
11	**1h**	Dioxane	6	89	91
12[d]	**1i**	Dioxane	4	93	70
13[d]	**1j**	Dioxane	6	85	84
14[d]	**1k**	Dioxane	4	90	71
15	**1l**	Dioxane	8	75	21
16[e]	**1h**	Dioxane	5	92	90
17	**1h**	Dioxane	4	92	91[f]

[a] Reactions were carried out on a 0.1 mmol of **2a** with 0.5 mmol of **3a** in 100 μL of solvent, unless stated otherwise.
[b] Determined by HPLC using chiral column.
[c] Reaction was carried out at rt.
[D] S-Enantiomer was obtained.
[e] 4 Å MS were used.
[f] 20 mol % of catalyst (1 h) was used.

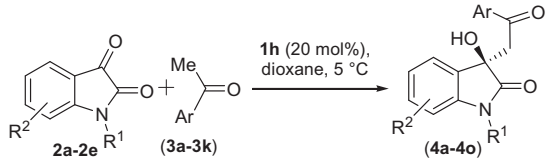
20 °C makes the reaction very sluggish. Thus, it was decided to perform rest of the reactions at 5 °C.

Among all solvents screened (Table 1, entries 3–9), dioxane proved to be the optimum choice for this reaction (entry 3) in terms of both rate of the reaction as well as enantioselectivity. At 5 °C using dioxane as a solvent, various bifunctional thiourea and urea catalysts (**1f–1l**) were screened. It was found that catalysts **1f** and **1g** provided enantioselectivities in the range of 81–83% with very good to excellent yields (Table 2, entries 1–10). Poor enantioselectivity with catalyst **1l** (entry 15), emphasizes the significance of the relative orientation and positions, respectively, of acidic and basic functional groups in the chiral scaffold. Among all the catalysts screened, urea derived catalyst **1h** proved to be the best in the direct aldol reaction (up to 91% ee, entry 11) at 5 °C with 10 mol % catalyst loading.[19] Addition of molecular sieves to the reaction did not make any difference in the enantioselectivity (entry 16). Increasing the catalyst loading to 20 mol % shortened the reaction time to four days without affecting the enantioselectivity (entry 11 vs 17). Thus it was decided to use 20 mol % of the catalyst for further substrate scope (Table 3).

Aldol reaction of isatin with a wide range of aromatic ketones was studied using the catalyst **1h** under standard conditions. In all the cases, the enantioselectivities obtained were good to very high (Table 3). A number of C-acetyl heterocyclic compounds, on reaction with isatins, gave a series of 3-hydroxy-3-substituted oxindoles (entries 11, 12 and 14). Interestingly, the product **4k**, formed from the reaction of 2-acetylthiophene **3h** and isatin, is active at 100 mg/kg in the maximal electroshock seizure test, and could also be obtained in 84% ee with 98% of yield (entry 11).[20]

Further, we were interested in using activated carbonyl compounds such as acetone and acetaldehyde as a donor in the aldol reaction. To our delight, a high level of enantioselectivities

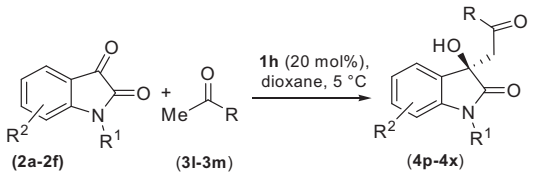
Table 3
Substrate scopes of aldol reaction[a]



Entry	R^1	R^2	Ar	Time (d)	Product	Yield (%)	ee[b] (%)
1	H	H/2a	Ph (3a)	4	**4a**	92	91
2	H	5-F/2b	Ph (3a)	4	**4b**	88	84
3	H	5-Cl/2c	Ph (3a)	4	**4c**	93	84
4	H	4,6-DiBr/2d	Ph (3a)	5	**4d**	92	91
5	H	H/2a	4-FC_6H_4 (3b)	4	**4e**	98	90
6	H	H/2a	4-ClC_6H_4 (3c)	4	**4f**	92	87
7	H	H/2a	4-BrC_6H_4 (3d)	4	**4g**	95	88
8	H	H/2a	4-MeOC6H4 (3e)	6	**4h**	83	89
9	H	H/2a	4-MeC_6H_4 (3f)	6	**4i**	80	85
10	H	H/2a	3-ClC_6H4 (3g)	4	**4j**	97	84
11	H	H/2a	2-Thienyl (3h)	4	**4k**	98	84
12	H	H/2a	2-Pyridyl (3i)	4	**4l**	91	78
13	H	H/2a	1-Naphthyl (3j)	4	**4m**	98	85
14	H	H/2a	2-Pyridyl-*N*-oxide (3k)	7	**4n**	85	91
15	Me	H/2e	Ph (3a)	4	**4o**	98	88

[a] Reactions were carried out by using 0.1 mmol of two with 0.5 mmol of three in 100 μL of dioxane at 5 °C, unless stated otherwise.
[b] Determined by HPLC using chiral column and absolute configuration was assigned according to Reference.[8a]

Table 4
Aldol reaction of activated carbonyls with isatins[a]

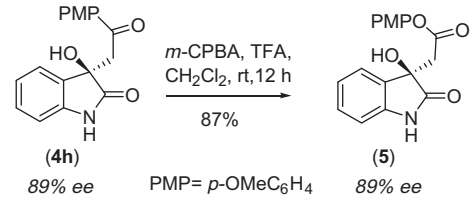


Entry	R^1	R^2	R	Time (d)	Product	Yield (%)	ee[b] (%)
1	H	H/**2a**	Me (**3l**)	4	**4p**	92	89
2	H	5-Br/**2f**	Me (**3l**)	5	**4q**	87	88
3	H	5-F/**2b**	Me (**3l**)	4	**4r**	88	89
4	H	5-Cl/**2c**	Me (**3l**)	4	**4s**	85	89
5	H	4,6-DiBr/**2d**	Me (**3l**)	5	**4t**	93	92
6	H	H/**2a**	H (**3m**)	6	**4u**	68	67[c]
7	H	5-F/**2b**	H (**3m**)	4	**4v**	73	72[c]
8	H	5-Cl/**2c**	H (**3m**)	4	**4w**	80	63[c]
9	Me	H/**2e**	H (**3m**)	4	**4x**	71	78[c]

[a] Unless otherwise stated, all reactions were carried out by using 0.1 mmol of **2** and 1 mmol of **3** in 100 μL of dioxane at 5 °C.
[b] Determined by HPLC using chiral column and the absolute configuration was assigned as per the literature method.[8a]
[c] Yield of corresponding diol after reduction of the aldehydes with $NaBH_4$.

(88–92% ee) was achieved when the reaction was performed using acetone with a variety of isatins (Table 4, entries 1–5). Modest enantioselectivity was also obtained in the case of acetaldehyde. It was heartening to note that 10 equiv of acetone and acetaldehyde gave good result as the large excess of these substrates usually required in its addition reactions.[8b,21]

While studying the scope of the reaction, we synthesized (*R*)-convolutamydine A **4t** in 92% ee and 93% yield (Table 4, entry 5).



Scheme 1. Baeyer–Villiger oxidations of Aldol adduct **4h**.

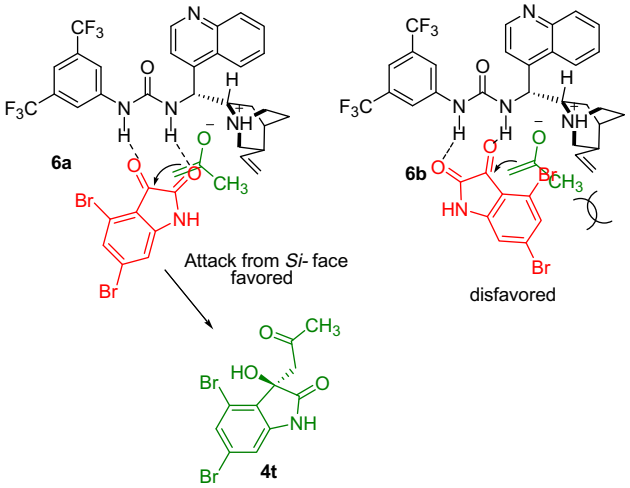


Figure 2. Proposed transition state model.

We have transformed an aldol adduct **4h** into the corresponding ester via Baeyer–Villiger oxidation[22] (Scheme 1) with no loss of enantiopurity. The ester obtained in this reaction could be used as intermediates for several convultamydins synthesis.[23]

A tentative mechanism has been proposed (Fig. 2) based on recent literature report,[5] where an enolate ion, derived from a

ketone, attacks the isatin which is activated by the H-bonding interaction with the urea moiety of the catalyst. It is clear from the transition state that attack of the enolate from *Re*-face of isatin is not preferred because of the possible steric repulsions between the aromatic part of the isatin and the quinuclidine ring, thus leading to the favorable *Si*-face attack.

In conclusion, we have developed a mild and facile soft enolate approach, which is complementary to enamine catalysis for direct aldol reaction of isatin with various unactivated and activated carbonyl compounds, catalyzed by cinchona alkaloid-based urea ligand. Employing our methodology, we have also synthesized (*R*)-convolutamydine A by an operationally simple procedure. Further studies in this direction are still under progress and will be reported in due course.

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Supplementary data

Supplementary data (general experimental procedures, characterization data including ^{1}H NMR spectra, ^{13}C NMR spectra for all new compounds and HPLC chromatograms for aldol adducts as sociated) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.013.

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