Primary 1,2-Diamine Catalysis (V): Efficient Asymmetric Aldol Reactions of Isatins with Cyclohexanone

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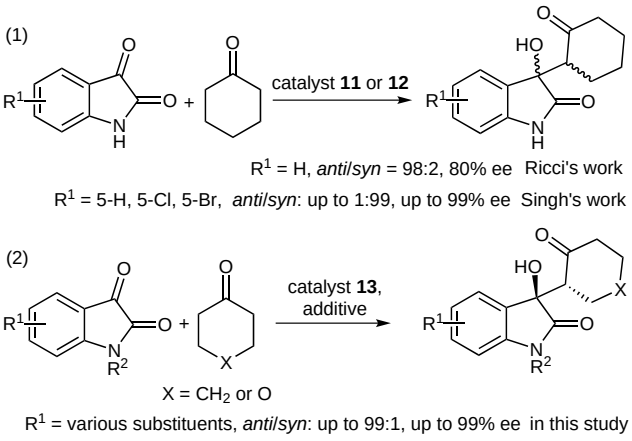
Abstract: 1,2-Diaminocyclohexane-hexanedioic acid has been demonstrated to catalyze the asymmetric aldol reactions of cyclo-ketones and various isatin derivatives efficiently in MeOH–H_2O. The corresponding products were obtained in good yields (70–90%) with high diastereoselectivity (up to 99:1 *anti*/*syn*) and enantio-selectivity (up to 99% ee).

Key words: asymmetric aldol reaction, diaminocyclohexane, organocatalyst, isatin

The 3-substituted-3-hydroxyindolin-2-ones **1**–**5** are a class of compounds (Figure 1) with an indole skeletal structure, which are found in several biologically active alkaloids and pharmacological agents.[1] Owing to the significance of this structural motif, numerous methodologies have been developed and continue to be explored for the construction of this structure.[2] Most methods involve the use of expensive or toxic metal reagents as catalysts.

In light of the great progress made in organocatalytic asymmetric aldol reaction, there has been an increasing interest in applying this reaction for the synthesis of chiral 3-substituted-3-hydroxyindolin-2-ones in recent years. For example, several efficient organocatalysts (Figure 2), such as **6**,[3] **7**,[4] **8**,[5] **9**,[6] **10**,[7] have been reported. While non-cyclic ketones and aldehydes as donors have been widely investigated, to the best of our knowledge, there are only two reports on the organocatalytic asymmetric aldol reaction of cyclohexanone and isatins. Moreover, examples of isatin derivatives as acceptors reacting with cyclic ketones are also scant. Ricci's group[8] only reported one example of cyclohexanone reacting with isatin to afford the oxindole in a *anti*/*syn* ratio of 98:2 with 80% ee during their investigation of using chitosan (**11**) as the asymmetric aldol reaction catalyst (reaction 1, Scheme 1). Singh's group[9] carried out the enantioselective synthesis of 3-substituted-3-hydroxy-indolin-2-ones, which are quite promising in the field of medicinal chemistry, with three isatin derivatives as acceptors by using a primary–tertiary diamine–Brønsted acid catalyst **12**.



Scheme 1 Aldol reactions of istans with various ketones or aldehydes

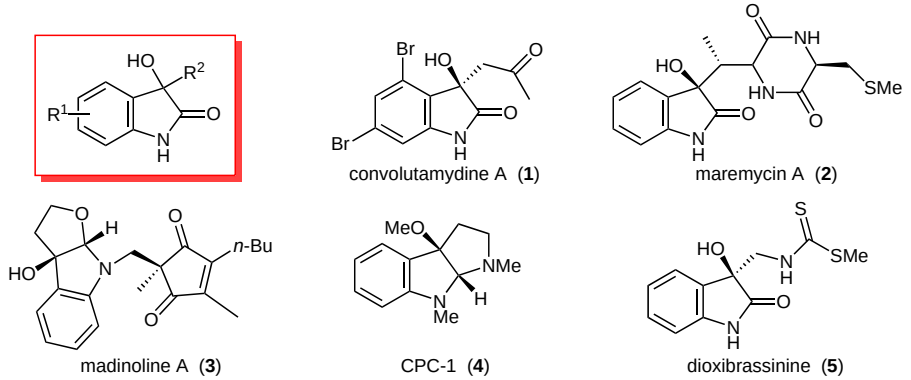


Figure 1 Examples of biologically active 3-substituted-3-hydroxy indole-2-ones

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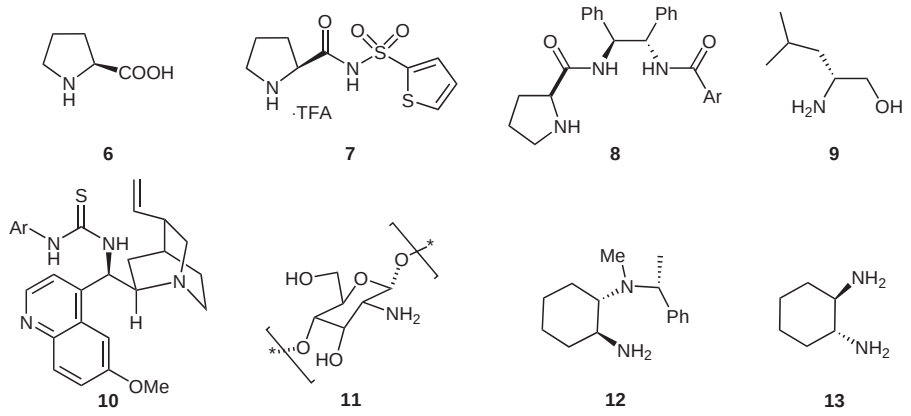


6 7 8 9 10 11 12 13

Figure 2 Structures of some organocatalysts

Because catalytic, intermolecular ketone–ketone cross-aldol reactions are still rare and represent a significant challenge for the chemists,[6] herein we report an efficient asymmetric aldol reaction of cycloketones with various isatin derivatives catalyzed by vicinal primary diamine salts in good yields, excellent diastereoselectivities and enantioselectivities.

In our previous studies, the simple and commercially available chiral 1,2-diaminocyclohexane (**13**) was found to be an effective organocatalyst in Michael addition reactions. Reactions of γ-butenolides[10] and cyclopentanone[11] with chalcones provided products with up to 99% ee. This catalyst was also found to be useful in the asymmetric aldol reactions of ketones and aromatic aldehydes.[12] Based on these results, we envisioned that the asymmetric aldol reaction catalyzed by **13** could be extended for the preparation of chiral 3-substituted-3-hydroxyindolin-2-ones using cyclohexanone and isatins (reaction 2, Scheme 1).

Our initial reaction of isatin (**14a**) with cyclohexanone (**15a**) was carried out using our previous optimized reaction conditions for asymmetric aldol reaction[12] [20 mol% of chiral 1,2-diaminocyclohexane (**13**) and 20 mol% co-catalyst hexanedioic acid (HDA), in a mixture of MeOH–H_2O (1:1) at r.t.; Table 1, entry 1]. To our surprise, the reaction proceeded smoothly to provide the desired aldol product **16a** in high yield with excellent diastereoselectivity and enantioselectivity (yield: 90%; dr >20:1; ee >99%). When single solvents were used instead of the co-solvent MeOH–H_2O, the corresponding yield and enantioselectivity decreased significantly (Table 1, entries 2–4). Similarly, reducing the amount of catalyst or lowering the reaction temperature also impacted the yields (Table 1, entries 5–8). It is worth noting that only a trace amount of product was detected in the absence of hexanedioic acid (Table 1, entry 9), which indicated that the co-catalyst plays an important role in this reaction.

We further examined the generality of the reaction using the optimized reaction conditions. As shown in Table 2, various substituted isatins reacted with cyclohexanone **15a** to afford the corresponding 3-cyclohexanone-3-hydroxy-2-oxindoles in good to excellent yields and dia-

Table 1 Optimization of the Reaction Conditions

14a 15a 16a

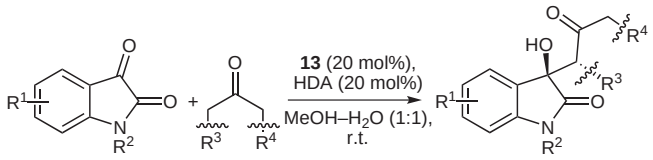
Entry	Solvent	**13** and HAD (mol%)	Yield (%)[a]	*anti*/*syn*[b]	ee (%)[b]
1	MeOH–H_2O	20	90	20:1	>99
2	MeOH	20	85	99:1	90
3	DMF	20	30	20:1	68
4	MeCN	20	50	20:1	72
5	MeOH–H_2O	5	30	20:1	95
6	MeOH–H_2O	10	65	99:1	96
7	MeOH–H_2O	20	43[c]	99:1	96
8	MeOH–H_2O	20	10[d]	99:1	97
9	MeOH–H_2O	20	trace[e]	–	–

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Carrying the reaction at 0 °C.
[d] Carrying the reaction at –10 °C.
[e] Only catalyst **13**.

stereo- and/or enantioselectivities (Table 2, entries 1–8).[13] It appeared that the introduction of substituents on the isatin could slightly decrease the yield and enantioselectivities, but the property and the position of substituents did not have a significant influence on the yields, diastereoselectivities, and enantioselectivities. We found that substituents such as 5-O_2N (Table 2, entry 2, 72% yield; *anti*/*syn* = 13:1; 87% ee), 6-Br (Table 2, entry 6, 82% yield; *anti*/*syn* = 20:1; 90% ee), or Me at 1-N (Table 2, entry 7, 78% yield; *anti*/*syn* = 10:1; 83% ee) gave similar results. In addition to cyclohexanone (**15a**), we also

examined tetrahydropyran-4-one (**15b**), acetone (**15c**), and cyclopentanone (**15d**) as donors. Tetrahydropyran-4-one (**15b**) was found to react with various substituted isatins **14a**–**h** and gave excellent results (Table 2, entries 9–14), except with N-substituted isatins, which gave moderate enantioselectivities (Table 2, entry 13, 51% ee and entry 14, 50% ee). However, the enantioselectivity was almost lost completely when acetone (**15c**) or cyclopentanone (**15d**) was used (Table 2, entries 15 and 16). The configuration of compounds was determined by comparing our Chiralcel HPLC profile with Ricci's result.[8] Interestingly, the compounds obtained by our method were *R*,*R* isomers, which are different from the *S*,*R* isomers reported.

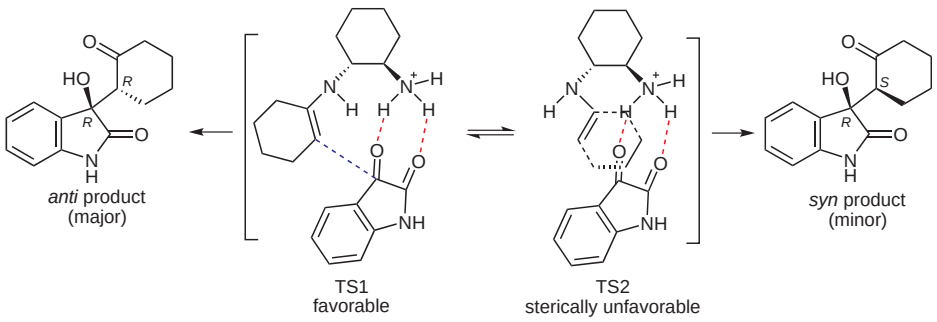
Table 2 Aldol Reactions of Isatin and Various Ketones



14 **15** **16**

Entry	R^1, R^2	R^3, R^4	Product	Yield (%)[a]	*anti*/*syn*[b]	ee (%)[b]
1	**14a** H, H	**15a** -$(CH_2)_3$-	**16a**	90	20:1	99
2	**14b** 5-O_2N, H	**15a**	**16b**	72	13:1	87
3	**14c** 5-MeO, H	**15a**	**16c**	70	20:1	77
4	**14d** 5-Cl, H	**15a**	**16d**	73	15:1	72
5	**14e** 6-Cl, H	**15a**	**16e**	75	20:1	91
6	**14f** 6-Br, H	**15a**	**16f**	82	20:1	90
7	**14g** H, Me	**15a**	**16g**	78	10:1	83
8	**14h** H, Bn	**15a**	**16h**	85	99:1	77
9	**14a**	**15b** -CH_2OCH_2-	**16i**[c]	80	20:1	87
10	**14c**	**15b**	**16j**[c]	68	20:1	82
11	**14d**	**15b**	**16k**[c]	76	20:1	83
12	**14f**	**15b**	**16l**[c]	81	20:1	71
13	**14g**	**15b**	**16m**[c]	72	10:1	51
14	**14h**	**15b**	**16n**[c]	78	10:1	50
15	**14a**	**15c** H, H	**16o**[c]	87	–	<5
16	**14a**	**15d** -$(CH_2)_2$-	**16p**[c]	83	2:1	16

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Carrying the reaction at 0 °C in MeOH–H_2O (10:1).



Scheme 2 Proposed mechanism for the reaction of cyclohexanone and isatin

Similar to our previous hypothesis,[12] we propose that both the aldol donor (ketone) and the receptor (isatin) could be activated simultaneously in this reaction system to form transition states TS1 and TS2 (Scheme 2). It is obvious that TS1 is sterically more stable than TS2, the size of the cyclic six-membered enamine ring was crucial for this steric restriction. Therefore, the *R*,*R* isomer is formed as the main product.

In conclusion, we have developed an efficient asymmetric aldol reaction of cycloketones and various isatin derivatives using a simple and commercially available chiral 1,2-diaminocyclohexane as the catalyst and hexanedioic acid as the co-catalyst. The corresponding 3-substituted-3-hydroxyindolin-2-ones have *R*,*R* configuration and were obtained in good to excellent yields (70–90%), diastereoselectivity (up to 99:1 *anti*/*syn*) and enantioselectivity (up to 99% ee). A possible mechanism of the reaction was proposed to proceed via the more stable TS1 intermediate leading to the *anti* product.

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References and Notes

(1) (a) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; *Angew. Chem.* **2007**, *119*, 8902. (c) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (d) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783. (e) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523. (f) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S. *Eur. J. Org. Chem.* **2001**, *66*, 261. (g) Hayashi, M.; Rho, M.-C.; Enomoto, A.; Fukami, A.; Kim, Y.-P.; Kikuchi, Y.; Sunazuka, T.; Hirose, T.; Komiyama, K.; Ōmura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14728. (h) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199.

(2) (a) Kamenecka, T. M.; Danishefsky, S. J. *Chem. Eur. J.* **2001**, *7*, 41. (b) Nicolaou, K. C.; Rao, P. B.; Hao, J.; Reddy, M. V.; Rassias, G.; Huang, X.; Chen, D. Y.-K.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1753. (c) Liao, Y.-J.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2003**, *59*, 3511. (d) Barroso, S.; Blay, G.; Cardona, L.; Fernandez, I.; Garcia, B.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 6821. (e) Cleghorn, L. A. T.; Cooper, I. R.; Fishwick, C. W. G.; Grigg, R.; MacLachlan, W. S.; Rasparini, M.; Sridharan, V. *J. Organomet. Chem.* **2003**, *687*, 483. (f) Schwaebisch, D.; Tchabanenko, K.; Adlington, R. M.; Cowley, A. M.; Baldwin, J. E. *Chem. Commun.* **2004**, *22*, 2552. (g) Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413. (h) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. (i) Toullec, P. Y.; Jagt, R. B. C.; De Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*, 2715. (j) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. (k) May, J. P.; Patrick, B. O.; Perrin, D. M. *Synlett* **2006**, 3403. (l) Yadav, J. S.; Reddy, B. V. S.; Reddy, C. S.; Krishna, A. D. *Tetrahedron Lett.* **2007**, *48*, 2029. (m) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593. (n) Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413. (o) Kumar, C. N. S. S. P.; Devi, C. L.; Rao, V. J.; Palaniappan, S. *Synlett* **2008**, 2023. (p) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kundig, E. P. *Chem. Commun.* **2008**, *34*, 4040. (q) Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369. (r) Lai, H.; Huang, Z.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283. (s) Jia, Y.-X.; Kundig, E. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1636. (t) Castaldi, M. P.; Troast, D. M.; Porco, J. A. *Org. Lett.* **2009**, *11*, 3362. (u) Tsuchikama, K.; Hashimoto, Y.; Endo, K.; Shibata, T. *Adv. Synth. Catal.* **2009**, *351*, 2850. (v) Beaumont, S.; Pons, V.; Retailleau, P.; Dodd, R. H.; Dauban, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 1634. (w) An, G.; Zhou, W.; Zhang, G.; Sun, H.; Han, J.; Pan, Y. *Org. Lett.* **2010**, *12*, 4482. (x) Urgaonkar, S.; Cortese, J. F.; Barker, R. H.; Cromwell, M.; Serrano, A. E.; Wirth, D. F.; Clardy, J.; Mazitschek, R. *Org. Lett.* **2010**, *12*, 3998. (y) Kothandaraman, P.; Rao, W.; Foo, S. J.; Chan, P. W. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 4619. (z) Zheng, K.; Yin, C.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 2573.

(3) (a) Corrêa, R. J.; Garden, S. J.; Angelici, G.; Tomasini, C. *Eur. J. Org. Chem.* **2008**, 736. (b) Angelici, G.; Corrêa, R. J.; Garden, S. J.; Tomasini, C. *Tetrahedron Lett.* **2009**, *50*, 814.

(4) (a) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 8079. (b) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2010**, *352*, 1621.

(5) Chen, J. R.; Liu, X. P.; Zhu, X. Y.; Li, L.; Qiao, Y. F.; Zhang, J. M.; Xiao, W. J. *Tetrahedron* **2007**, *63*, 10437.

(6) Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluháčková, K.; Kočovský, P. *Org. Lett.* **2007**, *9*, 5473.

(7) Guo, Q.; Bhanushali, M.; Zhao, C. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 9460.

(8) Ricci, A.; Bernardi, L.; Gioia, C.; Vierucci, S.; Robitzer, M.; Quignard, F. *Chem. Commun.* **2010**, *46*, 6288.

(9) (a) Raj, M.; Veerasamy, N.; Singh, V. *Tetrahedron Lett.* **2010**, *51*, 2157. (b) Popp, F. D.; Donigan, B. E. *J. Pharm. Sci.* **1979**, *68*, 519. (c) Pajouhesh, H.; Parson, R.; Popp, F. D. *J. Pharm. Sci.* **1983**, *72*, 318. (d) Joshi, K. C.; Dandia, A.; Sanan, S. *J. Fluorine Chem.* **1989**, *44*, 59.

(10) Wang, J. F.; Qi, C.; Ge, Z. M.; Cheng, T. M.; Li, R. T. *Chem. Commun.* **2010**, *46*, 2124.

(11) Wang, J. F.; Wang, X.; Ge, Z. M.; Cheng, T. M.; Li, R. T. *Chem. Commun.* **2010**, *46*, 1751.

(12) Liu, Y.; Wang, J. F.; Sun, Q.; Li, R. T. *Tetrahedron Lett.* **2011**, *52*, 3584.

(13) **Typical Procedure** To the mixed solvent (2 mL, MeOH–H_2O = 1:1) was added the corresponding isatin (0.2 mmol), cyclohexanone (0.6 mmol), and catalyst **13** (0.04 mmol) with equal amount of hexanedioic acid (0.04 mmol). The mixture was stirred at r.t. for 14 h, then quenched with additional H_2O. The organic matter was extracted with EtOAc, dried over Na_2SO_4, and the filtrate was concentrated to get the crude product, which was further purified by a silica gel chromatography.
3-Hydroxy-3-(2-oxocyclohexyl)indolin-2-one (16a)
Yield 90%; mp 159 °C; *anti*/*syn* = 20:1; 99% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (s, 1 H), 7.13–7.21 (m, 2 H), 6.75–6.87 (m, 2 H), 5.77 (s, 1 H), 3.07 (dd, *J* = 12.0, 4.0 Hz, 1 H), 2.53–2.58 (m, 1 H), 2.36–2.53 (m, 1 H), 2.27–2.34 (m, 1 H), 1.58–2.08 (m, 5 H), 1.43–1.50 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 209.8, 179.4, 144.1, 131.5, 129.3, 125.5, 121.5, 110.1, 74.6, 58.1, 42.1, 27.4, 27.3, 25.1. HRMS: *m*/*z* calcd for $C_{14}H_{16}NO_3$ [M + H$^+$]: 246.11247; found: 246.11184. The enantiomeric ratio was determined by chiral HPLC with AD-H column (hexane–2-PrOH = 80:20, 1 mL/min).

