Simple rhodium–chlorophosphine pre-catalysts for the ortho-arylation of phenols†

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Simple chlorodiisopropylphosphine adducts of rhodium, either pre-formed or formed *in situ*, prove to be highly effective catalysts for the ortho-arylation of phenols.

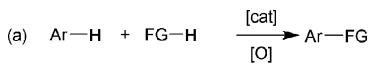
Aromatic functionalisation by catalytic C–H activation is rapidly establishing itself as a viable alternative to classical cross-coupling chemistry, not least because it obviates the need to introduce an organometallic leaving group onto either of the coupling partners.[1] In the absence of an organometallic fragment, two general C–H activation protocols can be envisaged; the first is to use oxidative coupling (Scheme 1, path a) and the second relies on the oxidative addition of an organic halide (path b). The first process is obviously more atom-economical than the second,[2,3] although this is dependent on the complexity of the oxidising agent, but can lack the selectivity inherent in the second reaction type.

An example of the second methodology is provided by the catalytic ortho-arylation of phenols (Scheme 2).[4,5] In this instance the phosphinite ligand is required as a co-catalyst; this is the species that undergoes C–H activation *via* ortho-metallation (Scheme 3), in effect acting as an intramolecular 'tether'. The phosphinite ligand then undergoes 'transesterification' with the starting phenol, in the presence of base, which liberates the 2-arylated phenol product and regenerates the starting phosphinite.

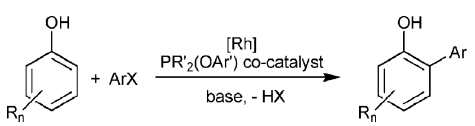
Unfortunately, the use of phosphinite co-catalysts presents some obvious problems. Firstly, these ligands are not generally commercially available and thus need to be pre-synthesised; secondly, the phosphinite used should ideally contain the same phenoxide residue as the substrate to avoid contamination of the product with coupled by-products. These issues can limit the appeal of the methodology in synthetic applications. One way around these problems would be to use rhodium systems with commercially available chlorophosphine complexes as pre-catalysts—this should lead to the formation of the desired phosphinite ligands *in situ*. We now report that simple rhodium chlorophosphine complexes, either pre-formed or produced *in situ* from commercially available materials, are indeed at least as active as phosphinite systems, making them the catalysts of choice for these reactions.

In the first instance, we examined the use of commercially available $^{i}Pr_2PCl$ as the ligand since we previously found the corresponding phosphinites $^{i}Pr_2P(OAr)$ to be particularly useful for the ortho-arylation of a range of phenols. Table 1 summarises the results obtained in the coupling of 2,4-di-*tert*-butylphenol with 4-bromoanisole. As can be seen, good activity is observed at 5 mol% Rh with $^{i}Pr_2PCl$, but changing to Ph_2PCl is deleterious. Similarly, the other dialkylchlorophosphines employed both perform poorly. It is obvious that nucleophilic attack of the phenol at a coordinated $ClP^{t}Bu_2$ is severely impeded by the bulk of the alkyl groups, however comparison of simple models of '$ClP^{i}Pr_2$–Rh' and '$ClPCy_2$–Rh' fragments also show the approach of the nucleophile to the latter to be sterically disfavoured.† It seems that the ^{i}Pr group holds a privileged position with sterically encumbered phenol substrates—it is sufficiently bulky to accelerate orthometallation by forcing the phenolic residue over the metal centre,[6] and yet provides an access route for the incoming phenolate during transesterification.

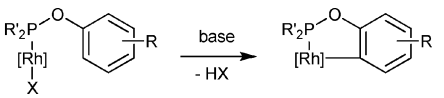
Changing the base to $NaO^{t}Bu$ or K_3PO_4 leads to reduced activity. Changing the rhodium precursor to Wilkinson's catalyst has little effect on performance, whereas $[\{RhCl(ethene)_2\}_2]$ behaves highly capriciously with poor



Scheme 1 Aromatic C–H functionalisation.



Scheme 2 The catalytic ortho-arylation of phenols.



Scheme 3 Orthometallation of the phosphinite ligand.

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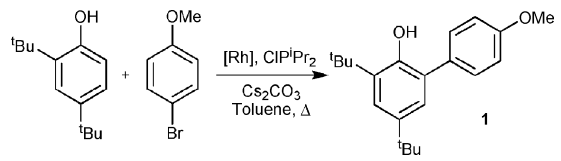
† Electronic supplementary information (ESI) available: Experimental details, models of $Rh–PClR_2$ fragments. See DOI: 10.1039/b718128k

Table 1 Catalyst optimisation[a]



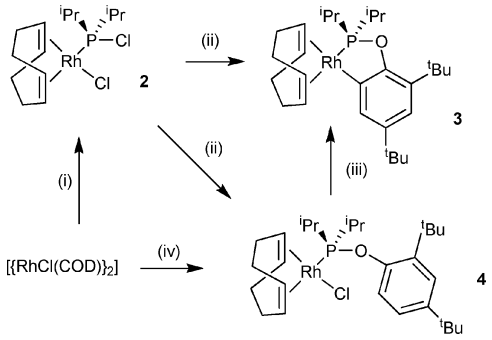
Entry	Rh precursor	Rh loading (mol%)	$ClPR_2$	Yield (%)[b]
1	$[\{RhCl(COD)\}_2]$	5	ClP^iPr_2	92
2		5	$ClPPh_2$	27
3		5	$ClPCy_2$	19
4		5	ClP^tBu_2	0
5		5	ClP^iPr_2	76[c]
6		5	ClP^iPr_2	66[d]
7	$[RhCl(PPh_3)_3]$	5	ClP^iPr_2	85
8	$[\{RhCl(C_2H_4)_2\}_2]$	5	ClP^iPr_2	55[e]
9	$[\{RhCl(COD)\}_2]$	2.5	ClP^iPr_2	90
10		1	ClP^iPr_2	80
11		0.5	ClP^iPr_2	23

[a] Conditions: 2,4-^{t}Bu$_2$C$_6$H$_3$OH (0.5 mmol), 4-BrC$_6$H$_4$OMe (0.6 mmol), catalyst loading 5 mol%, $ClPR_2$: Rh = 2 : 1, base (0.85 mmol), toluene (5 ml), 18 h, reflux. [b] Spectroscopic yield determined by ^{1}H NMR spectroscopy (1,3,5-(MeO)$_3$C$_6$H$_3$ internal standard), average of 2 runs. [c] NaO^{t}Bu used as base. [d] K_3PO_4 used as base. [e] Average of 9 runs, ±38%.

reproducibility across several runs. $[\{RhCl(COD)\}_2]$ was selected for the remainder of the studies as it is commercially available, easy to handle and, with fewer, less massive ligands, offers lower potential for product contamination than Wilkinson's catalyst. We were pleased to find that the catalyst loading could be reduced to 1 mol% Rh without too much loss in activity.

Having established the optimum catalyst and conditions, we next briefly examined the application of these to the coupling of a range of substrates and the results are summarised in Table 2.† In most cases the catalyst loading used was not optimised but held at 5 mol% Rh, although lowering the loading to 2.5 mol% and repeating the reactions shown in entries 1 and 3 led to only a modest decrease in yield (entries 2 and 4, respectively). In all cases the performances obtained were comparable within a few percent to those reported previously for the pre-formed phosphinite ligands,[4b] demonstrating that chlorodiisopropylphosphine is indeed an ideal and convenient substitute. The aryl bromide employed in entry 7, 2-bromo-*meta*-xylene, has not been used previously in this reaction and demonstrates that the process is tolerant of bulky aryl bromides.

As can be seen from entries 8–10, unsubstituted phenol represents more of a challenge. This is because the rate of orthometallation falls rapidly with decreasing bulk of the phenolic substrate. Replacing the ^{i}Pr$_2$PCl with ^{t}Bu$_2$PCl leads to some di-arylated product, however the conversion obtained is far from useful (entry 9). We reasoned that whilst $ClPCy_2$ is too large for bulky phenols to undergo rapid transesterification (see above) it may allow nucleophilic attack by smaller phenols; the increase in steric bulk may be sufficient to promote a good rate of C–H activation. Unfortunately, there appears to be little difference in activity on changing to this



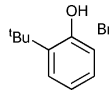
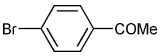
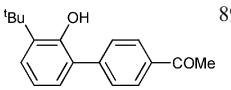
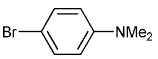
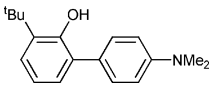
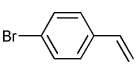
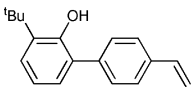
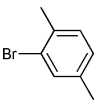
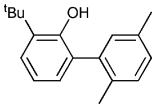
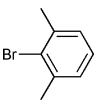
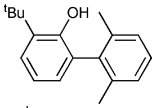
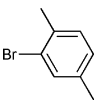
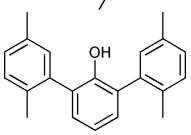
Scheme 4 Conditions: (i) ClP^iPr_2, CH_2Cl_2, rt, 2 h; (ii) HOC$_6$H$_3$-2,4-^{t}Bu$_2$, NaO^{t}Bu, toluene, 80 °C, 1 h; (iii) NaO^{t}Bu, toluene, 80 °C, 1 h; (iv) P^iPr_2(OC$_6$H$_3$-2,4-^{t}Bu$_2$), CH_2Cl_2, rt, 1 h.

chlorophosphine, implying that transesterification is achievable but that the rate of C–H activation is not enhanced. In all three cases, the only product observed is the di-arylated phenol.[7] A synthetically useful alternative, which yields the mono-arylated 6-*H* 2-arylphenols, is to exploit the 2-*tert*-butylphenol substrates which, as shown above, undergo highly selective reactions in good yields and then remove the *tert*-butyl group, a process which can easily be achieved using mild conditions.[8]

With regards to the mechanism, it seems likely that the chlorophosphine ligand, either free or coordinated to the rhodium centre, reacts with the phenolic substrates in the presence of base to generate phosphinite complexes *in situ*. In order to test this we prepared the rhodium chlorophosphine complex **2** (Scheme 4).† The $^{31}P\{^1H\}$ NMR spectrum of **2** shows a doublet at 173.2 ppm with a $^1J_{PRh}$ of 175 Hz, similar to the data reported for a related rhodium complex of a bulky dialkylchlorophosphine.[9] Complex **2** is air-stable in the solid state, showing no sign of decomposition after several days, while a $CDCl_3$ solution stored under air shows less than 5% decomposition within three days.[10] The crystal structure of **2** was determined and the molecule is shown in Fig. 1.‡ To the best of our knowledge this is the first structure of a chlorodiisopropylphosphine transition metal complex to be determined.

Complex **2** is catalytically competent, giving the coupled product **1** in 89% yield at 2.5 mol% loading, indicating that it is a viable model compound for mechanistic studies.[11] The reaction of complex **2** with 2,4-di-*tert*-butylphenol in the presence of excess NaO^{t}Bu generates a new complex assigned as the orthometallated complex **3** on the basis of the NMR spectroscopic and MS data.† Complex **3** can also be prepared by orthometallation of the κ^1-phosphinite complex **4**. When **2** is reacted with 2,4-di-*tert*-butylphenol in the presence of one equivalent of NaO^{t}Bu then a mixture of products is obtained; ^{31}P NMR spectroscopy reveals the major components to be **4** and **3**. The conversion of **4** to **3** reaction is dependent on the presence of base; no orthometallation is observed even at reflux temperature in toluene for 24 h in its absence. This suggests a base-assisted deprotonation mechanism for the C–H activation rather than either electrophilic displacement or oxidative addition of the C–H bond.[12]

Table 2 Coupling of selected substrates[a]

Entry	Phenol	Aryl halide	Product	Yield (%)[b]
1				89
2				87[c]
3				77
4				70[c]
5				74
6				94
7				91 (83)[d]
8				26[e]
9				10[e,f]
10				24[e,g]

[a] Conditions: ArOH (0.5 mmol), ArBr (0.6 mmol), [{RhCl(COD)}$_2$] (5 mol% Rh), ClP^{i}Pr$_2$ (10 mol%), Cs_2CO_3 (0.85 mmol), toluene (5 ml), reflux, 18 h. [b] Spectroscopic yield determined by ^{1}H NMR spectroscopy (1,3,5-(MeO)$_3$C$_6$H$_3$ internal standard), average of 2 runs. [c] 2.5 mol% Rh. [d] Isolated yield. [e] 2 Equiv. of aryl bromide. [f] ClP^{t}Bu$_2$ used as ligand. [g] ClPCy$_2$ used as ligand.

In summary, simple rhodium chlorodiisopropylphosphine complexes serve as excellent catalysts for the ortho-arylation of phenols. These complexes can be either pre-formed or produced *in situ*; the former has the benefit of simplicity whilst the latter yields an air-stable, easily handled species and requires a lower loading of chlorophosphine. Initial mechanistic studies indicate that the rhodium chlorophosphine complexes react with phenolic substrates in the presence of base to give phosphinite complexes that undergo orthometallation by base-assisted C–H activation. The good activity shown by these simple catalysts, comparable with the best reported previously, coupled with the commercial availability of both the rhodium precursors and the ClP^{i}Pr$_2$ ligand, considerably increases the attractiveness of the catalytic ortho-arylation of phenols in synthesis. We are currently exploring the application of this class of catalysts to a range of substrates; in particular we are exploring methodologies that allow the simple mono-arylation of *ortho*-unsubstituted phenols and probing the mechanism of the reaction further.

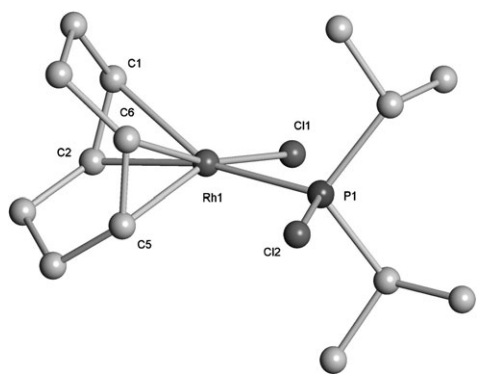


Fig. 1 X-Ray crystal structure of complex **2**. Selected bond lengths (Å) and angles (°): Rh1–Cl1, 2.3609(11); Rh1–P1, 2.2634(11); Rh1–C1, 2.232(4); Rh1–C2, 2.251(4); Rh1–C5, 2.120(4); Rh1–C6, 2.143(4); P1–Cl2, 2.0849(15); Cl1–Rh–P1, 88.04(4); Rh1–P1–Cl2, 114.71(6).

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Notes and references

‡ *Crystal data for* **2**: $C_{14}H_{26}Cl_2PRh$, $M = 399.13$, monoclinic, $a = 7.4343(4)$, $b = 20.7246(14)$, $c = 10.6522(7)$ Å, $\beta = 92.041(2)^\circ$, $V = 1640.17(18)$ Å, $T = 120(2)$ K, space group $P2_1/n$, $Z = 4$, $\mu = 1.447$ mm^{-1}, $R_{int} = 4.9\%$ (for 16 093 measured reflections), $R_1 = 4.4\%$ [for 3175 unique reflections with $>2\sigma(I)$], w$R_2 = 9.6\%$ (for all 3776 unique reflections). CCDC 669413. For crystallographic data in CIF format see DOI: 10.1039/b718128k

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