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Kinetic Investigation of a Ligand-Accelerated Sub-mol % Copper-Catalyzed C–N Cross-Coupling Reaction

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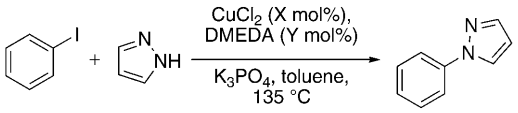
The C–N cross-coupling reaction is an important and versatile chemical transformation in organic chemistry. The development of efficient palladium-catalyzed protocols, for example, the Buchwald–Hartwig reaction, has increased the utility of the reaction tremendously.[1] More recently, there has been a renewed interest in protocols based on copper, namely the Ullmann[2] and Goldberg[3] reactions.[4] The latter reaction has had a reputation of being ineffective, requiring, for example, high temperatures, and near stoichiometric amounts of copper, and being limited in substrate scope. New highly efficient systems have been developed through the use of different simple amine ligands and/or additives, some of them effective at low temperatures and with low loadings of copper.[5] Dimethylethylenediamine (DMEDA) has proven to not only be a very efficient ligand in these type of transformations but also to exhibit unusual reaction behavior compared to other ligands in similar copper-catalyzed systems. The catalytic loadings of copper can be brought down as low as 0.001 mol % as long as the concentration of DMEDA is kept high (>20 mol %).[6] Recently, Zuidema and Bolm showed that the sub-mol % copper/DMEDA system can be extended to Sonogashira-type reactions, as exemplified by the cross-coupling between phenylacetylene and iodobenzene, further broadening the reaction scope and understanding of the unique role of DMEDA.[7]

In the present study, the cross-coupling reaction of pyrazole and iodobenzene was chosen as the standard reaction system for the kinetic investigation (Scheme 1). The reaction can be carried out under standard reaction conditions either with CuI, CuO, Cu_2O, or $CuCl_2$ without any apparent effect on the yield.[6] We have chosen to work here with the soluble and easily handled $CuCl_2$ to allow preparation of stock solutions. We have investigated the reaction order in all essential components of the reaction.



Scheme 1. Standard reaction for the kinetic investigation (X = 0.000625–0.64 mol %, Y = 10–160 mol %).

For copper, the reaction order was found to be approximately one in the interval 0.000625–0.04 mol % and zero from 0.16–0.64 mol % (Figure 1). The fairly sharp decrease in reaction order is unusual, and points to some type of inactivation at higher copper concentrations. Formation of inactive dimers would only be expected to reduce the reaction order to one half. A plausible hypothesis is that copper forms inactive heterogeneous material (which could be nanoparticular) in equilibrium with a saturated solution of homogeneous and catalytically active monomeric copper.[5o] Below a critical concentration of about 1 mM (depending on the amount of ligand present), the copper is completely homogeneous, whereas above this concentration, all excess copper goes into the heterogeneous phase.

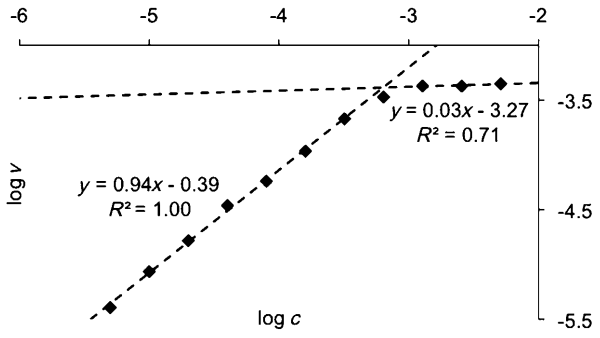


Figure 1. Reaction order for copper from 0.000625–0.64 mol %.

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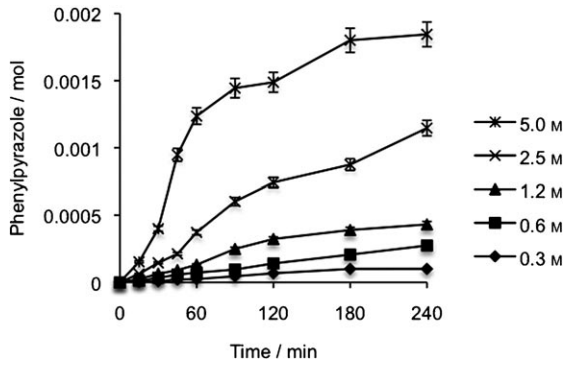


Figure 2. Reaction profile when varying the concentration of iodobenzene (5% error margin).

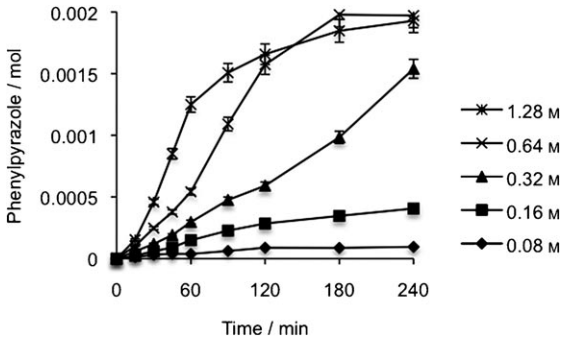


Figure 4. Reaction profile when varying the concentration of DMEDA (5% error margin).

The reaction order for iodobenzene was also found to be approximately one (Figure 2). Running the reaction using iodobenzene as solvent under standard reaction conditions gave full conversion in 1 h. This result was expected, and only shows that iodobenzene is involved in the rate-limiting step, in good agreement with previous studies.[8]

K_3PO_4 had a reaction order of approximately zero. Again, this is an expected result, since the solid base maintains a fairly constant equilibrium concentration in solution, independent of the actual amount added. Pyrazole displayed a variable reaction order, weakly positive when dilute, but strongly negative at higher concentrations (Figure 3). The most probable explanation is that pyrazole coordinates to copper in the rate-limiting step,[9] but that higher concentrations saturate the coordination sphere of Cu, causing inactivation.

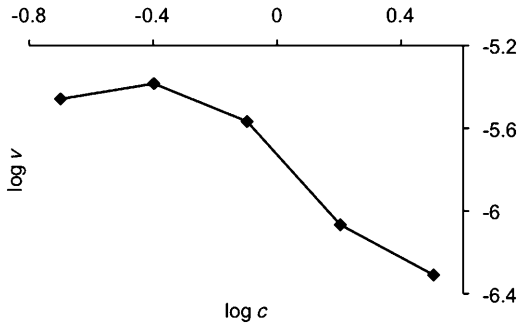
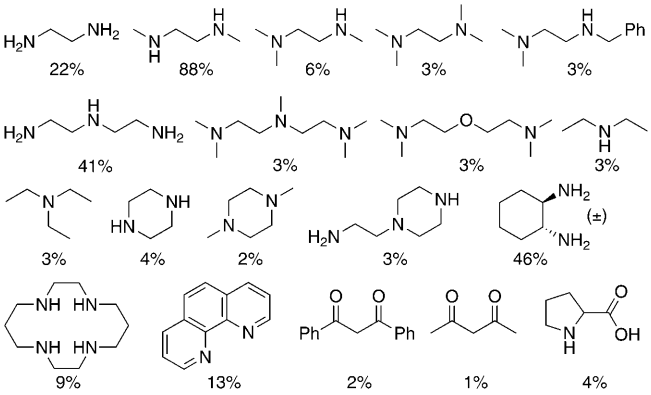


Figure 3. Reaction-order for pyrazole from 0.2–3.2 M.

Surprisingly the reaction order for DMEDA was approximately one over the entire range, up to 160 mol% relative to the substrate (Figure 4). The reaction can also be run in neat DMEDA with 0.01 mol% $CuCl_2$, yielding 91% product in 1 h at 135°C. Using these proportions, the reaction temperature could be lowered to 65°C, still yielding 88% product after 16 h. These conditions are among the mildest reported for this coupling,[5i,m] and unprecedented at this low concentration of Cu. These results were unexpected, since coordination of more than one DMEDA ligand to copper ought to deactivate the catalyst, in analogy with the behavior of pyrazole.

We cannot, at this stage, fully explain the positive reaction order in DMEDA even in a situation where copper should be completely saturated (>1000 equivalents relative to Cu). The experiments are conducted in the range where the reaction order is still positive in copper, and therefore cannot result from increasing the effective concentration of the catalyst. However, an alternative rationalization is that DMEDA assists in solubilizing the potassium phosphate, reducing the mass transfer problem with a heterogeneous base. To investigate whether DMEDA is unique as ligand in the ppm range, we screened a number of related ligands, some which are known to be effective in copper-catalyzed cross-coupling reactions at higher catalyst concentrations (Scheme 2).[4b]



Scheme 2. Yield of phenylpyrazole after 24 h at 135°C using 0.01 mol% $CuCl_2$ and 20 mol% ligand (yields determined by GC using dodecane as internal standard).

None of the ligands tested could match DMEDA, but three structurally similar ones gave low to moderate yields after 24 h at 135°C: ethylenediamine (EDA, 22%), diethylenetriamine (DETA, 41%) and 1,2-diaminocyclohexane (46%). Other ligands gave only traces of product. The reason for the unique ligand-accelerated behavior of DMEDA is unknown but could be rationalized by DMEDA

having more than one role in the reaction.[10] It is certainly a ligand to copper, but it could also help solubilizing the base and possibly serve as reducing agent. It is known that simple amines can reduce, for example, copper(II) and gold(III) salts to give nanoparticles.[11] However, recent observations of a related system indicates that DMEDA does not reduce Cu^{II}, at least not at room temperature.[12]

In the current case, the reaction order in copper (Figure 1) clearly shows that active copper is monomeric and homogeneous, but reduction, for example by pyrazole, can still play a role in keeping the copper in the catalytically active state. Mechanistic studies on similar systems are scarce in the literature, but recently both experimental and computational studies have been published.[5j,8,9,12] Our current results cannot differentiate between the various proposals, but are certainly compatible with a rate-limiting reaction between iodobenzene and a copper-ligand-pyrazolide complex, possibly by single-electron or atom transfer.[8d]

In summary, DMEDA is a unique ligand for the reaction with ppm levels of catalyst. The steric bulk must be perfectly balanced to allow formation of the active catalyst while avoiding over-coordination. Only a few known ligands can match the efficiency of DMEDA in allowing high conversions at very low concentrations of catalyst.[5i,m] High concentration of catalyst (> ca. 1 mM) does not increase the reaction rate, probably because of formation of an inactive, heterogeneous form of copper in equilibrium with a saturated active copper solution. The amine substrate can coordinate to and deactivate the catalyst, whereas the iodobenzene has a positive reaction order at all concentrations. The rate-limiting step is a reaction between iodobenzene and a copper–DMEDA complex, possibly also coordinating pyrazolide as an additional ligand.[8d,9]

Experimental Section

General: All experiments were carried out under a nitrogen atmosphere. The toluene was dried by distillation. DMEDA, iodobenzene, dodecane was distilled over calcium hydride. $CuCl_2$ (Aldrich, purity of 99.999% metal basis), K_3PO_4 (98%), and pyrazole (98%) were stored under air- and moisture-free conditions. A gas chromatograph with a flame ionization detector and a 30 m × 0.25 mm × 0.25 mm EQUITY™-5 fused silica capillary column was used, with hydrogen as carrier gas. General temperature program: 100 °C for 14 min, then up to 300 °C at 50 °C min^{-1} for 2 min. Dodecane was used as an internal standard.

General procedure for the kinetic investigation: The kinetic investigation was carried out by varying the concentration of one component and keeping the rest of the components constant under standard reaction conditions; pyrazole (136 mg, 2 mmol, 1 equiv), K_3PO_4 (849 mg, 4 mmol, 2 equiv), $CuCl_2$ (200 μL, 5 mM, 0.05 mol%), toluene (2.073 mL), DMEDA (43 μL, 0.4 mmol, 20 mol%), iodobenzene (334 μL, 3 mmol, 1.5 equiv), and dodecane (50 μL, 0.22 mmol). The log plots were constructed from data points ranging from 0 to a maximum of 25% yield. Into a microwave vial was added pyrazole (A mmol) and K_3PO_4 (B mmol). The vial was sealed and a $CuCl_2$ solution (C mL, 5 mM in THF) was added. The THF was removed by three cycles of vacuum followed by nitrogen, whereupon toluene (appropriate volume, total reaction volume equals 2.5 mL), DMEDA (D mmol), iodobenzene (E mmol), and dodecane (50 μL, 0.22 mmol) were added. The closed vial was placed in a pre-heated aluminum block at 135 °C. Samples (50 μL) were collected at certain time intervals, filtered through a small silica plug, and analyzed by GC. The GC yield was determined by using dodecane as internal standard.

Acknowledgements

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Keywords: copper · cross-coupling · kinetics · ligand acceleration · sub-mol% catalysis

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