

Stereodivergent Multicomponent Synthesis of Functionalized Pyrrolidines

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The pyrrolidine ring is an important motif found in many bioactive molecules. We have developed two complementary asymmetric multicomponent [C+NC+CC] reactions for the synthesis of highly functionalized pyrrolidines. The Ag(I) catalyzed [C+NC+CC] coupling reaction produces endo (4,5-cis) products, while the Cu(I)-dppb catalyzed version affords exo (4,5-trans) products.

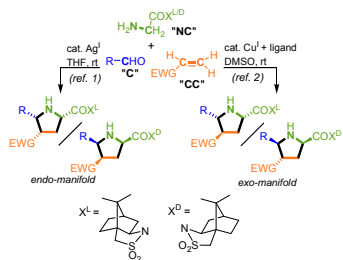
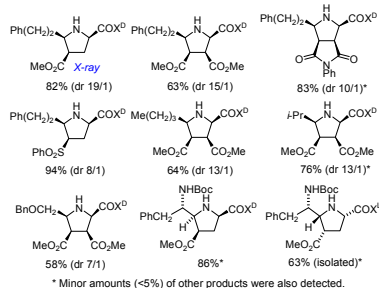


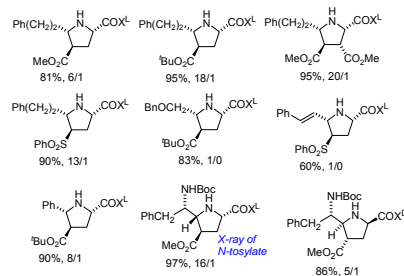
Figure 1. Stereocomplementary asymmetric [C+NC+CC] coupling reactions.

Chart 1. Endo-Selective [C+NC+CC] Coupling Reaction^a



^aAldehyde ("C", 1 equiv), glycyl sultam ("NC", 1.1 equiv), dipolarophile ("CC", 3.0 equiv) and AgOAc (0.05 equiv) were combined in THF and stirred at room temperature for 1-6 h. After extractive workup, the products were obtained by flash chromatography (combined yield, endo/exo ratio). The stereochemical assignments for the major cycloadducts were ascertained by NOE experiments.

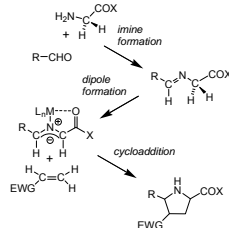
Chart 2. Exo-Selective [C+NC+CC] Coupling Reaction^b



^bAldehyde ("C", 1 equiv), glycyl sultam ("NC", 1.3 equiv), dipolarophile ("CC", 3.0 equiv) and Cu(MeCN)₄PF₆-dppb (0.05 equiv) were combined in DMSO and the mixture was stirred at room temperature for 1-3 h. Workup and purification as described in Chart 1.

Both reactions occur under very mild conditions and do not require special precautions. A key feature of these metal catalyzed [C+NC+CC] coupling reactions is that they are fairly general in terms of starting aldehyde and alkene components. It is particularly significant that enolizable/chiral aldehydes can be used. Oppolzer's chiral auxiliary controls the absolute stereochemistry of the product independent of existing chirality.

Scheme 1. The [C+NC+CC] Coupling Reaction Cascade



The [C+NC+CC] coupling reaction proceeds via a cascade imine→azomethine ylide→cycloaddition sequence (Scheme 1). It is believed that the sultam reduces the nucleophilicity of the amine component (preventing unwanted Michael addition) and facilitates azomethine ylide formation by enhancing the α-acidity of the intermediate glycyl imine.

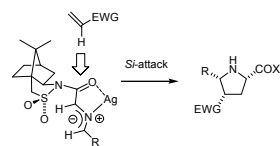


Figure 2. Oppolzer's sultam controls the diastereofacial selectivity of the 1,3-dipolar cycloaddition.

The camphor derived sultam controls the diastereofacial selectivity of the 1,3-dipolar cycloaddition in a predictable manner via the (E,E)-azomethine ylide. This is illustrated for the endo-selective process in Figure 2. It is believed that endo-selectivity is due in part to coordination of the dipolarophile carbonyl to the Ag(I). Thus, the D-sultam gives (2R)-pyrrolidines via Re-attack by the dipolarophile while the L-sultam afforded (2S)-pyrrolidines via Si-attack by dipolarophile.

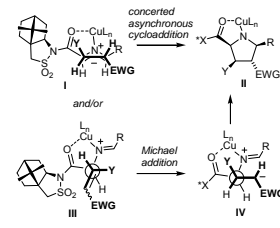
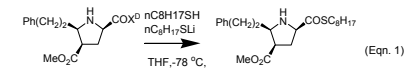


Figure 3. Dual mechanistic rationale for exo-selective asymmetric [C+NC+CC] Coupling (Y=H, EWG)

Two mechanistic hypotheses are advanced to explain the exo-selectivity of the Cu(I)-catalyzed reaction (Figure 3). The cycloaddition reaction may be concerted and proceed through an asynchronous [3+2] transition state (I → II). Alternatively, the reaction may also proceed in a step-wise manner via a zwitterionic intermediate such as III. If the alkene is β-substituted, the stereocenter at C3 would be set by an approach that places the smallest β-substituent above the chelate metalocycle. Rotation of C2-C3 bond in III brings the enolate carbon towards the iminium carbon as in structure IV. The 4,5-trans product results from the minimization of steric clash between the dipolarophile activating group (EWG) and the azomethine ylide R group.

To expand the practical utility of metal catalyzed [C+CN+CC] process, the chemoselective removal of the chiral auxiliary was demonstrated. Treatment of acylsultam with buffered thiolate produced the corresponding thioester (Equation 1).



In summary, we have developed two stereocomplementary metal-catalyzed asymmetric multicomponent [C+NC+CC] coupling reactions, providing convenient access to a variety of functionalized pyrrolidines.

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References

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