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# Direct Catalytic Asymmetric Amination of Aldehydes: Synthesis of Evans Oxazolidinones and $\alpha$ -Amino Acids

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Research by A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, and K.A. Jørgensen, *Angew. Chem. Int. Ed. Engl.* **2002**, 41, 1790; B. List, *J. Am. Chem. Soc.* **2002**, 124, 5656

Condensation and commentary by **Chambers C. Hughes** and **Dirk Trauner**, University of California, Berkeley

## Condensation of the Research

### Purpose of the Studies

*To explore the scope and utility of the proline-catalyzed asymmetric  $\alpha$ -amination of aldehydes with azodicarboxylates*

### Background

The catalysis of reactions with organic molecules void of transition metals has lately assumed a prominent role in asymmetric synthesis. Among different catalysts, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile.<sup>1</sup> The simultaneous presence of a carboxylic acid and amine bestows a unique bifunctional character to this chiral molecule.

Early contributions by Hajos and Parrish, as well as Eder, Sauer and Wiechert, focused on asymmetric Robinson annulations in the context of steroid synthesis (Scheme 1, Eq. 1).<sup>2</sup> The broad scope of proline-catalyzed reactions, however, was not realized until recently. It was only in the late 1990s that *intermolecular* variants, such as asymmetric aldol reactions (Eqs. 2 and 3)<sup>3,4</sup> and Mannich reactions (Eq. 4)<sup>5</sup> began to surface in the literature.

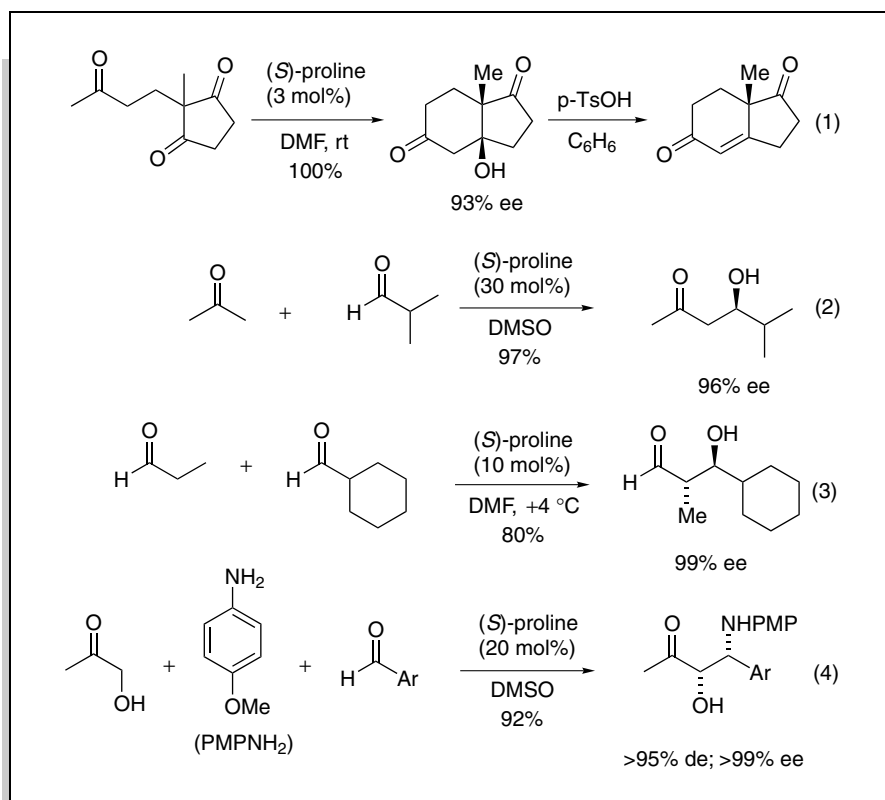
In all the reactions shown in Scheme 1, proline presumably condenses with a carbonyl compound to generate a chiral enamine and water (Scheme 2). The enamine subsequently reacts with a  $\pi$ -electrophile  $X = Y$ , which may be another carbonyl (aldol reaction), an imine (Mannich reaction), an activated olefin (Michael reaction), or an azodicarboxylate

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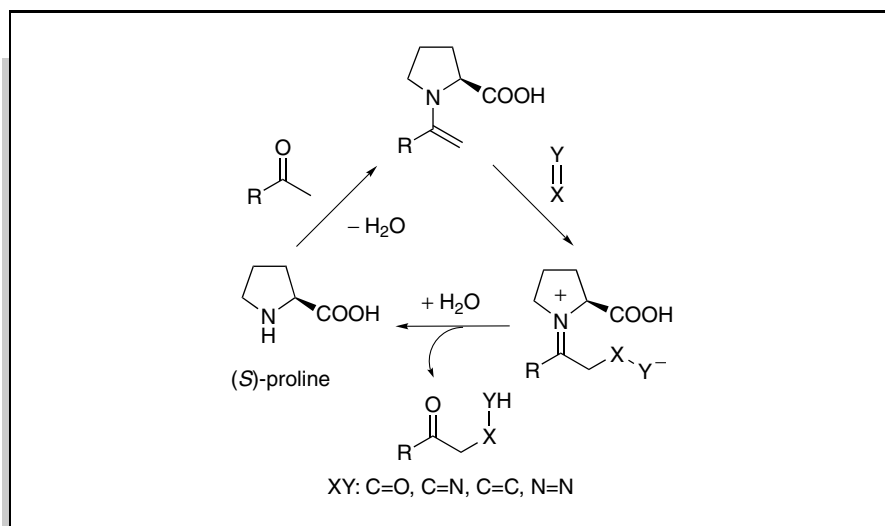
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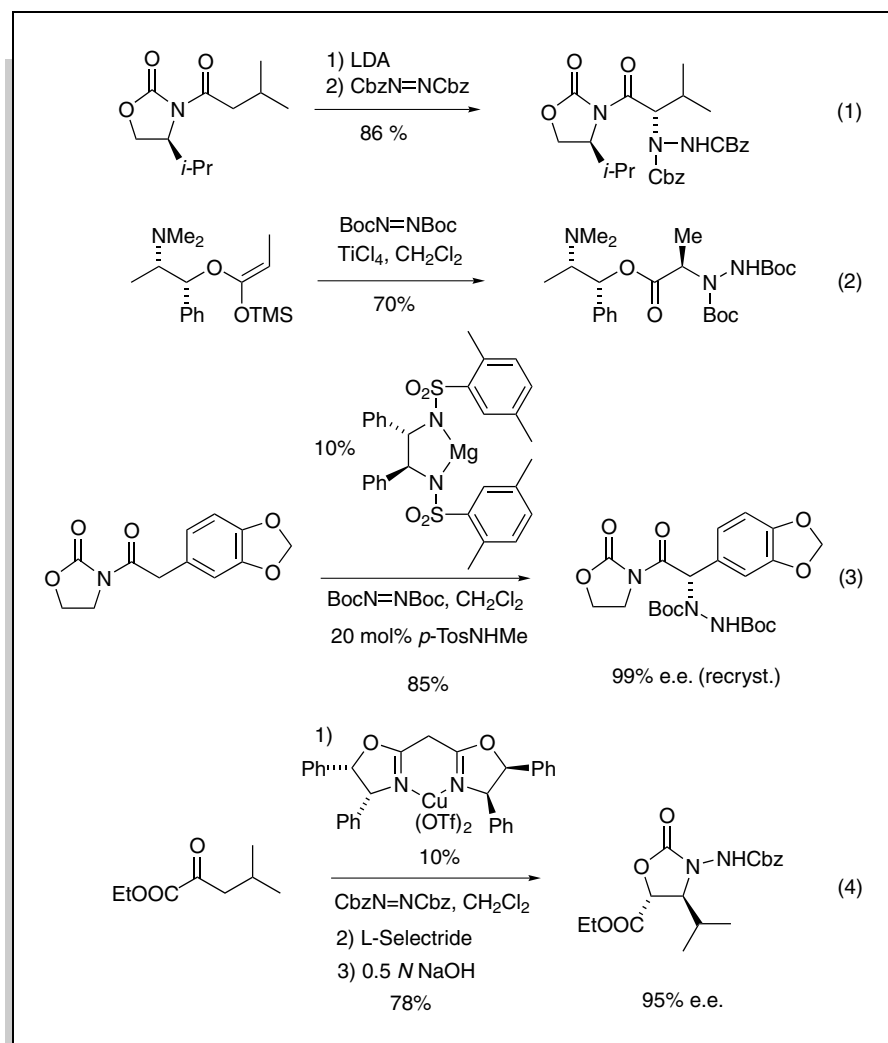


**Scheme 1.** Some representative proline-catalyzed asymmetric reactions.



**Scheme 2.** The enamine catalysis cycle.

( $\alpha$ -amination, *vide infra*). Subsequent hydrolysis of the resulting iminium ion liberates the product and regenerates the active catalyst. It is important to note that proline must remain either unreactive towards  $X = Y$  or react with the electrophile in a reversible fashion.



**Scheme 3.** Asymmetric electrophilic aminations using azodicarboxylates.

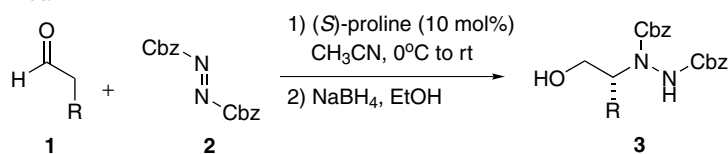
The electrophilic  $\alpha$ -amination of carbonyl compounds is a conceptually attractive method for the synthesis of nitrogenous compounds.<sup>6</sup> That this strategy is not more widely used may be partially due to a psychological barrier: nitrogen is usually thought of as the nucleophilic component in a reaction. Of course, the small number of suitable *N*-electrophiles also limits its popularity. Apart from sulfonyl azides, azodicarboxylates have proven to be the most successful aminating reagents. They are widely available, relatively cheap, and highly reactive. Several asymmetric aminations using azodicarboxylates have been disclosed (Scheme 3),<sup>7</sup> including direct catalytic enantioselective ones.<sup>7c-e</sup>

### What Researchers Accomplished

In the two articles discussed here, virtually published simultaneously, List and Jørgensen have recently shown that proline catalyzes the reaction of simple unbranched aldehydes with certain azodicarboxylates to furnish, directly, optically active  $\alpha$ -hydrazino aldehydes (Table 1). The reactions are reasonably fast at room temperature and the observed yields and ee's are good to excellent.

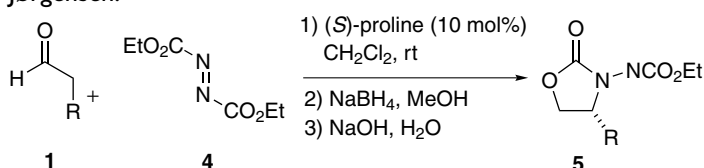
**Table I.** Proline-catalyzed asymmetric  $\alpha$ -amination of aldehydes

List:



Product	R	Yield (%)	ee (%)
<b>3a</b>	<i>i</i> -Pr	99	96
<b>3b</b>	<i>n</i> -Pr	93	>95
<b>3c</b>	<i>n</i> -Bu	94	97
<b>3d</b>	Me	97	>95
<b>3e</b>	Bn	95	>95

Jørgensen:

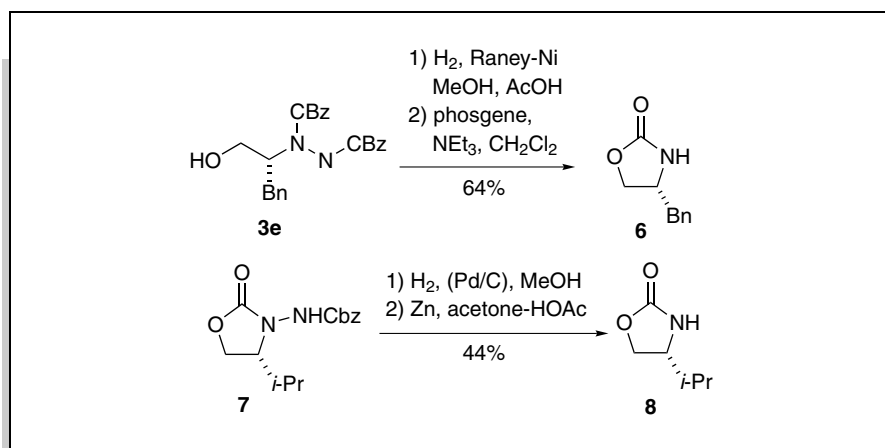


Product	R	Yield (%)	ee (%)
<b>5a</b>	Me	67	93
<b>5b</b>	Et	77	95
<b>5c</b>	<i>i</i> -Pr	83	93
<b>5d</b>	<i>t</i> -Bu	57	91
<b>5e</b>	allyl	92	93
<b>5f</b>	Bn	68	89

The enantiomeric excesses of the resulting  $\alpha$ -hydrazino aldehydes were observed to decrease slowly because of the  $\alpha$ -acidity of the carbonyl group. Assessing the inherent enantioselectivity of this process therefore required the reduction of the intermediate aldehyde with sodium borohydride prior to isolation. To further simplify isolation and purification, Jørgensen and colleagues cyclized the resulting  $\alpha$ -hydrazino alcohols under basic conditions to furnish stable *N*-amino oxazolidinones.

The efficiency of the reaction depends on the choice of azodicarboxylate, solvent, and temperature. High yields and enantioselectivities were obtained using several dialkyl azodicarboxylates. However, use of dibenzyl azodicarboxylate as the aminating agent yielded enantioenriched products bearing an easily removable and UV-detectable carbobenzyloxy (Cbz) protecting group. Acetonitrile or dichloromethane have emerged as the best solvents. Other solvents (e.g., dioxane, toluene, ethyl acetate) led to longer reaction times and lower enantioselectivities. Lowering the reaction temperatures only had a modest effect on enantioselectivities.

Both groups have shown that the enantioenriched  $\alpha$ -hydrazino alcohols (List) or *N*-amino oxazolidinones (Jørgensen) can be effectively transformed into important substrates like Evans oxazolidinones (Scheme 4).

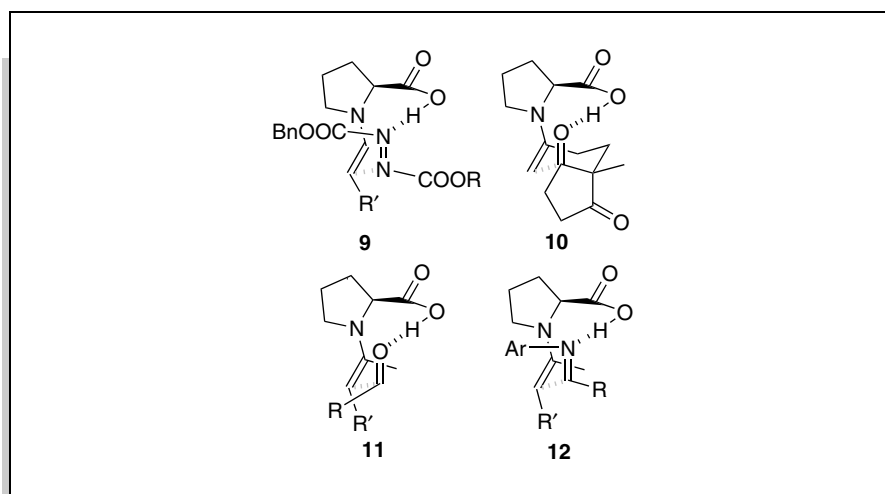


**Scheme 4.** Conversion of chiral  $\alpha$ -hydrazino alcohols and *N*-amino oxazolidinones to Evans auxiliaries.

For example, hydrogenolysis of alcohol **3e** followed by treatment of the resulting amino alcohol with phosgene furnished oxazolidinone **6** in good overall yield. Alternatively, hydrogenolysis of *N*-amino oxazolidinone **7** and subsequent Zn reduction afforded oxazolidinone **8**.

In principle, the  $\alpha$ -hydrazino aldehydes obtained can be converted into  $\alpha$ -amino acids, a process requiring both *N*–*N* bond cleavage and oxidation of the aldehyde function to a carboxylic acid. Although one such transformation has been demonstrated in Jørgensen's article, the generality and efficiency of his protocol remains to be seen.

The observed absolute stereochemistry can be rationalized in terms of a transition state **9** (Fig. 1), which resembles the Houk model for enantio-topos-differentiating intramolecular aldol additions (**10**).<sup>8</sup> This transition state is also consistent with those proposed by List for the proline-catalyzed intermolecular Mannich and aldol reactions (**11** and **12**, respectively).<sup>1</sup>



**Figure 1.** Stereochemical rationale.

## Commentary on the Research

The contributions by List and Jørgensen et al. are further testament to the remarkable scope and versatility of asymmetric aminocatalysis. The authors have opened what looks like one of the most practical routes to enantiomerically pure oxazolidinones,  $\alpha$ -amino alcohols, and possibly  $\alpha$ -amino acids. The starting materials (aliphatic aldehydes and diazocarboxylates) are widely available; the catalyst (proline) is relatively cheap, recyclable, and nontoxic; and the products—usually crystalline—are consistently formed in high enantiomeric excess. The reactions proceed on a convenient time scale with good to excellent yields.

This work will certainly increase the popularity of electrophilic aminations as a means to generate nitrogenous compounds. The immediate products,  $\alpha$ -hydrazino acids, occur as a structural motif in peptidomimetics<sup>9</sup> and natural products like sanglifehrin B<sup>10</sup> or himastatin.<sup>11</sup> The methodology also provides fast access to Evans oxazolidinones, arguably the most widely used chiral auxiliaries in asymmetric synthesis, and may prove useful for the synthesis of  $\alpha$ -amino acids that cannot be easily accessed by other catalytic methods. The fact that expensive D-amino alcohols and acids can be obtained from cheap L-proline is one of the nicer features of this work. It will be interesting to see whether the method can be extended to  $\alpha$ -branched aldehydes or dialdehydes, opening access to more specialized, yet important, compound classes. The efficient conversion of  $\alpha$ -hydrazino aldehydes into  $\alpha$ -amino acids on a large scale also remains to be fully demonstrated.

## References and Notes

1. For an extensive review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.
2. (a) Hajos, Z.G., Parrish, D.R. *J. Org. Chem.* **1974**, *39*, 1615; (b) Eder, U., Sauer, G., Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.
3. (a) List, B., Lerner, R.A., Barbas III, C.F. *J. Am. Chem. Soc.* **2000**, *122*, 2395; (b) Bahmanyar, S., Houk, K.N. *Chemtracts* **2000**, *13*, 904.
4. Northrup, A.B., MacMillan, D.W.C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.
5. (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336; (b) List, B., Pojarliev, P., Biller, W.T., Martin, H.J. *J. Am. Chem. Soc.* **2002**, *124*, 827; (c) Sheehan, S.M., *Chemtracts* **2002**, *15*, 384.
6. Reviews: (a) Genet, J.-P., Greck, C., Lavergne, C.D. In *Modern Amination Methods*, Ricci, A. ed., Wiley-VCH: Weinheim, 2000, ch. 3; (b) Krohn, K. In *Organic Synthesis Highlights*, VCH: Weinheim, 1991, pp. 45–53; (c) Greck, C., Genet, J.P. *Synlett* **1997**, *7*, 741.
7. (a) Trimble, L.A., Vederas, J.C. *J. Am. Chem. Soc.* **1986**, *108*, 6397; (b) Gennari, C., Colombo, L., Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394; (c) Evans, D.A., Nelson, S.G. *J. Am. Chem. Soc.* **1997**, *119*, 6452; (d) Evans, D.A., Johnson, D.S. *Org. Lett.* **1999**, *1*, 595; (e) Juhl, K., Jørgensen, K.A. *J. Am. Chem. Soc.* **2002**, *124*, 2420.
8. (a) Bahmanyar, S., Houk, K.N. *J. Am. Chem. Soc.* **2001**, *123*, 12911; (b) Bahmanyar, S., Houk, K.N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.
9. See for example: (a) Lam, L.K.P., Arnold, L.D., Kalantar, T.H., Kelland, J.G., Lane-Bell, P.M., Palcic, M.M., Pickard, M.A., Vederas, J.C. *J. Biol. Chem.* **1988**, *263*, 11814.

10. Sanglier, J.-J., Quesniaux, V., Fehr, T., Hofmann, H., Mahnke, M., Memmert, K., Schuler, W., Zenke, G., Gschwind, L., Maurer, C., Schilling, W. *J. Antibiot.* **1999**, *52*, 466.
11. Leet, J.E., Schroeder, D.R., Krishnan, B.S., Matson, J.A. *J. Antibiot.* **1990**, *43*, 961.