

Reaction Optimization of a Pd-Catalyzed N-Arylation

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Introduction

With the development of new palladium catalysts for the arylation of amines and alcohols¹, this elegant method has increasingly found use in the synthesis of scaffolds and building blocks for medicinal chemistry. Optimizing such coupling reactions commonly causes elevated experimental expense for uncovering the suitable catalyst system and process solvent. Tailored screening systems for parallel synthesis are used in particular when working out the reaction conditions. In the case of the couplings being addressed, the reaction mixtures are usually heterogeneous; thorough mixing must be assured during the reaction. The use of air-sensitive phosphine ligands and the often negative influence of moisture presume equipment that permits carrying out the reaction under inert conditions. The screening and optimization experiments described here were carried out in a *Synthesis 1* modified according to our specification (see **Fig. 1**). This equipment makes it possible to take out and install the reaction vessels excluding air and humidity by the use of flexible tubing connections and attachment to a vacuum/argon distributor. The use of conventional inert gas technology makes it possible to fill the vessel with argon during the reaction. The screening and optimization phase of a palladium-catalyzed N-arylation (**Diagram 1**) is described below.

Experimental work

In the example described here, a suitable ligand for the coupling reaction is first selected, using toluene as solvent and Cs₂CO₃ as base. The aniline participating in the reaction was used in excess in each case. The process solvent was then determined first, and then the stoichiometry of the reaction was thereupon optimized.

In all experiments, the reaction vessel was loaded in the glove box and was then placed in the *Synthesis 1*. After flushing the system with inert gas, the reaction vessels were then opened toward the inert gas distributor. Argon was used as a protective gas during the reaction. Samples were taken from the opened reaction vessels in a counterflow of argon.

The purpose of the project was to make it possible to produce the desired compound on a 100-gram scale in the shortest possible time. The process used here was to provide the target compound using < 5 mol-% palladium based on the aryl bromide used and with an isolated yield of > 70%.

¹ A. R. Muci, S. L. Buchwald, *Topics in Current Chemistry* **219** (2002) 131.

Fig. 1. Heidolph *Synthesis 1*

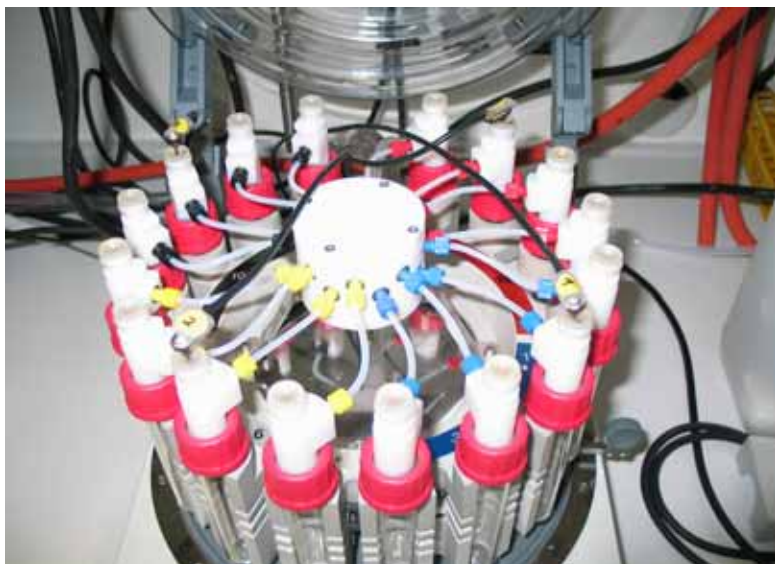


Diagram 1. Palladium-catalyzed N-arylation

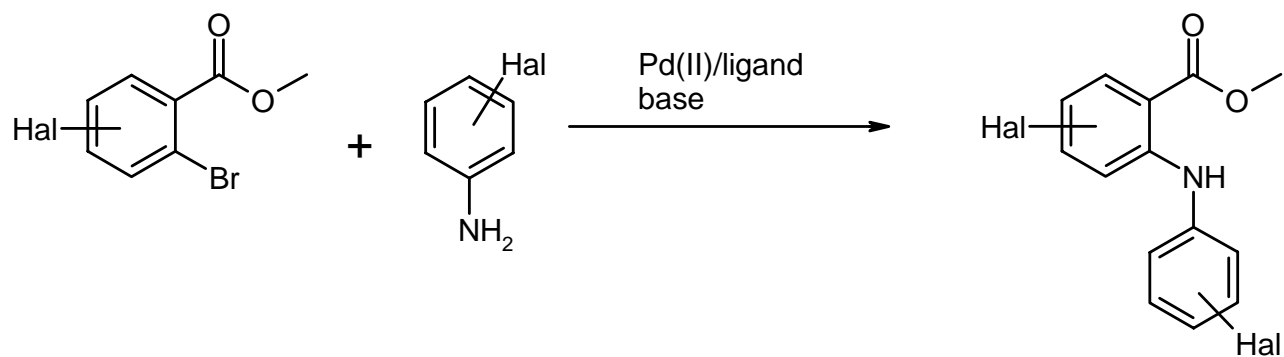


Fig. 2. Screening of various ligands

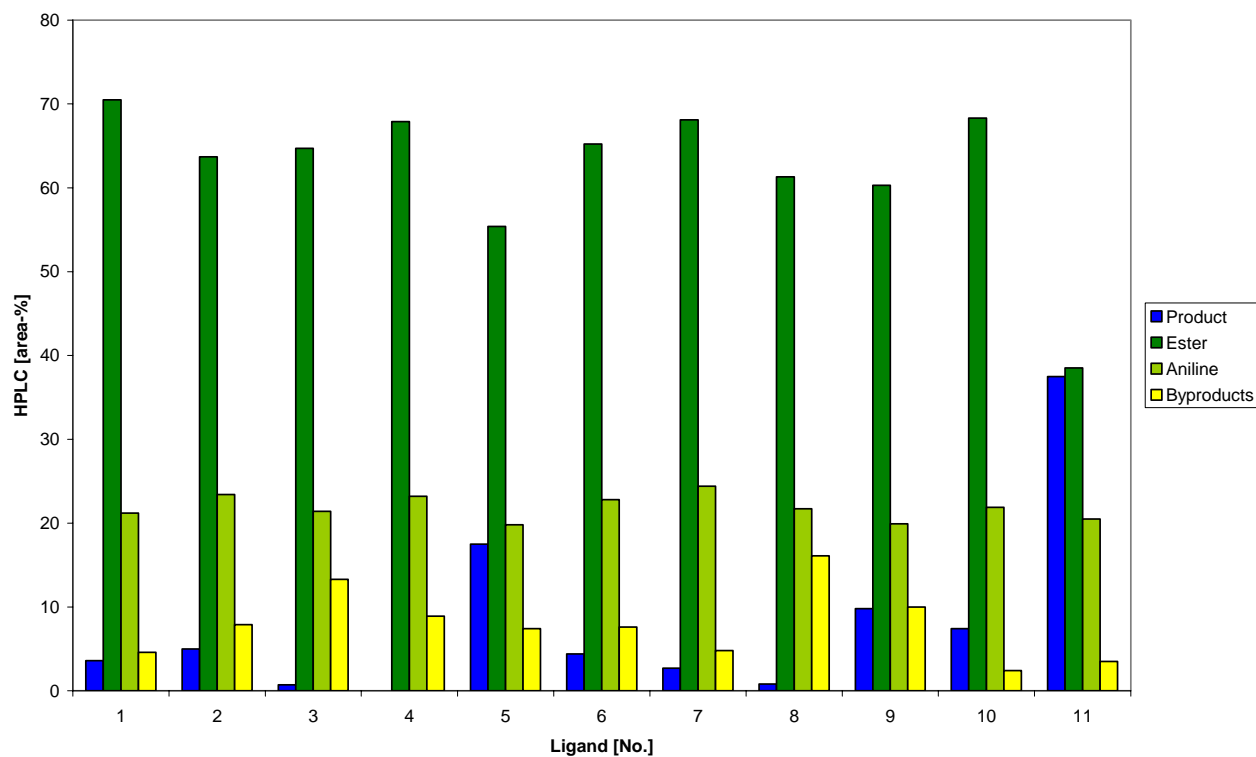


Fig. 3. Solvent screening

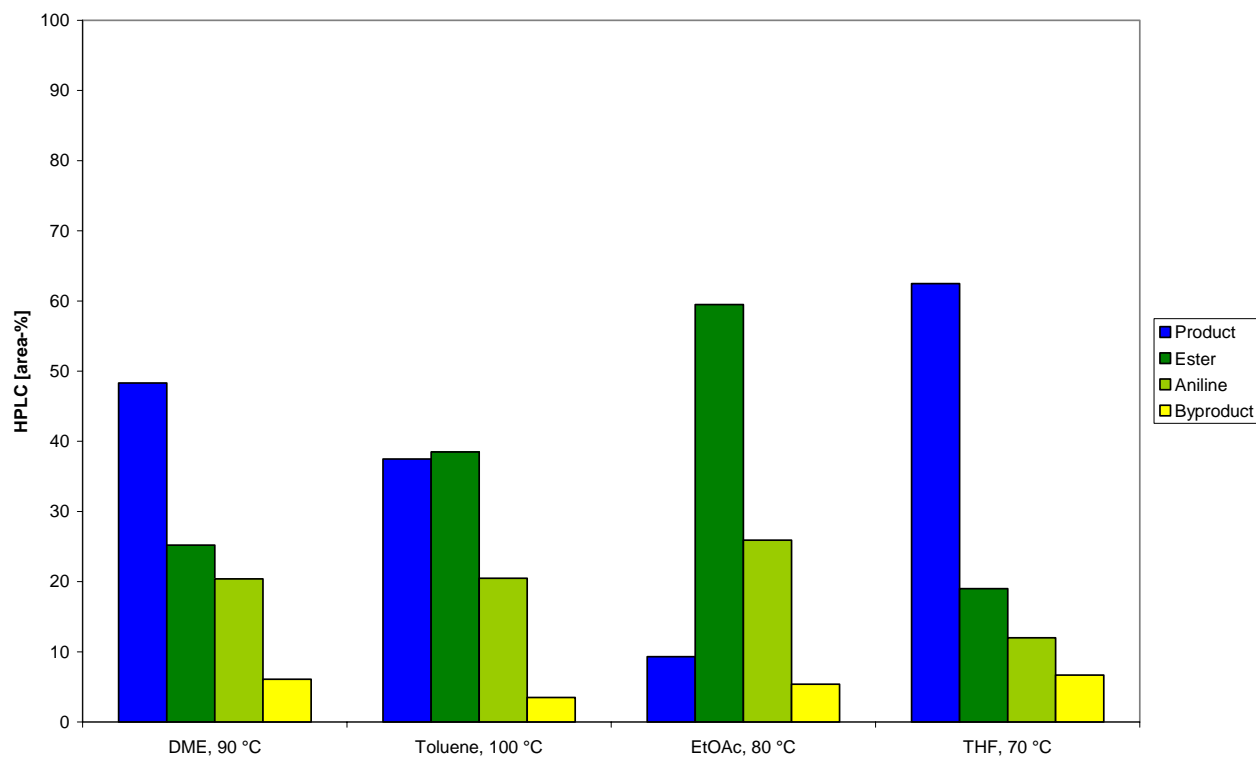


Fig. 4. Optimization of reaction conditions (aniline concentration in THF as solvent).

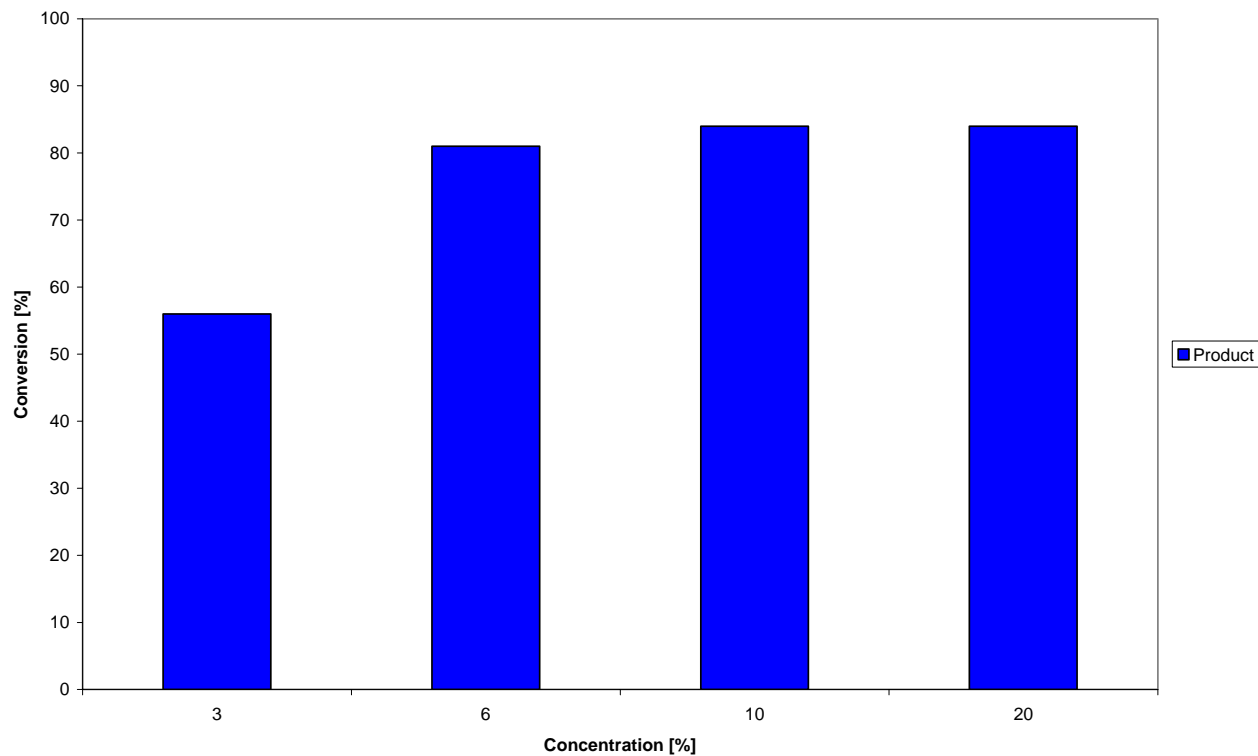
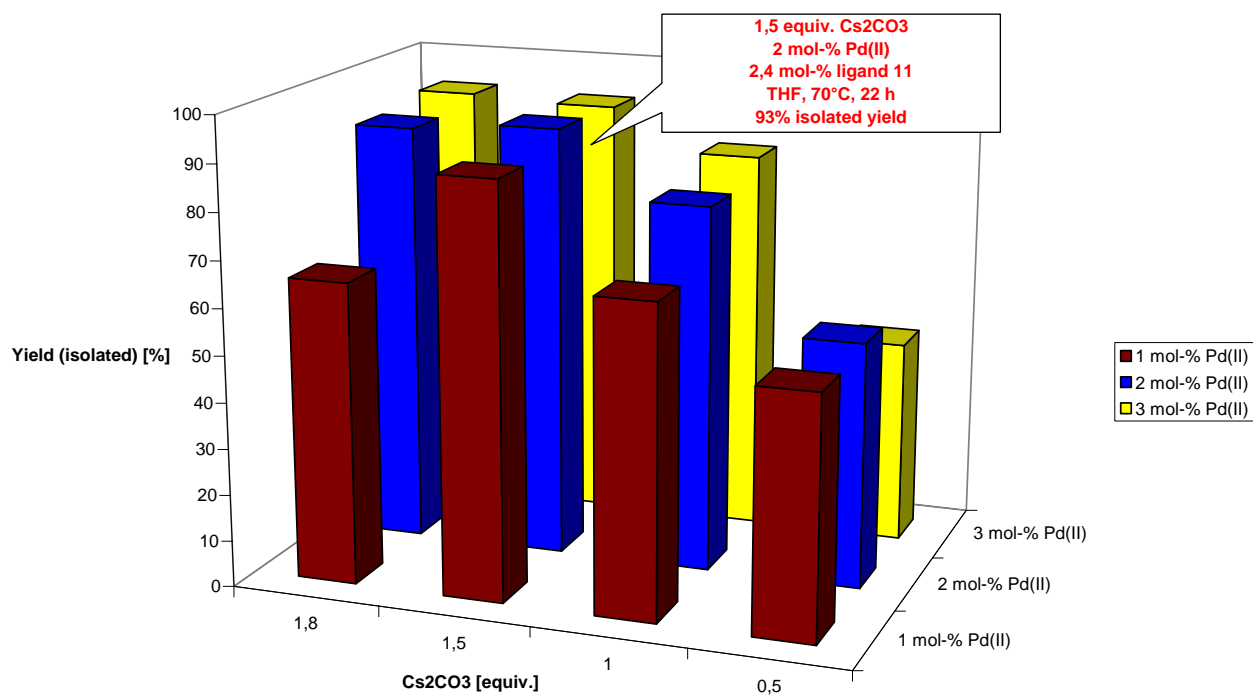


Fig. 5. Optimization of reaction conditions (equivalents of base and amount of Pd)



Ligand screening

In a first step, 11 readily available ligands for the reaction were tested. This screening was done with 5 mol-% Pd(II) and 5.5-6 mol-% of the particular ligand. For time reasons, no variation of solvent or base was tested in this step. The following experiments were performed with the best ligand (**Fig. 2**).

Screening of solvent

The reaction was carried out in four possible solvents, with four different dilutions of each of the solvents listed in **Fig. 3** being tested. THF proved to be the solvent of choice, since the variation of yield was small in this case over the dilution range tested (**Fig. 4**).

Optimization of reaction conditions

Systematic variation of the amounts of base and Pd used (**Fig. 5**) led to the optimized reaction conditions that were used successfully on a 100-gram scale for the subsequent synthesis.

Summary

Using *Synthesis 1*, the work described here could be carried out in three blocks of experiments. The desired method with the desired quality was worked out and the first 100 g of the substance was made available within one week.