SYNLETT
# Spotlight 168

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

## Proline: An Essential Amino Acid as Effective Chiral Organocatalyst

Compiled by Eric Lacoste

Eric Lacoste was born in 1978 in Bordeaux, France. He received a Master's degree from University Bordeaux 1 in 2002, and carried out Ph.D. studies under the supervision of Dr. Jean-Marc Vincent and Prof. Yannick Landais. His research interests are based in the field of asymmetric catalysis, including design of new organo- and organometallic catalysts.

Laboratoire de Chimie Organique et Organométallique, UMR CNRS 5802, Université Bordeaux 1, 33400 Talence, France
E-mail: lacoste.eric@gmail.com

### Introduction

Asymmetric organocatalysis can be considered a powerful tool for synthetic challenges because it involves mild reaction conditions and few protection/deprotection steps. The most commonly used organocatalyst for various asymmetric reactions is L-proline (Figure 1), which is one of the essential amino acids.[1] The number of studies has exploded in the past years and so this review is an update of Spotlight No. 60.[1a] Previous results will not be repeated, except to add recent comments.

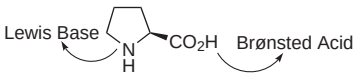



**Figure 1** L-proline, one of the essential amino acids.

The asymmetric organocatalyzed **aldol process**, which today leads to ee values up to 96%,[2] has been used to synthesize important bioactive compounds,[2a] intermediates for *de novo* carbohydrate synthesis,[2b] and 2-hydroxy 1,4-diketones.[2c]

The enantiomeric excess and the diastereomeric ratio for **cross coupling of aldehydes** can be increased by using ionic liquids such as 1-*n*-butyl-3-methylimidazolium-hexafluorophosphate ([bmim]$PF_6$), and the catalyst can be reused.[3]

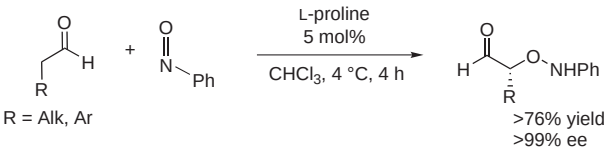
**Robinson annulation**, which affords Wieland–Miescher ketones (i.e., steroid precursors), is used industrially,[1d] and an acyclic version has been studied by Gryko in *N*-methylpyrrolidinone (NMP).[4]

For the **Mannich reaction**,[5] several aldehydes can be used, but *p*-methoxyphenylamine is often the protected amine of choice. The most commonly used ketone is acetone, but cyclopentanone, cyclohexanone and diethylketone have also been used. Preferred solvents are NMP and DMF to afford the products in 50–96% yield and 71–99% ee. The reaction is efficient on multigram scale.[5e] Recently, Bolm and co-workers, using microwaves, have decreased the amount of catalyst to 0.5 mol% and achieved 98% ee.[5f]

**α-Amination** affords non-natural α-amino acids or non-natural α-amino alcohols and has been used to obtain metabotropic glutamate receptor ligands, which are associated with various neurodegenerative diseases.[6]

### Abstracts

(A) If a nitroso compound is used as aldol acceptor, **α-aminoxylation** affords versatile synthons for natural product synthesis.[7]

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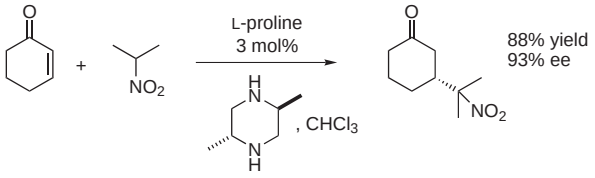
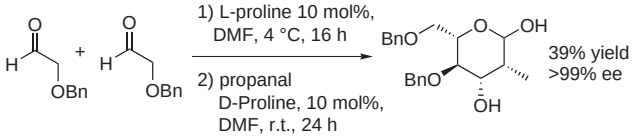
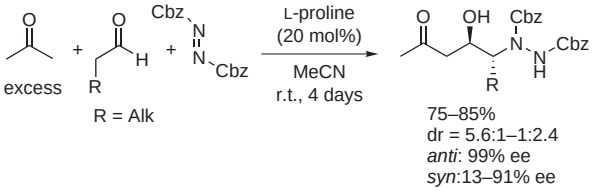
(B) If an additive is used, proline can catalyze the **Michael addition** of nitroalkanes to cyclic enones.[8] In ionic liquid, addition of thiophenols to chalcones is catalyzed by L-proline (up to 91% yield, ee not given).[8b]



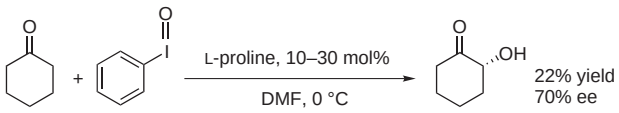

(C) Asymmetric organocatalysis is a powerful tool to **synthesize sugars** in two steps without protection or deprotection reactions, and to realize excellent enantiomeric excesses.[9]




(D) **Cascade reactions** such as the combination of α-amination of an aldehyde and an aldol reaction, are effectively catalyzed by L-proline.[10]




(E) New promising reactions are also in progress. Córdova and co-workers have developed an α-oxidation reaction.[11a] α-Fluorination of aldehydes and ketones with Selectfluor have been developed by Enders and Hüttl to afford the fluorinated cyclohexanone in 43% yield and with 29% ee.[11b]

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