Synthesis of α-Quaternary Pyrrolidines by Ru and Cu-Catalyzed Condensation of α-Diazo-β-Ketoesters and γ-Lactams and Efficient Access to 9-Membered-fused Pyrazoles

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Building and increasing molecular complexity in a few synthetic steps is a challenge in heterocyclic chemistry. Many transition metal complexes - including ruthenium, rhodium and copper catalysts - have been shown to promote diazo decompositions and subsequent reactions with various Lewis basic substrates, allowing the straightforward access to several types of heterocycles.[1]

In the particular case of α-diazo-β-ketoesters and γ-lactams as substrates, Ru and Cu catalysts exhibit complementary reactivities. Indeed, when reacted with N-aryl-γ-lactams, Cul promotes the formation of N-aryl-pyrrolidines carrying α-quaternary centers through a [1,2]-acyl migration on the carbon,[2] whereas Ru reacts with N-alkyl-pyrrolidinones to afford unsaturated pyrrolidines via a [1,2]-Brook-like rearrangement of the acyl group. The obtained products can then be transformed into highly substituted α-quaternary pyrrolidines through a one-pot O-alkylation/[3,3] sigmatropic rearrangement sequence.

In addition, using a combination of hydrazine and an acid source, N-aryl pyrrolidines are efficiently transformed into novel pyrazolo[3,4-e]azonines motifs in very high yield via a two-steps one-pot process. A mild Aza-Claisen rearrangement drives the concomitant formation of the pyrazole and the azonane core, affording substructures which might reveal as potential biologically relevant products.