Organocatalysis

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Quinidine Thiourea-Catalyzed Aldol Reaction of Unactivated Ketones: Highly Enantioselective Synthesis of 3-Alkyl-3-hydroxyindolin-2-ones**

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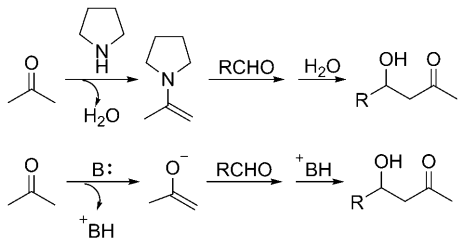
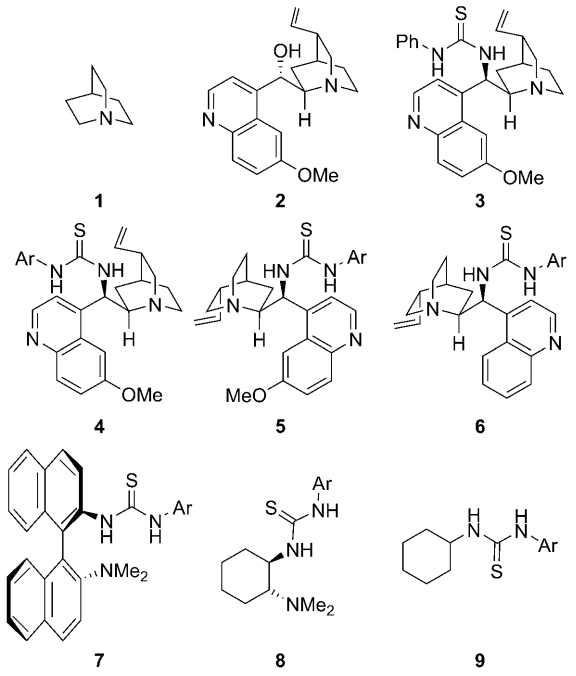
The aldol reaction is one of the most important carbon–carbon bond formation reactions[1] and, therefore, many asymmetric variants of this reaction have been developed in the past.[1] Since List and Barbas discovered the proline-catalyzed cross-aldol reaction of ketones and aldehydes,[2] many amine derivatives, mainly proline derivatives, have been developed for asymmetric cross-aldol reactions.[3] Mechanistically, these catalysts activate the ketones or enolizable aldehydes through the formation of an enamine intermediate (Scheme 1, upper equation).[3] The mechanism



Scheme 1. Aldol reactions involving the enamine or enolate intermediates.

is usually a combination of both covalent and noncovalent catalyses, since most of these catalysts also contain a hydrogen-bonding moiety to direct the approach of the enamine acceptor. In contrast, although enol and enolate (Scheme 1, lower equation) are the active intermediates in the original aldol reactions,[4] organocatalyzed enantioselective direct aldol reaction of unactivated ketones through the enolate mechanism is very difficult, because the acidity of the α proton in these ketones is very low. To our knowledge, there has been no such report.[5–7] Nevertheless, the enolate mechanism does have certain advantages, especially when the formation of an enamine is difficult. During our study of using activated ketone compounds as the enamine acceptors for organocatalyzed aldol reactions,[8] we envisioned that such an organocatalyzed enolate-mediated aldol reaction should be possible if the enolate acceptor is sufficiently activated, because the equilibrium favors the formation of the product with such a substrate. Herein, we report the first enantioselective aldol reaction of unactivated ketones involving the enolate mechanism, which may be used for the highly enantioselective synthesis of 3-alkyl-3-hydroxyindolin-2-ones.[9]

The enamine-mediated aldol reactions of isatins and ketones or enolizable aldehydes have been used in recent years for the synthesis of 3-alkyl-3-hydroxyindolin-2-ones,[10] which are important biologically active natural products and medicinal compounds.[11] Since isatin contains an activated ketone group, we tested our hypothesis with isatin (**10a**) and acetone (**11a**) as the model substrates, and some tertiary amines (**1**–**8**) as the catalysts (Scheme 2). The results of the catalyst screening and optimizations are presented in Table 1.



Scheme 2. Catalysts screened for the cross-aldol reaction of isatin and acetone [Ar = 3,5-$(CF_3)_2C_6H_3$].

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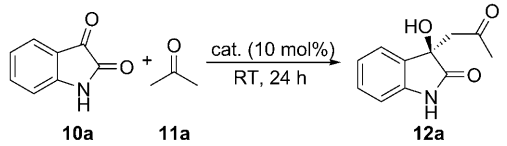
Table 1: Catalyst screening and reaction conditions optimization.[a]



10a **11a** **12a**

Entry	Catalyst	Solvent	**10a** [equiv]	Time [days]	Yield [%][b]	*ee* [%][c]
1	**1**	acetone	–	1	78	–
2	**2**	acetone	–	1	84	2
3	**3**	acetone	–	1	80	61
4	**4**	acetone	–	1	98	68
5	**5**	acetone	–	1	99	57[d]
6	**6**	acetone	–	1	98	57[d]
7	**7**	acetone	–	1	trace	–
8	**8**	acetone	–	1	98	40
9	**9**	acetone	–	1	0	–
10	**4**	benzene	7	4	56	56
11	**4**	CH_2Cl_2	7	4	46	53
12	**4**	THF	7	4	58	82
13	**4**	Et_2O	7	4	60	76
14	**4**	dioxane	7	4	64	70
15	**4**	CH_3CN	7	4	22	67
16	**4**	AcOEt	7	4	trace	–
17	**4**	DMSO	7	4	trace	–
18	**4**	hexane	7	4	trace	–
19	**4**	DME	7	4	15	77
20	**4**	MeOH	7	4	49	31
21	**4**	THF	30	4	98	80
22	**4**	THF	30	4	23	86[e]
23	**4**	THF	70	4	73	86[e]
24	**4**	THF	70	6	97	85[e]

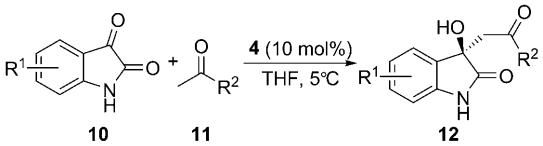
[a] Unless otherwise indicated, all reactions were carried out with isatin (0.10 mmol), acetone, and the catalyst (0.01 mmol, 10 mol%) in the specified solvent (1.0 mL for acetone; 2.0 mL for THF and other solvents) at room temperature. [b] Yield of the isolated product after column chromatography. [c] Determined by HPLC analysis. Absolute configuration was assigned according to reference [10c]. [d] The *S* enantiomer was obtained. [e] Carried out at 5°C. DMSO = dimethyl sulfoxide, DME = dimethoxyethane.

With acetone as the solvent, the reaction catalyzed by quinuclidine (**1**) gave a good yield of the desired **12a** (Table 1, entry 1). Quinidine (**2**) is similarly reactive, but the *ee* value obtained was poor (Table 1, entry 2). In contrast, quinidine-derived thioureas[12] **3** and **4** gave much improved *ee* values for the *R* enantiomer (61 and 68%, respectively; Table 1, entries 3 and 4). As expected, quinine thiourea (**5**) and cinchonidine thiourea (**6**) led to the formation of the *S* enantiomer (57% *ee*, Table 1, entries 5 and 6). High yields of **12a** were also obtained for these four catalysts. Nonetheless, with thiourea **7**, only a trace amount of **12a** was formed (Table 1, entry 7). This was probably because of the lower basicity of **7**. Takemoto thiourea **8** is more reactive, but the *ee* value obtained was lower (Table 1, entry 8). However, a simple thiourea **9** that has no basic moiety does not catalyze the reaction (Table 1, entry 9). This result excludes the possibility of the involvement of an enol intermediate in this reaction.

Since the reaction is catalyzed by **1** (Table 1, entry 1) and not by **9** (Table 1, entry 9), it most likely works through the enolate mechanism. If this is the case, the reaction must be a complete *noncovalent* catalysis. With the best catalyst **4**, further optimizations (Table 1, entries 10–20) identified THF as the best solvent for this reaction, in which the *ee* value was improved to 82% (Table 1, entry 12). All the other solvents screened led to less satisfactory results. The product yield could be improved to 98% by using more acetone (30 equiv, Table 1, entry 21). The *ee* value was improved to 86% when the reaction was carried out at 5°C, at the cost of the reactivity (Table 1, entry 22).[13] Luckily, the lost reactivity could be remedied by employing more acetone (70 equiv) and prolonging the reaction time to 6 days, without affecting the enantioselectivity (Table 1, entries 23 and 24).

Next the scope of this reaction was studied and the results are summarized in Tables 2 and 3. As shown in Table 2, with acetone as the substrate, various substituted isatins may be applied in this reaction. Excellent yields and high *ee* values (≥79% *ee*) of the expected products were obtained (Table 2, entries 1–6). The electronic nature of the substituent and its position on the isatin phenyl ring show some influences on the enantioselectivities. For example, the *ee* value of 4-bromoisatin **12c** (Table 2, entry 3) is much higher than that of 6-bromoisatin **12e** (Table 2, entry 5). Acetophenone (**11b**) is a tough substrate for the enamine mechanism because of its low electrophilicity[14] and it has never been used in the asymmetric aldol reaction with isatin. However, as is evident from the results in Table 2, **11b** is even more reactive than acetone under our conditions (only 10 equiv ketone is necessary), and

Table 2: Cross-aldol reaction of isatins and ketones.[a]

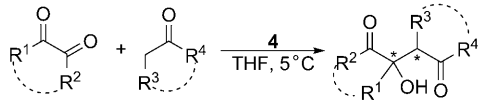


10 **11** **12**

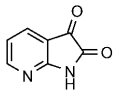
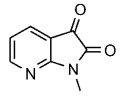
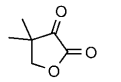
Entry	R^1/**10**	R^2/**11**	Time [days]	**12**/Yield [%][b]	*ee* [%][c]
1	H/**a**	Me/**a**	6	**a**/97	85
2	4-Cl/**b**	Me/**a**	4	**b**/98	87
3	4-Br/**c**	Me/**a**	4	**c**/99	91
4	5-F/**d**	Me/**a**	5	**d**/99	85
5	6-Br/**e**	Me/**a**	4	**e**/99	79
6	5,7-Br_2/**f**	Me/**a**	5	**f**/99	83
7	H/**a**	Ph/**b**	6	**g**/75	90
8	4-Cl/**b**	Ph/**b**	5	**h**/98	95
9	4-Br/**c**	Ph/**b**	5	**i**/98	97
10	5-F/**d**	Ph/**b**	4	**j**/99	86
11	6-Br/**e**	Ph/**b**	5	**k**/98	84
12	4,7-Cl_2/**g**	Ph/**b**	5	**l**/98	92
13	H/**a**	1-Np/**c**	6	**m**/70	86
14	H/**a**	2-Np/**d**	5	**n**/98	90
15	H/**a**	*E*-MeCH=CH/**e**	6	**o**/76	87
16	H/**a**	*E*-PhCH=CH/**f**	4	**p**/98	91
17	H/**a**	H/**g**	3	**q**/82[d]	73[e]

[a] All reactions were carried out with **10** (0.10 mmol), the ketone **11** (7.0 mmol for acetone and 1.0 mmol for acetophenone), and catalyst **4** (0.01 mmol, 10 mol%) in THF (2.0 mL) at 5°C. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analyses. [d] Yield of the corresponding diol after reduction of the primary product with $NaBH_4$. [e] Determined by HPLC analysis of the corresponding diol.

Table 3: Cross-aldol reaction of activated carbonyl compounds and ketones.[a]



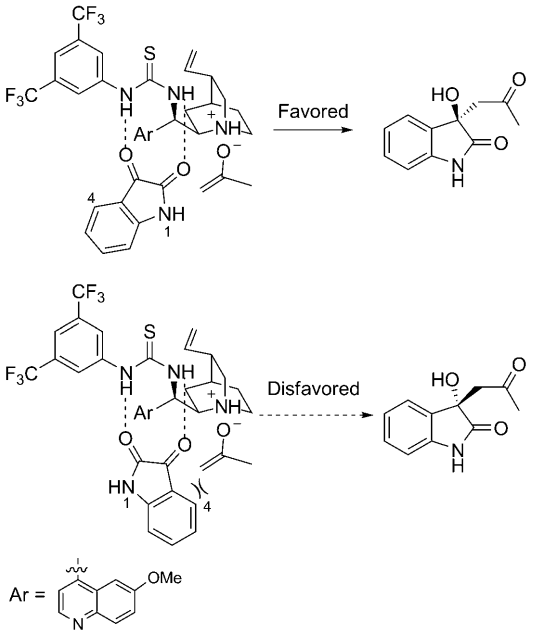
13 11 14

Entry	13		11		14/Yield [%][b]	*ee* [%][c]
1		/a	b		a/60	90
2		/b	a		b/90	61
3			b		c/78	76
4		/c	b[d]		d/41	74
5	$PhCOCHO{\cdot}H_2O$	/d	a[e]		e/46[f]	56
6	$PhCOCHO{\cdot}H_2O$	/d		/h	f/54[g,h]	93[i]

[a] Unless otherwise indicated, all reactions were carried out with **13** (0.10 mmol), **11** (7.0 mmol for **11a** and 1.0 mmol for **11b**), and catalyst **4** (0.01 mmol, 10 mol%) in THF (2.0 mL) at 5°C for 6 days. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analyses. [d] The reaction was carried out at room temperature. [e] The reaction was carried out for 4 days with THF (0.2 mL) as the solvent. [f] The product of this reaction is 2-hydroxy-1-phenylpentane-1,4-dione (**14e**). [g] The reaction was carried out in cyclohexanone (**11h**, 1.0 mmol) as the solvent for 2 days; the product of this reaction is 2-(1-hydroxy-2-oxo-2-phenylethyl)cyclohexanone (**14f**). [h] Total yield of two inseparable diastereomers; the diastereomeric ratio (*anti*/*syn*) was determined to be 86:14 according to ^{1}H NMR analysis of the crude product. The relative stereochemistry of these products was assigned according to reference [15]. [i] Value of the major *anti* diastereomer.

the *ee* values obtained for the products are also higher than those of the corresponding acetone products (Table 2, entries 7–12). The observed higher reactivity is in accord with the increased acidity of the acetophenone α proton. Other aryl methyl ketones, such as acetonaphthones **11c** and **11d**, also give very good results (Table 2, entries 13 and 14). Excellent results were also obtained for α,β-unsaturated ketones (*E*)-3-penten-2-one (**11e**) and (*E*)-4-phenyl-3-buten-2-one (**11f**) (Table 2, entries 15 and 16). Besides ketones, acetaldehyde (**11g**) may also be applied in this reaction. Since the corresponding aldol product **12q** is not very stable, it was reduced in situ with $NaBH_4$ to give the corresponding diol in 82% yield. The *ee* value of this diol was determined to be 73% (Table 2, entry 17).

In addition to isatins, other activated carbonyl compounds may also be used as the substrates in this reaction. As is evident from the results collected in Table 3, the aldol reaction of 7-azaisatin (**13a**) with acetophenone (**11b**) gives the expected **14a** in 60% yield and 90% *ee* (Table 3, entry 1). These results are comparable to those of isatin (Table 2, entry 7). Similarly, the aldol reaction of 1-methyl-7-azaisatin (**13b**) with acetone (**11a**) and acetophenone (**11b**) yields the desired products **14b** and **14c** in 90 and 78% yields, respectively. The *ee* values of these two products were determined to be 61 and 76% *ee*, respectively (Table 3, entries 2 and 3). The lower *ee* value obtained with **13b** (Table 3, entry 3) relative to **13a** (Table 3, entry 1) was most likely due to the steric effects of the *N*-methyl group in **13b**, which may be easily rationalized with our proposed mechanism in Scheme 3.



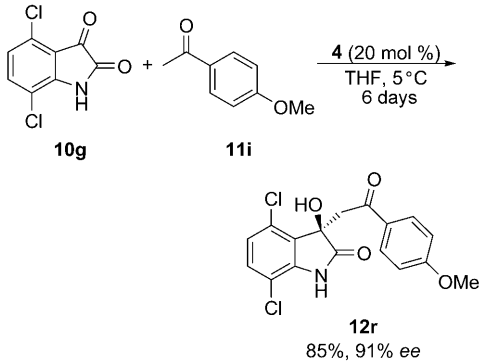
Scheme 3. Proposed transition states for the aldol reaction of isatin and acetone.

Other active carbonyl derivatives, such as 4,4-dimethyldihydrofuran-2,3-dione (**13c**) and phenylglyoxal hydrate (**13d**), may also be applied in this reaction. The reaction of **13c** with **11b** leads to the desired product **14d** in 41% yield and 74% *ee* (Table 3, entry 4). Compound **13d** has both a ketone and an aldehyde group; nonetheless, only the aldehyde group reacts in the cross-aldol reactions with acetone (**11a**) and cyclohexanone (**11h**). With acetone (**11a**) as the substrate, the product 2-hydroxy-1-phenylpentane-1,4-dione (**14e**) was obtained in 46% yield and 56% *ee* (Table 3, entry 5). When cyclohexanone (**11h**) was used as the substrate, the reaction gave **14f** as a mixture of *anti* and *syn* diastereomers[15] in 54% yield, with an *anti*/*syn* ratio of 86:14. The major *anti* diastereomer was obtained in a high *ee* value of 93% (Table 3, entry 6). To our knowledge, this is first example of an enantioselective cross-aldol reaction of phenylglyoxal hydrate that yields the *anti* diastereomer as the major product.[16]

A plausible mechanism of this reaction is proposed to account for the observed enantioselectivity in the isatin–acetone cross-aldol reaction. As shown in Scheme 3, acetone is deprotonated by the tertiary amine in the quinidine thiourea catalyst backbone. After deprotonation, the enolate associates closely with the catalyst through ionic interactions. On the other hand, two hydrogen bonds are formed between

the isatin carbonyl groups and the thiourea moiety of the quinidine thiourea catalyst. Besides activating the ketone group for the enolate attack, these hydrogen bonds also direct the approach of isatin. Among the two possible orientations of isatin, the *re* face orientation (Scheme 3, top left) is favored since the unfavorable interaction between the isatin benzene ring and the enolate is avoided. Attacking of the enolate to the *si* face of the isatin ketone group leads to the observed major *R* enantiomer. These proposed transition states predict that an increase of the steric bulkiness at position 1 of isatin will lead to lower enantioselectivity, while an increase of the steric bulkiness at position 4 will lead to higher enantioselectivity. As shown by the results (Table 3, entry 3 versus entry 1; Table 2, entries 2 and 3 versus entry 1), this is indeed the case, which lends some support to this mechanism.

To show the utility of the current method, we developed the first enantioselective synthesis of 3-hydroxyindolin-2-one **12r**, which is the lead compound for treating Ewing's sarcoma discovered most recently by Toretsky and co-workers.[17] As shown in Scheme 4, when isatin **10g** and 4′-methoxyacetophenone (**11i**, 20 equiv) were allowed to react in the presence of catalyst **4** (20 mol%) under optimized conditions, the desired product **12r** was obtained in 85% yield and 91% *ee*.[18]



Scheme 4. Enantioselective synthesis of 3-hydroxyindolin-2-one (**12r**).

In summary, we have developed the first organocatalyzed asymmetric aldol reaction of unactivated ketones and activated carbonyl compounds on the basis of a new noncovalent catalysis mechanism involving the enolate intermediate by using quinidine thiourea as the catalyst. The method is complementary to the enamine-based organocatalyzed aldol reactions and works well in cases where the enamine mechanism has difficulties. The reaction may be utilized for the highly enantioselective synthesis of biologically significant 3-alkyl-3-hydroxyindolin-2-ones.

Experimental Section

General procedure for the aldol reaction of isatins with ketones: The organocatalyst **4** (5.9 mg, 0.01 mmol, 10 mol%) and isatin **10** (0.10 mmol) were stirred in THF (2.0 mL) for 10 min at 5 °C. The corresponding ketone **11** (7.0 mmol for acetone or 1.0 mmol for other methyl ketones) was added and the mixture was stirred at 5 °C for the time given in the tables. The solvent was then removed under reduced pressure and the mixture was purified by flash column chromatography on silica gel (1:1 hexane/ethyl acetate) to give the desired aldol product.

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Keywords: aldol reaction · enantioselectivity · ketones · organocatalysis · reaction mechanisms

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