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Examination of Ligand Effects in the Heck Arylation Reaction

Maryiam Qadir, Tobias Möchel and King Kuok (Mimi) Hii*

Department of Chemistry, King's College London, Strand, London WC2R 2LS, United Kingdom

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Abstract—The Heck arylation reaction between aryl bromide and iodide with methyl acrylate was evaluated. A new class of ligands, R–N($CH_2CH_2PPh_2$)$_2$, is compared with conventional monodentate and bidentate ligands, and was found to confer greater catalyst stability. The nitrogen substituent (R) has a noticeable effect on the rate of the turnover. We believe this is the first report of the application of such hemilabile ligands in Heck arylation chemistry. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The development of catalysts for the Heck arylation reaction has been the subject of several recent high profile reports, which describe the discovery of a number of palladium metal complexes that are capable of achieving extremely high catalytic turnovers, even with fairly unreactive aryl bromides and chlorides.[1] Almost all of the catalysts reported to date contain cyclometalated palladacycles (Fig. 1).[2–4] Although impressive turnovers are attained, it can be envisaged that tuning the ligands sterically and/or electronically will not be a trivial exercise.

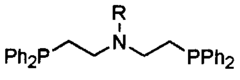
As part of our recent studies on a new class of 'tuneable' phosphorus–nitrogen–phosphorus containing ligands, **4** (Fig. 2), we postulated that these ligands will be able to stabilise fragile reactive intermediates via the hemilabile nitrogen site, which allows the ligand to switch between *cis* (PP) and *trans* (PNP) coordination modes easily without necessitating the cleavage of a Pd–P bond (Fig. 3).[5] If this is true we expect the palladium metal complex to be more stable in catalytic reactions, offering higher turnover numbers without compromising reactivity. In this paper we wish to compare the performance of these ligands with conventional mono- and bi-dentate ligands towards Heck arylation chemistry.

Results and Discussion

To appreciate the performance of these ligands in the Heck arylation reaction, studies were carried out in parallel with conventional monodentate and bidentate phosphine ligands, such that direct comparison might be achieved.

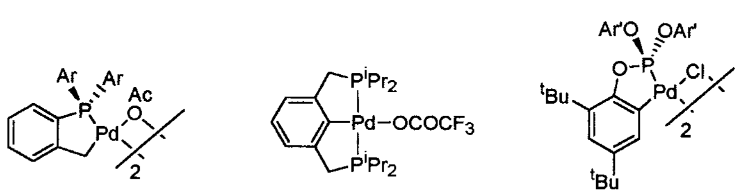
Coupling between iodobenzene and methyl acrylate

Our first chosen system was the catalysed reaction between iodobenzene and methyl acrylate (Table 1). To our great surprise, turnovers of about 1 million could be easily achieved with 'ligandless' catalysts such as palladium(0) and palladium(II) complexes (entries 2 and 3). Furthermore,



R = Ph, **4a**
4-$MeOC_6H_4$, **4b**
^{t}Bu, **4c**
^{n}Bu, **4d**
$PhCH_2$, **4e**

Figure 2. Different PNP ligands.



1 **2** **3**

Figure 1. Recently reported catalysts for highly efficient Heck arylation reactions.

Keywords: C–C coupling; Heck arylation; homogeneous catalysis; palladium; P ligands.

* Corresponding author. Tel./fax: +44-020-78482810; e-mail: mimi.hii@kcl.ac.uk

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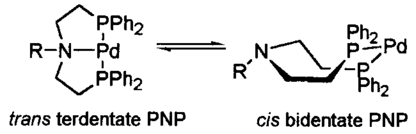
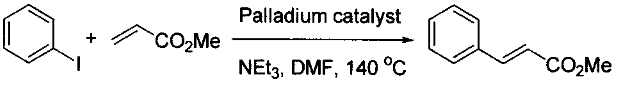


Figure 3. Different coordination modes adopted by PNP ligands.

Table 1. Effect of catalyst with/without phosphine ligands (reactions were carried out in pressure tubes, with 1 mg catalyst, 3 equiv. of methylacrylate with respect to iodobenzene, and 3 equiv. of NEt_3)



Entry	Catalyst	Reaction time/h	% Conversion	TON
1	$Pd(PPh_3)_4$5100	109,106		
2	$Pd_2(dba)_3.CHCl_3$	4	100	100,000
3	$Pd(OAc)_2$	4.5	95	95,000
4[a]	$Pd(OAc)_2$/**4a**	19.5	97	97,000
5	$Pd(OAc)_2/PPh_3$	19.5	100	100,000
6	[(dppp)Pd(dba)]	6	100	100,000

[a] **4b**–**4e** showed the same reactivity.

the addition of certain ligands such as 1,3-*bis*(diphenylphosphino)propane (dppp), PPh_3 or **4a** even appeared to slow down the rates of these reactions (entries 4–6). Although ligandless Heck arylation is nothing new,[6,7] we believe this provides direct evidence that the addition of phosphine ligands is unnecessary, and may indeed have a decelerating effect, on the Heck reactions involving aryl iodides.

Coupling reaction between 4-bromoacetophenone and methyl acrylate[8]

In dramatic contrast, the reaction between methyl acrylate and 4-bromoacetophenone is accelerated by the addition of phosphine ligands (Table 2). Compared to the results obtained with iodobenzene, this is quite a significant observation as it implies that different rate-limiting steps operate for Heck arylation reactions involving aryl iodides and bromides.

As shown in Table 2, the reactions with 'ligandless' palladium precursors have limited turnovers of less than 250 (entries 1 and 2), whereas the addition of monodentate phosphines seems to improve the catalyst's performance somewhat (entries 3 and 4). The addition of bidentate phosphines such as 1,2-*bis*(diphenylphosphino)ethane (dppe), 1,3-*bis*(diphenylphosphino)propane (dppp) and 1,1′-*bis*(diphenylphosphino)ferrocene (dppf) induce lower turnovers compared to the monodentate PPh_3 (entries 5–7).[9]

para-Substituents on the rate of the Heck arylation reaction

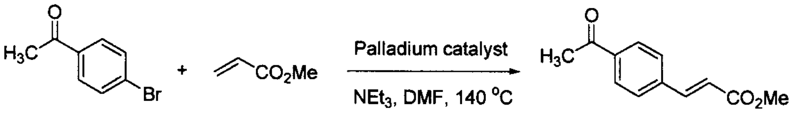
The relative rates offered by different *para*-substituted monodentate phosphines are summarised in Table 3. Percentage conversions were recorded after 7 h, from which the comparative rates were calculated. The reactions were then allowed to proceed for 31 h to determine the total number of turnovers achievable by the individual systems. From the results it is evident that the more electron-rich triarylphosphines induce faster reactions (entries 3 and 4). The *ortho*-substituted tris(methoxyphenyl)phosphine was much slower than the *para*-analogue (entries 3 and 5), implying an important steric effect on the rate of reaction. When the relative rates were plotted against the Hammett (σ_{para}) parameters, we obtained excellent linearity (Fig. 4). This forms an interesting comparison to the results of Jutand and Amatore,[10] in which the rates of oxidative addition (one of the possible rate-determining steps of the Heck catalytic cycle) of aryl halides to palladium complexes coordinated by triarylphosphines are reported *to follow a bell-shaped correlation.*

Effect of using phosphorus–nitrogen–phosphorus ligands, 4

In an earlier paper, we postulated that the introduction of a hemilabile nitrogen donor between two phosphorus donor atoms could improve the stability of palladium complexes of diphosphine ligands.[5] When ligands **4** were utilised in the coupling reaction of aryl bromides, we find that turnovers of 10,000 were achievable in all cases (Table 4).

The results show that the catalytic activity induced by the PNP ligands is indeed better than monodentate and bidentate diphosphine ligands. More importantly, the rate of

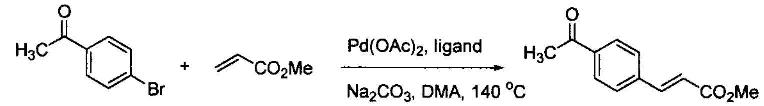
Table 2. Heck arylation of methyl acrylate with 4-bromoacetophenone using 'common' phosphine ligands (reactions were carried out in pressure tubes. Reagents: 3 equiv. of Et_3N with respect to the aryl bromide and 3 equiv. of methylacrylate in anhydrous DMF)

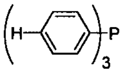
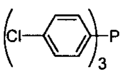
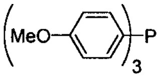
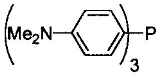
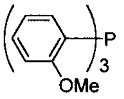


Entry	Catalyst	Reaction time/h	Catalyst loading/mol%	% Conversion	TON
1	$Pd(OAc)_2$	5	0.4	85	212.5
2	$Pd_2(dba)_3.CHCl_3$	5	0.4	75	187.5
3	$Pd(OAc)_2/2\ PPh_3$	2	0.4	100	250
4	$Pd(OAc)_2/2\ PPh_3$	19	0.01	97	9,700
5[a]	$Pd(OAc)_2$/dppe	24	0.01	85	8,540
6[a]	$Pd(OAc)_2$/dppp	24	0.01	86	8,550
7[a]	$Pd(OAc)_2$/dppf	24	0.01	96	9,580

[a] 3 equiv. of Na_2CO_3 as base in DMA.

Table 3. Effect of substituents on triarylphosphines (reactions were carried out in parallel in a reaction carousel. Reactions were left to run for 31 h to obtain optimum turnover. Reagents: 0.01 mol% catalyst, 3 equiv. of Na_2CO_3 with respect to the aryl bromide and 3 equiv. of methylacrylate)



Entry	Ligand	% Conversion (reaction time/h)	Relative rates ($k_{relative}$)
1		45(7) 96(31)	1
2		40(7) 98(31)	0.878
3		56(7) 98(31)	1.251
4		81(7) 100(31)	1.798
5		25(7) 100(31)	0.545

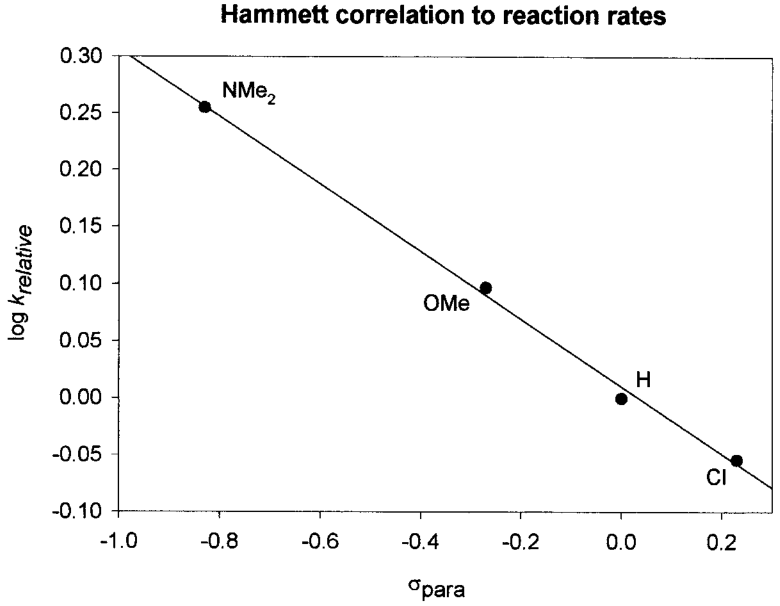
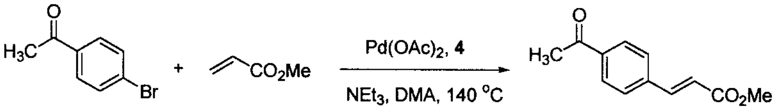


Figure 4. Hammett correlation between reaction rates and *para*-substituent of the triarylphosphine.

Table 4. Reaction using PNP phosphine ligands (reactions were carried out in pressure tubes. Reagents: 0.01 mol% catalyst, 3 equiv. of Et_3N with respect to the aryl bromide and 3 equiv. of methylacrylate)



Entry	Ligand	Reaction time/h	Catalyst loading /mol%	% Conversion	TON	TOF/h^{-1}
1	**4a**	15	0.01	100	10,000	667
2	**4b**	11	0.01	100	10,000	909
3	**4c**	8	0.01	100	10,000	1,250
4	**4d**	9	0.01	100	10,000	1,111
5	**4e**	10	0.01	100	10,000	1,000

reaction is dependent on the nature of the nitrogen substituent, increasing in the order: *tert*-butyl (**4c**)>*n*-butyl (**4d**)>benzyl (**4e**)>*p*-anisole (**4b**)>phenyl (**4a**). The trend seems to fit the electronic nature of the substituents, with the most electron-donating group imparting twice the TOF compared to the most electron-withdrawing group (entries 1 and 3). This is a very satisfying result as it confirms our theory that the presence of a hemilabile site could promote both the stability and reactivity of the metal complex.

Conclusion

The effect of different phosphine ligands has been studied for the Heck arylation reaction. The reaction of methyl acrylate with iodobenzene is **not** ligand accelerated, whereas the reaction with bromoacetophenone is. The palladium complexes of PNP ligands have also been examined, and the nature of the hemilabile nitrogen donor is observed to have a big effect on the turnover of the catalytic reaction. All of these ligands are better catalysts than monodentate and bidentate ligands in terms of greater catalyst stability (all achieving 10,000 turnovers without losing activity). Ligands **4c** afforded the fastest turnover than any of the ligands tested in this study.

Work is currently underway to prepare a second generation of PNP ligands with further modifications, in the hope of activating the metal complex for more difficult coupling reactions with other aryl bromides and chlorides. Further applications of these ligands in other transition-metal catalysed reactions are also being sought.

Experimental

The phosphines **4a–c** were prepared according to previously reported procedure.[5] Ligands **4d–e** were similarly prepared in our laboratory recently.[11] Iodobenzene (Avocado) was passed through a column of neutral alumina before use. All other phosphines and reagents were obtained from commercial sources and used without any prior purification. Solvents were degassed before use. Each catalytic run was duplicated. Percentage conversion of the initial aryl halide was monitored by GLC and/or ^{1}H NMR spectroscopy. When percentage conversion <100, it signifies that the reaction did not progress beyond the stated turnover number. TOF is only quoted for reactions that have achieved 100% conversion, and is thus an average value calculated by dividing the time for complete conversion by the TON for comparison of relative rates.

Pressure tube experiments

Typical catalytic reaction with iodobenzene: The appropriate palladium catalyst (1 mg) was carefully weighed out, transferred into a 10 mL volumetric flask and diluted to the mark with the appropriate solvent. Dilutions were carried out with the appropriate analytical pipettes and volumetric flasks as required. In a thick-walled tube fitted with a Teflon Young's tap, iodobenzene (1.38 mL, 0.0123 mol), methyl acrylate (3.3 mL, 0.036 mol), appropriate base and the appropriate amount of diluted catalytic solution (1 mL) were mixed. Additional solvent was added to give a total solvent volume of 2.5 mL, so as to achieve homogeneity throughout the reaction. A small magnetic stirrer was added, and the reaction vessel was sealed via the Teflon tap, before heating in an oil bath, with the reaction temperature carefully controlled by a digital thermostat (±1°C). For these reactions, sampling of reaction mixtures were performed at regular intervals by cooling the pressure tube down and extracting a small aliquot for GC/^{1}H NMR analyses.

Typical catalytic reaction with 4-bromoacetophenone (10,000 turnovers): Under a dry nitrogen atmosphere, Pd(OAc)$_2$ (2.8 mg, 1.25×10^{-2} mmol) and the ligand **4c** (6.2 mg, 1.25×10^{-2} mmol) were dissolved in 10 mL of DMA in a volumetric flask, and the solution was gently warmed to give a pale yellow solution. 4-Bromoacetophenone (2.45 g, 12 mmol), methyl acrylate (3.3 mL, 36 mmol) and the appropriate base (36 mmol) were placed in a Young's tube, to which 1 mL of the catalyst solution was added, together with additional 1.5 mL of DMA (to achieve homogeneity throughout the reaction). A small magnetic stirrer bar was added, and the tube was then sealed. The Young's tube was then heated in an oil bath, its temperature carefully controlled by a digital contact thermometer at 140°C (±1°C). Analytical samples were extracted as before.

Reaction carousel experiments: For comparison, the reactions were also carried out in a Radley's 12-placed reaction carousel on the same scale. Reaction mixtures were stirred and refluxed under N$_2$ atmosphere with a thermostated (140±1°C) heating block. Analytical samples of reaction mixtures were extracted at regular intervals via a syringe through a fitted septum.

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