Fluorophore tagged cross-coupling catalysts†

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Fluorophore tagged *N*-heterocyclic carbenes and the derived (NHC)Pd(allyl)Cl complexes were synthesized and the fluorescence signal was used to follow the course of a Suzuki coupling reaction.

The direct observation of catalyst complexes within the catalytic cycle is desirable in order to obtain a better understanding of homogeneous catalysis. Obviously, the amount of complex required to initiate a catalytic transformation is small. Thus, it is not surprising that the lack of selective and highly sensitive spectroscopic techniques has precluded the direct observation of homogeneous catalysts under real time conditions—unlike the situation in heterogeneous catalysis.[1]

Fluorescence spectroscopy has the potential to allow the detection of minute amounts of catalyst complexes. Fluorescence-based approaches have been used in cross-coupling reactions, but this has been limited mainly to examine product formation with fluorophores attached to coupling partners.[2–5] Tagging with a fluorescent dye enables the detection of Pd complexes down to the single molecule limit as demonstrated recently by Blum *et al*. with fluorescence microscopy.[6] Herten *et al*. have shown that the formation and dissociation of individual ligands from metal complexes can be monitored by single-molecule fluorescence spectroscopy.[7]

We assume that direct information about species in the catalytic cycle can be obtained when relevant ligands for homogeneous catalysis are tagged with fluorophores. A potential problem of such an approach is the occurrence of fluorescent emissions unrelated to the catalytic event following the dissociation of the fluorophore tagged ligands from the transition metal complexes during the course of the catalytic transformation. In this respect, *N*-heterocyclic carbenes are very useful as they are tightly bound to the metal center. Consequently, we report here on the synthesis of fluorophore tagged *N*-heterocyclic carbenes and of catalytically active (NHC)Pd complexes. We decided to use complexes of the type (NHC)Pd(allyl)Cl as model complexes, recently reported by Nolan *et al*.[8,9] The dansyl group appears to be suitable as a fluorophore since its functional groups should not interfere with cross-coupling chemistry.[10,11] We report here on a preliminary investigation of the fluorescence emission of the respective tagged complexes during catalysis.

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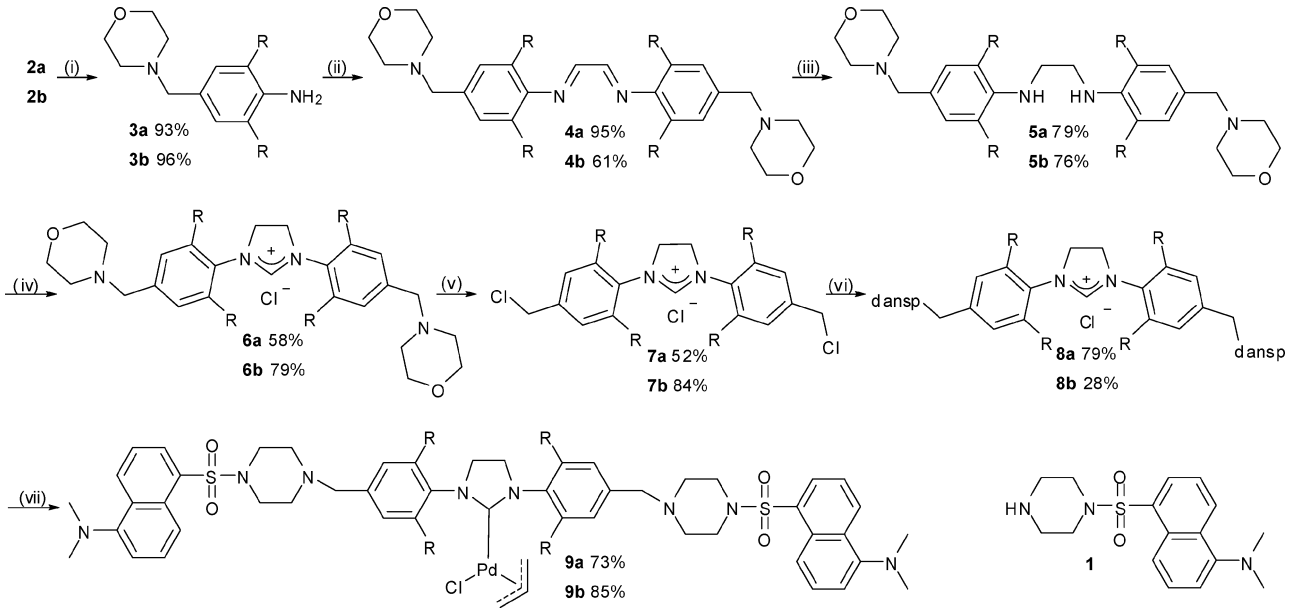
First the synthesis of a fluorophore tagged *N*-heterocyclic carbene was undertaken (Scheme 1). According to a procedure by Cooke *et al*.[12] 2,6-dimethylaniline **2a** and 2,6-diisopropylaniline **2b** were aminomethylated to obtain up to 100 g of the respective 4-morpholinomethyl-substituted anilines in excellent yields. The anilines **3a** and **3b** were converted into the imidazolium salt **6a** and **6b** in accordance with standard procedures.[13] Treatment of **3a** or **3b** with glyoxal gave the respective diimines **4a** and **4b**, whose reduction with $LiAlH_4$ resulted in the respective diamines **5a** and **5b**, followed by ring closure with $HC(OEt)_3$ and formation of **6a** and **6b**. The CH_2-*N*(morpholino) unit can be cleaved by prolonged treatment with ClCOOEt in acetonitrile,[14] to generate $–CH_2Cl$-substituted imidazolium salts **7a** and **7b**. These are the key compounds for the work reported here, as the presence of two $–CH_2Cl$ groups enables the facile introduction of various nucleophiles onto the NHC precursor. The methyl-substituted **7a** is produced in 52% yield after repeated treatment with chloroformate. Due to the poor solubility of the imidazolinium salt **6a** in CH_3CN (and in many other solvents suitable for this reaction) the reaction proceeds slowly. However, the starting material and the partially cleaved mono-morpholino salt can be isolated and again exposed to the cleavage conditions. The much better solubility of **6b** in CH_3CN enables the synthesis of dekagram amounts of **7b** in 84% yield. The facile substitution of the $–CH_2Cl$ group with a variety of nucleophiles allows the introduction of numerous functional units. In order to attach a dansyl-based fluorophore, the corresponding nucleophile was required. A large excess of piperazine (6 equiv.) was reacted with dansylsulfonylchloride and the monosulfonated piperazine **1** isolated in 93% yield. Reaction of the secondary amine **1** with the benzyl chloride **7** results in the facile formation of a dansyl-tagged NHC precursors **8a** and **8b**, respectively. The introduction of the fluorophore is equally efficient for both **8a** and **8b**. However, for the isopropyl-substituted species the difficult separation of **8b** and **1** results in a low yield of isolated **8b**. According to published procedures the carbenes resulting from **8a/8b** were converted to the Pd complexes **9a/9b**. The (NHC)PdCl(allyl) complex reported by Nolan *et al*. is useful in Suzuki cross-coupling and Buchwald–Hartwig amination reactions.[8,9] According to Nolan *et al*., the best catalytic conditions for such catalyst are the use of KO*t*Bu as a base and *i*PrOH as a solvent. Unfortunately, due to the low solubility of our Pd complex and the precipitation of inorganic salts during reaction we were prompted to search for other solvents. In polar solvents such as DMSO, DMF and DMA a very low catalytic activity was observed. With a view to the important role of *i*PrOH in the generation of active species, DMA–*i*PrOH mixture (1 : 5) was found as an optimal choice.

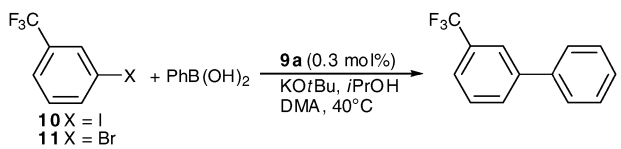


Scheme 1 Synthesis of fluorophore tagged Pd complex. *Reagents and conditions*: **2a** (2,6-dimethylaniline), **2b** (2,6-diisopropylaniline) (i) CH_2O, morpholine, EtOH, H_2O, reflux; (ii) HCOOH, glyoxal, MeOH, rt; (iii) $LiAlH_4$, THF, 0 °C, rt; (iv) NH_4Cl, $HC(OEt)_3$, 120 °C; (v) ClCOOEt, MeCN, reflux; (vi) **1**, DMF, rt (dansp-H = **1**); (vii) $[Pd(allyl)Cl]_2$, KO*t*Bu, THF, rt.

Iodo- and bromoderivatives **10** and **11** were chosen as model substrates. In this solvent medium the sterically less demanding catalyst **9a** is more active than **9b**. The next step was to establish the conditions needed for fluorescence monitoring measurements in a cuvette to enable *in situ* fluorescence measurements. Ideally all reagents and products should be soluble in the reaction medium.

We studied the Suzuki coupling reaction of 3-trifluoromethyl-bromobenzene and 3-trifluoromethyl-iodobenzene with phenyl boronic acid using 0.3 mol% (10^{-4} M) of the fluorophore tagged Pd complex **9a** at 40 °C in DMA–*i*PrOH (1 : 5) (Scheme 2).

After excitation at 365 nm, the monitoring of the fluorescence signal at 532 nm during the coupling reaction (Fig. 1) reveals interesting features of the catalytic transformation. During the first minutes the fluorescence signal of a mixture of Pd^{2+} precatalyst **9a** and phenylboronic acid is stable at 3100 a.u. According to Nolan *et al.*, the addition of KO*t*Bu leads to the formation of the catalytically active Pd^0 species. This process results in an immediate drop in the fluorescence intensity from 3100 to 2700 a.u. within a few seconds. We believe that this drop in intensity is due to a change in the fluorescence quenching behavior of Pd^{2+} *vs.* Pd^0. It was recently reported that Pd^0 nanoparticles cause fluorescence quenching in Alexa Fluor dyes.[15] Again, the fluorescence remains stable over the next *ca.* 20 min until the aryl halide was added. This substrate induced a slower but much more pronounced decrease in the fluorescent intensity from 2630 to



Scheme 2 Suzuki coupling reactions of **10** and **11**.

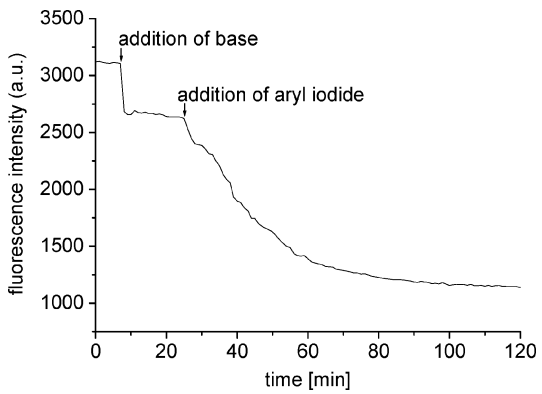


Fig. 1 Fluorescence *vs.* time curve of the Suzuki coupling of 3-trifluoromethyl-iodobenzene and $PhB(OH)_2$ using Pd complex **9a**.

1100 a.u.. The exponential decay of the fluorescence intensity corresponds to the shape of the GC derived conversion–time curve of this Suzuki coupling reaction. This shows that monitoring the fluorescence signal allows one to directly follow the course of the coupling reaction. Since it is unlikely that the organic coupling product formed is responsible for the change in fluorescence intensity and since the distribution of Pd complexes should be constant throughout the catalytic transformation, other species must be responsible for the decay of the fluorescence signal.

It is known that heavy atoms can quench the fluorescence (heavy atom effect).[16] A hint that iodide is responsible for this in the cross-coupling experiments comes from the analogous reaction of **11** with $PhB(OH)_2$ from which qualitatively the same curve was obtained. However, the slow exponential drop in the fluorescence intensity is much less pronounced after the addition of aryl bromide. This points to the formation of iodide as being responsible for the strong decay of the fluorescence signal during the coupling of **10**. To confirm this,

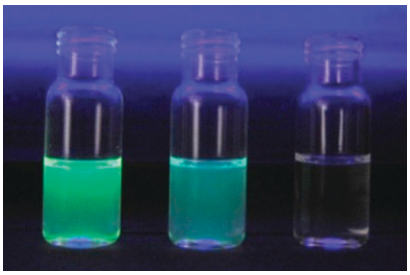


Fig. 2 Residual fluorescence of product solutions: after silica gel plug filtration (left vial); after ethyl acetate chromatography (central vial); after cyclohexane chromatography (right vial).

stoichiometric amounts of KI were added to the reaction mixture. With solid KI, the fluorescence slowly decays due to the slow dissolution of the salt; upon addition of a KI solution an instant drop in the fluorescence intensity was observed.

Another aspect of NHC fluorophore tagging is that it allows the visual detection of palladium impurities in the cross-coupling products. An example of the qualitative estimation of palladium content using the precatalyst **9b** in isopropanol is shown below (Fig. 2). Initially, the reaction mixture was passed over a short silica plug to remove salts, and all of the (NHC)Pd species remain in the product solution. Next, chromatography with ethyl acetate led to a significant reduction in the (NHC)Pd level, but only after cyclohexane chromatography were all of the (NHC)Pd species removed, as evidenced by the absence of noticeable fluorescence. It is worth noting that the smallest visually detectable concentration of **9b** was determined to be *ca.* 2×10^{-7} mol L^{-1}, which corresponds to 64 ng of Pd in 3 mL of solvent (volume of cuvette).

It is important to confirm that the observed fluorescence originates from the fluorophore tagged NHC ligand attached to the metal and not from dissociated ligand. This was shown by probing the reaction mixtures of the Suzuki coupling reactions by TLC. Among the fluorescent products a primary dominant fluorescent spot besides other more polar ones of much lower intensity was observed. Based on fluorescence intensity, the predominant portion of the fluorescence resides in a single species denoted as **9c**, which (according to TLC) is not the initial Pd complex **9b**. To learn more about the identity of this fluorescent species, we did the following experiment: for the coupling reaction of phenylboronic acid with 2,6-dimethylchlorobenzene, 20 mol% of catalyst **9b** and 1.4 equiv. of base (KO*t*Bu) were used. Again, the main fluorescent product is **9c**, which was purified by column chromatography and isolated. Based on the NMR spectra the identity of **9c** was not resolved, but **9b** and **9c** are quite similar.

In conclusion, we have synthesized two imidazolinium salts (**7a**, **b**) which possess functional groups ($-CH_2Cl$) allowing the facile introduction of various nucleophiles into *N*-heterocyclic carbenes. A dansyl fluorophore was attached *via* a piperazine linker and the corresponding (NHC)Pd(allyl)Cl complex was prepared. The fluorescence signal of the dansyl group experiences characteristic changes on forming the catalytically active species from the precatalyst and during the actual cross-coupling reaction. The presence of a fluorescent tag firmly attached to Pd furthermore allows the detection of minute amounts of (NHC)Pd species down to a concentration of *ca.* 2×10^{-7} mol L^{-1}. Future studies are aimed towards using the variations in the fluorescent tag signal to learn more about the nature and the concentration of the (NHC)Pd species in the catalytic cycle. The tagging of various metal complexes with the fluorophore NHC ligand should also enable the facile detection of such complexes in trace amounts.

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