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Dipeptide-Catalyzed Asymmetric Aldol Condensation of Acetone with (N-Alkylated) Isatins

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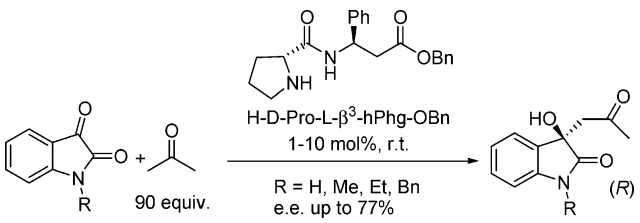

The aldol condensation of acetone with several isatins is described. The desired compound was obtained in quantitative yield and with good enantioselectivities up to 77%. The best results were obtained with 10 mol % H-D-Pro-L-β^3-hPhg-OBn as a catalyst, resulting in the preferential formation of the (*R*)-enantiomer. The absolute configuration of the newly formed chiral center has been assigned by an X-ray diffraction study and CD spectra analysis of the molecules.

The aldol condensation is an important reaction for the formation of new carbon−carbon bonds, both in synthetic organic chemistry and in nature. The use of the inexpensive and nontoxic proline as a catalyst in reactions involved in enamine formation was first introduced by Hajos and Parrish and also independently by Eder, Sauer, and Wiechert.[1] This reaction has subsequently been widely studied by List.[2] Recently, many research groups have tested various oligopeptides containing proline as an N-terminal amino acid as catalysts in the aldol condensation and related reactions of aldehydes, but to the best of our knowledge no reactions have been reported on ketones yet.[3]

SCHEME 1. Aldol Reaction of Isatin with Acetone

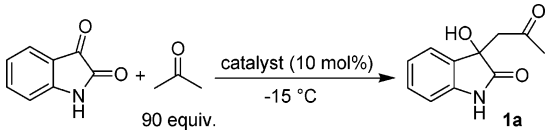

TABLE 1. Enantiomeric Excesses and Yields of 1a Formed in the Aldol Reaction of Isatin with Acetone Catalyzed by L-Proline and L-Prolinamide[a]

entry	catalyst	time (h)	temp (°C)	yield (%)	ee (%)[b]	configuration
1	H-L-Pro-OH	90	−15	quantitative	33	*S*
2	H-L-Pro-NH_2	2	20	82	23	*S*
3	*cis*-4-OH-D-Pro-OH	16	20	25	30	*R*
4	*trans*-3-OH-L-Pro-OH	16	20	48	17	*S*

[a] Conditions: concentration of isatin in acetone is 0.15 M, and 10 mol % catalyst was used. [b] Ee values were determined by HPLC.

In this paper we want to describe the results obtained on the aldol condensation of acetone with isatin and N-alkylated isatins. This reaction enables the formation of a quaternary stereogenic center with good enantioselectivity (Scheme 1). The product **1a** had already been prepared in the racemic form, but no synthesis of the enantiopure form has yet been described.[4]

Highly polar solvents such as DMSO and DMF are often used in organocatalysis reaction due to the low solubility of proline, which is routinely used as a catalyst in up to 20−30 mol %. Since such high-boiling solvents are difficult to remove at the end of the reaction, the use of acetone not only as a reagent but also as a solvent is advantageous due to its ease of removal. Further, the identification of new catalysts with increased solubility is highly desirable.

The reaction was initially investigated using L-proline as a catalyst (Table 1, entry 1). In a typical reaction, the catalyst (0.03 mmol) was dissolved in acetone and the mixture stirred at −15 °C. After 15 min, solid isatin (0.3 mmol) was added and the mixture stirred at −15 °C for 90 h. After this time, the mixture was concentrated and analyzed by HPLC equipped with a chiral column.

The reaction using L-proline as a catalyst afforded the desired compound 3-(2-oxopropyl)-3-hydroxyindolin-2-one

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(1) (a) Hajos, Z. G.; Parrish, D. R.. *J. Org. Chem.* **1974**, *39*, 1615−162. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497.

(2) List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557, and refs therein. For a recent review, see: Dalko, P.; Moisan, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

(3) Organocatalytic reactions mediated by oligopeptides, see: (a) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bio. Chem. Med. Lett.* **2003**, *13*, 2445−2447. (b) Jarvo, E.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495. (c) Shi, L.-X.; Sun, Q.; Ge, Z.-M.; Zhu, Y.-Q.; Cheng, T.-M.; Li, R.-T. *Synlett* **2004**, 2215−2217. (d) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285−2287. (e) List, B.; Martin, H. J. *Synlett* **2003**, 1901−1902.

(4) For the racemic aldol condensation of isatins with methylketones, see: (a) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493−3503. (b) Garner, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399−8412. (c) Beccalli, E. M.; Marchesini A.; Pilati, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 579−587.

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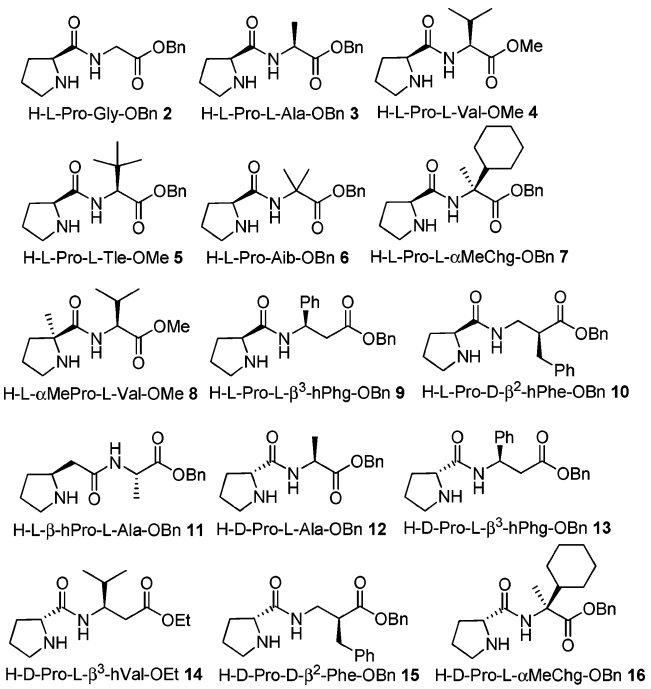

FIGURE 1. Dipeptides evaluated in this study.

1a in quantitative yield but with low enantioselectivity, 33%. A disappointing outcome was also obtained not only using L-prolinamide [5] as a catalyst but also using different hydroxyprolines (entries 2−4). In these cases, the reactions were carried out at 20 °C because only starting material was recovered at −15 °C, probably owing to the low solubility of the catalysts at low temperature.

In view of these results, we investigated the use of dipeptides containing N-terminal proline residues as catalysts: 15 dipeptides with the general formula L- or D-"Pro"-Xaa-OR, where Xaa is a natural or an unnatural amino acid (Figure 1), were prepared by conventional peptide synthesis starting from the Boc-protected "proline"-amino acid. After synthesis, the Boc-protecting group was removed using TFA in methylene chloride. Thus, dipeptides containing α,α-disubstituted amino acids such as L-(αMe)Pro [L-(α-methyl)proline], Aib (α-aminoisobutyric acid), or L-(αMe)Chg [L-(α-methyl)cyclohexylglycine][6] and dipeptides containing β-amino acids such as L-β^3-hVal (L-β^3-homovaline), L-β^3-hPhg (L-β^3-homophenylglycine), or D-β^2-hPhe (D-β^2-homophenylalanine)[7] were tested as catalysts for the reaction of isatin with acetone under the same reaction conditions as reported above, and the results are shown in Table 2.

TABLE 2. Enantiomeric Excesses and Yields of 1a Formed in the Aldol Reaction of Isatin with Acetone Catalyzed by Dipeptides 2−16[a]

entry	catalyst[b]	time (h)	temp (°C)	yield (%)	ee (%)[c]	configuration
1	**2**	19	−15	80	46	*S*
2	**3**	19	−15	quantitative	56	*S*
3	**4**	20	−15	92	43	*S*
4	**5**	20	−15	96	22	*S*
5	**6**	17	−15	quantitative	43	*S*
6	**7**	16	20	quantitative	20	*S*
7	**8**	26	20	0		
8	**9**	16	−15	96	67	*S*
9	**10**	17	−15	quantitative	47	*S*
10	**11**	17	−15	23	4	*R*
11	**12**	19	−15	quantitative	49	*R*
12	**13**	15	−15	92	72	*R*
13	**13**	23	20	quantitative	55	*R*
14[e]	**13**	64	20	70	56	*R*
15[d]	**13**	16	−15	quantitative	73	*R*
16[d,e]	**13**	16	−15	45	64	*R*
17[d,e]	**13**	64	−15	quantitative	73	*R*
18	**13**	64	−50	30	63	*R*
19[d]	**13**	64	−50	60	68	*R*
20	**14**	16	−15	88	48	*R*
21	**15**	17	−15	quantitative	49	*R*
22	**16**	16	20	42	32	*R*

[a] Unless otherwise specified, the concentration of isatin in acetone was 0.15 M. [b] Unless otherwise stated, the catalyst loading was 10 mol %. [c] Ee values were determined by HPLC. [d] Performed with a 1 M concentration of isatin in acetone. [e] Catalyst loading was 1 mol %.

These results are a substantial improvement on those reported in Table 1: an enantiomeric excess as high as 73% was obtained when H-D-Pro-L-β^3-hPhg-OBn **13** was used as a catalyst. Remarkably, the concentration of the isatin has nearly no effect on the ee, probably due to the high solubility of the catalyst. Hence, similar ees were obtained whether using 0.15 or 1 M solutions (cf. entry 12 with 15 and entry 18 with 19). However, attempts to increase the enantiomeric excess by lowering the temperature (cf. entry 12 with 18 and entry 15 with 19) were unsuccessful.

Noteworthy results were obtained with 1 mol % catalyst (cf. entry 13 with 14 and entry 15 with 16 and 17): at −15 °C, after prolonged reaction times (entry 17), the reaction occurred in quantitative yield and with the same enantiomeric excess as obtained with 10 mol % catalyst (entry 15). It is also noteworthy that the reaction catalyzed by H-L-Pro-L-β^3-hPhg-OBn **9** (epimer of **13**) (entry 8) produced the opposite enantiomer, although with a slightly lower ee.

Some interesting conclusions can be drawn: The absolute configuration of proline is determining the sign of the enantiomeric excess, but an accurate choice of the amino acid in the second position is indispensable: indeed, highly hindered amino acids furnish mediocre results (cf. entry 2 with 4). Furthermore, replacing proline with β-homoproline yields the worst results, while β-amino acids in the second position in general give better results than α-amino acids.

To determine the absolute configuration of the newly formed stereogenic center, two samples of **1a** (those obtained from entries 8 and 15) were purified with silica gel chromatography (eluent = cyclohexane/ethyl acetate 8:2). During the purification, an enantiomeric enrichment

(5) For the use of prolinamide as a catalyst, see: (a) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *PNAS* **2004**, *101*, 5755−5760. (b) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A. Jörgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, 43, 5507−5510. (c) Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817−2820.

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(7) (a) Boesten, W. H. J.; Moody, H. M.; Kaptein, B.; Seerden, J. P. G.; van der Sluis, M.; de Lange, B. (DSM). PCT Pat. Appl. WO 01/42173. (b) Broxterman, Q. B.; Kaptein, B.; Kierkels J. G. T.; Milcent, T. J. A. (DSM) Eur. Pat. Appl. No. 04075597.7 (patent pending).

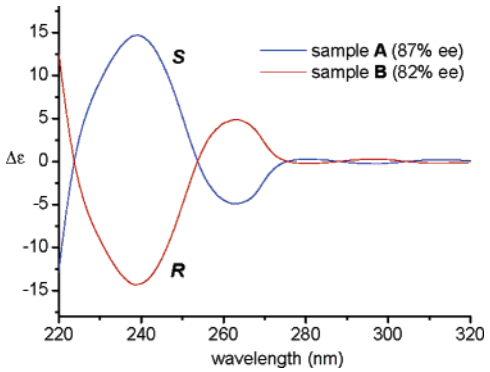


FIGURE 2. CD spectra of sample **A** and sample **B** of **1a** (solution 5 mM in methanol).

of the products occurred, and a sample from entry 8 with 87% ee (sample **A**) and a sample from entry 15 with 84% ee (sample **B**) of the opposite enantiomer could be isolated. Similar enantiomeric enrichment of nonracemic mixtures during chromatographic purifications has already been observed by other research groups and has been ascribed to stable diastereomeric interactions between the two enantiomers.[8]

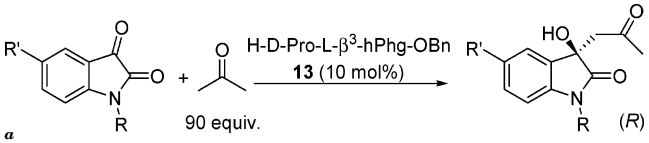
The two samples were analyzed by CD spectroscopy (Figure 2): in the CD spectra, sample **A** exhibits a negative Cotton effect in the long-wave region (300−255 nm) and a positive effect in the short-wave region (260−220 nm), while sample **B** exhibits exactly the opposite behavior.

This outcome has been compared with the CD spectra of the two diastereomers of (2*S*,3*R*)- and (2*S*,3*S*)-3-hydroxytryptophan reported by Aimi and co-workers.[9] They assigned the absolute configuration of the quaternary stereogenic center of isorhynchophylline by comparing the CD spectra of both enantiomers (of a known derivative) with the CD spectra of (2*S*,3*R*)- and (2*S*,3*S*)-3-hydroxytryptophan. Indeed (2*S*,3*S*)-hydroxytryptophan ($[\alpha]_D$ −19.9°) exhibits a negative Cotton effect in the long-wave region (280−255 nm) and a positive effect in the short-wave region (260−220 nm), while the other diastereomer ($[\alpha]_D$ +36.7°) having the (2*S*,3*R*)-configuration showed exactly the opposite behavior.

Thus, comparison of the CD spectra of our samples with the reported data allows us to state that sample **A** has (*S*)-absolute configuration and sample **B** has (*R*)-absolute configuration and thus that the catalysts containing L-Pro induce the formation of the (*S*)-enantiomer, while the catalysts containing D-Pro induce the formation of the (*R*)-enantiomer.

Finally, we tested the efficiency of H-D-Pro-L-β^3-hPhg-OBn **13** in the addition of acetone to N-alkylated isatins and 5-bromoisatin (Table 3).[10] The syntheses of the racemic products **1b** and **1d** have already been described.[4b,11] Entries 1−4 show that in each case a good ee was obtained with the preference for the (*R*)-enantiomer.

TABLE 3. Aldol Reaction of N-Alkylated Isatin Derivatives with Acetone-Catalyzed by Dipeptide 13



a

entry	R	R′	product	time (h)	temp (°C)	concn (M)	yield (%)	ee (*R*) (%)[b]	configuration
1	Me	H	**1b**	17	−15	0.15	quantitative	77	*R*
2	Et	H	**1c**	16	−15	0.15	92	74	*R*
3	Bn	H	**1d**	17	−15	0.15	90	74	*R*
4	H	Br	**1e**	17	−15	0.15	quantitative	73	*R*

[a] Concentration of the isatin in acetone was 0.15 M. [b] Ee values were determined by HPLC.

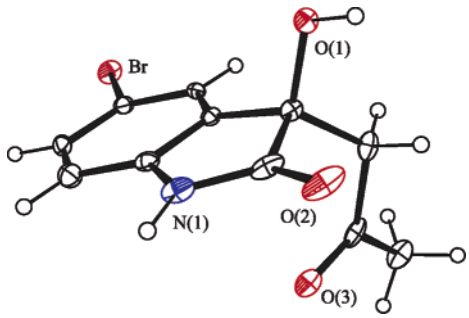


FIGURE 3. ORTEP drawing of the (*R*)-enantiomer of **1e** (30% thermal ellipsoids).

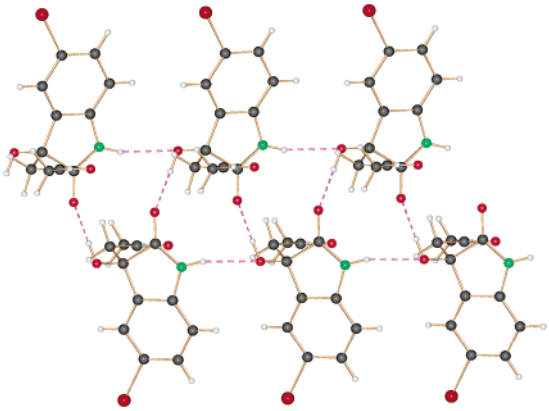


FIGURE 4. Crystal packing of **1e** showing the zigzag chain generated by the intermolecular hydrogen bonds running along the *b*-axis.

The absolute configuration of **1e** was unambiguously determined by single-crystal X-ray investigations carried out on crystals grown from slow evaporation of a chloroform solution. We obtained two sets of crystals, having different habits, which turned out to be the racemic mixture (as platelets) and the pure enantiomer (as needles). X-ray analysis of the needles showed that the absolute configuration of the stereogenic center was (*R*)- (Figure 3). HPLC analysis of the crystal confirmed that it is the more abundant enantiomer, which is the second to be eluted.

Interestingly, in the crystal packing of the (*R*)-enantiomer, the molecules formed zigzag chains via intermolecular N−H...O and O−H...O hydrogen bonds (Figure 4) not involving the ketonic oxygen of the lateral chain.

(8) See for example: (a) Stefani, R.; Cesare, V. *J. Chromat. A.* **1998**, *813*, 79−84. (b) Loža, E.; Loïa D.; Íemme, A.; Freimanis, J. *J. Chromatogr. A.* **1995**, *708*, 231−243.

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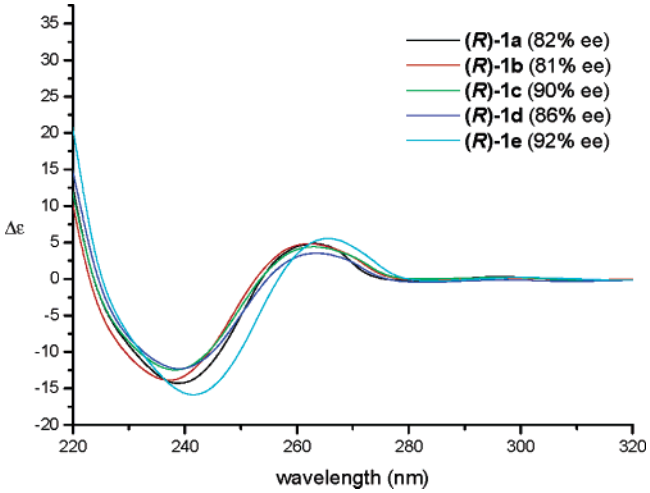

FIGURE 5. CD spectra of samples of **1a**−**e** (concentration 5 mM in methanol).

Chiral HPLC analysis showed a general preference for the formation of the (*R*)-isomer, analogously to what was observed for **1a**. To corroborate this deduction, enriched fractions of **1b**−**e** were obtained by silica gel chromatography, thus showing that the enantiomeric enrichment during chromatographic purifications of nonracemic mixtures of these (N-alkylated) isatins is a general effect for these isatin derivatives, and the CD spectra were recorded and compared with those of **(*R*)-1a** and **(*R*)-1e**. The spectra shown in Figure 5 are nearly superimposable.

In summary, we have described the asymmetric aldol condensation of acetone with isatin, its N-alkylated derivatives, and 5-bromoisatin. A new quaternary stereocenter is obtained with good enantioselectivity (up to 77%), which can easily be enriched by silica flash chromatography; this effect proved to be general for this class of compounds. The best dipeptide catalysts turned out to be derived from proline and β^3-homophenylglycine.

Experimental Section

General Method for the Synthesis of 1-Alkyl 3-(2-Oxopropyl)-3-hydroxyindolin-2-ones. The ligand (0.03 mmol) was stirred in acetone (2 mL) for 15 min at the temperature described in Table 1, 2, or 3. Solid isatin (0.3 mmol) was added, and the mixture was stirred for the time described in the appropriate table. After this time, acetone was removed under reduced pressure, and the mixture was purified by flash chromatography (cyclohexane/ethyl acetate 1:1) to eliminate the catalyst. The enantiomeric excesses were determined by chiral HPLC prior to purification. Analytical high-performance liquid chromatography (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. x 25 cm) (Daicel, Inc.) (for the analysis of **1a**) or a Daicel CHIRALCEL OD column (0.46 cm i.d. x 25 cm) (Daicel, Inc.) (for the analysis of **1b**−**d**). Hexane CHROMASOLV and 2-propanol CHROMASOLV for HPLC were purchased from Riedel-de Haën and used as the eluting solvents. The CD spectra were obtained on a Jasco J-810 spectropolarimeter. Cylindrical fused quartz cells of 0.05 and 0.02 cm path length were used. The values are expressed in terms of molecular CD.

3-(2-Oxopropyl)-3-hydroxyindolin-2-one 1a. IR (Nujol): ν = 3363, 3318, 1719, 1624 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.03 (d, 1H, J = 17.1 Hz), 3.23 (d, 1H, J = 17.1 Hz), 4.81 (bs, 1H), 6.91 (d, 1H, J = 7.5 Hz), 7.07 (t, 1H, J = 7.5 Hz), 7.24−7.39 (m, 2H), 8.43 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.4, 48.8, 74.5, 110.5, 123.1, 124.2, 128.5, 130.1, 140.6, 178.2, 207.5. MS (EI) *m/z* (rel intensity): 206 (M^+ + 1), 188, 146. HRMS (EI): calcd for $C_{11}H_{11}NO_3$ (M^+ + 1) 206.0817, found 206.0829.

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Supporting Information Available: Experimental details and characterization of the isatin derivatives **1a**−**d** and the catalysts **2**−**16**; ^{1}H NMR and ^{13}C NMR spectral data for **1a**−**d**; and X-ray crystallographic data (CIF), experimental crystallographic details, and ORTEP drawings for **1e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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