Iridium- and Ruthenium-Catalyzed N-alkylation of Amines with Alcohols and Amines

Many biologically active molecules contain one or more nitrogen atoms. Consequently, C-N bond formation is a crucial area in the development of pharmaceuticals. The main part of this thesis is devoted to environmentally benign syntheses of different nitrogen scaffolds. Iridium and ruthenium catalysts have been employed for the N-alkylation of amines with either alcohols or amines.

**Synthesis of secondary amines**

Self-condensation of primary amines afforded secondary amines in good to high yields. The reaction is catalyzed by the commercially available [Cp*IrCl2]2 complex. The procedure is environmentally benign as it is performed in the absence of both solvent and additives and the only by-product is ammonia. Additionally, the work-up procedure is a simple distillation of the product directly from the reaction mixture.

**Synthesis of piperazines**

In the Madsen group it has previously been demonstrated that condensation of diamines and diols catalyzed by [Cp*IrCl2]2 furnishes the piperazine skeleton. The only by-product of the reaction is water. The substrate scope was extended and the limitations of the reaction were studied. It was established that the Thorpe-Ingold effect plays a central role in the reaction, as ethyleneglycol and 1,2-ethylenediamine failed to produce piperazine. Introduction of a C-substituent on one or both of the starting materials gave substituted piperazines in high yields. Synthesis of N-benzylpiperazine from ethyleneglycol and N-benzylethylenediamine was also successful. Self-condensation of ethanolamine was unsuccessful due to polymerization of the starting material. α-Phenylendiamine was a difficult substrate as it furnished an equimolar mixture of 1,2,3,4-tetrahydroquinoxaline and 2-benzimidazolomethanol in the reaction with ethylene glycol. Ammonium tetrafluoroborate as the nitrogen source in reaction with 1,2-cyclohexanediol afforded the morpholine derivative. Finally, attempts to switch to ruthenium catalysis were unsuccessful since neither a RuCl3-PPh3 complex nor a RuCl3-xantphos complex was able to catalyze the reaction between 1,2-cyclohexanediol and ethylene glycol. Mechanistic experiments of the iridium catalyzed reactions revealed that the Voigt isomerization of the α-imino alcohol intermediate to the corresponding α-imino ketone plays a significant role.

**Synthesis of indoles**

Anilines and vicinal diols were reacted in the presence of a ruthenium complex (RuCl3 with PPh3 or xantphos) to give indoles in good yields. In this case water and dihydrogen are the only by-products. When unsymmetrical diols were employed the corresponding indole with the largest substituent in the 2-position was favored. It is believed to proceed through a Bischler-like reaction pathway. Mechanistic experiments were conducted and emphasized the importance of the Voigt reaction in the formation of the product.

**Protein folding**

During an external stay at The Scripps Research Institute, San Diego, California, USA, folding of the well-known protein CI2 was studied. Several mutants were synthetically prepared via folding assisted ligation. One segment was synthesized as the C-terminal thioester by Boc-SPPS and the other segment as a C-terminal acid by Fmoc-SPPS. The sites of mutation were all in the α-helical region of the protein and the mutation choices were alanine and Aib, which both possess a high α-helical propensity. Hereby, it was believed that more stable proteins would be obtained. Folding of the mutants was studied in terms of thermodynamics and kinetics by guanidine hydrochloride denaturation monitored by fluorescence. The results were unfortunately unreliable due to errors in the spectrofluorometer.

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