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Polymer supported palladium *N*-heterocyclic carbene complexes: long lived recyclable catalysts for cross coupling reactions

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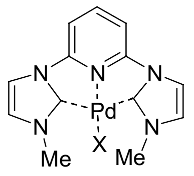
Abstract—Polymer supported palladium complexes, containing a pyridyl bis *N*-heterocyclic carbene ligand system derived from isonicotinic acid, provide highly stable catalysts for Heck and Suzuki cross coupling reactions. These heterogenous catalysts can be recycled ⩾14 times with no loss of activity.

The immobilisation of active homogeneous catalysts to insoluble supports has become a popular strategy to facilitate the recovery and recycling of potentially expensive ligands and complexes.[1] Whilst numerous examples of this approach have been reported, many of these exhibit only limited lifetimes and levels of recyclability with the principal problems being complex/ligand degradation and metal leaching from the supported ligand. These problems are particularly prevalent for complexes based on phosphines in which fast ligand exchange occurs or a dissociative mechanism is required to generate the active catalyst from the stable precursor species. Consequently, in order to function effectively in this regard, ligand systems are required, which stabilise not only the catalyst precursor, but also the catalyst rest state and all species involved in the catalytic cycle. In this respect *N*-heterocyclic carbene ligands have been shown to provide much stronger binding than the corresponding phosphines and unlike the latter remain bound to the metal centre throughout catalytic cycles.[2] With this in mind we were attracted by a report, which indicated that the CNC pyridyl bis carbene–palladium complex **1** exhibits extreme thermal, air and moisture tolerance and functions as an effective catalyst for a range of cross coupling processes.[3] In this letter we demonstrate that simple modifications to this system provide robust immobilised catalysts capable of promoting both Suzuki and Heck coupling reactions through repeated cycles.[4]



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Initial work commenced with commercially available dichloroisonicotinic acid **2** and explored the effect of the C-4 carbonyl group on the catalytic activity and stability of the complex (Scheme 1).[5] Following conversion to the acid chloride a number of simple amides were generated. Subsequent heating with *N*-alkyl or aryl imidazoles at 160 °C for 24 h afforded the desired imidazolium salts **3**. Attempts to accelerate this process through the use of microwave activation were successful (140 °C, 10 min, 91%) in the case of the *N*-methyl imidazole but failed with higher *N*-alkyl derivatives. We believe that with these latter substrates *N*-dealkylation via halide promoted elimination is competitive under microwave promotion. Complexation was then achieved by simple ligand exchange with $Pd(OAc)_2$. Initially this was undertaken by prolonged heating (160 °C, 16 h) in thoroughly degassed DMSO but can be more efficiently achieved under microwave initiation (160 °C, 15 min). In

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Keywords: Polymer; C–C coupling; Palladium; *N*-Heterocyclic carbene; Heck; Suzuki.

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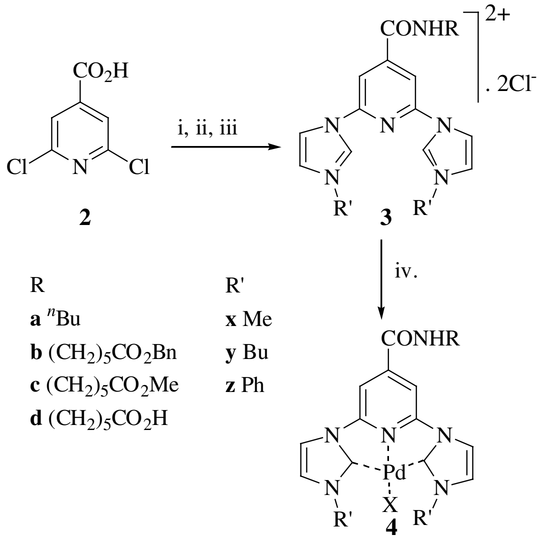
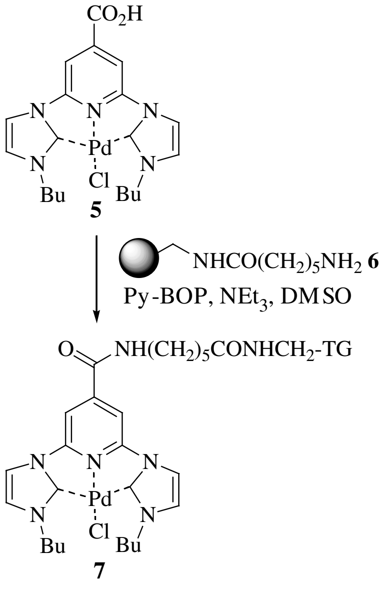


Scheme 1. Reagents and conditions: (i) $(COCl)_2$, $DMF_{(cat)}$, DCM; (ii) RNH_2, Et_3N, DCM 79–89% (two steps); (iii) imidazole, DMSO, 160 °C (79–96%) or *N*-methyl imidazole, μ-wave, 140 °C, 10 min (**4ax**, 90%); (iv) $Pd(OAc)_2$, μ-wave, DMSO, 160 °C, 15 min (90–95%).



Scheme 2.

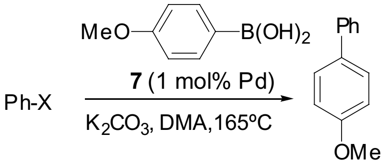
all cases the complexes could be isolated by simple precipitation and recrystallisation. Simple model studies in both the Heck and Suzuki cross coupling with bis *N*-methyl complex **4ax** showed that the incorporation of an amide unit at C-4 had little effect on the overall yield and that the reaction rate was only marginally slower than with the parent compound.[6]

Having demonstrated that an amide group could be tolerated we then investigated the coupling to a polymer support. In order to minimise both steric interference from the bulk polymer and the possibility of adverse site–site interactions we opted for a relatively short spacer unit in the form of a caproate linker. Although the ester terminated caproate complexes **4by** and **4cy** could be prepared, attempts to generate the free acid **4dy** [$R' = Bu$, $R = (CH_2)_5CO_2H$] and couple this to a variety of polymeric amines proved unsuccessful. The alternative approach of initially generating the supported ligand followed by complex formation was frustrated by poor efficiencies in the complexation step leading to considerable amounts of precipitated palladium, which proved to be difficult to separate from the resin. Ultimately a reliable and reproducible loading of the complex was achieved by coupling preformed complex **5** with a polymer supported caproate **6** derived from amino terminated Tenta Gel® resin (0.26 mmol/g), Scheme 2. Complete loading of all the available amine groups (bromophenol blue stain[7]) was consistent with the loading determined by elemental analysis ($0.22\,mmol\,g^{-1}$, 3.04% Pd [theoretical maximum 3.05%]).

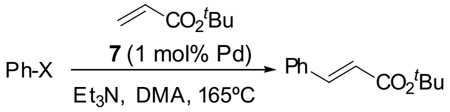
With the resin in hand we then explored applications in cross coupling strategies. Simple Suzuki and Heck reactions could be achieved in moderate to excellent yields without any recourse to the exclusion of air or moisture with iodides affording considerably better yields of product than the equivalent bromides.[8] As with the solution phase versions of this catalyst, attempts to carry out these reactions at lower temperatures were not successful. Having demonstrated that the polymeric complexes retained catalytic activity we then turned to explore the viability of recycling and reuse. Following complete consumption of starting material (GC) the reaction mixture was filtered and the residual resin washed with THF/water (1:1) to remove any precipitated salts and then dried under vacuum before being recharged with reagents. Although initial attempts at running the reaction under an atmosphere of air were successful, only limited repeats were possible before precipitation of Pd black was observed and the overall yield began to fall off. These problems could simply be circumvented by purging the reaction mixture with an inert gas (argon) for ~30 min prior to commencing heating. Under these modified conditions the polymeric catalyst appears to be robust giving no evidence for a drop in overall yield or a diminution of the reaction rate even after a minimum of 14 recycles, Table 1.

Analysis of the product mixture following separation and washing of the resin by ICP-MS indicated that after the initial run (~3 ppb) there were very low levels of leaching (<0.05 ppb) of Pd from the resin. This was confirmed by analysis of the resin following 14 recycles (3.02% Pd). In order to confirm that the active catalysts remained bound to the polymer during the course of the reaction we undertook experiments in which the reaction mixture was filtered after ~50% conversion (GC). No further conversion occurred despite heating for a further 48 h. Moreover, following the procedure developed by Davies,[9] a three phase reaction involving a polymer supported aryl iodide **8** (Wang resin 2.7 $mmol\,g^{-1}$), polymer supported catalyst **7** and 4-methoxyphenyl-boronic acid failed to produce any Suzuki coupling product.

Table 1. Suzuki and Heck reactions carried out using polymer supported catalyst **7**



Entry	X	Recycles[a]	Yield[b]
1	Br	1[c]	57
2	Br	4[c]	55
3	I	1[c]	95
4	I	5[c]	95
5	I	>14[d]	95



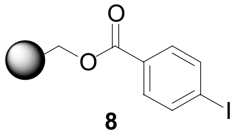
Entry	X	Recycles[a]	Yield[b]
6	I	1[c]	87
7	I	8[c]	82
8	I	>14[d]	83

[a] Recycles before >5% drop in isolated yield.

[b] Yield of purified product after chromatography.

[c] Reactions carried out in air.

[d] Reactions carried out under Ar.



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In conclusion, these pincer CNC systems provide very effective ligands for supported catalysis showing enhanced stability and functioning at low loading levels of catalyst.[10] Limitations do exist in the lower activity of aryl bromides and the (related) need for high activation temperatures. We suspect that these are due to the very high ligand binding in the precatalyst system and the difference in rate determining step between aryl iodides and bromides. More active equi-stable supported catalyst systems that address these issues are being developed in our laboratory and results will be reported in due course.

Acknowledgements

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4. Recently and concurrent with this work Peris et al. have demonstrated the immobilisation of **1** on various clays and the application of this combination as a supported catalyst for Heck and Sonagashira reactions. (a) Mas-Marza, E.; Segarra, A. M.; Claver, C.; Peris, E.; Fernandez, E. *Tetrahedron Lett.* **2003**, *44*, 6595–6599; (b) Poyatos, M.; Marquez, F.; Peris, E.; Claver, C.; Fernandez, E. *New J. Chem.* **2003**, *27*, 425–431.
5. (a) Dijkstra, H. P.; Slagt, M. Q.; McDonald, A.; Kruithof, C. A.; Kreiter, R.; Mills, A. M.; Lutz, M.; Spek, A. L.; Klopper, W.; van Klink, G. P. M.; van Koten, G. *Eur. J. Inorg. Chem.* **2003**, *22*, 830–838; (b) van de Kuil, L. A.; Grove, D. M.; Gossage, R. A.; Zwikker, J. W.; Jenneskens, L. W.; Drenth, W.; van Koten, G. *Organometallics* **1997**, *16*, 4985–4994.
6. Complete coupling of phenyl iodide with 4-methoxyphenylboronic required 36 h at 165 °C. In contrast the unfunctionalised complex promoted this transformation in <24 h at the same temperature. Conversions after 1 h **1** 66%, **4ax** 58%; 4 h **1** 81%, **4ax** 70%; 24 h **1** 100%, **4ax** 94%; 36 h **4ax** 100%.
7. Krchnak, V.; Vagner, J.; Lebl, M. *Int. J. Pept. Prot. Res.* **1988**, *32*, 415–416.
8. The reactions for Suzuki coupling studies were typically conducted as follows: catalyst **7** (50 mg, ~1 mol%), K_2CO_3 (270 mg, 1.95 mmol), boronic acid (1.50 mmol), aryl halide (1.31 mmol), diethylene glycol dibutyl ether (323 μL, 1.31 mmol, GC standard), dry DMA (10 mL) and a magnetic stirrer were added to a Radley's Carousel® parallel synthesis reaction tube. The reaction mixture was degassed by bubbling argon through the reaction tube contents for 30 min prior to use. The tube was then sealed with a Teflon screw cap and heated to 165 °C for 48 h. After cooling to room temperature the reaction contents were filtered and the supported resin washed with DCM (3 × 10 mL). For GC analysis the filtrate was made up to 50 mL in a standard volumetric flask with DCM and a small aliquot taken for GC analysis of the reaction. For an isolated yield the organic filtrate was extracted with water (3 × 20 mL) and dried with $MgSO_4$. The mixture was filtered and the solvent removed in vacuo and the product purified by flash column chromatography. The catalyst was washed further with THF/water (1:1, 3 × 10 mL) and diethyl ether (3 × 10 mL) and dried in vacuo for further use. All products were characterised by comparison with

commercially available samples. The reactions for Heck coupling studies were typically conducted as follows: catalyst **7** (90 mg, ~1 mol%), K_2CO_3 (610 mg, 4.41 mmol), acrylate (3.14 mmol), aryl halide (2.23 mmol), dry DMA (10 mL) and a magnetic stirrer were added to a Radley's Carousel® parallel synthesis reaction tube. The reaction mixture was degassed by bubbling argon through the reaction tube contents for 30 min prior to use. The tube was then sealed with a Teflon screw cap and heated to 165 °C for 48 h. After cooling to room temperature the reaction contents were filtered and the supported resin washed with DCM (3 × 10 mL). The organic filtrate was extracted with water (3 × 20 mL) and dried with $MgSO_4$. The mixture was filtered and the solvent removed in vacuo and the product purified by flash column chromatography. Regeneration of the catalyst followed an identical procedure as described above.

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10. Although in this study we have routinely used ~1 mol% of the polymer supported catalyst this simply reflects the ease in handling of the resin (~50 mg) on the scale of the reactions undertaken. However, we have been able to run similar reactions using 0.1 mol% loadings with no loss in yield and recyclability.