Combining Organometallic Catalysis and Organocatalysis for the Synthesis of Heterocyclic Scaffolds - DTU Orbit (21/10/2019)

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The main work presented in this thesis describes the development of efficient and novel methodologies for the synthesis of pharmaceutically interesting indole-containing alkaloids, i.e., the 1,2,3,4-tetrahydro-β-carboline and the 1,2,3,4-tetrahydrocarbazole scaffolds. The synthesis of 1,2,3,4-tetrahydro-β-carbolines was based on a transition metal/Brønsted acid-catalyzed tandem isomerization/N-acyliminium ion cyclization of N-acylated allylic tryptamines. First, the reaction conditions for the tandem reaction were optimized to high efficiency, culminating in the use of the ruthenium hydride catalyst RuHCl(CO)(PPh3)3 combined with diphenyl phosphate at elevated temperature (refluxing toluene). The optimized reaction conditions were, in most cases, successfully applied to a broad range of Nacylated allyltryptamines, and the desired products were obtained in good yields (68–96%). With highly electron-withdrawing substituents, the reaction resulted in the formation of the corresponding enamides. When substituents capable of coordinating the catalyst were used, no conversions of the starting materials were observed. In an enantioselective version of the reaction, the substituent α to the nitrogen in the allylic system proved to be highly important for the enantioselectivity. Enantiomeric excesses up to 57% was obtained.

The synthesis of 1,2,3,4-tetrahydrocarbazole relied on novel Brønsted acid-catalyzed Friedel-Crafts-type reactions. Three different kinds of 1,2,3,4-tetrahydrocarbazole could be synthesized from one common carbonyl starting material. Type 1 reactions involved direct intramolecular cyclization from an indole moiety to an aldehyde resulting in the corresponding alcohols. The reaction was limited to electron-rich nucleophiles. Type 2 reactions deal with addition of nucleophiles, either to the cyclized alcohol obtained from type 1 reactions or directly to the carbonyl followed by cyclization. The reaction conditions were dependent on whether the addition of the nucleophile occurred before or after cyclization. An enantioselective version of the reaction was highly dependent on the substitution pattern, as enantiomeric excesses between 6 and >99% were obtained in 35–94% isolated yield. Type 3 reactions aimed for addition of organometallic reagents to the carbonyl with subsequently cyclization. No one-pot reaction directly from the carbonyl species to the 1,2,3,4-tetrahydrocarbazole was developed. A two-step synthetic route, via the alcohols, was investigated and found to be highly dependent on the presence of carbocation stabilizing groups around the alcohol; therefore only three final type 3 products were synthesized in good yields (64–95%).

A small project, which attempted to take advantage of the above described to be use as a novel cleavage strategy for solid support linkers, is also presented here. Unfortunately, no successful conditions were developed.

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