Asymmetric Organocatalysts
Asymmetric organocatalysts have emerged as a powerful synthetic tool that is complementary to metal-catalyzed reactions. Pioneering work in this area dates back to the 1970s, in which Eder et al. and Hajos et al. separately reported an intramolecular asymmetric aldol reaction which employed L-proline \([\text{P0481}]\) as catalyst.\(^1\) This reaction was considered to be a special case at that time. Later in 2000, List et al. reported an L-proline-catalyzed intermolecular asymmetric aldol reaction.\(^3\) The same year, MacMillan et al. documented the first highly enantioselective amine-catalyzed Diels-Alder reaction.\(^4\) These reports received a great deal of attention and the research in the area of asymmetric organocatalysts has since thrived.\(^5\)

Later, the significance of these proline-catalyzed reactions was luminously demonstrated by MacMillan for the application to carbohydrate synthesis.\(^6\) Córdova et al. reported a proline-catalyzed asymmetric conversion of protected glycol aldehydes into hexoses in one step.\(^7\)

Compared with conventional transition metal complex catalysts, asymmetric organocatalysts offer several advantages including operational simplicity, their availability, and low toxicity which confer a direct benefit in the production of pharmaceuticals and contribution to green chemistry.

In the initial spectacular advances in asymmetric organocatalysis, proline and its analogues have been predominantly employed. Generally organocatalytic aldol reactions with ketones as acceptors require high catalyst loadings, however a recent development in this area enables the reaction with a lower catalyst loading. Nakamura et al. reported the enantioselective synthesis of (R)-convolutamydine by using 5 mol% of newly developed novel \(N\)-heteroaryl-sulfonylprolinamide \([\text{T3080}]\).\(^8\) In this reaction, amounts of the catalyst can be reduced to 0.5 mol% with retention of the enantioselectivity even though the time takes longer to complete the reaction.

Singh et al. also developed a new class of proline-based organocatalysts and reported asymmetric direct aldol reactions with excellent enantioselectivities (>99% ee). A variety of ketones and aldehydes could be employed using 0.5 mol% of catalyst \([\text{H1407}]\).\(^9\)

Due to the various advantages including ready availability and versatility, the asymmetric reactions using other amino acids as organocatalysts were also intensively studied. More recently, the group of Lu explored the possibility of deriving a wide array of novel multifunctional organocatalysts from amino acid structural scaffolds.\(^10\) The new catalyst, dipeptide-derived phosphine \([\text{T2937}]\), was proven to promote enantioselective \([3+2]\) cycloadditions of allenes to acrylates or acrylamides.
Cinchona alkaloids and their derivatives have been intensively used as chiral ligands for metal-catalyzed reactions or as organocatalysts as demonstrated in Sharpless asymmetric dihydroxylation with an OsO₄-cinchona alkaloids complex. It is considered as one of the most privileged chiral inducers. Cinchona alkaloids-derived catalysts could be effectively applied for nearly all classes of organic reactions. The quinuclidinyl moiety as a tertiary amine could serve as an active center for Brønsted base catalysis, Lewis base catalysis, and nucleophilic catalysis. Upon alkylation of the quinuclidine nitrogen, the resulting ammonium salts could serve as phase transfer catalysts, another class of organic catalysis. Hatakeyama, Ishihara, et al. have developed α-isocupreine (α-ICPN) [E0974], a pseudoenantiomer of β-isocupreidine [I0728] and reported the application to an efficient asymmetric Morita-Baylis-Hillman (MBH) reaction. Since the pioneering work on asymmetric synthesis of amino acids using N-benzyl cinchoninium halide as a chiral phase transfer catalyst in 1980s, numerous cinchona alkaloids-derived chiral phase-transfer catalysts have been developed. In the late 1990s, a totally new aspect on the design of chiral phase-transfer catalyst, based on the C₂-symmetrical chiral binaphthyl moiety, has emerged. The ongoing efforts towards the simplification of the catalyst have led to the novel catalyst which could be employed under even milder conditions with excellent enantioselectivities. Maruoka et al. reported an enantioselective conjugate addition of 3-substituted oxindoles to Michael acceptors under neutral conditions in a water-rich solvent in the presence of a newly developed morpholine-derived chiral phase-transfer catalyst [B3970] without base additives.

Nucleophilic carbene is an emerging class of asymmetric organocatalysis. Since the report of the first asymmetric intramolecular Stetter reaction by Enders et al., there have been many reports on asymmetric carbon-carbon bond formation reactions via umpolung of aldehydes mediated by N-heterocyclic carbene (NHC) catalysts. Bode et al. have reported highly enantioselective Diels–Alder reactions to afford dihydropyridinones using an NHC catalyst [D3983] generated in situ.

The imidazolidinone derivatives [B4137] [B4138] are asymmetric organocatalysts developed by MacMillan et al. To date, various types of asymmetric reactions using B4137 and B4138 have been reported, such as Mukaiyama-Michael addition, epoxidation of α,β-unsaturated aldehydes, 1,3-addition of aldehydes, and the Diels-Alder reaction. The desired products are realized in high yields and selectivity in all the cases. These reactions are often utilized in total syntheses of natural products to construct complex condensed-ring structures such as in spinosyn. Thus, B4137 and B4138 are powerful tools and their use in new asymmetric reactions is anticipated.

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The two prolinol derivatives D3867 and D3843, known as Hayashi-Jørgensen catalysts are utilized in various types of asymmetric reactions. For instance, Hayashi et al. have reported an asymmetric Michael addition of nitroalkenes and aldehydes, which gives syn adducts with high enantio- and diastereoselectivities. Furthermore, utilizing this reaction as a key early-stage step allowed them to achieve a short synthesis of the anti-flu drug oseltamivir phosphate. Additionally, Jørgensen’s group have reported a tandem Michael/intramolecular Morita-Baylis-Hillman reaction to afford cyclohexanone derivatives.

Ishihara’s group has developed a new iodoarene catalyst $[I1122]$ for the enantioselective spirolactonization. The given spirolactone has a diene moiety, so that it affords an optically active fused ring compound in one-pot synthesis through Diels-Alder reaction with an olefin. Furthermore, $I1122$ is also utilized in the construction of asymmetric cyclic acetals.
References


(b) V. Maya, M. Raj, V. K. Singh, Org. Lett. 2007, 9, 2593.

(c) S. G. Hentges, K. B. Sharpless, J. Am. Chem. Soc. 1980, 102, 4263.
The list of products

We introduce our products according to their structure.

<table>
<thead>
<tr>
<th>Product</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolines, Proline Analogs</td>
<td>7</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>8</td>
</tr>
<tr>
<td>Cinchona Alkaloids</td>
<td>8</td>
</tr>
<tr>
<td>Chiral Imidazolidinones</td>
<td>9</td>
</tr>
<tr>
<td>Chiral Oxazaborolidines</td>
<td>9</td>
</tr>
<tr>
<td>Chiral Isothioureas</td>
<td>9</td>
</tr>
<tr>
<td>Chiral Diols</td>
<td>9</td>
</tr>
<tr>
<td>Chiral Phosphoric Acids</td>
<td>9</td>
</tr>
<tr>
<td>Chiral Sulfonic Acids</td>
<td>10</td>
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<tr>
<td>Chiral Amines</td>
<td>10</td>
</tr>
<tr>
<td>Chiral Ammonium Salts</td>
<td>10</td>
</tr>
<tr>
<td>Chiral N-Heterocyclic Carbenes (NHC)</td>
<td>10</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
</tr>
</tbody>
</table>
Asymmetric Organocatalysts

Prolines, Proline Analogs

- **α-Methyl-L-proline**
  - CAS RN: 42856-71-3

- **trans-4-(tert-Butyl-diphenylsilyloxy)-L-proline**
  - CAS RN: 259212-61-8

- **(R)-(+)-Indoline-2-carboxylic Acid**
  - CAS RN: 98167-06-7

- **(S)-(-)-Indoline-2-carboxylic Acid**
  - CAS RN: 79815-20-6

- **2-Aminomethyl-1-ethyl-indole-2-carboxylic Acid**
  - CAS RN: 22795-99-9

- **2,5-Diphenylpyrrolidine**
  - CAS RN: 80875-98-5

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Please inquire for pricing and availability of listed products to our local sales representatives.
Asymmetric Organocatalysts

Chiral Imidazolidinones

Chiral Oxazaborolidines

Chiral Isothioureas

Chiral Diols

Chiral Phosphoric Acids

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Asymmetric Organocatalysts

Please inquire for pricing and availability of listed products to our local sales representatives.
### Others

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