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Asymmetric cross aldol addition of isatins with α,β-unsaturated ketones catalyzed by a bifunctional Brønsted acid–Brønsted base organocatalyst

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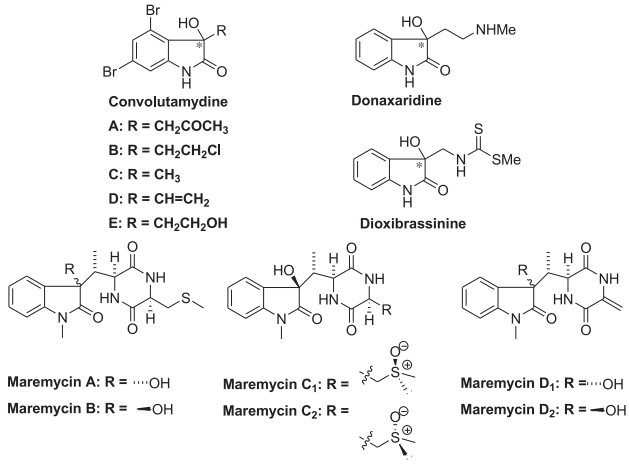
ABSTRACT

The asymmetric cross-aldol reaction of isatins with α,β-unsaturated ketones has been developed under catalysis by a *Cinchona alkaloid*-derived bifunctional Brønsted acid–Brønsted base catalyst, affording the aldol adducts in moderate to good yields (18–98%) with moderate to good enantioselectivities (30–97%). The noncovalent organo-catalyzed asymmetric cross-aldol reaction displays a broad substrate scope and wide functional-group tolerability, albeit the electronic and steric properties of both reaction partners have considerable and regular effects on the reactivity and stereocontrol.

1. Introduction

The asymmetric intermolecular cross-aldol reactions between aldehydes and aldehydes or aldehydes and ketones have been proved important access to carbon–carbon formation, which has been extensively explored for construction of chiral β-hydroxy aldehydes or β-hydroxy ketones in organically synthetic chemistry.[1] In contrast, enantioselective intermolecular cross-aldol reaction between ketones, which produces 3-substituted-3-hydroxy ketones with quaternary stereogenic centres, is much more demanded and challenged.[2]

The 3-hydroxyindolin-2-one structural cores with quaternary stereogenic centres are widely existed in natural products, pharmaceuticals, agrochemicals, indole alkaloids and synthetic indole derivatives.[3] Moreover, these natural products containing 3-hydroxyindolin-2-one cores display invaluable biological and pharmacological activity,[4] such as convolutamydines A–E,[5a] donaxaridine,[5b] dioxibrassinine,[5c] maremycins A–D,[5d] diazonamide A,[5e] leptosin D,[5f] spiro-isoxazolidynyl oxindole,[5g] witindolinone C,[5h] madindoline A and B,[5i,j] and CPC-1,[5k] and efavirenz mimics[5l] (selected structures see Scheme 1). In addition, recent structure–activity relationship studies have shown that the quaternary configuration of the C3 hydroxyl group and the substituent of the oxindole greatly affects the biological and pharmacological activities of those compounds.[3a]



Scheme 1. Selected 3-hydroxyindolin-2-one structures in natural products.

As convolutamydine A shows the potent inhibitory activity towards the differentiation of HL-60 human promyelocytic leukaemia cells, the construction of stereocontrolled tetrasubstituted 3-hydroxyindolin-2-one motifs has attracted great interests of the chemists.[6] Particularly, the methods for enantioselective synthesis

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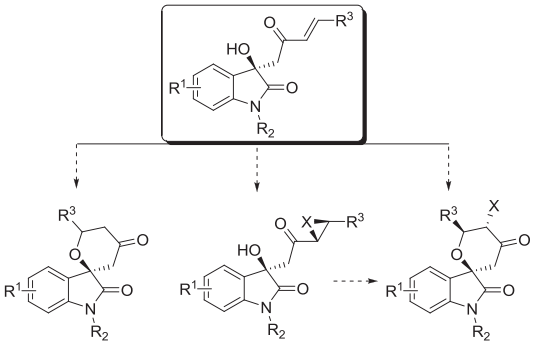
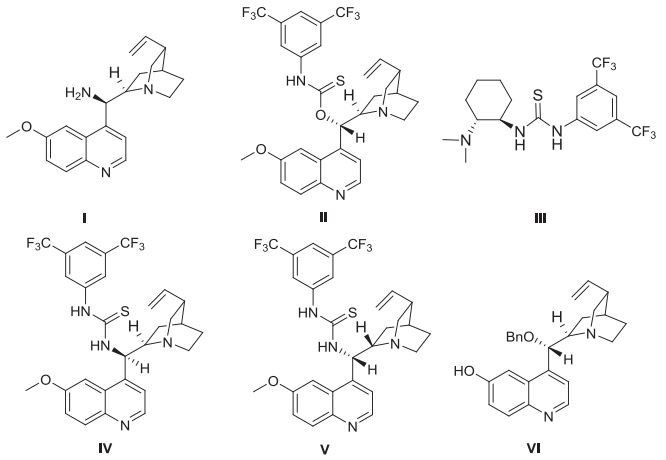
of convolutamydine became very prevalent in the presence of organocatalyst. In 2006, Tomasini[7] and co-workers pioneerly reported the cross-aldol reaction of isatins with acetone by using dipeptide organocatalyst derived from D-proline and L-β-homophenylgricine. Xiao,[8] Malkov, Bella and Kočovský,[9] Nakamura and Toru[10] independently reported enantioselective cross-aldol reaction of isatins with acetone catalyzed by primary or secondary amine catalysts. Recently, Zhao disclosed that quinidine thiourea as a new noncovalent catalyst could efficiently catalyzed the cross-aldol reaction of isatins with unactivated ketones in THF at −5 °C for 3–6 days, which provided the 3-alkyl-3-hydroxyindolin-2-ones in high yields with high enantioselectivities.[11] Although the enantioselective cross-aldol reaction between isatins and ketones has been extensively studied, few examples of the corresponding aldol reactions of various α,β-unsaturated ketones with isatins were found in the literature.

The aldol addition of α,β-unsaturated ketone to isatin leads to 3-aryl-3-hydroxyindolin-3-one with an additional enone moiety, to provide a chance for further elaboration of the products (Scheme 2). In addition, the obvious difficulty in using α,β-unsaturated ketones as a nucleophile is arising from the inherent multiple reactivity that involve ketone, β-carbon (electrophilic sites) and active methylene unit (nucleophilic site). In order to selectively achieve targeted cross aldol-type reaction chemoselective activation of the carbonyl in isatin should be a key point. In virtue of limited examples reported by Zhao, herein, we investigate the asymmetric cross-aldol reaction between α,β-unsaturated ketones and isatins in the presence of thiourea-modified *Cinchona alkaloids* as bifunctional Brønsted acid–Brønsted base catalysts, which provides enantiomerically enriched 3-hydroxy-3-(2-oxo-4-arylbut-3-en-1-yl) indolin-2-ones in moderate to high yields (up to 98%) and moderate to good enantioselectivities (up to 97% ee). Both enantiomers of the 3-hydroxyindolin-3-one adducts can be prepared by using two epimers of the quinidine-derived thiourea catalysts. An investigation of the electronic and steric effect on the stereochemical outcome is also detailed.



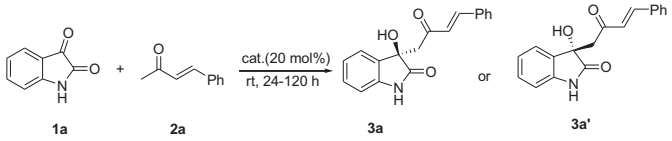
Scheme 2. Further elaboration of 3-hydroxy-3-(2-oxo-4-arylbut-3-enyl)indolin-2-one product.

Initially, several common organocatalysts (Scheme 3) bearing a quinuclidine and/or a thiourea moiety,[12] were examined for the catalysis of the cross-aldol reaction of isatin **1a** as an acceptor and (*E*)-4-phenylbut-3-en-2-one **2a** as a donor with a catalyst loading of 20 mol % in THF at ambient temperature. The results of the screening and optimizations are shown in Table 1. At the beginning, we examined the reaction substrates of isatin **1a** with the benzylideneacetone **2a** with the molar ratio of 1:1 in the presence of 20 mol % of quinidine-derived primary amine or combination with 40 mol % of trifluoro acetic acid (TFA) as Brønsted acid additives. No expected cross aldol adducts were observed after direct determination by TLC (entries 1 and 2). This indicated that it is impossible for the cross-aldol reaction in which the primary amine



Scheme 3. Catalysts screened for the cross-aldol reaction of isatins with α,β-unsaturated ketones.

Table 1
Catalyst screening and reaction conditions optimization[a]



Entry	Cat.	Solv.	Ratio (**1a**/**2a**)	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	**I**	THF	1:1	24	NR	—
2[d]	**I**+**TFA**	THF	1:1	24	NR	—
3[d]	**II**	THF	1:1	120	Trace	—
4[d]	**III**	THF	1:1	48	70	63
5[d]	**IV**	THF	1:1	24	46	75
6	**IV**	THF	1:2	24	51	79
7	**IV**	THF	1:2	48	82	80
8[d]	**V**	THF	1:1	48	75	60
9	**V**	THF	1:2	48	78	71
10	**VI**	THF	1:2	48	34	31
11	**IV**	Toluene	1:2	48	52	33
12	**IV**	DCM	1:2	48	58	47
13	**IV**	Et_2O	1:2	48	56	38
14	**IV**	*n*-Hexane	1:2	48	35	45
15	**IV**	EtOH	1:2	48	68	47
16	**IV**	Dioxane	1:2	48	69	76

[a] Unless otherwise indicated, all reactions were carried out with isatin **1a** (0.10 mmol), benzylideneacetone **2a** (0.20 mmol) and the catalyst (0.04 mmol, 20 mol %) in the specified solvent (1.0 mL) at room temperature.
[b] Yield of the isolated product after column chromatography.
[c] Determined by HPLC analysis. Absolute configuration of **IV** for *R* enantiomer and **V** for *S* enantiomer were determined according to the literature reported.[11,14]
[d] Carried out with isatin **1a** (0.20 mmol) and **2a** (0.20 mmol).

catalyst unilaterally activates the benzylideneacetone **2a** to form an enamine intermediate. Then, we turned our attention to other chiral Brønsted acid–Brønsted base bifunctional catalysts. The *Cinchona alkaloid* derived bifunctional catalyst **II** was found to be ineffective for the reaction, affording essentially only trace amount of the desired products after prolonged reaction times (5 days, entry 3). Pleasingly, the reaction proceeded smoothly in the presence of 20 mol % Takemoto thiourea catalyst **III** to afford the desired aldol product **3a** in 70% yield with 63% ee after 48 h (entry 4).[13] Subsequently, the quinidine-derived thiourea catalyst **IV** and its pseudo-enantiomer **V** were investigated for this transformation, which furnished the desired product with improvement in both yields and enantioselectivities (**IV**: 82% yield and 80% ee; **V**: 78% yield and 71% ee, respectively) after 48 h of reaction time, while the reactant's molar ratio of **1a**/**2a**=1:2 was employed (entry 7 vs