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# Asymmetric aldol reaction of isatins with acetone in the presence of terpene amino alcohols

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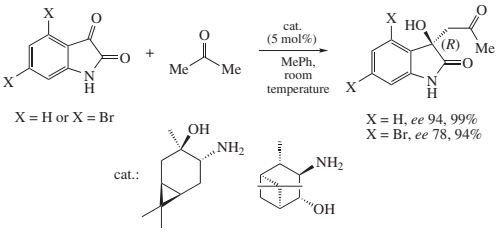
**Asymmetric aldol reactions of isatin and 4,6-dibromoisatin with acetone are efficiently catalyzed by β-amino alcohols derived from α-pinene and 3-carene. The target compounds can be isolated by crystallization from toluene, which eliminates the need for using chromatography and makes the asymmetric synthesis of (*R*)-convolutamydine A (up to 94% *ee* and yield 75%) simple and convenient.**

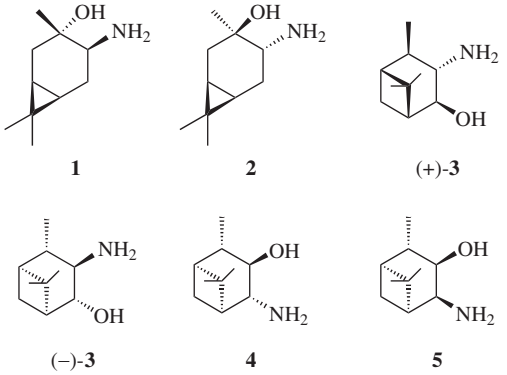



*Keywords*: aldol reaction, β-amino alcohols, 3-carene, α-pinene, isatin, 4,6-dibromoisatin, convolutamydine A.

Asymmetric aldol reaction is a simple and convenient method for enantioselective formation of the carbon–carbon bond in organic compounds.[1] Effective organocatalysts for this reaction are proline and some of its derivatives,[1] as well as a number of other chiral amines of natural origin.[2] The metal complex compounds with terpene ligands are also successfully applied in reactions of this type.[3]

Among the various aldol condensations, enantioselective reactions between two ketones in which one acts as donor and the other as acceptor are of considerable interest as a source of compounds valuable for pharmacology.[4] In particular, products of aldol reactions of ketones with isatin-derived acceptors,[5] which contain the motif of 3-substituted 3-hydroxy-2-indole, are useful biologically active compounds, *e.g.*, TMC-95 (A-D), celogentin K, dioxibrassinine.[6] (*R*)-Convolutamydine A, a product of reaction of 4,6-dibromoisatin and acetone,[7] was isolated from the marine bryozoa of the genus *Amathia convoluta*. It inhibits the differentiation of promyelocytic leukemia cells of human line HL-60 and exhibits potent anticancer activity.[8]

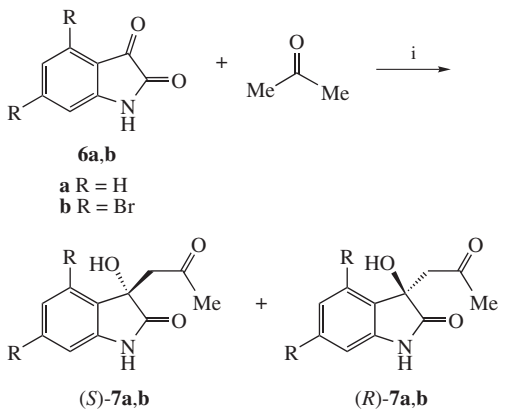
Asymmetric aldolization of isatin derivatives with acetone are efficiently catalyzed by chiral β-amino alcohols, *viz.* leucinol and valinol,[2(a)] where the corresponding aldols are formed with up to 95% *ee*. Recently we have shown[9] that β-amino alcohols **1**–**5** derived from α-pinene and 3-carene are also capable of catalyzing these reactions.




Herein, catalysts of this type were applied to the stereoselective synthesis of (*R*)-convolutamydine A.

At first, the model reaction of isatin **6a** with acetone (Scheme 1) was carried out at ambient temperature in the presence of amino alcohol **1** (20 mol%), which previously[9(a)] exhibited promising stereoinduction (84% *ee*) in dichloromethane (Table 1, entry 1). However, in 1,2-dichloroethane and *tert*-butyl methyl ether a substantial decrease in the yield and *ee* of aldol (*S*)-**7a** were recorded (entries 2 and 3).

The best enantioselectivity (90% *ee*) was achieved in acetone (entry 4), though at the expense of prolonged reaction time (110 h). Interesting results were attained in toluene, where a major part of generated aldol (*S*)-**7a** precipitated in the course of the reaction (entry 5). After filtration, the pure product was obtained in 77%




**Scheme 1** *Reagents and conditions*: i, catalyst **1**–**5**, solvent, $H_2O$ (2 equiv.), room temperature, 24–180 h.

**Table 1** Asymmetric aldol reactions of isatins **6a**,**b** with acetone.[a]

| Entry | Isatin | Solvent | Catalyst (loading, mol%) | *t*/h | Product | Yield (%)[b] | *ee* (%)[c] (configuration) |
|---|---|---|---|---|---|---|---|
| | | | | | | solution/precipitate | solution/precipitate |
| 1 | **6a** | $CH_2Cl_2$ | **1** (20) | 24 | **7a** | 95/– | 84 (*S*)[8(a)] |
| 2 | **6a** | $Cl(CH_2)_2Cl$ | **1** (20) | 40 | **7a** | 76/– | 68 (*S*) |
| 3 | **6a** | $Bu^tOMe$ | **1** (20) | 24 | **7a** | 87/– | 67 (*S*) |
| 4 | **6a** | $Me_2CO$ | **1** (20) | 110 | **7a** | 93/– | 90 (*S*) |
| 5 | **6a** | PhMe | **1** (20) | 20 | **7a** | 11/77 | 29/78 (*S*) |
| 6 | **6a** | PhMe | **1** (10) | 24 | **7a** | 21/79 | 10/90 (*S*) |
| 7 | **6a** | PhMe | **1** (5) | 20 | **7a** | 31/63 | 73/94 (*S*) |
| 8 | **6a** | PhMe | **1** (1) | 90 | **7a** | 14/86 | 52/91 (*S*) |
| 9 | **6a** | PhMe | **2** (5) | 42 | **7a** | 6/65 | 58/94 (*R*) |
| 10 | **6a** | PhMe | (+)-**3** (5) | 72 | **7a** | 3/69 | 59/89 (*S*) |
| 11 | **6a** | PhMe | (–)-**3** (5) | 20 | **7a** | 4/76 | –7 (*S*)/99 (*R*) |
| 12 | **6a** | PhMe | **4** (20) | 72 | **7a** | 30/70 | 93/93 (*R*) |
| 13 | **6a** | PhMe | **5** (20) | 180 | **7a** | 66/30 | 57/72 (*R*) |
| 14 | **6b** | PhMe | **2** (5) | 72 | **7b** | 20/55 | 84/78 (*R*) |
| 15 | **6b** | PhMe | (–)-**3** (5) | 72 | **7b** | 11/75 | 68/94 (*R*) |

[a] Conditions: **6a** (0.07 mmol) or **6b** (0.09 mmol), acetone (2.1 mmol, except for entry 4), solvent (144 equiv.), $H_2O$ (2 equiv.), room temperature. [b] Isolated yields. [c] Determined by chiral HPLC.

yield and with 78% *ee*. Additional crop (~ 11%) of (*S*)-**7a** isolated from the mother liquor by column chromatography had significantly lower *ee* (29%) compared to the precipitated crystals. Enantiomeric enrichment of product (*S*)-**7a** *via* spontaneous crystallization provides an efficient tool for facile product isolation without usage of column chromatography. Therefore, we further studied the reaction between **6a** and acetone in toluene at 1–10 mol% catalyst loadings and succeeded in improving enantiomeric enrichment of crystals to 94% with 5 mol% of **1** (entries 6–8).

Next, we examined 3-carene- and α-pinene-derived catalysts (**2**–**5**) (5, 20 mol%) in the model reaction between **6a** and acetone in toluene (see Table 1, entries 9–13).[†] A significant portion of product **7a** was also precipitated from MePh and could be isolated with up to 99% *ee* without use of chromatography. Reactions catalyzed by amino alcohols **2** and **3** efficiently proceeded at 5% catalyst loading (entries 9–11), whereas the corresponding transformations catalyzed by **4** and **5** were rather sluggish even at 20% catalyst loading (entries 12 and 13). Remarkable inversion of configuration of product **7a** isolated from the toluene solution (–7% *ee vs.* 99% *ee* for precipitated crystals) was observed in the reaction catalyzed by antipode (–)-**3** (entry 11). Another important finding is that although the stereocenters at the amino group in catalysts **4** and **5** have different configurations, the same product (*R*)-**7a** was formed in both cases; the optical rotations were $[\alpha]_D = +21.2$ (*c* 0.2, MeOH) and $[\alpha]_D = +20.1$ (*c* 0.2, MeOH), respectively; lit.[5(a)] $[\alpha]_D = +27.3$ (*c* 0.5, MeOH) for (*R*)-**7**.

To synthesize the target convolutamydine A **7b**, we carried out the reaction of 4,6-dibromoisatin **6b**[10] with acetone (see Table 1, entries 14 and 15) in the presence of catalysts **2** and (–)-**3** (5 mol%), which showed the best stereoinduction in the model reaction between **6a** and acetone in MePh. Here too, a major portion of product **7b** precipitated from the reaction mixture and could be isolated in analytically pure state without chromatography. The crystalline substance **7b** obtained in the presence of catalyst **2** (5 mol%) had enantiomeric purity of 78%, whereas in the (–)-**3**-catalyzed reaction it reached 94%, a value competitive to best previously reported results[2(a)] (see Table 1).

In summary, β-amino alcohols derived from α-pinene and 3-carene act as efficient stereoinductors in asymmetric aldol reactions of isatin and 4,6-dibromoisatin with acetone. Carrying out these reactions in MePh significantly simplifies workup excluding labor-consuming chromatography. The developed procedure may be considered as the most convenient enantioselective (up to 94% *ee*) synthesis of anticancer agent (*R*)-convolutamydine A.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.005.

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[†] *General procedure for the aldol reactions of isatin and 4,6-dibromoisatin with acetone.* A solution of catalyst **1**–**5** (for the catalyst loading, see Table 1) in acetone (0.15 ml)/water (0.14 mmol) mixture was added to a solution of isatin **6a** or **6b** (0.07 mmol and 0.09 mmol, respectively) in MePh (1.2 ml). The mixture was stirred for specified time under the conditions given in Table 1. The precipitate formed was filtered, washed with MePh (3 x 0.3 ml) and dried in air to afford pure compound **7a** or **7b**. The mother liquor was subjected to silica gel column chromatography (EtOAc/*n*-hexane, 3:1) to afford additional crop of compound **7a** or **7b**. The *ee* values of products **7a** and **7b** (mother liquors and precipitates) were determined by HPLC on a chiral column Chiralpak AD-H. The spectral data of compounds **7a** and **7b** corresponded to those described previously.[2(a)]

HPLC-chromatograms of aldols **7a** and **7b** are presented in Online Supplementary Materials.

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