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Rhodium-catalysed aryl transfer to aldehydes: counterion effects with nitrogen containing ligands

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Abstract—Cationic rhodium complexes of certain nitrogen-containing ligands exhibit excellent catalytic activity in the addition of arylboronic acids to aldehydes. The counterion had a notable effect with the weakly coordinating carborane anion affording a highly active catalyst. © 2001 Elsevier Science Ltd. All rights reserved.

The transition metal-catalysed addition of aryl groups to a carbon–heteroatom double bond remains a relatively undeveloped process compared to the related addition to carbon–carbon double bonds.[1] Miyaura has described the efficient addition of aryl boronic acids to aldehydes in aqueous solution employing phosphane complexes having a large P–Rh–P angle and also with bulky and donating trialkyl phosphines.[2] The necessary transmetalation to rhodium has also been reported to occur with aryltrifluoroborates, trimethyl(phenyl)-stannane and sodium tetraphenylborate allowing the successful arylation of aldehydes and *N*-arylsulfonyl imines.[3] Until recently, active catalytic systems that contain supporting ligands other than phosphines had not been identified. A report by Fürstner revealed a very convenient system comprising $RhCl_3 \cdot 3H_2O$ and a sterically hindered imidazolium salt for effecting the efficient arylation and alkenylation of aldehydes.[4] The emergence of this elegant study prompts us to report our findings concerning the influence of nitrogen-containing ligands, counterion and solvent on the rate and scope of this synthetically useful process.

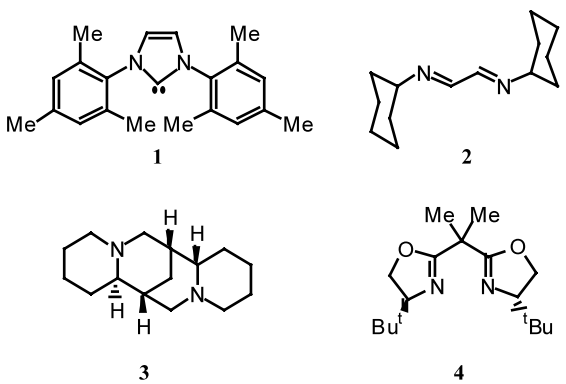

Figure 1. Nitrogen containing ligands used in study.

At the outset of the project our primary goal was to develop an efficient catalyst capable of affording high turnovers in the arylation reaction. To this end, we combined four nitrogen-containing ligands **1**–**4** (Fig. 1) with different rhodium salts and tested the complexes for activity in the addition of boronic acid **6** to aldehyde **5** to afford product **7** after work-up.[5] A selection of results that illustrate the optimisation procedure are shown in Table 1. As expected the reaction was sensitive to changes in Rh source, ligand, counterion and solvent.

The first point to note is that in the absence of ligand no product formation was observed. In the presence of ligands **1**–**4**, under the conditions first reported by Miyaura [boronic acid (2 equiv.), 80°C, DME:H_2O (1:1), 16 h] we were disappointed to similarly note no product formation with any of our catalysts.[2a] On changing the reaction solvent to distilled dimethoxyethane (DME) the catalysts started to show some activity. However, the addition of just 1 equiv. of water to the reaction leads to a complete loss of activity. This is in stark contrast to rhodium(I)/phosphine complexes were the reaction is extremely slow in the absence of water. The carbene ligand **1** and the *N*,*N*′-dicyclohexyl-1,4-diazabutadiene (DAB-Cy) ligand **2** have previously been used as supporting ligands for the

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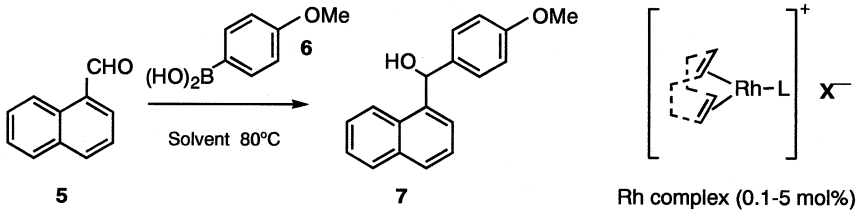
Table 1. Ligand effects in rhodium-catalysed addition of boronic acid **6** to aldehyde **5**



Entry	Metal salt	Loading (mol%)	Ligand	Solvent	Counterion	Yield (%)
1	$[RhCl(ethylene)]_2$	5	–	DME/H_2O (1:1)	–	0
2	$[RhCl(ethylene)]_2$	5	–	DME	–	0
3	$[RhCl(ethylene)]_2$	5	–	DME	PF_6	0
4	$[RhCl(ethylene)]_2$	5	**1**	DME	PF_6	24
5	$[RhCl(ethylene)]_2$	5	**2**	DME	PF_6	5
6	$[RhCl(ethylene)]_2$	5	**3**	DME	PF_6	41
7	$[RhCl(cod)]_2$	5	**3**	DME	PF_6	84
8	$[RhCl(cod)]_2$	0.5	**3**	DME	PF_6	20
9	$[RhCl(cod)]_2$	5	**4**	DME	PF_6	76
10	$[RhCl(cod)]_2$	0.5	**4**	DME	PF_6	73
11	$[RhCl(cod)]_2$	0.1	**4**	DME	PF_6	43
12	$[RhCl(cod)]_2$	0.5	**4**	Dioxane	PF_6	79
13	$[RhCl(cod)]_2$	0.5	**4**	THF	PF_6	64
14	$[RhCl(cod)]_2$	0.5	**4**	Toluene	PF_6	27
15	$[RhCl(cod)]_2$	0.5	**4**	CH_2Cl_2	PF_6	8
16	$[RhCl(cod)]_2$	0.5	**4**	DME/H_2O (1:1)	PF_6	0
17	$[RhCl(cod)]_2$	0.5	**4**	DME	OTf	29
18	$[RhCl(cod)]_2$	0.5	**4**	DME	BF_4	43
19	$[RhCl(cod)]_2$	0.5	**4**	DME	$CB_{11}H_{12}$	85
20	$RhCl_3 \cdot 3H_2O$	1	**1**	DME/H_2O (1:1)	–	88

Suzuki–Miyaura cross-coupling reaction and provide an alternative to the use of tertiary phosphine ligands.[6] In our hands both ligands afforded low yields of product **7** which whilst disappointing was subsequently validated by the work of Fürstner (for **1** with $[RhCl(cod)]_2$).[4] Under optimised conditions ligand **1** was effective (entry 20). A more promising result was obtained with (−)-sparteine **3**, a commonly used chiral base but less exploited as a ligand in catalysis.[7] At 5 mol% loading the complex [Rh(cod)**3**]PF_6 promoted the formation of **7** in 84% isolated yield.[8] On lowering the loading to 0.5 mol% the yield fell dramatically (entries 6–8). The most active complex was derived from the bis(oxazoline) ligand **4** which afforded a 76% yield of product **7** using 5 mol% of catalyst and pleasingly the catalyst loading could be lowered to just 0.5 mol% with no loss in efficiency.[9] The reaction (**5**–**7**) proceeded less efficiently in other solvents including DME:H_2O (0%), dichloromethane (8%), toluene (18%), ether (27%) and tetrahydrofuran (64%). However, the use of dioxane resulted in a comparable 79% conversion to product after 2 h (entries 12–16).

The speculated mechanism suggests that the carbonyl group coordinates to the metal prior to insertion. The addition step is thus influenced by both the Lewis acidity of the metal and the polarisation of the rhodium–aryl bond which in turn is biased by the ligand. Although often overlooked it is well-documented that many catalytic processes involving charged organometallic complexes are dependent on the nature of the counterion.[10] We anticipated that in the presented catalysts, the counterion would influence the Lewis acidity and to test this theory we prepared complexes with varying counterion (OTf^-, BF_4^-, PF_6^-, $CB_{11}H_{12}^-$) and compared their activity in the addition of **5** to **7** in distilled DME at 80°C using 0.5 mol% of catalyst (entries 10 and 17–19).

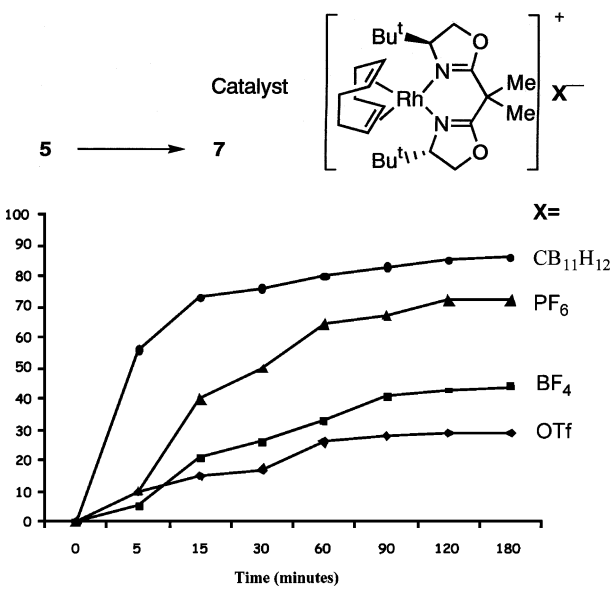
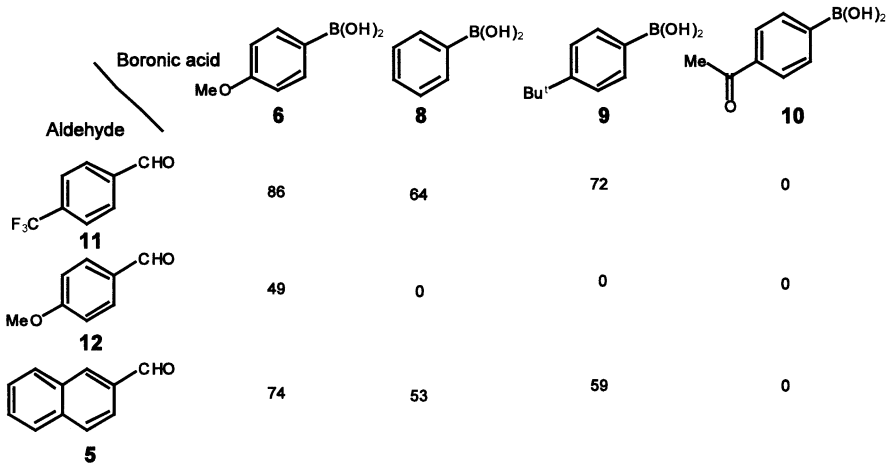


Figure 2. Effect of changing counterion.

Table 2. Scope of the reaction



With all other variables being constant, the counterion had a dramatic effect on the rate of reaction (Fig. 2). The trend appeared to reflect the increasing Lewis acidity of the metal centre with weaker coordinating anions. The best results were obtained with the extremely weakly coordinating carborane anion ($CB_{11}H_{12}^-$) which after only 5 min showed 56% conversion to product and within 15 min was over 70% complete. The unique nature of the carborane anion has previously been exploited in stabilising reactive cations, catalysis and crystal engineering.[11]

The use of enantiopure ligands such as **3** and **4** presents the possibility of asymmetric induction in the addition reaction. Although high enantioselectivity has been achieved in the Rh(I)-catalysed asymmetric 1,4-addition reaction of boronic acids to enones, enoates and alkenylphosphonates, the corresponding addition to aldehydes has not met with the same success.[12] We were similarly disappointed to obtain no enantioselectivity (<10% ee) using any of the enantiopure catalysts. The use of the carborane counterion enabled the reaction to be run at room temperature but still afforded racemic product. Pre-treatment of the catalysts with hydrogen to remove the cod ligand did not improve the results. The lack of enantioselectivity observed in our case and with enantiopure diphosphines suggests the mechanism is not as straightforward as in the 1,4-addition process.

As illustrated in Table 2, the reaction was sensitive to electronic influences in both coupling partners. The optimum combination was an electron-donating group on the boronic acid **6** and an electron-withdrawing group on the aldehyde **11**. This is again consistent with the proposal by Miyaura implying the nucleophilic attack of the aryl group on the coordinated carbonyl group. The lack of any observed reactivity with boronic acid **10** could either be due to electronic deactivation due to the withdrawing acyl group or the coordination of the carbonyl group in **9** to the Lewis acidic metal centre may prevent reaction.

In summary, we have developed new catalysts with good activity at low catalyst loadings for this important synthetic process. A definite counter-ion effect is observed which stimulates further investigation into the mechanism of the reaction and importantly what factors contribute to enantioselection.

Acknowledgements

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5. *Typical procedure*: A mixture of aldehyde **5** (1 mmol), boronic acid **6** (2 mmol) and performed Rh(I) complex (0.1–5 mol%) in solvent (5 ml) was stirred for 2 h at 80°C. The product was then extracted with ethyl acetate (5 ml), washed with water (5 ml), brine (5 ml) then dried over $MgSO_4$. Flash chromatography on silica gel using hexane/ethyl acetate (8:2) as the eluent afforded the desired alcohol **7**.
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7. For an excellent review, see: Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.
8. *Selected data* for **7**: δ_H ($CDCl_3$, 400 MHz) 2.32 (1H, br s), 3.76 (3H, s), 6.49 (1H, s), 6.83 (2H, d, $J=9.0$), 7.30 (2H, d, $J=9.0$), 7.40–7.51 (3H, m), 7.68 (1H, d, $J=7.0$), 7.79–7.86 (2H, m), 7.95–7.86 (1H, m); δ_C ($CDCl_3$, 100 MHz) 55.6 ($\underline{C}H_3$), 114.1 ($\underline{C}H$-OH), 124.2 (Ar $\underline{C}H$), 124.4 (Ar $\underline{C}H$), 124.9 (Ar $\underline{C}H$), 125.5 (Ar $\underline{C}H$), 126.2 (Ar $\underline{C}H$), 128.5 (Ar $\underline{C}H$), 128.6 (Ar $\underline{C}H$), 128.9 (Ar $\underline{C}H$), 130.7 (Ar $\underline{C}$), 134.1 (Ar $\underline{C}$), 135.6 (Ar $\underline{C}$), 139.1 (Ar $\underline{C}$), 159.2 (Ar $\underline{C}$).
9. *Selected data* for [Rh(cod)**4**]PF_6: δ_H ($CDCl_3$, 400 MHz) 0.89 (18H, s), 1.68–1.83 (2H, m), 1.95–2.10 (2H, m), 2.08 (6H, s), 2.28–2.42 (2H, m), 2.56–2.73 (2H, m), 3.66 (2H, dd, $J=4.4$, 9.7), 4.31–4.49 (6H, m), 4.62 (2H, dd, $J=2.4$, 9.7); δ_C ($CDCl_3$, 100 MHz) 25.4 ($\underline{C}H_3$), 25.6 ($\underline{C}H_3$), 29.4 ($\underline{C}H_2$ cod), 31.3 ($\underline{C}H_2$ cod), 34.3 ($\underline{C}$-$(CH_3)_3$), 40.8 ($\underline{C}$-$(CH_3)_2$), 72.5 ($\underline{C}$H-N), 73.1 ($\underline{C}H_2$-O), 80.5 ($\underline{C}$H cod), 82.8 ($\underline{C}$H cod), 178.2 ($\underline{C}$=N); δ_P ($CDCl_3$, 161 MHz) –143.5 (1P, septet, PF_6); m/z (FAB^+) 505 (100%, M^++H) [found 505.22345 M^++H $C_{25}H_{42}N_2O_2Rh$ requires M 505.23013].
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12. The use of enantiopure bidentate phosphines such as DIOP and BINAP result in the formation of racemic products. Only the monodentate ligand 2-diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl ((*S*)-MeO-MOP) affords any asymmetric induction (41% ee), see Ref. 2a.