

Copper-Catalyzed Construction of Quaternary Stereocenters

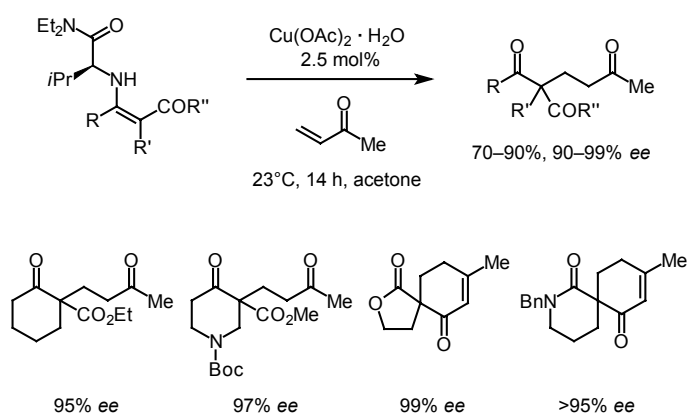
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Introduction

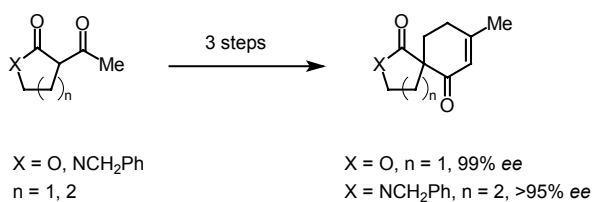
The copper(II)-catalyzed asymmetric Michael reaction with L-valine diethylamide as the chiral auxiliary allows the construction of quaternary carbon centers^[1] with up to 99% *ee* selectivity.^[2] The outstanding features of this procedure are:

- high selectivities even at ambient temperature,
- quantitative recovery of the auxiliary by extraction after workup,
- neither inert nor anhydrous conditions required,
- acetone as the solvent,
- wide substrate range: acyclic and cyclic β -oxo esters and β -diketones and heterocyclic β -diketones,
- compatibility of substrates with donor functions, e.g. carbamate moieties.



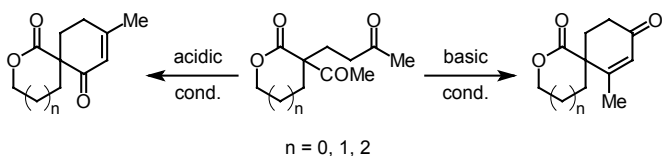
Tandem Michael-Aldol Reactions

In the case of α -acetylactones^[3] and -lactams^[4] as Michael donors, a reaction sequence of Michael reaction and subsequent Robinson annulation yields spirocyclic annulation products with high enantiomeric purity.



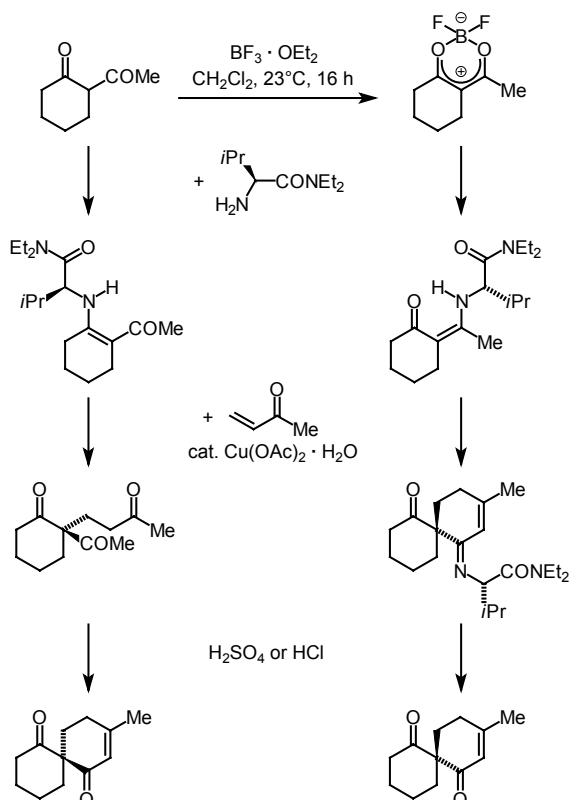
Regioselective Spiroannulations

Robinson annulation could lead to regioisomeric β - or δ -dicarbonyl compounds. By varying the annulation conditions the regioselectivity of spiroannulation of Michael addition products derived from α -acetylactones can be controlled to give exclusively either β -oxo- or δ -oxo lactones. The β - and δ -dicarbonyl constitutions are confirmed by X-ray crystallographic analysis.^[5]



Regioselective Enamine Formation

β -Diketones react with L-valine diethylamide to exo- and endocyclic enamines, respectively. Regioselectivity of enamine formation can be achieved as follows: β -diketones are converted into borate betaines which afford exclusively exocyclic enamines as the kinetic products, while direct, acid-catalyzed reactions yield endocyclic enamines as the thermodynamic products.^[6] Exo- and endocyclic enamines are complementary with respect to stereochemistry of the subsequent Michael reactions, resulting in stereocenters with opposite configurations.



Conclusion

- Excellent selectivities up to 99% *ee* for *quaternary stereocenters* are achieved at *ambient temperature* in the copper-catalyzed Michael reaction.
- Control of the regiochemistry in spiroannulations of α -acetylactone-derived Michael adducts by variation of reaction conditions enables the selective formation of β -oxo- and δ -oxo lactones.
- Regioselective formation of exo- or endocyclic enamines could be realized.
- Exo- and endocyclic enamines are complementary with regard to stereochemistry of subsequent Michael reactions, giving either enantiomer of the product with the same chiral auxiliary.

Literature

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- [2] a) J. Christoffers, A. Mann, *Angew. Chem.* **2000**, *112*, 2871–2874; *Angew. Chem. Int. Ed.* **2000**, *39*, 2752–2754. b) J. Christoffers, U. Röbler, T. Werner, *Eur. J. Org. Chem.* **2000**, 701–705. c) J. Christoffers, A. Mann, *Chem. Eur. J.* **2001**, *7*, 1014–1027. d) J. Christoffers, H. Scharl, *Eur. J. Org. Chem.* **2002**, 1505–1508.
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