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General and efficient methodology for the Suzuki–Miyaura reaction in technical grade 2-propanol

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Abstract

The reaction profile of a series of palladium-based catalysts was examined in the Suzuki–Miyaura reaction using technical grade 2-propanol as solvent and potassium *t*-butoxide as base. The results generally show high activity. The method allows for the coupling of electron-rich aryl chlorides with sterically hindered aryl boronic acids to produce tri-ortho-substituted biaryls in high yields using very mild conditions and short reaction times.

Keywords: Suzuki–Miyaura reaction; Palladium; Catalysis; *N*-heterocyclic carbene

1. Introduction

Palladium-catalyzed cross-coupling reactions represent one of the most employed modern synthetic methods [2] useful in fields ranging from polymer chemistry to synthetic organic chemistry [3]. Within this group, the Suzuki–Miyaura reaction [4,5] involving the coupling of an aryl or alkyl halide (or pseudo-halide) with an organoboron reagent to form a new C–C bond, is gaining a dominant position among these reactions both in academic and industrial laboratories; in view of significant advantages related to the ease of use of organoboron reagents. These represent simple coupling partners that are readily available, thermally stable, tolerant towards various functional groups and display low toxicity [6]. As a result, research focusing on the use and development of catalysts mediating the Suzuki–Miyaura reaction has become extremely attractive.

Numerous groups have developed efficient systems for the Suzuki–Miyaura reaction; a fact that accounts for the extensive literature available on this topic [7]. The determination of multiple variables in the optimum selection of coupling partners, palladium source/ligand versus well-defined catalysts, solvents, temperatures and additives in a multi-step synthesis can be a challenging task.

Recently, our group has reported the synthesis of a well-defined air stable palladacycle complex (**1**) that was found highly active in aryl amination and α-arylation of ketones using very low catalyst loadings [8]. Shortly after, we reported on the performance of the same complex in the Suzuki–Miyaura reaction [9]. The catalytic system makes use of technical grade 2-propanol as solvent and Na^{t}OBu as base and allows for the coupling of electron-rich aryl chlorides with sterically hindered boronic acids yielding di- and tri-ortho-sustituted biaryls with high yields at room temperature. We proposed that a key feature of this system was a rapid activation of the pre-catalyst by the *in situ* formation of *iso*-propoxide anion, leading to the reductive elimination of the biphenyl-dimethylamine and formation of the active form of the catalyst, [(IPr)Pd(0)] (IPr = (*N*, *N*′-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene), at room temperature. While that may account for the reactivity of the catalyst at room temperature, it is further known

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that additives in the form of an alcohol or water enhance dramatically the performance of the system: firstly, by improving the solubility of the organoboron reagent [10] and secondly, by forming hydroxyl-bound "ate" adducts [11,12] believed to play a key role in transmetallation [4c].

From an economical and industrial point of view, these conditions are very appealing, specially regarding to the use of an inexpensive and environmentally friendly solvent. Those facts led us to examine whether these same simple conditions are compatible with different palladium(0) and palladium(II) complexes (Fig. 1) to confirm a generality of the effect observed for the palladacycle complex. A detailed report comparing reaction profiles of various Pd complexes bearing *N*-heterocyclic carbene (NHC) or phosphine ligands is presented.

2. Results and discussion

A variety of commercially available and in-house complexes was used in a screening involving a Suzuki–Miyaura reaction. Two new complexes were synthesized for this study to evaluate the effect of substitution on the allyl moiety of the (NHC)Pd(allyl)Cl architecture. Crystal structures for the new compounds (IPr)Pd(η^3-2-methylallyl)Cl (**5**) and (IMes)Pd(η^3-2-methylallyl)Cl (**6**) (IMes = (*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol)-2-ylidene), are shown in Figs. 2 and 3.

In previous experiments using the palladacycle complex **1**, we observed that the stronger base KO^{t}Bu allowed the catalyst loading to be reduced by half (1 mol %) with no significant decrease on the yields or reaction times. An initial screening was performed using a model reaction composed of 4-chlorotoluene and phenylboronic acid in technical grade 2-propanol at two different temperatures, 50 °C and room temperature (Table 1). The reactions were monitored at short time intervals to allow comparison of catalyst performance. Reactions reached completion within 1 h for this model reaction.

Results in Table 1 show high activity for most of the complexes at 50 °C, with the exception of **9** and **10**. This might be in part due to a high stability of the complex induced by a chelate effect. These mild conditions for activation and catalysis do not appear to be restricted to NHC-bearing palladium complexes but appear also compatible with phosphine-bearing palladium complexes (**11**). As a general trend, (IPr)Pd complexes perform better than (IMes)Pd complexes with the

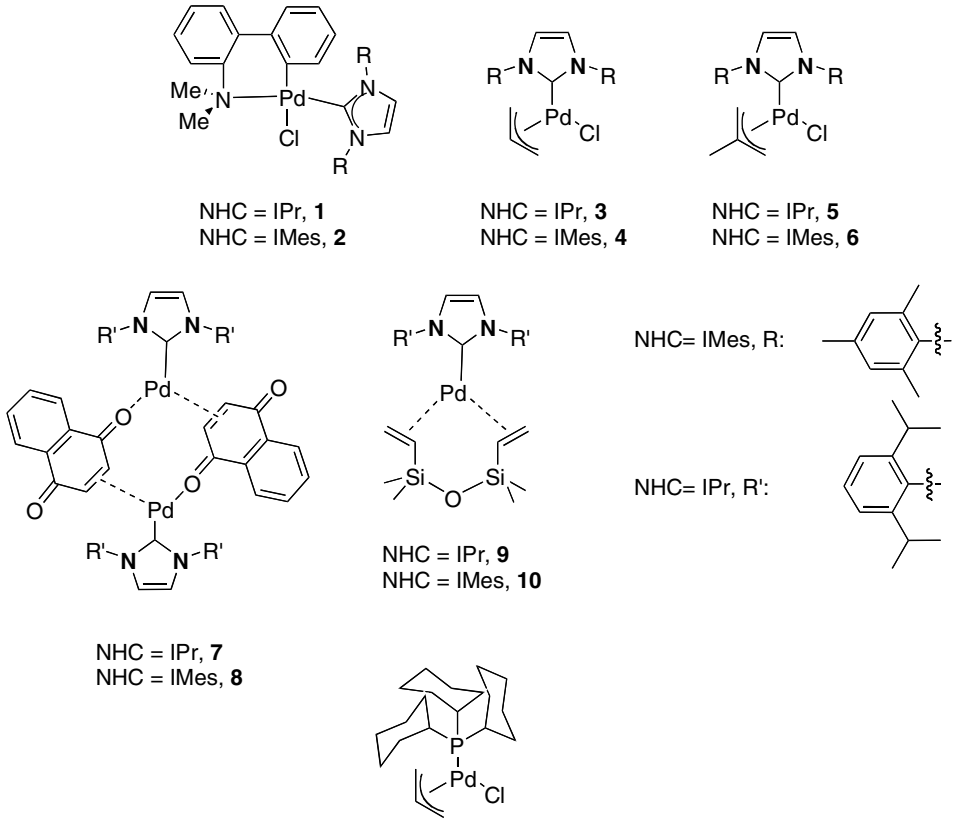


Fig. 1. Complexes tested in the Suzuki–Miyaura reaction.

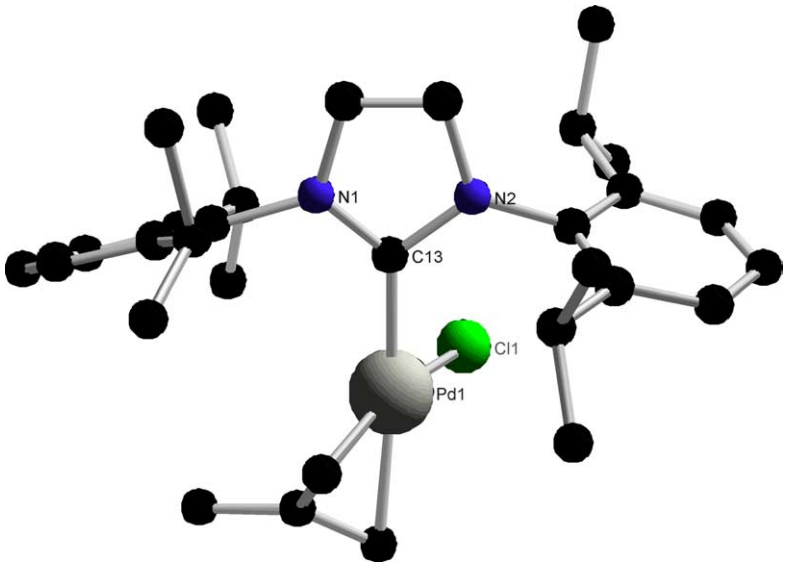


Fig. 2. Crystal stucture of (IPr)Pd(η^3-2-methylallyl)Cl (**5**). Hydrogens omitted for clarity.

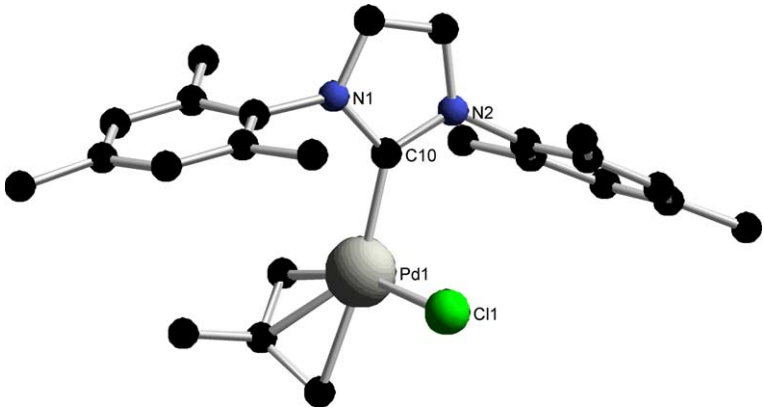


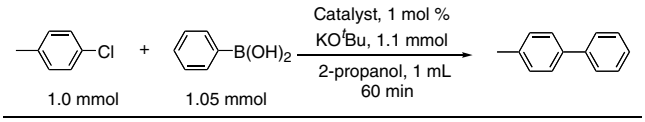
Fig. 3. Crystal stucture of (IMes)Pd(η^3-2-methylallyl)Cl (**6**). Hydrogens omitted for clarity.

exception of **8** which, like **1**, allowed the coupling at room temperature in high yield. The difference between **8** and the other (IMes)Pd complexes might be a result of the rapid formation of the active species [IMes-Pd(0)]. It is also worthy to note the conversions obtained with **3** and **5**, achieving nearly total coupling of the chloride in half the time required for others. Unfortunately, both of these catalysts failed to mediate the room temperature reaction. The different activity displayed by various (NHC)Pd complexes appears to be greatly influence by the other ancillary ligands and we feel an activation step required to generate the active [Pd(0)(NHC)] species is the origin of the different reaction profiles displayed by various related catalysts.

These complexes were then further tested with very challenging substrates. Electron-rich aryl halides (especially bearing chlorides) have historically been difficult substrates to activate by palladium centers [13]. When steric congestion provided by ortho substituents to the halide are added to the mix along with similar substitution patterns on the organoboron reagent then high temperature and long reaction times become mandatory to observe any product formation [7a,14]. There are only two reported examples in the literature for the Suzuki–Miyaura synthesis of di- and tri-ortho-substituted biaryls at room temperature, including the one recently reported by our group [9,15]. To truly observe marked differences in reaction profiles between these various catalysts, they were subjected to a reaction leading to a tri-ortho-substituted product. Coupling involving 2,6-dimethylphenyl chloride and 1-naphthaleneboronic acid was examined. The results are presented in Table 2.

As in the previous table, (IPr)Pd complexes perform better than (IMes)Pd complexes, however the differences in reactivity are much greater now for sterically de-

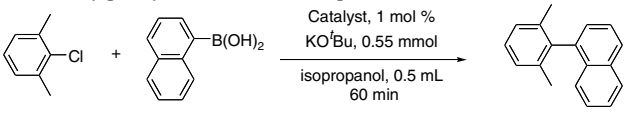
Table 1
Catalyst performance comparison for the Suzuki–Miyaura coupling of 4-chlorotoluene and phenylboronic acid[a]



Catalyst	$T = 50$ °C yield (%)	RT yield (%)
1	89	87
2	89	15
3	93[c]	12
4	73	23
5	95[c]	26
6	78	20
7[b]	88	23
8[b]	86	86
9	0	0
10	0	0
11	78	14

[a] GC yields, average of two runs.
[b] 0.5 mol% catalyst.
[c] 0.5 h.

Table 2
Catalyst performance comparison for the Suzuki–Miyaura coupling of 2,6-dimethylphenyl chloride and 1-naphthaleneboronic acid[a]



Catalyst	$T = 50$ °C yield (%)	RT yield (%)
1	96	93
2	34	29
3	92	39
4	34	31
5	94	27
6	34	24
7[b]	95	42
8[b]	35	24
11	85	13

[a] GC yields, average of two runs.
[b] 0.5 mol% catalyst.

manding substrates. While **8** performed the previous coupling at room temperature in high yield, the use of sterically demanding coupling partners leads to more modest yields even at 50 °C. All (IPr)Pd complexes performed the desired coupling in high yields at 50 °C, as did (PCy_3)Pd(allyl)Cl, interestingly.

Since all NHC-bearing Pd complexes are expected to lead to the same active [NHC–Pd(0)] species, it seems logical to observe two separate trends in the result tables: one for (IMes)Pd and one for (IPr)Pd. The difference in performance at room temperature and at 50 °C can then be directly linked to the activation of the catalyst. If we take for instance the (IPr)Pd group, it is evident that all complexes perform equally well at 50 °C, but only **1** allows for the couplings at room temperature due to the simple activation process previously described. For Pd-allyl complexes (**3**, **4**, **5** and **6**), these have been shown to participate in an activation step involving either nucleophilic attack at the allyl moiety followed by reductive elimination or substitution of the Pd-chloride into a Pd-alkoxide species followed by reductive elimination [16]. The slightly better performance of **7** in comparison to the allyl complexes might be attributed to the presence of a reduced palladium species at the onset of the reaction.

3. Conclusions

In the numerous catalyst optimization studies that have been published the principal focus is oftentimes to test the robustness of the catalytic system as a function of reaction conditions and substrate scope. Here, we have reported on a related series of NHC–Pd complexes and their relative activity in a Suzuki–Miyaura protocol making use of 2-propanol as solvent. The solvent is not innocent in these systems as reactions in dioxane require longer reactions times. These simple reaction conditions allow for the cross-coupling of aryl chlorides with aryl boronic acids yielding di- and tri-ortho-substituted biaryls in high yields, in short times and in an environmentally friendly solvent used without pre-drying or purification. We have also shown that temperature in this system has a minimal effect on the coupling itself, but principally on the generation of the active catalytic species. Efforts focused on identifying the effects of base and solvent in the boronic acid, as well as a detailed study on phosphine-bearing palladium catalysts and catalyst generated *in situ* are ongoing.

4. Experimental

4.1. General considerations

All aryl halides and boronic acids were used as received (Aldrich, Acros, Combi-Blocks). Technical grade isopropanol was used to carry out catalytic reactions (Mallinckrodt Chemicals). Potassium *tert*-butoxide (Acros) was stored under Argon in an MBraun glovebox. Complexes **1** and **2** [8], **3** and **4** [17], **7**, **8** [18], **9**, **10** [19] and **11** [20] were prepared according to the reported procedures. All reactions were carried out under an atmosphere of argon in screw cap vials. ^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in C_6D_6 (Cambridge Isotope Laboratories, Inc.). Elemental analyses were performed at Robertson Microlit Laboratories, Madison, NJ.

4.2. Synthesis of (IPr)Pd(η^3-2-Methylallyl)Cl (**5**)

A Schlenk flask equipped with a magnetic bar was loaded with the imidazolium salt IPr · HCl (17.5 g, 41.3

mmol) and Na^{t}OBu (3.4 g, 35.4 mmol). The flask was flushed with argon, technical grade isopropanol (350 ml) was added and the mixture was stirred for 2 h at 50 °C. After allowing it to cool to room temperature (Pd(2-methylallyl)Cl)$_2$ (5.39 g, 14.74 mmol) was added slowly, and the reaction mixture was stirred again for 2 h at room temperature. The mixture was filtered in air and washed with THF (2 × 10 ml). The solvent was evaporated in a rotoevaporator and redissolved in the minimum amount of CH_2Cl_2. The solution was passed through a plug of silica gel, previously wetted with hexane, and the silica was washed with CH_2Cl_2 (2 × 10 ml). All liquid portions were placed together in a round-bottom flask and the solvent was evaporated in a rotoevaporator. The solid obtained was collected by filtration and washed with cold hexane. This procedure yields 15.89 g (92%) of (IPr)Pd(η^3-2-methylallyl)Cl.

^{1}H NMR (400 MHz, C_6D_6): 7.125–7.226 (m, 6H), 6.656 (s, 2H), 3.731 (d, $J = 2.4$ Hz, 1H), 3.351 (p, $J = 6.8$ Hz, 2H), 3.191 (p, $J = 6.8$ Hz, 2H), 2.774 (d, $J = 2.4$ Hz, 1H), 2.650 (s, 1H), 1.761 (s, 1H), 1.483 (d, $J = 2.4$ Hz, 6H), 1.414 (d, $J = 2.4$, 6H), 1.064 (s, 3H), 1.061 (d, $J = 2.4$ Hz, 6H), 1.024 (d, $J = 2.4$ Hz, 6H). ^{13}C-NMR (100 MHz, C_6D_6): 189.638, 147.021, 146.884, 137.205, 130.453, 124.521, 71.496, 49.391, 29.197, 29.091, 26.876, 26.481, 23.599, 23.401, 22.901. Elemental analysis: Anal. Calc. C, 63.59; H, 7.40; N, 4.78. Found: C, 63.47; H, 7.42; N, 4.58.

4.3. Synthesis of (IMes)Pd(η^3-2-methylallyl)Cl (**6**)

A Schlenk flask equipped with a magnetic bar was charged with the imidazolium salt IMes · HCl (12.6 g, 41.3 mmol) and Na^{t}OBu (3.4 g, 35.4 mmol). The flask was flushed with argon, technical grade isopropanol (350 ml) was added and the mixture was stirred for 2 h at 50 °C. After allowing it to cool to room temperature, (Pd(2-methylallyl)Cl)$_2$ (5.39 g, 14.74 mmol) was added slowly, and the reaction mixture stirred again for 2 h at room temperature. The mixture was filtered in air and the solids washed with THF (2 × 10 ml). The filtrate was evaporated in a rotoevaporator and the solid residue redissolved in the minimum amount of CH_2Cl_2. The solution was passed through a plug of silica gel, previously wetted with hexane, and the silica was washed with CH_2Cl_2 (2 × 10 ml). All liquid portions were placed together in a round-bottom flask and the solvent was evaporated in a rotoevaporator. The solid obtained was collected by filtration and washed with cold hexane. This procedure leads to the isolation of 9.16 g (62%) of (IMes)Pd(IPr)Pd(η^3-2-methylallyl)Cl.

^{1}H NMR (400 MHz, C_6D_6): 6.757 (s, 4H), 6.203 (s, 2H), 3.661 (d, $J = 2.8$ Hz, 1H), 2.861 (d, $J = 2.8$ Hz, 1H), 2.684 (s, 1H), 2.267 (d, $J = 5.2$ Hz, 12H), 2.07 (s, 6H), 1.153 (s, 3H).

^{13}C-NMR (100 MHz, C_6D_6): 186.467, 139.101, 137.099, 136.370, 136.219, 129.619, 122.913, 70.692, 49.542, 22.688, 21.399, 18.971, 18.880. Elemental analysis: Anal. Calc. C, 59.89; H, 6.23; N, 5.59. Found: C, 59.45; H, 6.18; N, 5.38.

4.4. Suzuki–Miyaura cross-coupling of 4-chlorotoluene with phenylboronic acid. General procedure

In a glovebox, catalyst (1 mol%), potassium *tert*-butoxide (1.1 mmol, 123 mg) and phenylboronic acid (1.05 mmol, 128 mg) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, technical grade isopropanol (1 ml) was injected into the vial and the mixture stirred on a stirring plate at room temperature (or at 50 °C when noted) for 15 min. 4-Chlorotoluene (1 mmol, 118 μl) was then injected at a rate of 20 μl/30 s. The reaction was monitored by gas chromatography.

4.5. Suzuki–Miyaura cross-coupling of 2,6-dimethylphenyl chloride with 2-naphthaleneboronic acid. General procedure

In a glovebox, catalyst (1 mol%), potassium *tert*-butoxide (0.55 mmol, 62 mg) and 2-naphthaleneboronic acid (0.525 mmol, 90 mg) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, technical grade isopropanol (0.5 ml) was injected into the vial and the mixture stirred on a stirring plate at room temperature (or at 50 °C when noted) for 15 min. 2,6-Dimethylphenyl chloride (0.5 mmol, 66 μl) was then injected at a rate of 10 μl/30 s. The reaction was monitored by gas chromatography.

5. Supporting information

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Center, CCDC, No. 234157 for compound **5** and No. 234158 for compound **6**. Copies of this information may be obtained free of charge from the Director, CCDC, 12, Union Road, Cambridge CB2 1EZ UK [fax: +44-1223-336-033] or e-mail deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

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