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The Cu^{I}-catalyzed *exo*-selective asymmetric multicomponent [C+NC+CC] coupling reaction

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Abstract—A novel Cu^{I}-catalyzed *exo*-selective asymmetric [C+NC+CC] coupling reaction is reported that provides unprecedented access to a variety of highly functionalized 4,5-trans disubstituted pyrrolidines in a single operation. The reaction complements and extends our Ag^{I}-catalyzed *endo*-selective [C+NC+CC] asymmetric coupling reaction.

We recently disclosed a mild and efficient Ag^{I}-catalyzed [C+NC+CC] coupling process for the asymmetric synthesis of functionalized pyrrolidines.[1] At the heart of the reaction cascade was the *endo*-selective [3+2] cycloaddition of a metalated azomethine ylide that led to 4,5-cis disubstituted pyrrolidines (Fig. 1).[2] Oppolzer's camphor sultam not only enforced absolute stereocontrol but also enabled the underlying reaction cascade (presumably by lowering the pK_a of the glycyl α-proton). A particular advantage of this methodology is the ability to incorporate structurally rich and enolizable aldehydes into the reaction sequence. Azomethine ylide [3+2] cycloaddition reactions, particularly asymmetric variants,[3] have attracted considerable attention because they provide synthetic access to substituted pyrrolidines.

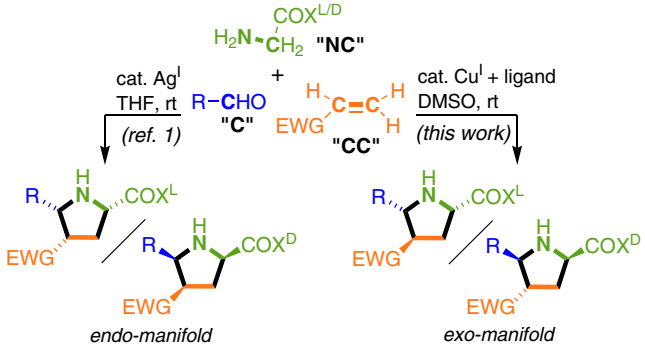

Figure 1. Stereocomplementary asymmetric [C+NC+CC] coupling reactions (X^{L} = Oppolzer's L-camphorsultam).

While the Ag^{I}-catalyzed cycloaddition of stabilized (*E*,*E*)-azomethine ylides generally proceeds through an *endo* transition state, reliable access to 4,5-trans disubstituted pyrrolidines via the corresponding *exo* cycloaddition manifold still remains a challenge. Progress toward this goal has been achieved on the asymmetric catalytic front, with Komatsu (Cu^{II}–BINAP),[4] Zhang (Cu^{I}–P, N-ferrocenyl),[5] Carretaro (CuI–fesulphos[6] and Cu^{I}–taniaphos),[7] and Hou (Cu^{I}–P, N-ferrocenyl)[8] all reporting examples of *exo*-selective [3+2] cycloaddition reactions using copper-based catalysts.[9] These reactions do not appear to be general in terms of starting aldehyde and dipolarophile. Moreover, low temperatures and/or long reaction times were used. We now report an *exo*-selective [C+NC+CC] coupling reaction that provides access 4,5-trans disubstituted pyrrolidine systems (Fig. 1). The procedure is general in terms of starting aldehyde and dipolarophile and operationally simple to perform. This reaction could serve as the basis for syntheses of pyrrolidine-containing targets such as DX-52-1,[10,11] A-315675,[12,13] and spirotryprostatin[14,15] (Fig. 2).

Our quest for *exo*-selectivity commenced with an analysis of the pre-TS ensemble that had been proposed to account for the *endo*-selective [3+2] cycloaddition (Fig. 3). *endo*-Selectivity is generally observed in these reactions when M = Ag, an outcome presumably due in part to

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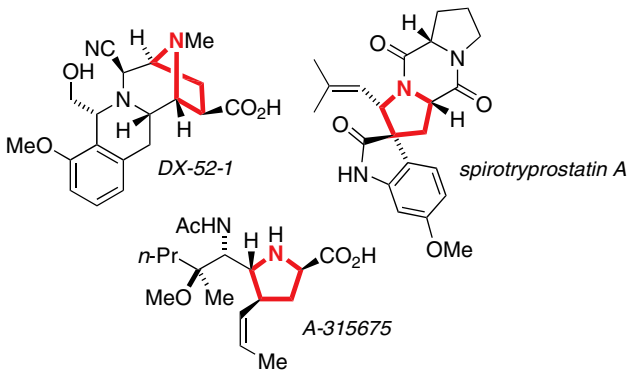

Figure 2. Representative natural product targets for the *exo*-selective asymmetric [C+NC+CC] coupling reaction.

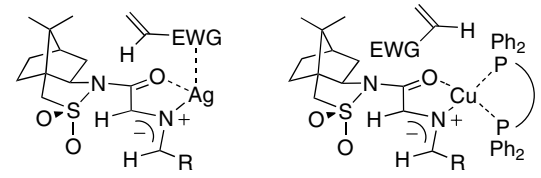

Figure 3. Design rationale for the *exo*-selective asymmetric [C+NC+CC] coupling reaction.

coordination of the dipolarophile carbonyl to the metal center. However, as noted above, the use of copper salts in combination with bidendate ligands often results in *exo*-selective [3+2] cycloaddition reactions. It was reasoned that the use of a Cu^{I}-bisphosphine catalyst system would likewise favor an *exo*-TS in our [3+2] cycloaddition on steric grounds (Fig. 3). A survey of commercially available copper salts, achiral bisphosphine ligands, and solvents was conducted to establish the most favorable reaction conditions. The optimal procedure involved simply stirring a mixture of aldehyde, glycylsultam, and dipolarophile (1.0/1.3/3.0 molar ratio) with the catalyst (5 mol % $Cu(MeCN)_4PF_6$ or CuOAc + 5 mol % dppb or dppf)[16] in reagent grade DMSO at ambient temperature. There was no need to dry the solvent since an equivalent of water is formed during the reaction. However, reactions were routinely performed in the dark to minimize degradation of the catalyst.

As illustrated by the examples collected in Chart 1, the *exo*-selective [C+NC+CC] coupling reaction provides access to a diverse array of highly functionalized pyrrolidines. Of particular significance is the ability to employ enolizable and α-chiral aliphatic aldehydes in the reaction. The [C+NC+CC] coupling reaction of hydrocinnamaldehyde, L-glycylsultam, and variety of standard dipolarophiles (methyl and *t*-butyl acrylate, dimethyl fumarate, dimethyl maleate, and phenylvinylsulphone) produced *exo*-adducts **1**–**4** in excellent yield. The

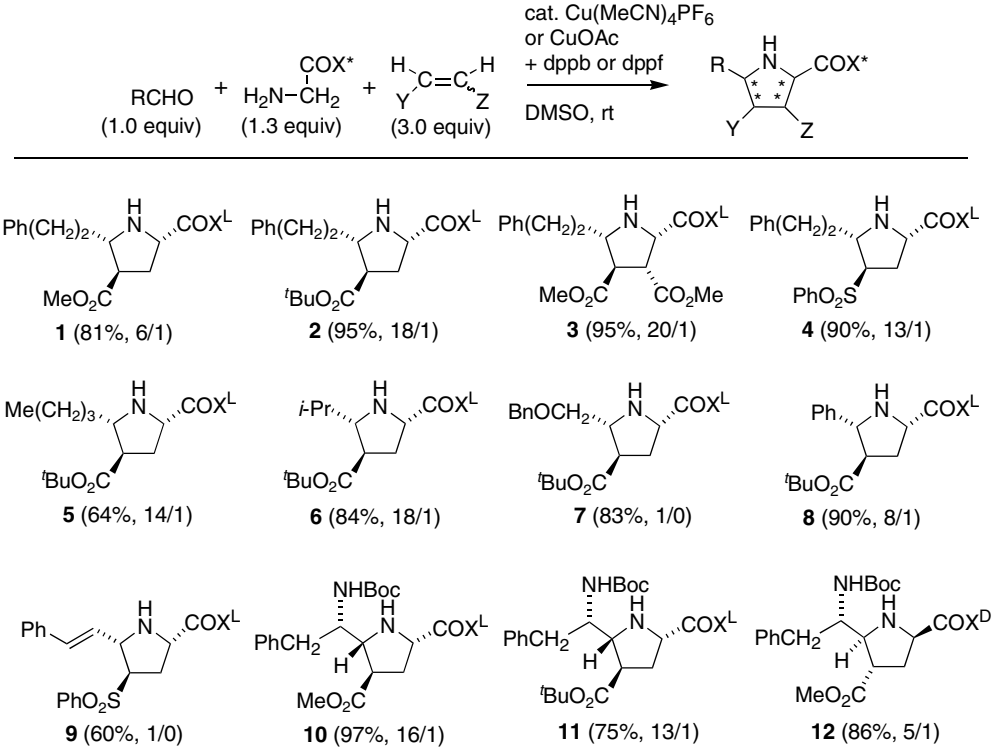

Chart 1. *exo*-Selective [C+NC+CC] coupling reaction examples. Procedure: the catalyst was prepared by stirring the copper salt ($Cu(MeCN)_4PF_6$ or CuOAc, 5 mol %) and bisphosphine ligand (dppb or dppf, 5 mol %) in DMSO (6 mL/mmol aldehyde) at rt for 1 h. To this mixture was added aldehyde (1.0 equiv), glycyl sultam (1.3 equiv), and dipolarophile (3.0 equiv). After stirring at rt for 1–3 h (monitoring by NMR and TLC), the mixture was partitioned between satd NH_4Cl and DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under vacuum to give the crude product. Further purification was accomplished using flash chromatography (see Supplementary data for experimental details).

remaining examples illustrate that variation of the aldehyde component (alkyl, aryl, and vinyl) is possible. Three examples using *N*-Boc-phenylalanal also demonstrate that, as was the case with the Ag^{I}-catalyzed process, the diastereofacial selectivity is controlled by the chiral auxiliary. These [C+NC+CC] coupling reactions resulted in the formation of the *exo* (4,5-trans) pyrrolidine as the predominant stereoisomer. When detected, the *endo* isomer consituted a very minor component of the reaction mixture. The *exo* stereochemical assignments for the major cycloadducts were ascertained by NOE experiments (see Supplementary data), and in one case, by chemical correlation.[17] The absolute configuration of cycloadduct **10** was established by an X-ray crystallographic analysis of its *N*-tosylate **14** (Fig. 4),[18] allowing the remaining cycloadducts to be assigned by analogy.

These experimental results are consistent with either of the following two mechanistic hypotheses (Fig. 5). On one hand, the cycloaddition reaction may be concerted and proceed through an asynchronous [3+2] transition state (**I**→**II**). An unsymmetrical TS—with C2–C3 bond formation (pyrrolidine numbering) being more advanced than C4–C5 bond formation—would be expected given the polarized nature of metalated azomethine ylide. Alternatively, the reaction may also proceed in a step-wise manner via a zwitterionic intermediate such as **III**.[19] 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 metallocycle. Rotation of the C2–C3 bond in **III** brings the enolate carbon toward the iminium carbon as in structure **IV**. The 4,5-trans product results from the minimization of a steric clash between the dipolarophile activating group (EWG) and the azomethine ylide R group. Support for this step-wise mechanism is provided by the reaction with dimethyl maleate, which produced

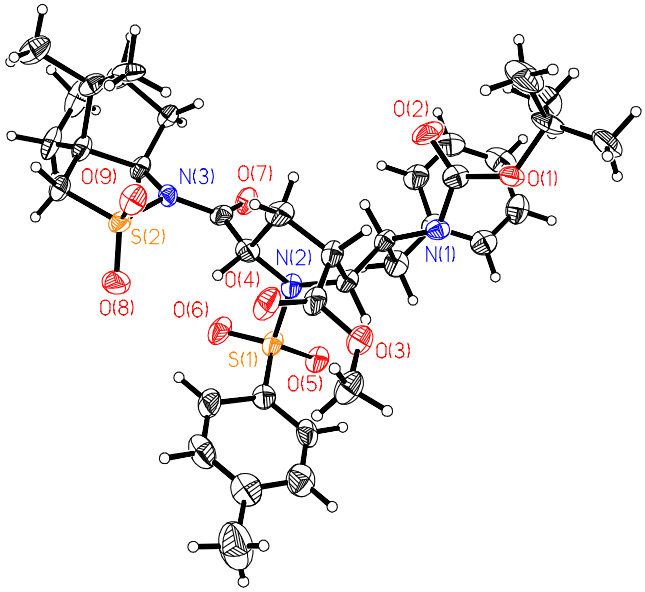

Figure 4. ORTEP diagram from the X-ray crystallographic analysis of **14**.

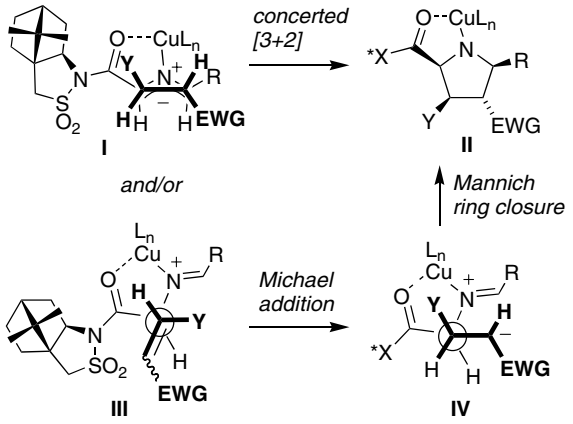

Figure 5. Dual mechanistic rationale for *exo*-selective asymmetric [C+NC+CC] coupling (Y = H or EWG).

the same cycloadduct **3** as the fumarate reaction.[20] Both mechanistic schemes would account for DMSO being the optimal organic solvent for this reaction, since this high dielectric ($\varepsilon = 48$) solvent would be expected to stabilize charged transition states.

In conclusion, the Cu^{I}-catalyzed *exo*-selective [C+NC+CC] coupling reaction provides convenient access to a variety of functionalized 4,5-trans disubstituted pyrrolidine-2-carboxylate systems that are not readily accessible by other routes. Oppolzer's readily removed camphor sultam auxiliary both enables the reaction cascade and controls the absolute sense of asymmetric induction. The described methodology complements and extends our Ag^{I}-catalyzed *endo*-selective [C+NC+CC] coupling reaction and represents a valuable addition to the synthetic chemist's arsenal for the synthesis of highly functionalized pyrrolidines.

Acknowledgments

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Supplementary data

Supplementary data (characterization data for compounds **1**–**14**) associated with this article can be found in the online version at doi:10.1016/j.tetlet.2007.03.145.

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16. Abbreviations: dppb = 1,4-bis(diphenylphosphino)butane and dppf = 1,1′-bis(diphenylphosphino)ferrocene.
17. The mixture of cycloadduct **1** and a minor diastereomer (**dia-1**) was converted to their *n*-octylthiol esters using the buffered thiolate conditions described previously (Ref. 1). The proton NMR spectrum of the major component (compound **13** in the Supplementary data) did not match the previously prepared *endo n*-octylthiol ester. The signals for the minor component did match the *endo n*-octylthiol ester, proving that the mixture of **1**/**dia-1** consisted of *exo* and *endo* isomers and not diastereofacial isomers.
18. CCDC-642220 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.
19. Michael additions of stabilized *N*-metalated azomethine ylides are known (see Refs. 2a,b). Step-wise [3+2] cycloadditions of stabilized *N*-metalated azomethine ylides and nitroalkenes have been predicted computationally and demonstrated experimentally. See: (a) Tatsukawa, A.; Kawatake, K.; Kanemasa, S.; Rudzinski, J. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2525; (b) Ayerbe, M.; Arrieta, A.; Cossío, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795; (c) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078; (d) Ref. 8.
20. Additional support for this interpretation comes from experiments using *N*-phenylmaleimide, which led to the *endo* product exclusively. In this case, the EWG and Y groups in structure **III** are constrained to be cis to each other.