

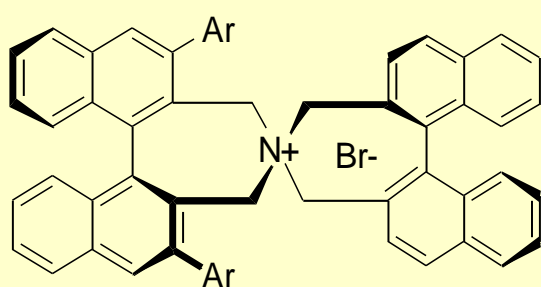
## Nagase Provides Unnatural Amino Acids Using Maruoka Asymmetric Catalyst Technology

Aug. 2008

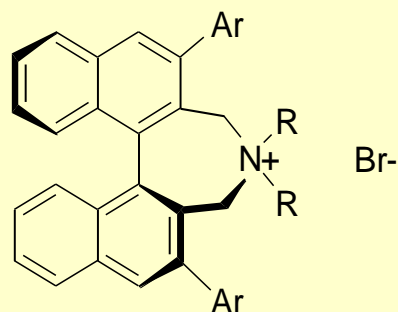
In cooperation with Prof. Keiji Maruoka, Kyoto University, Nagase successfully commercialized Prof. Maruoka's Asymmetric Phase Transfer Catalysts for such industrial applications as unique unnatural amino acids and derivatives thereof. Since the original structure of Prof. Maruoka's catalyst (1) is relatively complex, a new, simpler catalyst (2) was designed and synthesized. This simpler catalyst compared favorably with (1) in terms of intrinsic catalytic activity and stereoselectivity. Using the newly identified catalyst (2), Nagase has now established industrially viable conditions to produce  $\alpha$ -monosubstituted  $\alpha$ -amino acids and  $\alpha$ - $\alpha$ -disubstituted  $\alpha$ -amino acids. In parallel, Nagase has also explored applicability of Maruoka's catalysts to stereocontrolled access to  $\beta$ -hydroxy- $\alpha$ -amino acids and  $\gamma$ -amino acids. To achieve reactions I – IV listed below, less than 0.5 mol% of catalyst (2) sufficed. These reactions have been conducted on an industrial scale at Nagase Chemtex Corporation, Nagase's manufacturing subsidiary, to supply several unnatural amino acids of more than 99.0% ee.

Allylglycine, a versatile intermediate for pharmaceutical products, is one of a library of unnatural amino acids commercially available from Nagase Chemtex Corporation.  $\alpha$ -Methyl  $\alpha$ -amino acids, or  $\alpha$ -substituted alanine derivatives, are also available as building blocks for drug discovery. These unnatural amino acids and many others can also be supplied on a custom basis to support drug development programs. If you have any questions or would like to discuss a specific unnatural amino acid, please contact Nagase's representatives listed on the last page.

## Structures of Maruoka Catalyst<sup>TM</sup>



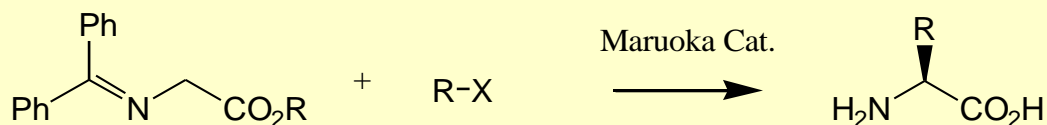
(1)



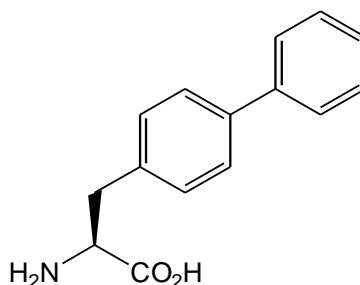
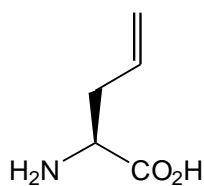
(2)

## Application of Maruoka Catalysts for Assymmetric Reactions

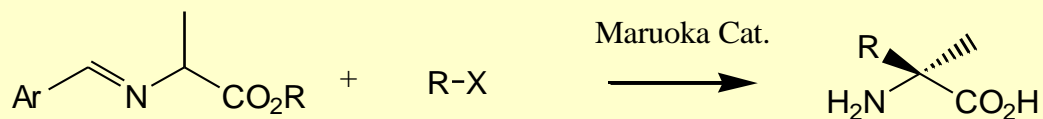
### I. $\alpha$ -Mono-Substituted Amino Acids by Alkylation of Glycine



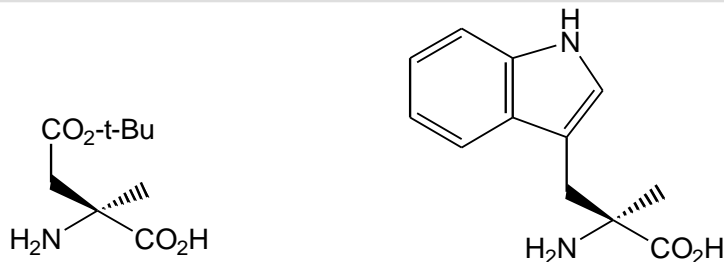
Examples



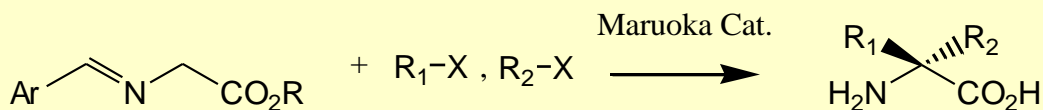
## I I . $\alpha, \alpha$ -Di-Substituted Amino Acids by Alkylation of Alanine



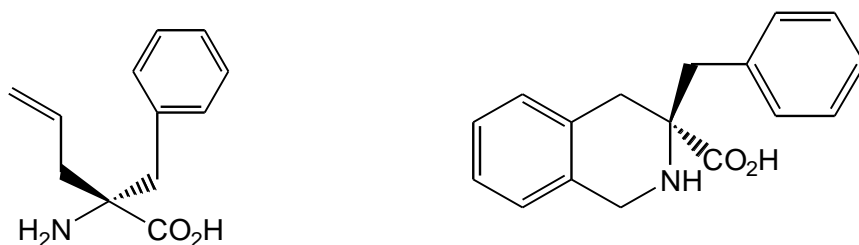
Examples



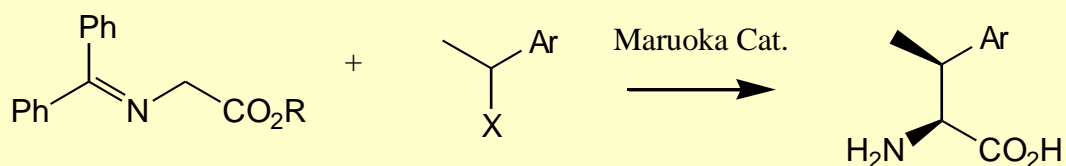
## I I I . $\alpha, \alpha$ -Di-Substituted Amino Acids by Di-alkylation of Glycine



Examples



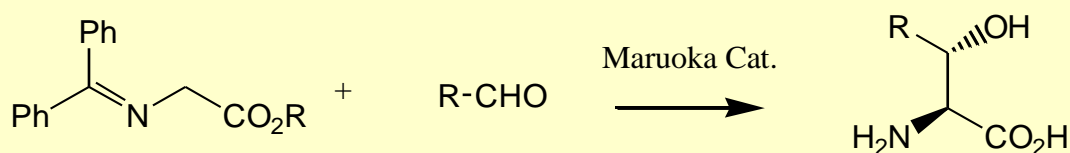
## I V . $\beta$ -Methyl- $\alpha$ -Amino Acids by Alkylation of Glycine



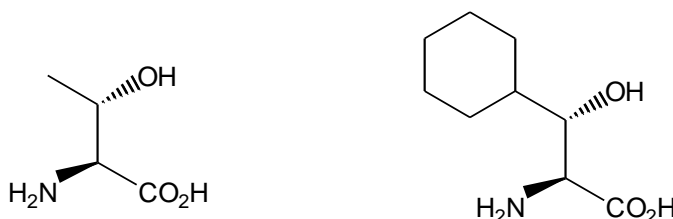
Example



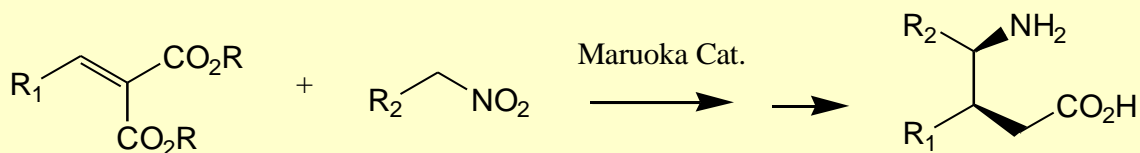
## V. $\beta$ -Hydroxy- $\alpha$ -Amino Acids by Aldol Reaction



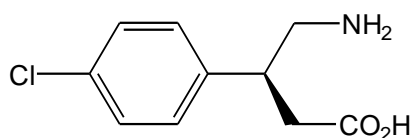
Examples



## V I. $\gamma$ -Amino Acids by Michael Addition

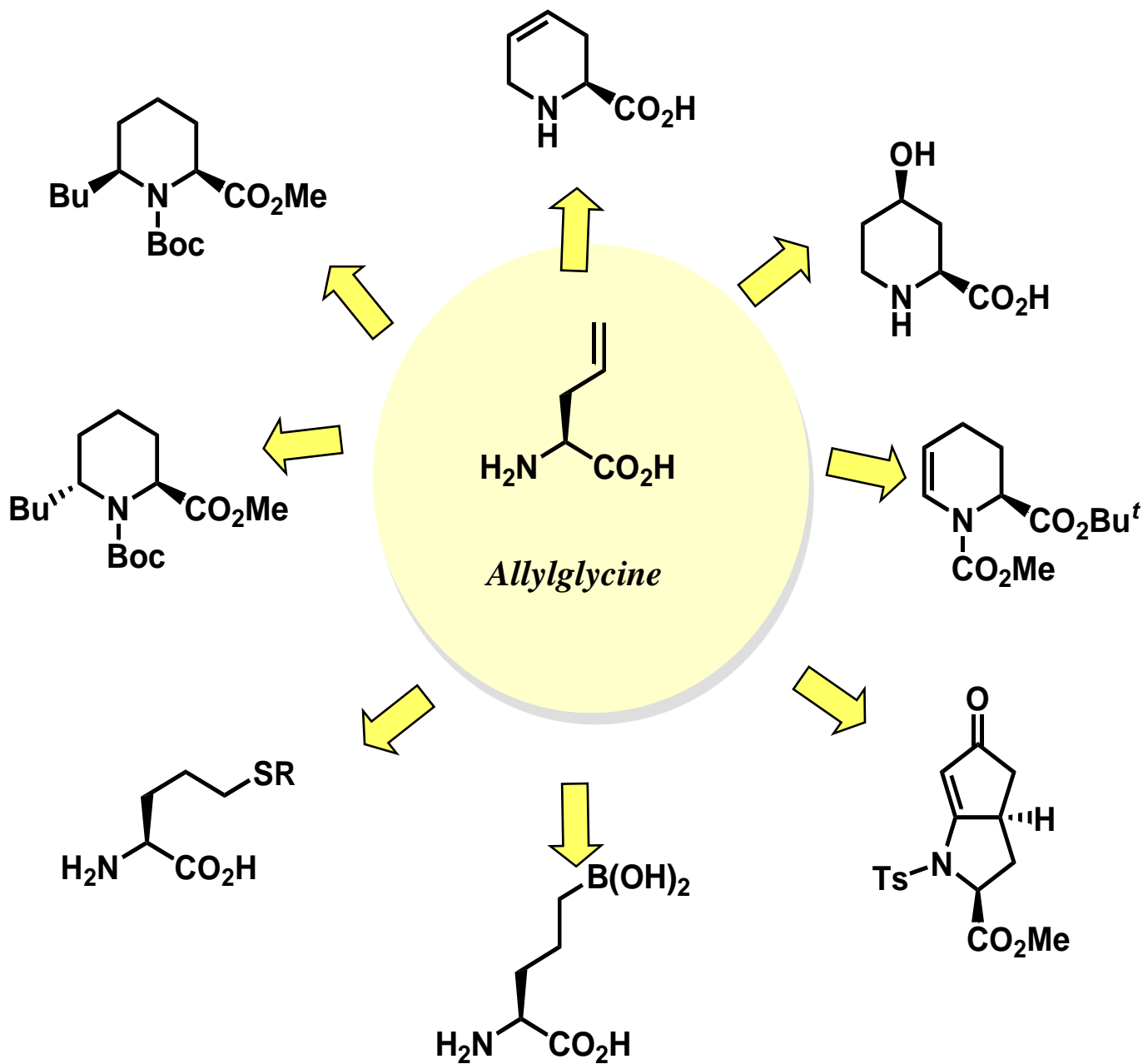


Example



# NAGASE

*Application of Allylglycine to the pharmaceutical intermediates  
Nagase can provide Allylglycine Et ester p-TsOH for grams to MTs scale.*



(References)

1. Rutjes, F.P.J.T. et.al. J.Org.Biomol.Chem. 2005,3,3435
2. Rutjes, F.P.J.T. et.al. J.Chem.Soc.,Perkin Trans 1, 2000,4197

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