# Quaternary Stereocenters by Asymmetric Michael Reactions: Enamine Regiochemistry as Configuration Switch

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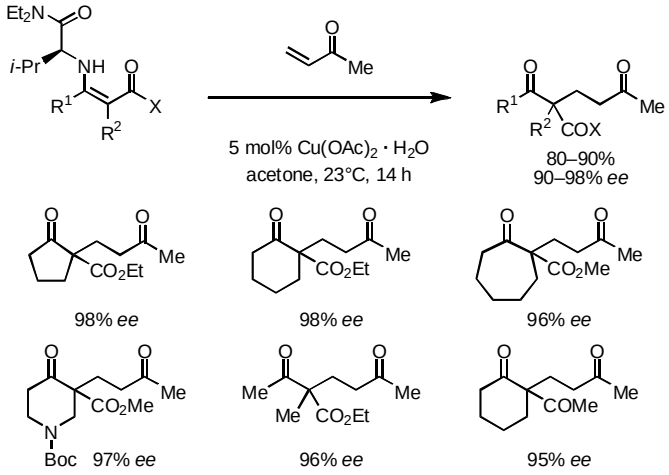
Quaternary stereocenters were obtained with high enantioselectivity by copper-catalyzed Michael reactions using L-valine diethylamide as chiral auxiliary. Starting with β-diketones, either *endo*- or *exo*-cyclic enamines could be obtained by proper choice of the activating agent (Brønsted or Lewis acid). These regioisomers behaved complementary with respect to the absolute configuration of the product in the conjugate addition. With the same configuration of the auxiliary, *endo*-enamines gave the (*R*)-configurated product, whereas *exo*-enamines gave the (*S*)-configuration.

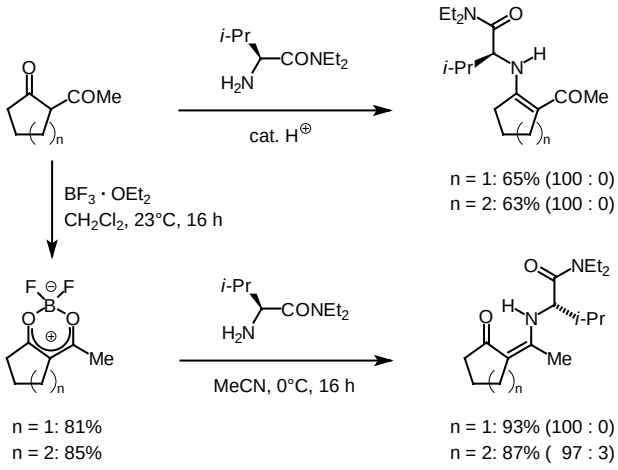
## Asymmetric Michael Reaction

Reaction of L-valine diethylamide with β-dicarbonyl compounds yielded enamines, which could be further converted in copper-catalyzed asymmetric Michael reactions with enones.[1] Products with a quaternary stereocenter were obtained with almost quantitative stereoselectivity.[2]



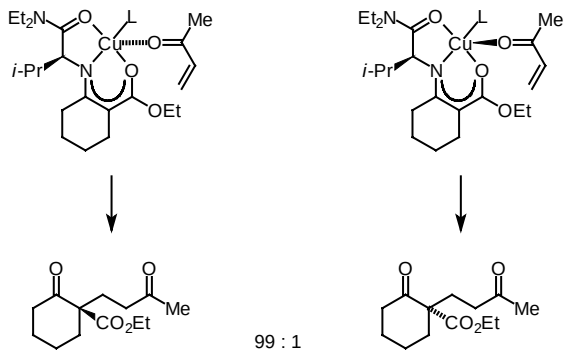

## Regioselective Enamine Formation

Brønsted acid catalyzed reaction of L-valine amide with cyclic α-acetyl ketones yielded *endo*-cyclic enamines as thermodynamic products. In contrast, treatment with $BF_3 \cdot OEt_2$ gave water and air stable betaines, which react under formation of the *exo*-cyclic enamines as the kinetic products.[3]



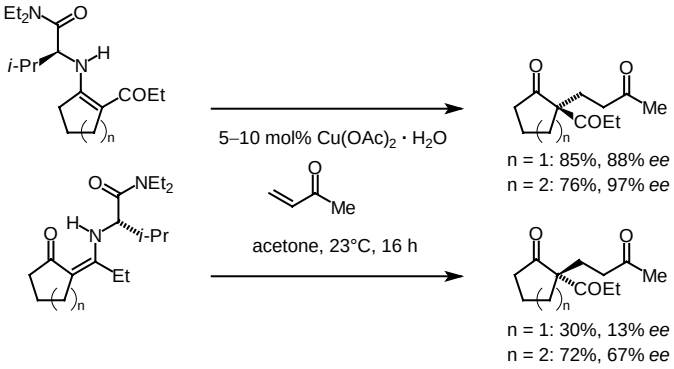

## Mechanistic Proposal

Copper(II)-complexes with tridentate aza-diketonato ligands are proposed as reaction intermediates. The front face of the six-membered ring is shielded by the isopropyl group and the acceptor reacts from the back face.




## Configuration Switch by Regiochemistry

In copper-catalyzed Michael reactions with methylvinylketone, *endo*-cyclic enamines gave products with (*R*)-configuration. The (*S*)-enantiomeric products are formed from the reaction of *exo*-cyclic enamines.[4]




[1] (a) J. Christoffers, *Chem. Eur. J.* **2003**, *9*, 4862–4867. (b) J. Christoffers, K. Schuster, *Chirality* **2003**, *15*, 777–782.

[2] (a) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. (b) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726–1728.

[3] J. Christoffers, B. Kreidler, S. Unger, W. Frey, *Eur. J. Org. Chem.* **2003**, 2845–2853.

[4] (a) J. Christoffers, B. Kreidler, H. Oertling, S. Unger, W. Frey, *Synlett* **2003**, 493–496. (b) B. Kreidler, A. Baro, W. Frey, J. Christoffers, *Chem. Eur. J.* **2005**, *11*, 2660–2667.