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Crown-ether functionalised second coordination sphere palladium catalysts by molecular imprinting†

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Functionalisation of the second coordination sphere of a molecularly imprinted Pd complex was achieved by localising within the polymeric cavity a crown-ether receptor capable of altering the catalytic activity of the reactive site.

High activities and selectivities in enzymatic reactions are normally achieved by imposing precise geometric controls on the enzyme–substrate complex; in the active site key catalytic group(s) converge on the substrate to guide and manipulate chemical reactivity. Metallo-enzymes function similarly and utilise both their *inner* and *outer spheres* to control the metal's reaction profile.[1] The same manipulation of the second coordination sphere of synthetic organometallic catalysts, while desirable, is challenging and often requires considerable synthetic efforts.[2]

Molecular imprinting has recently emerged as a promising alternative method for achieving this goal.[3] This technique relies on a three-dimensional transfer of information from a polymerisable template to a porous highly cross-linked organic polymer matrix. To date most *MIP* transition metal catalyst reports have dealt with developing methods for associating specifically shaped cavities to influence chemical reactivity and/or selectivity.[3,4] We sought access to polymer active sites that additionally contained a receptor (recognition site) displayed in the outer sphere of the metal center (reactive site), and report herein 1) preliminary results validating a synthetic strategy for achieving this goal and 2) a proof of principle that functionalised cavities can indeed influence chemical reactivity.

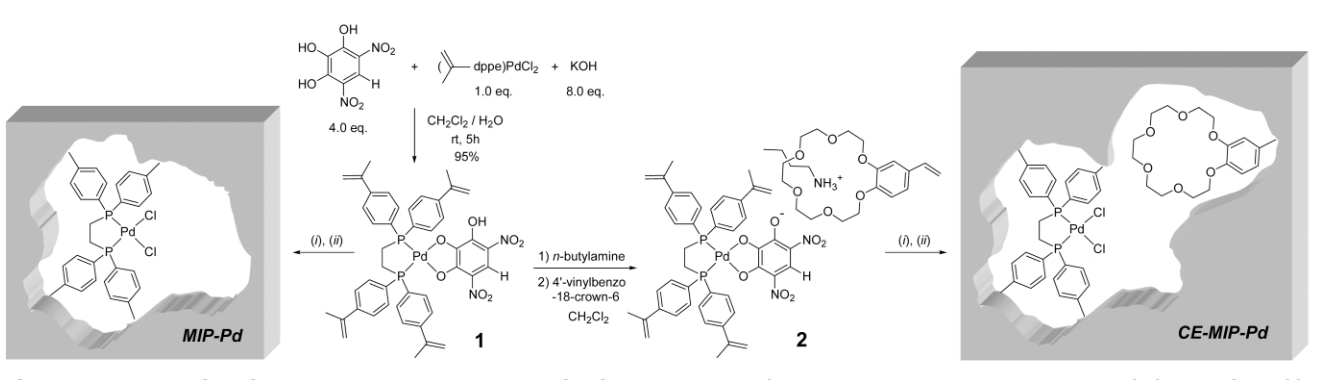
To test the feasibility of outer sphere recognition occurring in concert with catalysis, we chose to investigate a hybrid palladium catalyst/crown-ether receptor system, since crown-ethers (CE) have rich host–guest properties,[5] and Pd-catalysts have been demonstrated to be influenced by secondary interactions in the coordination sphere (including CEs).[6] These factors coupled with Cammidge's recently reported P_2Pd(catecholate)-based *MIP* catalysts for Suzuki reactions,[7] stimulated the design of a synthetically straightforward route to CE palladium *MIP* catalysts. Non-covalent interactions enable the assembly of a polymerisable ternary complex **2** which would hopefully lead to a hybrid crown-ether functionalised active site (Scheme 1).[8]

Treating **1**‡§ with a primary amine and crown-ether was expected to generate an ion-pair that acted to electrostatically associate the metal complex with a polymerisable CE. Indeed, ternary complex **2** was obtained by combining **1** with 1.0 equiv. of *n*-butylamine and 1.0 equiv. of 4′-vinylbenzo-18-crown-6 in CH_2Cl_2 which maintained its compositional integrity after trituration and precipitation.[9] In the absence of CE, the ion pair is nearly insoluble.

1 and **2** were copolymerised with ethylene dimethacrylate (Pd : EDMA = 1 : 99) in the presence of a porogen (C_6H_5Cl).[10] The pyrogallol template was then cleaved with HCl and removed[11] (Soxhlet, CH_2Cl_2) giving the white-yellow highly crosslinked porous polymer precatalysts ***MIP–Pd*** and ***CE–MIP–Pd***,[12] which should have similar inner-spheres, and different outer-spheres (Scheme 1). During the preparation of ***CE–MIP–Pd*** no leaching of the polymerisable crown-ether was observed. A control polymer missing the *n*-butylamine was also synthesised to test the effect of unassociated CE sites.

The Suzuki reaction (Table 1) was chosen to assess the presence and/or effect of the crown-ether in ***CE–MIP–Pd***, since the effect of coordinating the cation by the associated crown-ether could be manifested in several points in the catalytic cycle (highlighted in Fig. 1).[13]

A series of alkali metal bases were tested with both *MIP* catalysts. As reported in Table 1, the reaction rate was closely related to the nature of the base with the CE-modified catalyst being more active in every case. More importantly, the magnitude of the rate increase was strongly dependent on the nature of the cation. Indeed, while almost no increase was observed with Li_2CO_3 (g_{Li^+} ~1), a much higher "gain" was obtained with K_2CO_3 (g_{K^+} ~2.5). In fact, the order ($K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$) fits exactly the known affinity of alkali metal cations for an 18,6-crown-ether.[5] Control experiments



Scheme 1 *Reagents and conditions*: (*i*) a) **1** or **2**, EDMA, C_6H_5Cl (Pd : EDMA : C_6H_5Cl = 1 : 99 : 100), AIBN (1%), 60 °C, 24 h; b) CH_2Cl_2 Soxhlet extraction, 16 h; (*ii*) a) HCl in dioxane (4 M), CH_2Cl_2, rt, 6 h; b) CH_2Cl_2 Soxhlet extraction, 16 h.

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† Electronic supplementary information (ESI) available: synthesis and characterisation of compounds **1–3**, *MIP–Pd* and *CE–MIP–Pd*; molecular structure of **3**. See http://www.rsc.org/suppdata/cc/b3/b309072h/

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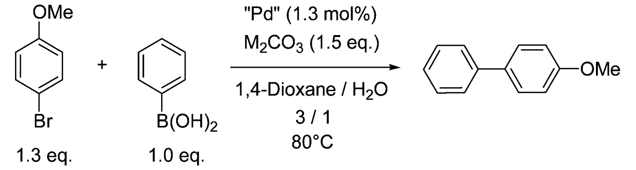
Table 1 Suzuki reaction catalysed by ***MIP–Pd*** or ***CE–MIP–Pd***



Entry	M_2CO_3	Conversion (%)[a] "Pd" = ***MIP–Pd***	 "Pd" = ***CE–MIP–Pd***	g_{M^+}[b]
1	K_2CO_3	26	66 (36)[c]	2.5 (1.4)[c]
2	Rb_2CO_3	48	77	1.6
3	Cs_2CO_3	49	70 (54)[c]	1.4 (1.1)[c]
4	Na_2CO_3	57	71	1.2
5	Li_2CO_3	42	44	1.1

[a] Determined by GC after 6 h. [b] g_{M^+} = conv[***CE–MIP–Pd***]/conv[***MIP–Pd***]. [c] A control polymer, prepared from **1** and the polymerisable CE in the absence of *n*-butylamine, was used.

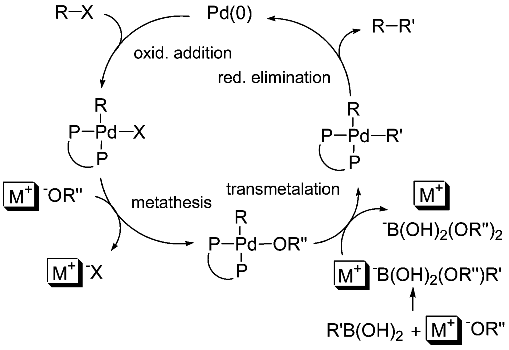
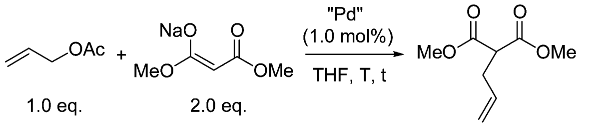


Fig. 1 Catalytic cycle for a typical Suzuki reaction.

with non-associated crowns (Table 1, bracketed entries 1 and 3) indicate that both the rate acceleration and the metal ion dependence are attenuated.

To further compare the catalytic behavior of ***MIP–Pd*** and ***CE–MIP–Pd*** we examined the allylation of dimethyl malonate with allyl acetate (Table 2).[14] The course of this reaction was somewhat impaired by deactivation of the catalysts after prolonged reaction times. However, conversion after short periods of time clearly showed the higher activity of ***CE–MIP–Pd***. And more interestingly, a decrease in temperature led to an increased activity-gap between ***MIP–Pd*** and ***CE–MIP–Pd***.[15]

Table 2 Allylic alkylation catalysed by ***MIP–Pd*** or ***CE–MIP–Pd***



Entry	"Pd"	*T*/°C	*t*/h	Conversion (%)[a]
1	***MIP–Pd***	60	2	10[b]
2	***CE–MIP–Pd***	60	2	39[b]
3	***MIP–Pd***	rt	8	9[b]
4	***CE–MIP–Pd***	rt	8	59[b]

[a] Determined by GC using *n*-decane as internal standard. [b] Formation of the disubstituted product was observed; [mono/di] = 93/7.

It is tempting to ascribe the rate enhancement in the above experiments to beneficial binding between the CE and the cation of the nucleophile as has shown by Ito in bifunctional chiral ligands.[6]

Together, these results show that molecular imprinting can be used to functionalise the second coordination sphere of a transition metal complex and subsequently affect its catalytic behavior. However, a consideration of the comparative rates of metal/CE association/dissociation (fast) and polymerisation (slow), along with the structural impreciseness of ion pairing, suggest that the imprinted CE effect emanates despite a broad distribution of structures in the active site of ***CE–MIP–Pd***. While clearly beneficial in a heterogeneous state, these considerations suggest that more defined imprinting assemblies will lead to even better synergism between the metal and the recognition site, much like metallo-enzymes.

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Notes and references

‡ The polymerisable palladium complex **1** with a pyrogallol ligand was synthesised in high yield from the corresponding (isopropenyl dppe)$PdCl_2$ and 4,6-dinitropyrogallol under biphasic CH_2Cl_2/aq. KOH conditions. **3**, the non-polymerisable analogue of **1**, was structurally characterised (see Supporting Information).

§ *Crystal data for* $C_{32}H_{26}N_2P_2O_7Pd$ **3**: M = 718.91, orthorhombic, space group *Pbca* (no. 61), a = 17.173(3), b = 17.584(3), c = 20.164(3) Å, U = 6088.8(18) Å^3, Z = 8, μ(Mo-Ka) = 0.77 mm^{-1}, T = 173 K, 55123 reflections measured, 5389 unique and 3967 observed [$I > 2.5\sigma(I)$, R_{int} = 0.047] which were used in all calculations. The final $\omega R(F2)$ was 0.053 (observed data). CCDC 216871. See http://www.rsc.org/suppdata/cc/b3/b309072h/ for crystallographic data in .cif or other electronic format.

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