Transition metal catalyzed synthesis and functionalization of ketonitrones

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Nitrone chemistry plays an important role in modern organic synthesis. These compounds are characterized by broad reactivity, which was applied in the syntheses of natural compounds and alkaloids. Nitrones can be divided into subgroups such as aldonitrones and ketonitrones, which are derivatives of aldehydes and ketones, respectively. Aldonitrones are a widely available group of compounds and usually their synthesis is not problematic. In the case of ketonitrones, there are only a few methods for their synthesis, very often limited to specific structures. Moreover, ketonitrones can be valuable precursors in the synthesis of highly functionalized compounds containing tetrasubstituted carbon atoms and nitrogen atoms. In this thesis, I described the results of three interconnected research projects, concerning both the synthesis of ketonitrones using palladium catalysis, as well as their further functionalization leading to spirocyclic isoxazolidines, catalyzed by a Co(III) complex.

In the first project, I focused my attention on the intramolecular C–H activation of aldonitrones, leading to strained analogues of benzocyclobutenones - benzocyclobutenitrones. Using a catalyst based on a palladium complex and aldonitrones bearing a bromoaryl substituent at the *C*-terminus of the nitrone, I obtained ketonitrones under mild conditions, which I further functionalized by 1,3-dipolar cycloaddition or nucleophilic addition. Moreover, I presented an efficient method for the synthesis of a spirocyclic fluorinated derivative of β-lactam - a motif commonly found in pharmaceutical compounds.

In the next part of the research, I focused on the analogous concept of the synthesis of cyclic ketonitrones, but in this case the final products were isoindole *N*-oxides. Wide applicability and high efficiency of the developed methodology makes it useful also in the case of sterically hindered substrates. I also carried out further transformations of isoindole *N*-oxides, such as the Rh(III)-catalyzed tandem C–H activation/1,3-dipolar cycloaddition or the reduction of isoindole *N*-oxide combined with subsequent oxidative cyclization, leading to an isoquinoline salt which exhibited fluorescent properties.

In the last project, I used the previously obtained isoindole *N*-oxides in the synthesis of spirocyclic isoxazolidines using the $Cp^*Co(CO)I_2$ catalyst. The cobalt(III) complex has lower toxicity and is more available than similar in terms of reactivity rhodium(III) complex. In my concept, *C*-arylisoindole *N*-oxides were first subjected to the C–H activation process and then reacted with allenylmethyl carbonates. The nitrone oxygen atom, acting as a directing group, played a key role in this concept. In the next step of the tandem process, the formed dienes underwent a 1,3-dipolar cycloaddition, leading to the spirocyclic isoxazolidine. Moreover, only one diastereoisomer is formed during the 1,3-dipolar cycloaddition step. I successfully transformed isoxazolidine into an aminoalcohol derivative, which was then cyclized to a fluoroderivative of tetrahydrofuran. I also performed mechanistic studies confirming the directing role of the nitrone oxygen atom and determining the kinetic isotope effect.