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Organocatalytic Enantioselective Cross-Aldol Reactions of Aldehydes with Isatins: Formation of Two Contiguous Quaternary Centered 3-Substituted 3-Hydroxyindol-2-ones

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Efficient catalytic asymmetric methods with the ability to create a chiral quaternary center in biologically significant molecular frameworks are of considerable importance and challenge in organic synthesis.[1] The 3-hydroxyindol-2-one structure constitutes a core unit of a number of natural products and pharmaceuticals (see Figure 1).[2] Among them

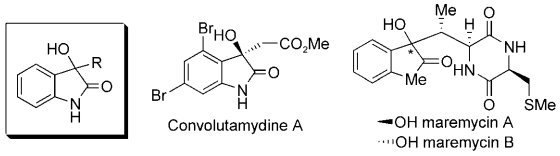

Figure 1. 3-Hydroxyindol-2-one structure.

are convolutamydines,[3a] maremycins,[3b] diazonamide A,[3c] leptosin D,[3d] *o*-hydroxyglucoisatisin,[3e] witindolinone C,[3f] TMC-95A-D,[3g] and celogentin K,[3h] arundaphine,[3i] paratunamides A–D,[3j] and neuroprotectins A and B.[3k] The reaction of readily available isatins as electrophile with an appropriate nucleophile affords a straightforward access to the chiral quaternary centered molecular architectures. The studies in this field have received increasing interest recently.[1] Notably, Malkov, Bella, and Kočovský, and Nakamura and Toru have independently reported organocatalytic asymmetric aldol reaction of isatins with acetone.[4] However, the use of aldehydes as nucleophiles for cross-aldol reactions has not been reported.[5] In this communication, we wish to disclose an organocatalytic enantioselective aldol reaction of α-branched aldehydes with isatins. Significantly, two adjacent quaternary centers are created simultaneously with high efficiency.

Aldol reactions are one of the most general and versatile methods for the formation of C–C bonds in organic synthesis.[6] The plethora of reagents, catalysts, and protocols have been developed for the synthesis of structurally diversified building blocks and targets. In recent years, significant efforts have focused on developing organocatalytic asymmetric aldol reactions.[7,8] We envision that the application of enolizable aldehydes as aldol donors and α-ketoamide isatins as acceptors in the presence of a chiral amine organic catalyst will generate 3-substituted 3-hydroxyindol-2-ones.

To demonstrate the working hypothesis, we carried out a model reaction of isatin (**1a**) with isobutyraldehyde (**2a**) in the presence of a chiral amine under neat conditions (Table 1). It was found that under the reaction conditions, the reaction efficiency varied significantly. L-Proline (**I**)[8a] and diaryl prolinol TMS ether (**II**),[9] both are the effective promoters in iminium/enamine catalysis, failed to catalyze the reaction (entries 1 and 2). The same result was observed for bisthiourea (**VII**) (entry 7).[10] Primary amine thioureas **V** and **VI**[11] could catalyze the reaction, but the product was racemic (entries 5 and 6). Among the catalysts probed, only (*S*)-pyrrolidine tetrazole (**III**)[12] exhibited 20% enantioselectivity in 18% yield (entry 3).

We then turned our attention to the optimization of **III**-catalyzed reaction conditions aimed at improving the cross-aldol reaction efficiency. Screening of solvents revealed that protic solvents were better than aprotic ones. Low reaction yields and poor *ee*s were obtained when the reaction was conducted in CH_3CN (entry 8), $CHCl_3$ (entry 9), and DMSO (entry 10). Among the protic solvents surveyed (entries 11–15), the best result was achieved in *i*PrOH. The process proceeded fast (2 h) to give the product **3a** in 70% yield and with 40% *ee* (entry 11).

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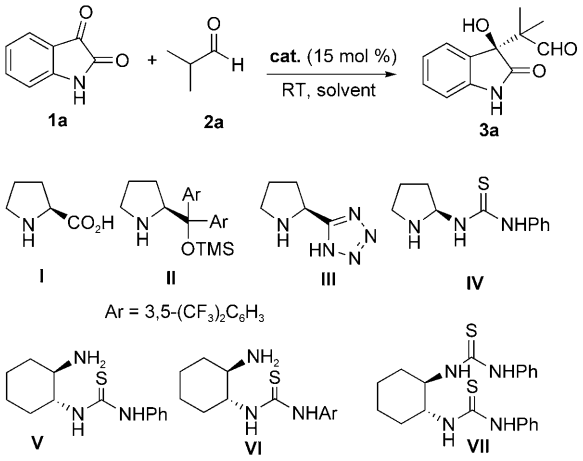
Table 1. Exploratory study of chiral amine catalyzed aldol reaction of isatin (**1a**) with isobutyraldehyde (**2a**).[a]



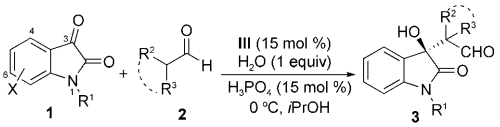
Entry	Cat	Solvent	*t* [h]	Yield [%][b]	*ee*[c]
1	**I**	–[d]	2	<5	nd[e]
2	**II**	–[d]	24	<5	nd[e]
3	**III**	–[d]	24	18	20
4	**IV**	–[d]	24	20	0
5	**V**	–[d]	4	73	0
6	**VI**	–[d]	4	89	0
7	**VII**	–[d]	24	<5	nd[e]
8	**III**	CH_3CN	24	55	27
9	**III**	$CHCl_3$	24	<5	nd[e]
10	**III**	DMSO	24	20	50
11	**III**	*i*PrOH	2	70	40
12	**III**	H_2O	24	<5	nd[e]
13	**III**	EtOH	2	91	30
14	**III**	$(CH_3)_3COH$	2	68	33
15	**III**	$HO(CH_2)_2OH$	1.5	68	19

[a] Reaction conditions: unless specified, see Experimental Section. [b] Yields of isolated product. [c] Determined by chiral HPLC analysis. [d] Under neat conditions. [e] Not determined.

Further optimization of reaction conditions using *i*PrOH as solvent was carried out next. A survey of additives revealed that they played a certain role in governing reaction yields and enantioselectivity (Table 2). Water as an additive was beneficial to the process in terms of enantioselectivity (entry 1). Among the acids probed (entries 2–5), it was observed that phosphoric acid was the best (entry 5) and both reaction yield (92%) and enantioselectivity (73%) were improved dramatically. Lowering the reaction temperature resulted in a further improvement of the enantioselectivity (84%) without sacrificing the yield although with an extension of the reaction time (24 h, entry 6). In addition, it was noted that slow addition of isatin (**1a**) was necessary for obtaining a higher *ee* without affecting the yield. These studies provided the optimal reaction conditions: addition of isatin (**1a**) to a solution of isobutyraldehyde (**2a**) in *i*PrOH in the presence of 15 mol% **III**, 100 mol% water, and 15 mol% phosphoric acid at 0°C.

Having established the optimal reaction conditions, we determined the scope of the reaction with a variety of isatins (**1**) and aldehydes (**2**) (Table 3). In general, the **III**-catalyzed asymmetric cross-aldol reactions proceeded smoothly to generate products with the formation of two contiguous quaternary centers, which are otherwise very difficult to construct. It appears that the electronic effect and steric hindrance have an influence on the reaction yield and enantioselectivity (entry 1 vs 2–6). The steric effect slowed down the reaction (entry 5) and also affected the enantioselectivity. The substitution pattern also had roles in the reaction yield and enantioselectivity (entries 2–6), indicative of the sensitive nature of the substrate structures. A cyclic aldehyde could engage in the process ef-

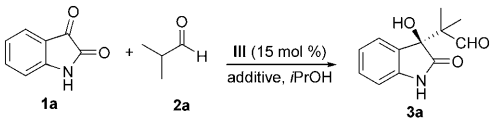
Table 3. Scope of **III**-catalyzed cross-aldol reactions of isatins (**1**) with aldehydes (**2**).[a]



Entry	X, R^1, R^2, R^3, **3**	*t* [h]	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	H, H, Me, Me, **3a**	24	92	84(>97)[e]	–
2	4-Me, H, Me, Me, **3b**	48	50	75	–
3	5-F, H, Me, Me, **3c**	26	74	60	–
4	5-Cl, H, Me, Me, **3d**	29	83	80	–
5	7-Cl, H, Me, Me, **3e**	72	46	49	–
6	6-Br, H, Me, Me, **3f**	120	69	79	–
7	H, H, -$(CH_2)_4$-, **3g**	40	86	70[f]	–
8	H, Bn, Me, Me, **3h**	52	92	76	–
9	H, H, H, Me, **3i**	3	80	98[g]	3:2
10	H, H, H, *n*Bu, **3j**	3	69	90[g]	7:5
11	4-Br, H, H, Me, **3k**	3	86	90	8:1
12	4, 6-Br_2, H, H, Me, **3l**	3	70	93[g]	7:1

[a] Reaction conditions: unless specified, see Experimental Section and Supporting Information. [b] Yields of isolated product. [c] Determined by chiral HPLC analysis. [d] Determined by ^1H NMR. [e] After recrystalization. [f] Determined by converting to corresponding alcohol. [g] 2 equiv of aldehyde used.

Table 2. Effect of additives on the **III**-catalyzed cross-aldol reaction of isatin (**1a**) and isobutyraldehyde (**2a**) in *i*PrOH.[a]



Entry	Additives	*t* [h]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	100 mol% H_2O	4	RT	72	50
2	15 mol% HOAc+100 mol% H_2O	5	RT	68	60
3	15 mol% TFA+100 mol% H_2O	4	RT	75	76
4	15 mol% H_3BO_3+100 mol% H_2O	4	RT	85	65
5	15 mol% H_3PO_4 (85%)+100 mol% H_2O	4	RT	92	73
6	15 mol% H_3PO_4 (85%)+100 mol% H_2O	24	0	92	84

[a] Reaction conditions: unless specified, see Experimental Section. [b] Yields of isolated product. [c] Determined by chiral HPLC analysis.

ficiently (entry 7). We also probed the effect of the substituents on the nitrogen on the reaction and it was found that such an influence was minimal (entries 1 and 8). Finally, the structural variation of aldehyde donors was examined with linear structures (entries 9–12). The reactions occurred faster (3 h) and two stereogenic centers were created in high yields (69–86%) and with high enantioselectivities (90–98% *ee*), albeit low *dr*. It appeared that the *dr* was significantly influenced by the steric effect. A high *dr* was observed with more sterically hindered substrates (entries 9 and 10 vs 11 and 12). The absolute and relative stereochemistry of the products were determined by a comparison with a known compound **3l** in terms of optical rotation value and sign.[5] It was realized that the *ee* value could be readily improved by recrystallization (entry 1), thus enhancing its synthetic utility.

In conclusion, we have a (*S*)-pyrrolidine tetrazole catalyzed cross-aldol reactions of isatins with aldehydes. In the process, two highly hindered contiguous quaternary centers and one chiral carbon are created with good efficiency. The protocol, which is applicable for both α-branched and linear aldehydes as aldol donors, is complementary to that reported recently by Nakamur, Toru, and co-workers, which is only effective for linear aldehydes.[5] Further investigations of the valuable catalytic asymmetric aldol reactions aimed at improving yields and enantioselectivity are currently being pursued in our laboratory.

Experimental Section

Typical procedure for the aldol reaction using **3a** as an example (Table 3, entry 1): To a mixture of **III** (15 mol%, 4.3 mg), isobutyraldehyde (**2a**) (1.0 mmol, 90 μL), and water (0.20 mmol, 3.6 μL), and 85% phosphoric acid (15 mol%, 1.6 μL) in *i*PrOH (0.5 mL) was added isatin (**1a**) (30 mg, 0.20 mmol) over 1 h in portions at 0 °C. After stirring for 24 h, the solvent was removed under reduced pressure to give a residue that was directly purified by column chromatography (hexane/ethyl acetate = 3:1) giving **3a** (41 mg, 92%). Single recrystallization of **3a** from hexane/ethyl acetate afforded > 97% *ee*.

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Keywords: aldehydes · aldol · isatins · organocatalysis

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