HETEROCYCLES, Vol. 68, No. 11, 2006, pp. 2327 - 2333. © The Japan Institute of Heterocyclic Chemistry
Received, 3rd August, 2006, Accepted, 19th September, 2006, Published online, 22nd September, 2006. COM-06-10856

L-PROLINE-CATALYZED ASYMMETRIC ALDOL CONDENSATION OF *N*-SUBSTITUTED ISATINS WITH ACETONE

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Abstract – L-proline-catalyzed asymmetric aldol condensation of several isatin derivatives with acetone is reported. The desired products were obtained in highly yield with the ee among 30–79%. The substitutes of N can deeply effect the ee value of products, and a novel mechanism is also described.

INTRODUCTION

The aldol condensation is one of the most powerful C–C bond forming reactions,[1-3] and many catalysts[4-6] were used in this reaction. Proline has been widely used in asymmetric aldol condensation and related reactions of aldehydes as a bifunctional catalyst.[7-9] Recently proline and *N*-terminal proline-contained dipeptides catalyzed aldol condensation of isatin and *N*-alkylated isatins with acetone was reported:[10] at –15 ℃, the reaction catalized by L-proline afforded the desired compound 3-(2-oxopropyl)-3-hydroxyindolin-2-one with low enantioselectivity, 33%; the best results were obtained with 10 mol % H-D-Pro-L-β^3-hPhg-OBn as a catalyst, resulting in the preferential formation of the (R)-enantiomer with a enantioselectivity of 77%. In this paper, we describe L-proline catalyzed directly these reactions with a novel mechanism.

RESULTS AND DISCUSSION

The reaction was investigated using L-proline as a catalyst. In a typical reaction, isatin (0.3 mmol) and L-proline (0.03 mmol) were dissolved in 3mL acetone and the mixture stirred at room temperature for 12h. The mixture was concentrated, and the product, 3-(2-oxopropyl)-3-hydroxyindolin-2-one, was isolated and analyzed by HPLC equipped with a chiral column.

The reaction at room temperature furnished aldol product in high yield, but the enantioselectivity is low, 23%. While *N*-methyl isatin reacted with acetone, a exciting result was obtained: the ee rised up to 54%. We investigated the effect of catalyst loading on the condensation of *N*-methyl isatin and acetone. In **Figure 1**, it was found that the optimum amount was 15–20 mol %.

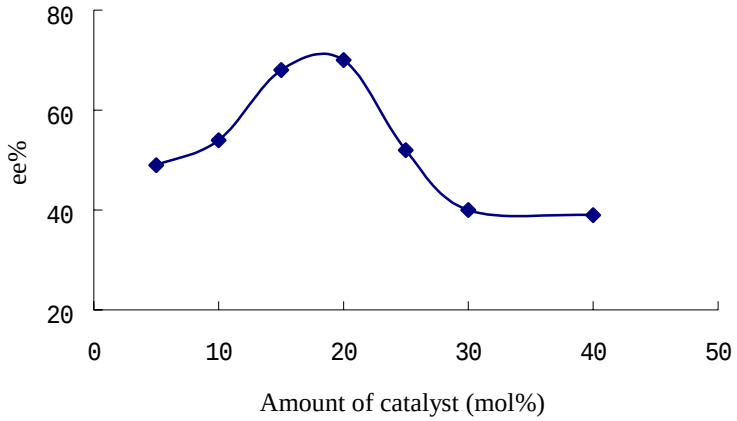


Figure 1. Effects of catalyst loading on the asymmetric addition of acetone to N-methyl isatin

On the basis of the above-mentioned results, we carried out a series of reactions with different (*N*-substituted) isatins catalyzed by 20 mol % L-proline, and got the result shown in **Table 2**.

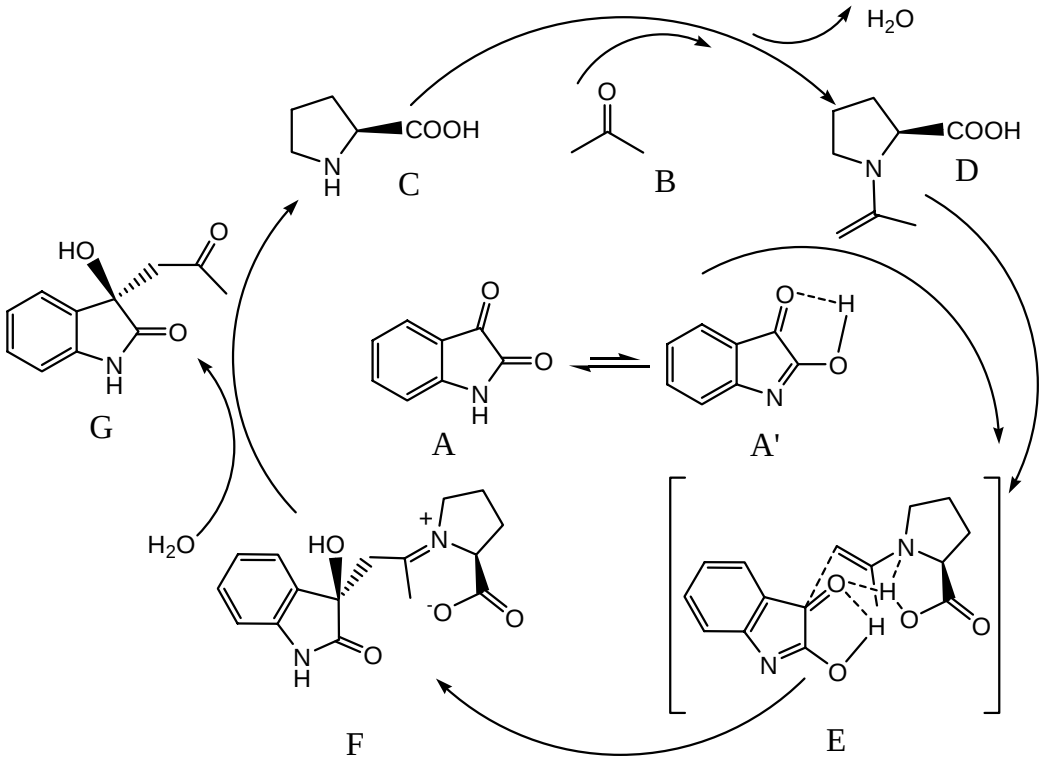
Entry	R	Time (h)	Tempera-ture (°C)	Yield (%)	ee (%)	Configur-ation[10]
1	H	72	-20	76.4	30	R
2	CH_3	24	-20	83.3	79	R
3	C_2H_5	24	-20	85.2	77	R
4	$CH_2CH{=}CH_2$	12	-20	91.8	68	R
5	$(CH_2)_3CH_3$	24	-20	95.4	57	R
6	$(CH_2)_5CH_3$	24	-20	95.7	60	R
7	Bn	12	-20	96.2	65	R
8	$COCH_3$	8	-20	83.9	45	R

9	COC_2H_5	8	-20	90.1	46	R
10	CH_2OH	12	-20	80.5	40	R

Table 2. Enantiomeric excesses and yields of the product formed in the aldol reaction of (*N*-substituted) isatins with acetone catalyzed by L-proline

Some interesting results can be found: the reaction between acetone and (*N*-substituted) isatins goes on much faster than that of acetone and isatin, and the ee all rise, the highest is 79%.

Why the substitutes can effect the stereoselectively so greatly? Houk and List[11,12] proposed a one-proline enamine mechanism, in which the carboxylic acid proton fulfils a crucial roles in the catalytic cycle. We proposed a mechanism shown in **Scheme 1**. Initially, isatin (A) might isomerize to a much active form – 2-hydroxylindol- 3-one (A'), meanwhile enamine intermediate D results from the condensation of acetone (B) and L-proline (C), then D combines with A' proceeding transition state E. In this bimolecular complex E, the carboxylic acid proton enables hydrogen bonding between the reaction partners. Several theoretical

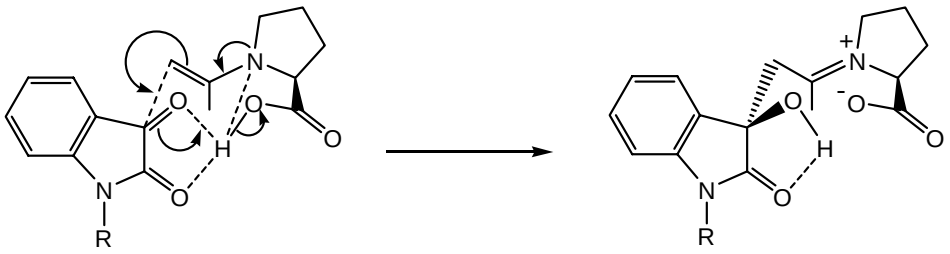


Scheme 1. Proposed mechanism for the L-proline catalyzed aldol condensation of isatin with acetone.

studies[7-9,13,14] have highlighted the importance of the carboxylic acid functionality of proline in this reaction: it orients the incoming isatin through a hydrogen bond, which ensures that the reaction proceeds on

only one face of the pyrrolidine ring; it lowers the activation barrier of the reaction by charge stabilization along the C–C bond formation by means of the intramolecular hydrogen bond. Based on the proposed mechanism, we assumed that the intramolecular hydrogen bond in A' makes it hard to form the hydrogen bond between the proton of carboxylic acid and the carbonyl group of C 3, even the two protons might repel to each other, which decreases the stability of the transition state, thus leads to low ee.

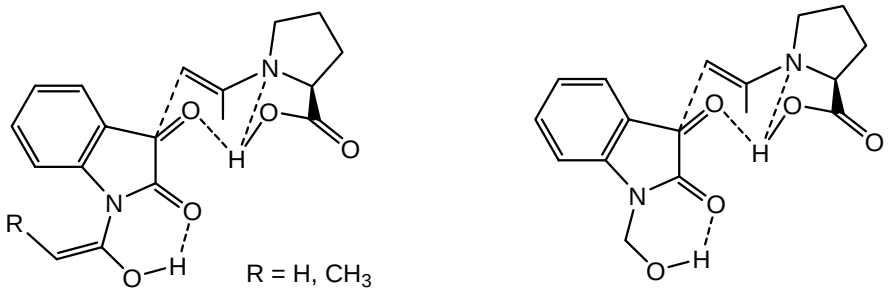
While the H of amide is substituted, the intramolecular hydrogen bond disappears, in transition state E' the proton of carboxylic acid is binded tightly by the two carbonyl groups of (*N*-substituted) isatins (**Scheme 2**). After a series of electrons transfer, E' converts to F', and hydrolysis of F' releases aldol product with much higher ee.



E' F'

Scheme 2. Proposed transition state in the reaction of L-proline catalyzed aldol condensation of (*N*-substituted) isatins with acetone.

Why $–COCH_3$, $–COC_2H_5$ and $–CH_2OH$ resulted in shorter reaction time but low ee? We proposed that these electron withdrawing groups can activate the carbonyl group, which lead to shorter reaction time. And these groups can also help founding other transition states (**Scheme 3**), which decrease the hydrogen bond between the proton of carboxylic acid and the carbonyl group of C 2. So reactions between $–COCH_3$, $–COC_2H_5$ and $–CH_2OH$ substituted isatins and acetone give low ee.



Scheme 3. Proposed transition state in the reaction of L-proline catalyzed aldol condensation of *N*–$COCH_3$, $–COC_2H_5$ and $–CH_2OH$ substituted isatins with acetone.

Antti[14] presumed that a stronger hydrogen bond donor should lower the energy of the transition state, and thus lead to increased reactivity. We can conclude from the result that a stronger hydrogen bond receptor can lower the energy of the transition state and stabilize the transition state, leading to a higher ee if catalized by a chiral catalyst.

In conclusion, this paper describes L-proline catalyzed Aldol condensation of isatin / *N*-substituted isatins with acetone. The reaction between *N*-substituted isatins and acetone is much faster than that of isatin and acetone, presenting the desired products with 30–79% ee. The mechanism was proposed, and we concluded that a stronger hydrogen bond receptor, as well as a stronger hydrogen bond donor, in the transition state can also lower the energy of the transition state.

EXPERIMENTAL

General Method for the Synthesis of *N*-substituted-3- (2-oxopropyl)-3-hydroxy- indolin-2-ones. 0.3 mmol of isatin / (*N*-substituted) isatins and 0.06 mmol of L-proline were dissolved in 6 mL of acetone and the mixture was stirred at –20 ℃ for the time stated in **Table 1**. Then acetone was evaporated under reduced pressure, and the mixture was purified by flash chromatography (petroleum ether/AcOEt 8:1–5:1). The products are all colorless crystals.

Analytical HPLC was performed on an HP 1090 liquid chromatograph equipped with a variable-wavelength UV detector (deuterium lamp 190–600 nm), using a Daicel CHIRALPAK AD column (0.46 cm i.d. × 25 cm) (Daicel, Inc.) (for the analysis of 3-(2-oxopropyl)-3-hydroxyindolin-2-one) or a Daicel CHIRALCEL OD column (0.46 cm i.d. × 25 cm) (Daicel, Inc.) (for the analysis of *N*-sustituted-3-(2-oxopropyl)-3- hydroxyindolin-2-one). Hexane CHROMASOLV and 2-propanol CHROMASOLV for HPLC were purchased from MERCK and used as the eluting solvents.

3-(2-Oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3360, 3303, 1719, 1617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$-CD_3OD): δ 9.57 (1H, s), 7.46 (2H, m), 7.20 (1H, t, *J* = 7.2), 6.95 (1H, d, *J* = 7.6), 4.64 (1H, s), 3.33 (1H, d, *J* = 17.2), 3.09 (1H, d, *J* = 17.2), 2.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD): δ 206.5, 179.1, 141.3, 130.1, 129.6, 123.5, 122.5, 110.2, 73.6, 49.6, 30.6; EI-MS: *m/z* 205 (M^+); HR-ESI-MS: *m/z* 228.0630 (calcd for $C_{11}H_{11}NNaO_3^+$ 228.0637)

1-Methyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3356, 1701, 1687, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (1H, d, *J* = 7.6), 7.23 (1H, t, *J* = 7.6), 7.01 (1H, t, *J* = 7.6), 6.87 (1H, d, *J* = 7.2), 5.88 (1H, s), 3.98 (3H, s), 3.27 (1H, d, *J* = 16.4), 3.11 (1H, d, *J* = 16.4), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 176.1, 143.4, 129.9, 129.6, 123.7, 123.0, 108.5, 74.1, 48.7, 31.3, 26.2; EI-MS: *m/z* 219 (M^+); HR-ESI-MS: *m/z* 242.0784 (calcd for $C_{12}H_{13}NNaO_3^+$ 242.0793)

1-Ethyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3302, 1705, 17695, 1616 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, d, *J* = 7.2), 7.43 (1H, t, *J* = 7.6), 7.16 (1H, t, *J* = 7.2), 6.98 (1H, d, *J* = 7.6), 4.53 (1H, s), 3.85 (2H, m), 3.33 (1H, d, *J* = 17.2), 3.0 (1H, d, *J* = 17.2), 2.27 (3H, s), 1.39 (3H, t, *J* = 7.2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 175.8, 142.7, 129.9, 129.8, 123.9, 122.9, 108.7, 74.0, 49.0, 34.8, 31.2, 12.3; EI-MS: *m/z* 233 (M^+); HR-ESI-MS: *m/z* 256.0948 (calcd for $C_{13}H_{15}NNaO_3^+$ 256.0950)

1-Allyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3317, 1716, 1699, 1621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, d, *J* = 7.6), 7.29 (1H, t, *J* = 7.6), 7.06 (1H, d, *J* = 7.6), 6.84 (1H, t, *J* = 7.6), 5.88 (1H, m), 5.34 (1H, s), 5.26 (1H, m), 4.39 (1H, dd, *J* = 16.4, 5.2), 4.26(1H, dd, *J* = 16.4, 5.2), 3.23 (1H, d, *J* = 17.2), 3.01 (1H, d, *J* = 17.2), 2.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 175.9, 142.8, 130.9, 129.9, 129.6, 123.8, 123.1, 109.5, 74.0, 48.9, 42.4, 31.3; EI-MS: *m/z* 245 (M^+); HR-ESI-MS: *m/z* 268.0941 (calcd for $C_{14}H_{15}NNaO_3^+$ 268.0950)

1-Butyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3354, 1712, 1688, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (1H, d, *J* = 7.2), 7.31 (1H, t, *J* = 7.6), 7.05 (1H, t, *J* = 7.6), 6.85 (1H, d, *J* = 7.6), 4.41 (1H, s), 3.64 (2H, m), 3.19 (1H, d, *J* = 16.8), 2.95 (1H, d, *J* = 16.8), 2.17 (3H, s), 1.68 (2H, m), 1.34 (2H, m), 0.94 (3H, t, *J* = 7.6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 176.0, 142.9, 129.9, 129.8, 123.9, 122.8, 108.8, 74.1, 48.8, 40.1, 31.4, 28.9, 26.8, 22.3; EI-MS: *m/z* 261 (M^+); HR-ESI-MS: *m/z* 284.1260 (calcd for $C_{15}H_{19}NNaO_3^+$ 284.1263)

1-Hexyl-3-hydroxy-3-(2-oxopropyl)indolin-2-one. IR (Nujol): ν = 3361, 1712, 1688, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, d, *J* = 7.2), 7.32 (1H, t, *J* = 7.6), 7.06 (1H, t, *J* = 7.6), 6.85 (1H, d, *J* = 7.6), 4.28 (1H, s), 3.60 (2H, m), 3.17 (1H, d, *J* = 16.8), 2.93 (1H, d, *J* = 16.8), 2.18 (3H, s), 1.69 (2H, m), 1.30 (4H, m), 0.88 (3H, t, *J* = 7.2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 176.0, 142.9, 129.9, 129.8, 123.9, 122.8, 108.8, 74.1, 48.8, 40.1, 31.4, 28.9, 26.8, 22.3; EI-MS: *m/z* 289 (M^+); HR-ESI-MS: *m/z* 312.1571 (calcd for $C_{17}H_{23}NNaO_3^+$ 312.1576)

1-Benzyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3317, 1716, 1699, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33- 7.38 (6H, m), 7.18 (1H, d, *J* = 7.6), 7.04 (1H, t, *J* = 7.6), 6.70 (1H, t, *J* = 7.6), 4.96 (1H, d, *J* = 16.4), 4.85(1H, d, *J* = 16.4), 4.44(1H, s), 3.27 (1H, d, *J* = 16.8), 3.05 (1H, d, *J* = 16.8), 2.19 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.3, 176.3, 142.7, 135.3, 129.9, 129.7, 128.8, 127.6, 127.2, 123.8, 123.1, 109.7, 74.1, 48.8, 43.8, 31.3; EI-MS: *m/z* 295 (M^+); HR-ESI-MS: *m/z* 318.1112 (calcd for $C_{18}H_{17}NNaO_3^+$ 318.1106)

1-Acetyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3431, 1715, 1623, 1574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (1H, d, *J* = 7.6), 7.34 (3H, m), 7.18 (1H, d, *J* = 7.6), 3.36 (1H, d, *J* = 17.6), 3.33 (1H, d, *J* = 17.6), 2.64 (3H, s), 2.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 178.0, 171.1, 140.5, 130.1, 129.0, 125.3, 122.8, 116.8, 72.9, 51.1, 30.3, 26.3; EI-MS: *m/z* 247 (M^+); HR-ESI-MS: *m/z* 270.0739 (calcd for $C_{13}H_{13}NNaO_4^+$ 270.0742)

1-Propionyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3433, 1716, 1620, 1577 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (1H, d, *J* = 8.0), 7.29 (3H, m), 7.15 (1H, d, *J* = 7.6), 3.32 (1H, d, *J* = 17.6), 3.24 (1H, d, *J* = 17.6), 3.01(2H, q, *J* = 7.2), 2.00 (3H, s), 1.17 (3H, 3H, t, *J* = 7.2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 177.8, 175.0, 140.7, 130.1, 129.1, 125.2, 122.8, 116.7, 73.0, 51.1, 31.6, 30.3, 8.14; EI-MS: *m/z* 261 (M^+); HR-ESI-MS: *m/z* 284.0891 (calcd for $C_{14}H_{15}NNaO_4^+$ 284.0899)

1-Hydroxymethyl-3-(2-oxopropyl)-3-hydroxyindol-2-one. IR (Nujol): ν = 3394, 1777, 1713, 1675, 1607 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.31 (1H, d, *J* = 7.6), 7.23 (1H, m), 6.99 (1H, m), 6.88 (1H, d, *J* = 7.6), 5.17 (2H, m), 3.36 (1H, d, *J* = 16.8), 3.16 (1H, d, *J* = 16.8), 2.04 (1H, s), 1.90 (3H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 206.1, 173.0, 142.7, 130.7, 125.1, 124.9, 123.5, 123.4, 111.3, 74.9, 51.2, 30.7, 24.2; EI-MS: *m/z* 235 (M^+); HR-ESI-MS: *m/z* 258.0747 (calcd for $C_{12}H_{13}NNaO_4^+$ 258.0742)

ACKNOWLEGEMENTS

This work was financially supported by two grants from National Science Foundation of China (No. 30370957) and Natural Science Foundation of Yunnan province (No. 2003 C0061M).

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