CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000138

Structure–Activity Relationship Analysis of Pd–PEPPSI Complexes in Cross-Couplings: A Close Inspection of the Catalytic Cycle and the Precatalyst Activation Model

Joanna Nasielski,[a] Nilofaur Hadei,[a] George Achonduh,[a] Eric Assen B. Kantchev,[a] Christopher J. O'Brien,[a] Alan Lough,[b] and Michael G. Organ*[a]

Abstract: A series of Pd–N-heterocyclic carbene (Pd–NHC) complexes with various NHC, halide and pyridine ligands (PEPPSI (pyridine, enhanced, precatalyst, preparation, stabilisation and initiation) precatalysts) were prepared, and the effects of these ligands on catalyst activation and performance were studied in the Kumada–Tamao–Corriu (KTC), Negishi, and Suzuki–Miyaura cross-coupling reactions. The lowered reactivity of more hindered 2,6-dimethylpyridyl complex **4** in the Negishi and KTC reactions is consistent with slow reductive dimerisation of the organometallic reaction partner during precatalyst activation. Comparative rate studies of complexes **1**, **4** and **5** in the KTC and Suzuki–Miyaura reactions verify that **4** activated more slowly than the others. A potential on/off mechanism of pyridine coordination to NHC–Pd^0 is also plausible, in which the more basic pyridine stays bound for longer.

Keywords: catalyst activation · cross-coupling · heterocycles · kinetics · palladium

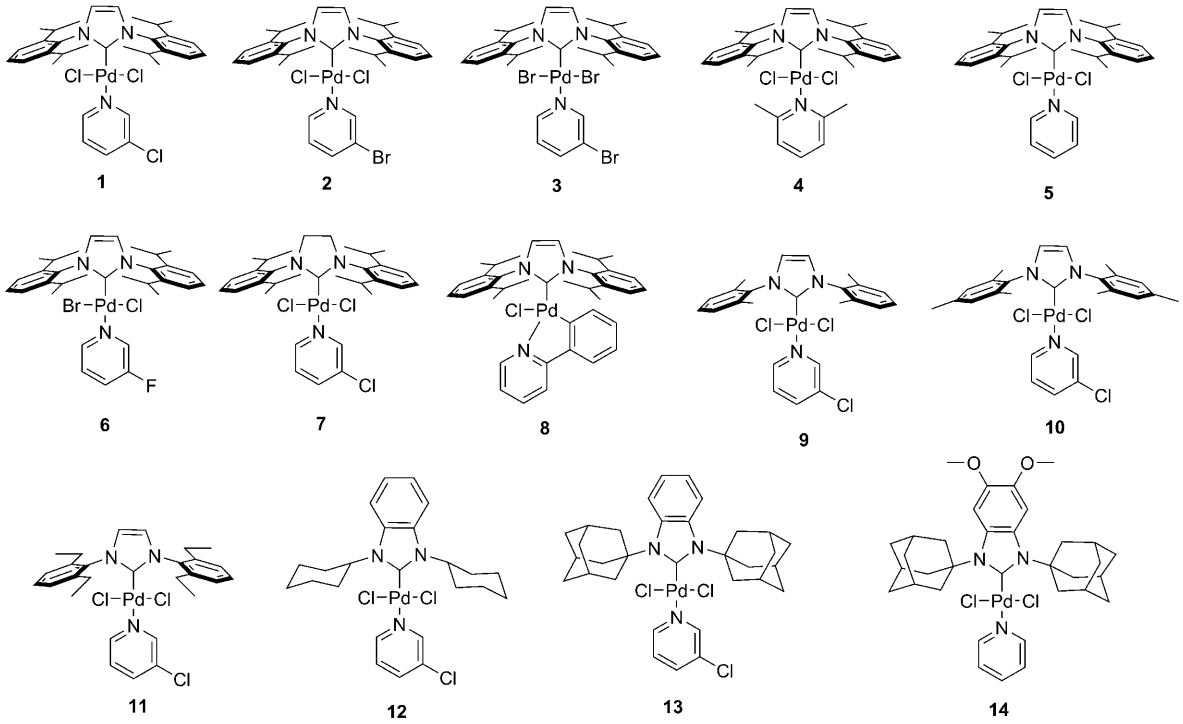
Introduction

N-Heterocyclic carbenes (NHCs) were discovered independently by Öfele[1] and Wanzlick,[2] and later investigations by Arduengo et al.[3] and Denk et al.[4] probed their stability and physical properties. Subsequent studies by Herrmann and co-workers revealed that NHCs are suitable ligands for metals and that the resultant complexes are catalytically active.[5–7] Owing to their very strong σ-donating properties, the replacement of phosphine- and arsine-based ligands by NHCs in Pd-catalysed cross-coupling reactions has led to a number of exciting discoveries, although their adoption by the broader synthetic community has so far been limited.[8] The highly reactive nature of free carbenes necessitates their use under strictly anhydrous conditions, which lessens their attractiveness when compared to their aryl phosphine counterparts that generally have better air and moisture stability. Consequently, much Pd–NHC chemistry has been conducted with in situ-derived catalysts in which a precursor azolium salt is stirred with a suitable base to generate the free carbene in the presence of a Pd source; cross-coupling substrates are either present during catalyst formation, or they are added after catalyst formation is believed to have taken place.[9,10] Although the in situ generation of Pd catalysts with phosphines is quite routine, this is not the case for NHC-based ligands. The high reactivity of carbenes limits compatible solvents owing to deleterious insertion reactions, and leads to uncertainty about both the rate of catalyst formation and the amount of final active catalyst that is formed; this leads to large variations in performance and wastes precious precursor ligand and palladium salts.[11,12] Even the structure of the catalyst formed during in situ studies is uncertain. There was a general assumption made in early Pd–NHC literature that the active species had two NHCs per Pd atom,[5] which would seem reasonable compared to the related, well-characterised phosphine analogues. In fact, studies with isolated [$Pd(NHC)_2$] complexes

[a] J. Nasielski, Dr. N. Hadei, G. Achonduh, Dr. E. A. B. Kantchev, Dr. C. J. O'Brien, Prof. M. G. Organ
Department of Chemistry, York University
4700 Keele Street
Toronto, Ontario, M3J 1P3 (Canada)
Fax: (+1) 416-736-5313
E-mail: organ@yorku.ca

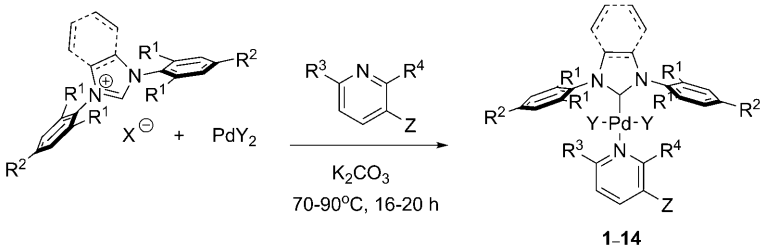
[b] A. Lough
Department of Chemistry, University of Toronto
80 St. George Street
Toronto, Ontario, M5S 3H6 (Canada)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000138, and includes the general coupling conditions used, the preparation of compounds **1**–**32** and full characterisation data.



have revealed that these species are completely inactive in Negishi reactions and that the active catalyst must therefore be a palladium complex with only one NHC ligand.[9,13,14] With the uncertainty of the in situ protocol in mind, our group[12,15] and others[7,16] embarked on the development of well-defined NHC–Pd precatalysts (**1**–**14**).

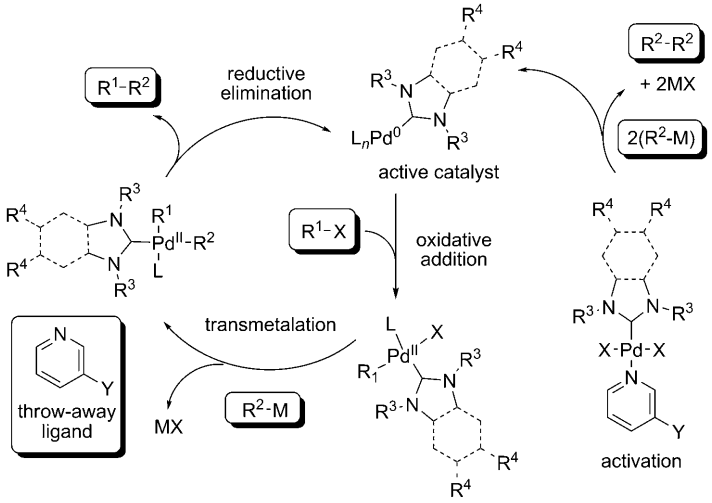
Our initial studies involved the preparation and evaluation of precatalysts **1**, **7**, **10** and **11**,[12] which belong to a growing series of easily-prepared, air- and moisture-stable Pd–PEPPSI precatalysts. The complexes were prepared in air by heating their precursor azolium salts with either $PdCl_2$ or $PdBr_2$ and K_2CO_3 in neat pyridine to provide good to excellent yields of the corresponding PEPPSI (pyridine, enhanced, precatalyst, preparation, stabilisation and initiation) complex (Scheme 1). Of these four complexes (**1**, **7**, **10**, **11**), two have sterically encumbered isopropyl groups at the ortho positions of the *N*-phenyl substituent (i.e., **1** and **7**) and these have proven to be highly reactive in Suzuki–Miyaura,[12,17] Negishi,[15] and Kumada–Tamao–Corriu (KTC)[18] cross-couplings, and Buchwald–Hartwig–Yagupol'skii amination.[19] We have been studying the origin of the reactivity of these NHC-based catalysts by using a variety of techniques, including computation[14] and NMR spectroscopy,[20] and all analyses indicate that increasing bulk at the *ortho* position of *N*-phenyl NHCs should lead to an in-



1: R^1 = *i*Pr, R^2 = H, $R^{3,4}$ = H, X, Y, Z = Cl; 97%
2: R^1 = *i*Pr, R^2 = H, $R^{3,4}$ = H, X, Y = Cl, Z = Br; 80%
3: R^1 = *i*Pr, R^2 = H, $R^{3,4}$ = H, X = Cl, Y, Z = Br; 97%
4: R^1 = *i*Pr, R^2 = H, $R^{3,4}$ = Me, X, Y = Cl, Z = H; 61%
5: R^1 = *i*Pr, R^2 = H, $R^{3,4}$ = H, X, Y = Cl, Z = H; 70%
6: R^1 = *i*Pr, R^2 = H, $R^{3,4}$ = H, X = Br, Y = Cl, Z = F; 91%
7: R^1 = *i*Pr, R^2 = H, $R^{3,4}$ = H, X, Y = Cl, Z = Cl; *SI*Pr·HCl; 88%
8: R^1 = *i*Pr, $R^{2,3}$ = H, R^4 = 2-Ph, X,Y = Cl, Z = H; 73%
9: R^1 = Me, $R^{2,3,4}$ = H, X, Y, Z = Cl; 80%
10: $R^{1,2}$ = Me, $R^{3,4}$ = H, X, Y, Z = Cl; 91%
11: R^1 = Et, $R^{2,3,4}$ = H, X, Y, Z = Cl; 98%
12: N-Cy, $R^{3,4}$ = H, X, Y, Z = Cl; BzICy·HCl; 55%
13: N-Ad, $R^{3,4}$ = H, X, Y, Z = Cl; BzIAd·HCl; 60%
14: N-Ad, $R^{3,4}$ = H, X, Y = Cl, Z = H; $(MeO)_2$BzIAd·HCl; 88%

Scheme 1. Synthesis of NHC–PdY_2–pyridine PEPPSI complexes **1**–**14**.

crease in reactivity. Of course, catalyst activation is another very important aspect of overall catalyst reactivity; similarly to the in situ-derived catalysts, if the active reduced catalyst does not form, turnover is not possible. A general mechanism for the catalytic cycle of the cross-coupling of alkyl or aryl halides with alkyl or aryl organometallic reagents by using NHC–Pd^{II} complexes is shown in Scheme 2. We have



Scheme 2. The proposed mechanism for Pd-catalysed cross-coupling reactions.

evidence to suggest that reduction of Pd occurs first, quickly followed by halide dissociation during reductive dimerisation of the organometallic reaction partner, which is then followed by dissociation of the pyridine. When precatalyst **1** was treated with two equivalents of heptylzinc bromide, one equivalent of tetradecane was produced followed by liberation of 3-chloropyridine. Secondly, the heterolytic dissociation energies of 3-chloropyridine from NHC complexes of Pd^0 and Pd^{II} were calculated, and dissociation from the electron-poor Pd^{II} complex was found to be 5 kcal mol^{-1} higher.[12] Therefore, assuming this model for catalyst activation is correct, the rate-limiting step would be reduction of Pd and liberation of the halides. To examine this, we created an array of PEPPSI complexes in which the halide and pyridine ligands were varied (compounds **1**–**8**) to see if their dissociation affects catalyst reactivity and overall conversion. We also varied the NHC ligand itself (compounds **9**–**14**) to see if any enhancement in performance over existing NHCs could be realised in the Negishi, KTC and Suzuki–Miyaura reactions.

Results and Discussion

KTC sp^2–sp^2 study: We began our structure–activity relationship (SAR) analysis of the different complexes in the KTC cross-coupling reaction (Figure 1).[18] As expected,

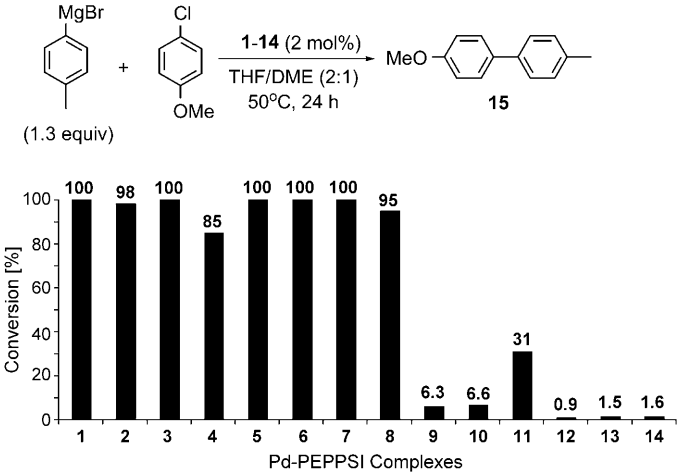


Figure 1. Results of KTC cross-coupling to form **15**. Conversion was determined by using GC/MS/MS against a calibrated internal standard (undecane). All experiments were performed in triplicate; control experiments with no catalyst showed no conversion.

complexes with IPr groups (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) showed excellent conversion to product **15**; with the exception of **9**, **10** and **11**, all other NHCs failed completely. The carbenes in IXy (**9**), IMes (**10**) and IEt (**11**) are presumed to have at least the same σ-donating ability as the IPr ligand, which would allow the oxidative addition step to be equally facile. However, the different steric topography that they impart around the palladium centre would have a greater impact on the rate of transmetalation and/or reductive elimination.[14] We have been studying the relationship between sterics and electronics brought about by the N substituents on the NHC by examining the ^{109}Ag NMR carbene chemical shifts of analogous NHC–Ag complexes. With increasing steric bulk on the NHC, the carbene chemical shifts were observed to be more downfield, which suggests a more electron-deficient metal centre.[20,21] The yields dramatically decrease on going from IPr (**1**–**8**) to IEt (**11**) to IXy (**9**) or IMes (**10**). These results support the idea that more σ-donating ligands on palladium facilitate oxidative addition,[22] and promote complex stability (no blacking-out of Pd^0 was observed), whereas the more sterically bulky ligands facilitate reductive elimination (or transmetalation).[12,14,23] However, there appears to be a limit to the amount of bulk tolerated because the bulkier adamantyl groups (**14**) form an altogether different topography around the metal that may cause them to be virtually ineffective as cross-coupling catalysts (see Figure 3).

Although some conversion was observed, at this point it is difficult to conclude with these particular sp^2 cross-coupling

substrates whether oxidative addition did in fact occur to a reasonable degree with complexes **12**, **13** and **14**; a more detailed investigation on this aspect is given in the sp^2–sp^2 and sp^3–sp^3 Negishi cross-coupling section (vide infra). The anionic ligands on palladium (Cl^- vs. Br^-) showed no notable effects on catalytic activity (**1**–**3**, **6**), whereas the electronics of pyridine throw-away ligands revealed some dependence. Complex **4** consistently provided a slightly lower yield, which is probably the result of the bulky methyl groups slowing down the halide–aryl exchange during catalyst generation/reduction. To explain the lower reactivity of lutidine derivative **4**, we decided to conduct a rate study on the formation of **15** in the hope of gaining some insight into the details of this reaction (Figure 2).

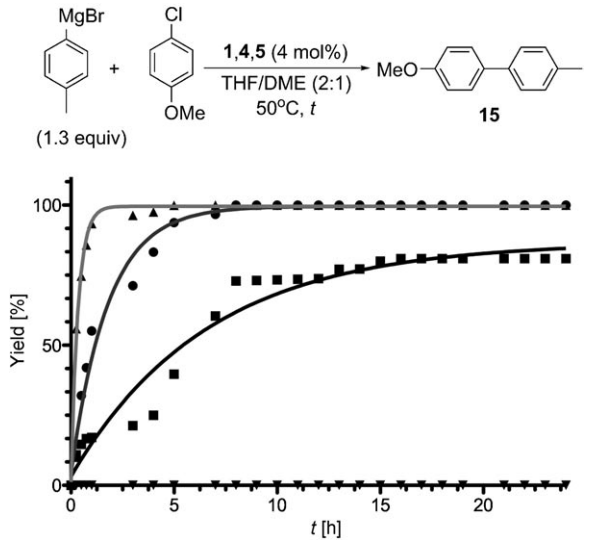
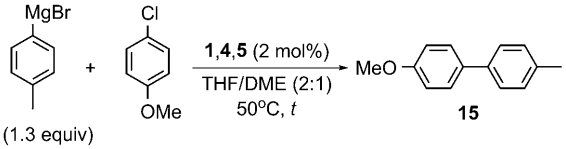


Figure 2. Rate of formation of **15** by using catalysts **1** (●), **4** (■), **5** (▲) and $PdCl_2$ (▼; control). The relative rates (initial) are as follows: **1**: $2.11\times10^{-4}\,mol\,L^{-1}\,s^{-1}$; **4**: $5.15\times10^{-5}\,mol\,L^{-1}\,s^{-1}$; **5**: $7.89\times10^{-4}\,mol\,L^{-1}\,s^{-1}$. Conversion was determined by using GC/MS against a calibrated internal standard (undecane). All experiments were performed in triplicate. Control experiments with no catalyst showed no conversion.

At a 4% loading, our results indicate that complex **5** forms the same active catalyst as **1** in solution, albeit at about one quarter of the rate, which indicates that there is some difference between the dissociation of pyridine and 3-chloropyridine. Alternatively, complex **4** displayed a more obvious reduction in activity that led ultimately to a lower conversion percentage after 24 h. Because **4** did successfully form product **15**, lutidine dissociation undoubtedly did take place. To test whether catalyst death was occurring at any time during the 24 h study, we next addressed the lifetime of the three catalysts (Table 1). After an initial period of 24 h, which gave quantitative conversion to **15** for **1** and **5**, we injected a second aliquot of the coupling partners into the same reaction vial, allowed the contents to stir for a further 24 h with the remaining catalyst of the previous reaction. After the initial complete conversion to the product, catalysts **1**, **4** and **5** remained highly active and suffer only a

Table 1. Evaluation of catalyst turnover for consecutive KTC cross-coupling reactions to form **15**.[a,b]



Catalyst	Conversion after 24 h [%] (Yield [%])	Conversion after 48 h [%] (Yield [%])
1	100 (93)	90 (87)
4	85 (81)	78 (75)
5	100 (91)	91 (87)

[a] Conditions: PEPPSI complex **1**, **4** or **5** (2 mol%), *p*-chloroanisole (0.5 mmol), *p*-tolylmagnesium bromide (0.65 mmol), total solvent volume = 2.1 mL. After 24 h and complete conversion to **15**, additional *p*-chloroanisole (0.5 mmol) and *p*-tolylmagnesium bromide (0.65 mmol) were added and the reaction continued for an additional 24 h. Control experiments with no catalyst showed no conversion in all cases. [b] The procedure was repeated three times and the isolated yields were obtained with < 5% variation.

modest loss of activity after one reaction cycle. Note that, as observed in the previous study, complex **4** was comparatively less active despite the theoretical generation of an identical NHC–Pd^0 species in each reaction vial. This lagging activity could suggest that it is not just activation that is problematic with the hindered pyridine derivative, but that perhaps the pyridine ligands attach to and detach from the NHC–Pd^0 complex in solution. Although lutidine is more bulky, it is also more electron rich, which means that it could be a stronger σ-donating ligand than simple pyridine, and most certainly a better coordinator than electron-poor 3-chloropyridine. The crystal structures of complexes **1** and **4** (Figure 3) provide further evidence to support both the steric congestion argument during reduction and the better coordination of lutidine; the Pd–N bond of complex **4** (2.086 Å) is comparatively shorter than that of **1** (2.137 Å), despite unfavourable sterics that direct the methyl groups in toward the metal centre. Additionally, the fact that no blacking-out of Pd occurs supports the notion that the pyridines reattach to the Pd centre, which stabilises it and lengthens the catalyst lifetime.

In the next KTC study, we subjected the more active IPr-NHC catalysts (**1**–**8**) to a more challenging KTC cross-coupling reaction to see if any further differences in performance could be detected with different substrates (Figure 4). Complex **5** showed a 20% yield enhancement over **1** for the formation of **16**, and although the previous two studies suggested that the same active species forms in solution with similar ease, this may not be the case with this particular group of substrates. One of our initial theories was that pyridine, being less electron-withdrawing than 3-chloropyridine, would have a higher dissociation energy from Pd^{II}/Pd^0 and thus allow more precatalyst to be conserved in **5** than in **1**. Assuming that conversion in this reaction is slower than in Figure 1, catalyst lifetime would become an important issue. The dissociated pyridine ligand could now re-coordinate with the NHC–Pd^0 complex after a

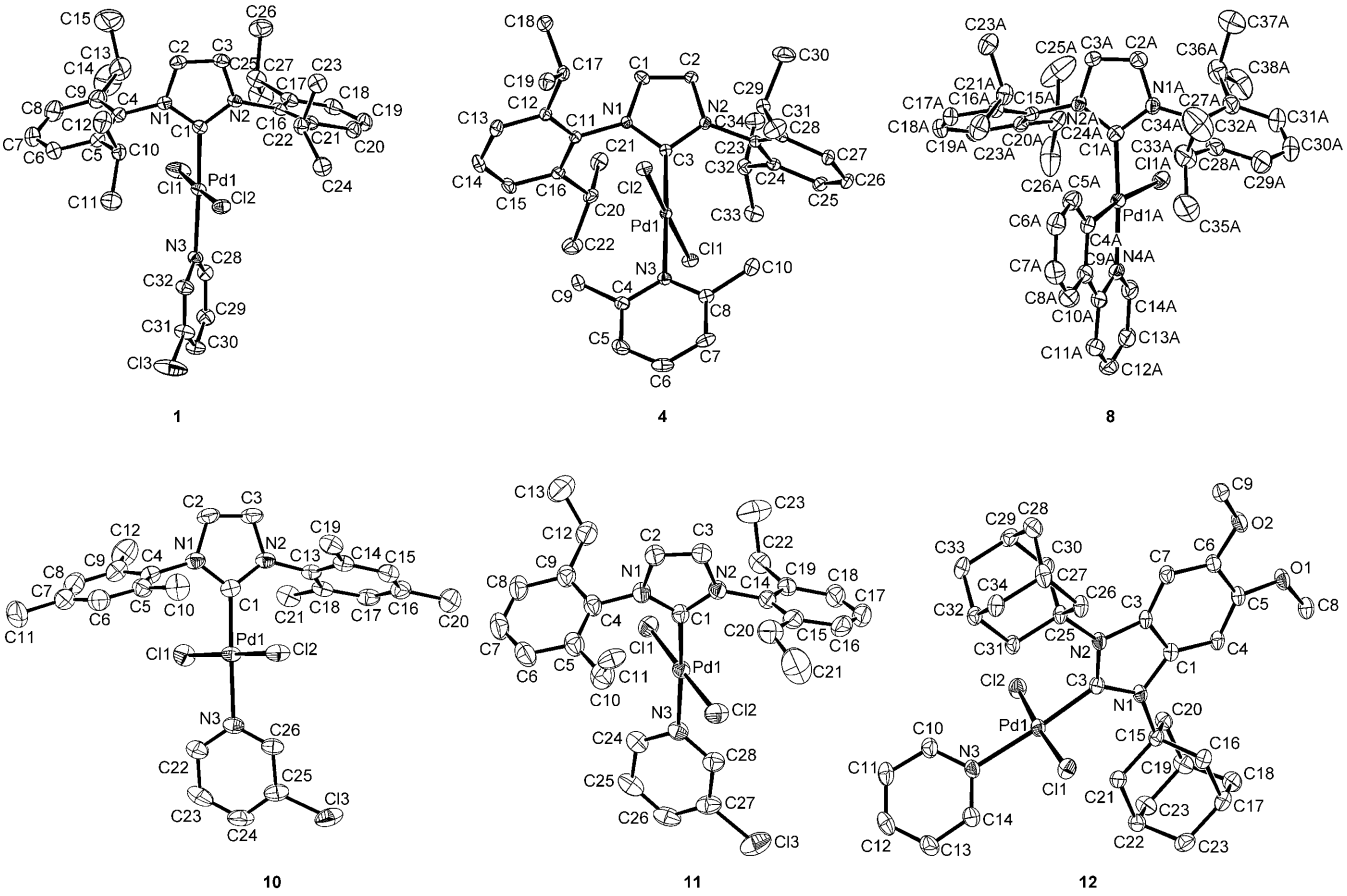


Figure 3. ORTEP representations of the crystal structures of **1**, **4**, **8**, **10**, **11** and **14**. Ellipsoids were drawn at the 30% level and hydrogen atoms have been omitted for clarity.

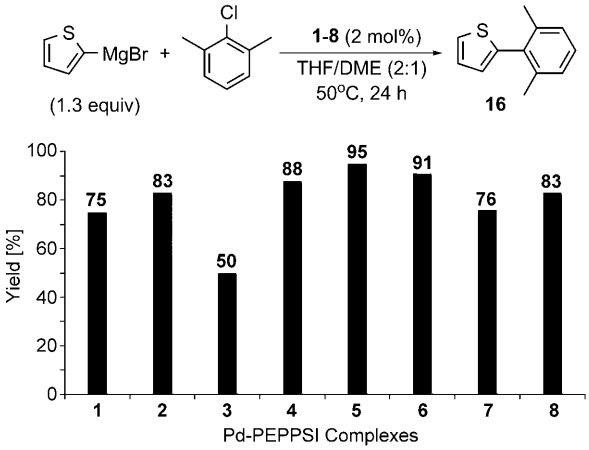


Figure 4. Isolated yields for KTC cross-coupling to form **16**. Reactions were performed in duplicate with <5% error. Control experiments with no catalyst resulted in no product formation. Reactions performed with **1** at RT gave a yield of 35%.

significant amount of **16** had formed, slowing down catalyst decomposition significantly and allowing for continued conversion to product with this difficult coupling. Whether catalyst death is a lot slower with **5**, or whether simply more catalyst is made available to the substrates under these particular conditions is still not fully understood.

Negishi sp^3–sp^3 study: Continuing the SAR analysis for complexes **1**–**14**, we investigated the Negishi sp^3–sp^3 reaction, once again using conditions we had previously used with **1** (Figure 5).[15] Due to competing β-hydride elimination following oxidative addition (Scheme 3), we know that oxidative addition is not problematic. Indeed, complexes **9**–**14** all appear to smoothly undergo oxidative addition as shown by the formation of alkene byproduct **18** concurrent with the consumption of all starting materials. When a control experiment was performed without catalyst, only the starting alkyl halide was recovered, which confirmed that elimination of the alkyl halide does not occur as a consequence of the basic reaction conditions and reduction to **20** is a Pd^0-mediated process. Interestingly, complexes **4** and **8** did not perform as well in the room-temperature Negishi reaction as they did in the sp^2–sp^2 study (vide infra). The major product observed in the reactions with both **4** and **8** was reduced phenylpropane **20**. In the case of **8**, it is possible that only a portion of the catalyst was activated because more than 60% of the alkyl halide starting material was recovered. This is somewhat surprising because only one equivalent of

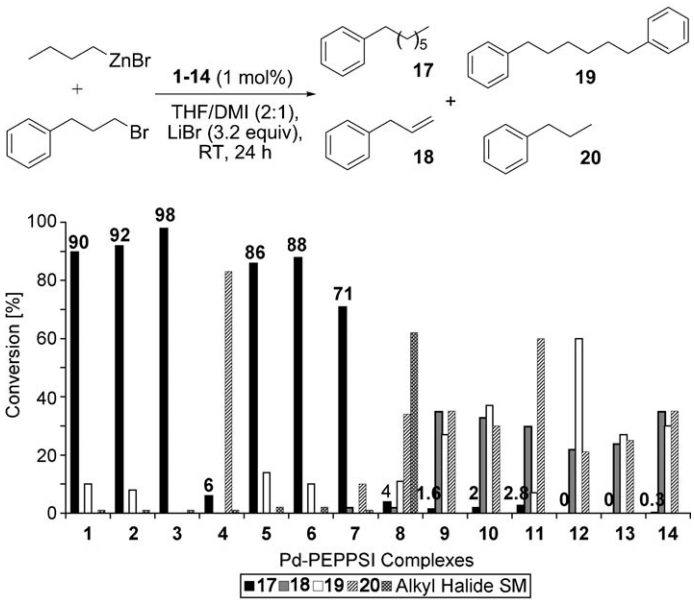
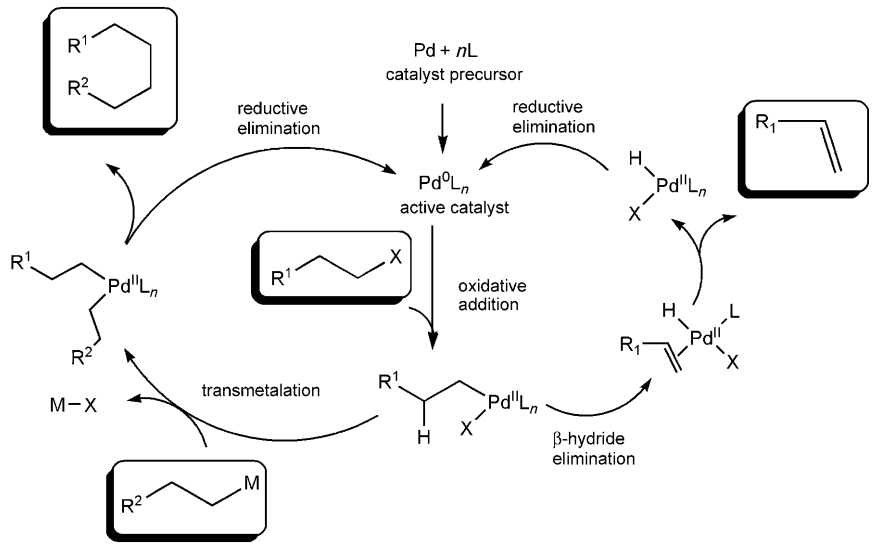


Figure 5. Results for Negishi cross-coupling to form **17**. Conversion was determined by using GC/MS against a calibrated internal standard (undecane). All experiments were performed in triplicate and the average value is reported. Control experiments with no catalyst resulted in no product formation.



Scheme 3. The β-hydride elimination pathway known to occur in sp^3 substrates.

organometallic reagent is required to activate the palladacycle to Pd^0, and we had achieved quantitative conversion to product **15** with **8** in our sp^2–sp^2 KTC (vide supra) and sp^2–sp^2 Negishi studies (vide infra). At the same time, this result also indicates the greater difficulty of cross-coupling alkyl reagents as compared with organic electrophiles that contain π electrons, such as allyl, alkenyl, alkynyl, benzyl or acyl groups, that coordinate to the metal centre with less difficulty prior to the catalytic steps. Despite complex **4** showing evidence of activation to Pd^0 at room temperature, it gave only 6% of cross-coupled product. Additionally, a slower reduction of the halides on the precatalyst by the alkylzinc reagent as compared with the unsaturated zinc reagents may also be responsible. Because no alkyl halide starting material was recovered, a plausible explanation for the presence of **20** is the alkyl halide undergoing metal–halogen exchange with the organozinc reagent followed by subsequent protonolysis upon workup. Similar to the KTC study, IPr-NHC catalysts (**1**–**8**) were subjected to a more challenging alkyl–alkyl Negishi cross-coupling reaction (Figure 6). A similar trend was discovered with complex **5** because it was again found to be the most active catalyst, outperforming **1** to a noticeable extent. It is worth noting that saturated analogue **7** performed poorly despite possessing greater flexibility, which has previously been linked to high reactivity during reductive elimination.[24] We noted in our earlier studies that **7** was the more active catalyst when forming aryl–aryl bonds at ambient temperatures. This led us to reason that the enhanced flexibility imparted by the saturated NHC bound to Pd was beneficial when placed against the demanding steps of the catalytic cycle.[24] The aromatic groups attached to the nitrogen atoms rock back and forth to accept the incoming substrates and expel the cross-coupled products.[18] In our earlier studies, this beneficial flexible steric bulk was noted with more rigid aryl substrates, but results from this work suggest that long and flexible alkyl chains are not compatible with more flexible NHCs.

Negishi sp^2–sp^2 study: By using similar substrates as in the KTC study, we compared the transmetalation step by employing *p*-tolylzinc bromide as the organometallic reagent (Figure 7). Unexpectedly, complexes that had previously proven inactive (**9**–**14**) were able to generate significant cross-coupled product, which perhaps indicates that something unique occurs with aryl organozinc reagents.

To rule out the possibility of reaction conditions (e.g., solvent) playing a role in the transformation, we reacted identical Grignard reagents under optimised Negishi conditions with less sterically hindered **11** and more hindered **14** to form product **15** (Table 2). Only upon heating did conversion improve for the Grignard, but the analogous Negishi couplings were still higher.

To evaluate this theory, we reacted sterically congested coupling partners with PEPPSI precatalysts that had previously been shown to be inactive (against **1** as a control)

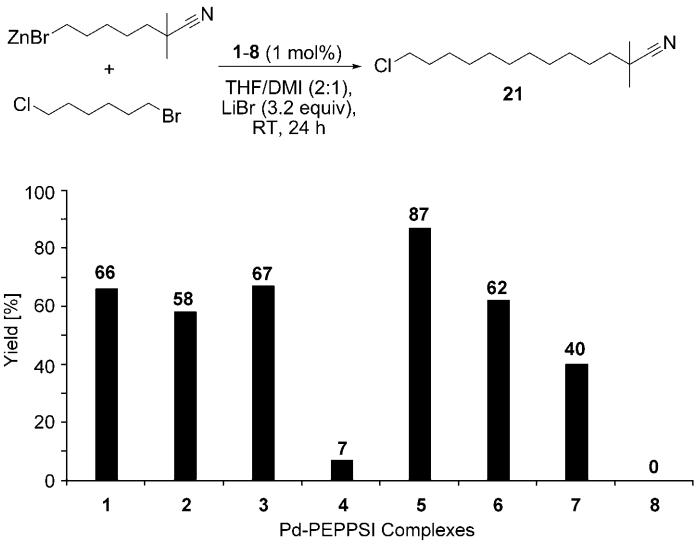


Figure 6. Isolated yields for Negishi cross-coupling to form **21**. Reactions were performed in duplicate and the average value is reported with <5% error. Control experiments with no catalyst showed no conversion.

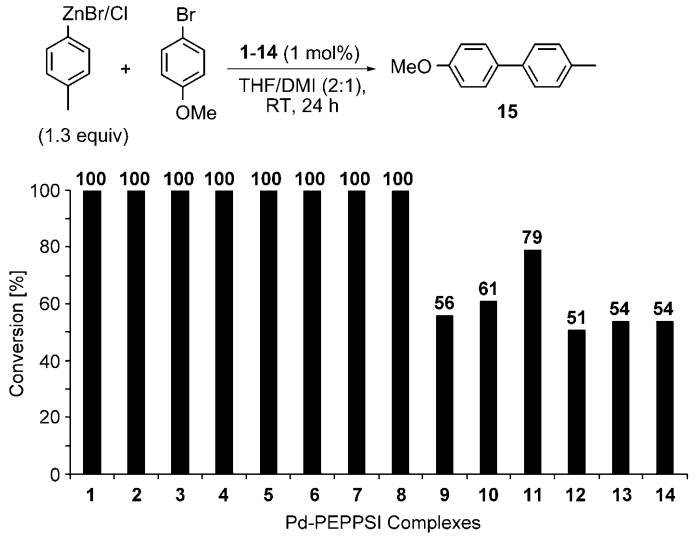
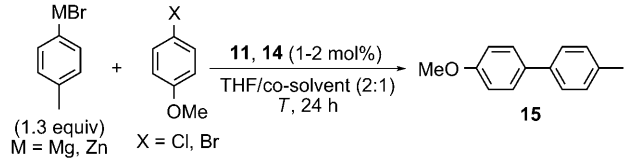


Figure 7. Results of Negishi cross-coupling to form **15**. Conversion was determined by using GC/MS against a calibrated internal standard (undecane). All experiments were performed in triplicate and control experiments with no catalyst showed no conversion.

under optimised Negishi conditions at elevated temperatures (Table 3). The similar yields obtained with **9**, **10** and **11** suggested nearly equal activity. However, when the cross-coupling partners were switched, which should presumably lead to the same reductive elimination intermediate, the reduced conversion with **10** suggested that either oxidative addition or transmetalation is rate-limiting (Table 4). The enhanced yield of **22** at both 60°C and room temperature with catalyst **1** and the less bulky organozinc (Table 4, entry 1) suggested that transmetalation was the critical step in this process. To further probe the reactivity of **1** and **10** and to

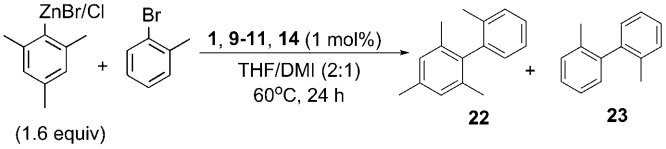
Table 2. Comparison of transmetalating agents in the formation of **15**.[a]



Entry	Catalyst	M	Conditions	Conversion [%]
1	**11**	Mg	DMI, RT	4
2	**11**	Mg	DME, 50°C	31
3	**11**	Zn	DMI, RT	79
4	**11**	Zn	DME, 50°C	43
5	**14**	Mg	DMI, RT	0
6	**14**	Mg	DME, 50°C	2
7	**14**	Zn	DMI, RT	54
8	**14**	Zn	DME, 50°C	29

[a] Reactions were performed in duplicate and the average value is reported. Control experiments with no catalyst showed no conversion.

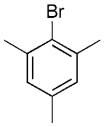
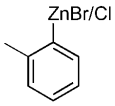
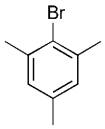
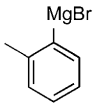
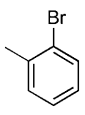
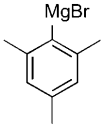
Table 3. Isolated yields for Negishi cross-coupling reactions to form **22**.[a]



Catalyst	Yield [%]
1	81 (76)[b]
9	73
10	77
11	80
14	0

[a] Reactions were performed in duplicate and the average value is reported. Control experiments with no catalyst showed no conversion. [b] Yield achieved when the reaction was performed at RT appears in parentheses.

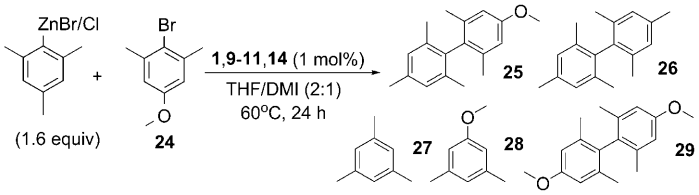
Table 4. Isolated yields for Negishi cross-coupling reactions to form **22**.[a]

Entry	Ar–Br	Organometallic reagent	Catalyst	Yield [%]
1			**1**	97[b]
			10	14[c]
2			**1**	87
			10	0[d]
3			**1**	88
			10	50[e]

[a] Reactions were performed in duplicate and the average value is reported. Control reactions with no catalyst showed no conversion. [b] The product was obtained in 94% yield when the reaction was carried out at RT. [c] No product was obtained when the reaction was carried out at RT. Byproducts included **23** and 12% unreacted Ar–Br. [d] Recovered reaction components: 86% Ar–Br and Grignard dimerisation product **23**. [e] Recovered reaction components: 13% Ar–Br and protonated Grignard (xylene).

look for more clues into the mechanism, the corresponding Grignard reagents were used (Table 4, entries 2, 3). The effects were pronounced with complex **10**, which was less reactive towards the bulkier aryl bromides and allowed for less ambiguity in the determination of the rate-limiting step. The complete absence of the cross-coupled product, along with significant amounts of **23**, suggests that a second transmetalation step that competes with reductive elimination may be in effect, leading to the homocoupled products as suggested recently by Lei et al.[25] Taken together, the abovementioned coupling results are consistent with transmetalation being the rate-limiting step, with the organozincs being more active. This higher activity observed with organozinc reagents may be attributed to better solubility than the Grignard reagents and/or the principle of hard and soft Lewis acids and bases.[26] The zinc metal, which has d orbitals and thus a larger size, presumably makes the carbanion more active and nucleophilic if it is mismatched with a softer Zn cation, which is supported by higher yields even with less active catalysts. In regards to the construction of more difficult tetra-*ortho*-substituted biaryls, complexes **9**–**11** were less tolerable (Table 5).

Table 5. Isolated yields for Negishi cross-coupling reaction to form **25**.[a]



Entry	Catalyst	Yield of **25** [%]	Starting material **24** [%]	Byproduct **27** [%]	Byproduct **28** [%]	Byproduct **29** [%]
1	**1**	65[b]	0	0	13	21
2	**9**	0[c]	99	0	0	0
3	**10**	0	79	9	12	0
4	**11**	0	98	2	0	0
5	**14**	0	64	18	18	0

[a] Reactions were performed in duplicate and the average value is reported. Control reaction with no catalyst showed no conversion. [b] Remaining reaction component includes organozinc dimerisation product **26**. [c] Remaining reaction component is the zinc dimerisation product **26**.

Suzuki–Miyaura sp^2–sp^2 study: We have also analysed the Suzuki–Miyaura reaction by using our catalyst library (Figure 8) and found no notable differences between any of our IPr-based catalysts with the exception of **8**. Palladacycle **8** was presumably not activated to Pd^0 because only aryl halide starting material was recovered. Conceptually, palladacycles can be viewed as the oxidative addition products of an aryl halide to palladium, however, the mechanism of their activation and the exact nature of the catalytic species in solution continue to be questioned by many researchers. Most literature examples describing palladacycle use for unactivated aryl chlorides in the Suzuki–Miyaura reaction are either at high reaction temperatures or use phosphine-based

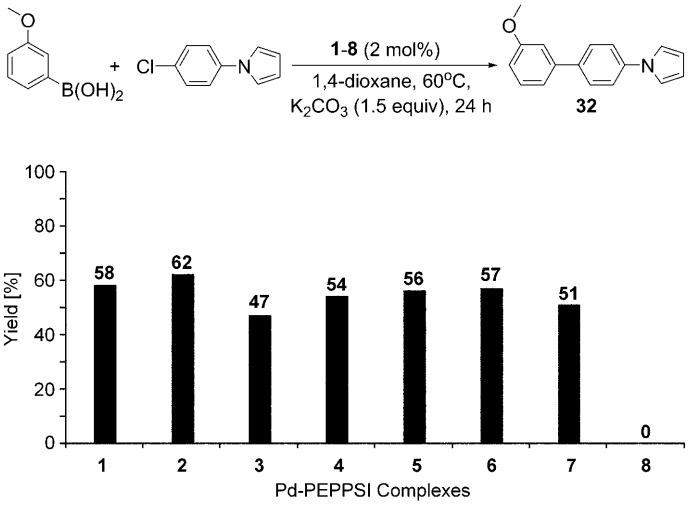


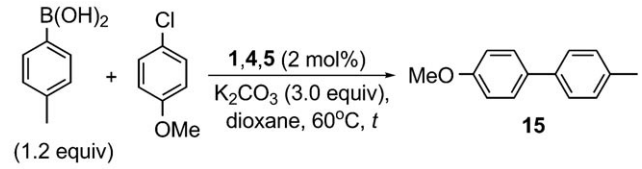
Figure 8. Isolated yields for Suzuki–Miyaura cross-coupling with K_2CO_3 to form **32**. Reactions were performed in duplicate and the average value is reported. The reaction carried out by using **1** also gave a yield of 46% when stopped after 15 h. Control experiments with no catalyst resulted in no product formation.

derivatives.[29] Nolan and co-workers suggested isopropoxide coordination followed by an ensuing β-hydride elimination to liberate acetone as key steps in the activation of an NHC palladacycle similar in structure to **8**;[29] such a mechanistic feature would limit the use of palladacycle-based catalysts.

To better draw comparisons with other coupling types, we conducted a rate study under these conditions with analogous substrates used in the KTC rate study (Figure 9). Again, lutidine complex **4** performed noticeably poorly, whereas complexes **1** and **5** showed similar rates. However, as shown in Figure 8, after 24 h only moderate conversion to the product was observed. When the same reaction was performed at room temperature under more strongly basic conditions (i.e., *t*BuOK, Figure 10), a much higher conversion to **15** occurred quite rapidly; interestingly, no turnover with **4** was observed at all.

Conclusion

In summary, we have demonstrated the high activity of IPr-based NHC ligands of the PEPPSI catalyst precursors in a variety of useful cross-coupling reactions. In the KTC and Negishi reactions, precatalyst activation most likely involves slow reduction of the halides by the organometallic reagent followed by fast pyridine dissociation. During the catalytic cycle, the transmetalation step appears to be rate-limiting, with the unsaturated organozinc reagents being the more active nucleophiles. High catalyst turnover numbers and higher turnover frequencies are possible with non-coordinating and non-bulky throw-away ligands, as demonstrated with complexes **1**, **4** and **5** in forming cross-coupled product in excellent yields after catalyst activation had taken place. The lowered rates and yields with complex **4** demonstrates



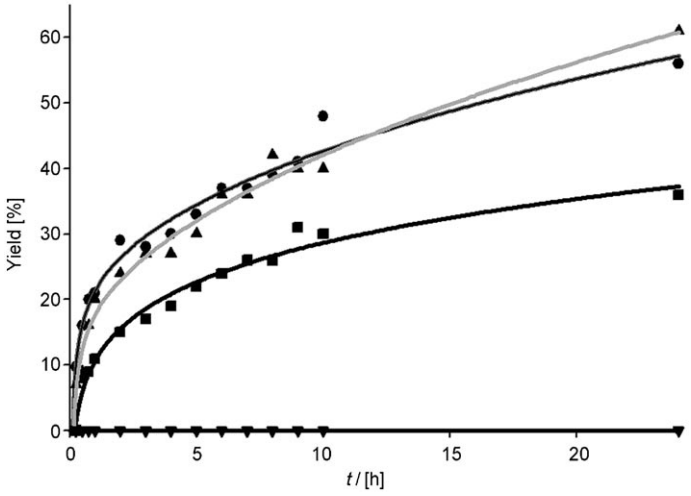
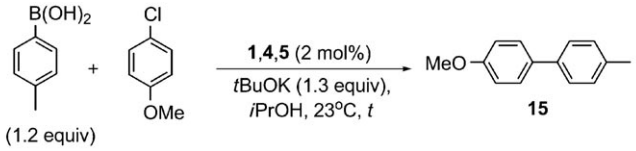


Figure 9. Rate of formation of **15** by using the Suzuki–Miyaura reaction with K_2CO_3 in 1,4-dioxane with catalysts **1** (●), **4** (■), **5** (▲) and $PdCl_2$ (▼; control). The relative rates (initial) are as follows: **1**: 5.0×10^{-6} mol L^{-1} s^{-1}; **4**: 1.7×10^{-6} mol L^{-1} s^{-1}; **5**: 3.2×10^{-6} mol L^{-1} s^{-1}. Conversion was determined by using GC/MS against a calibrated internal standard (undecane). All experiments were performed in triplicate. Control experiments with no catalyst showed no conversion.



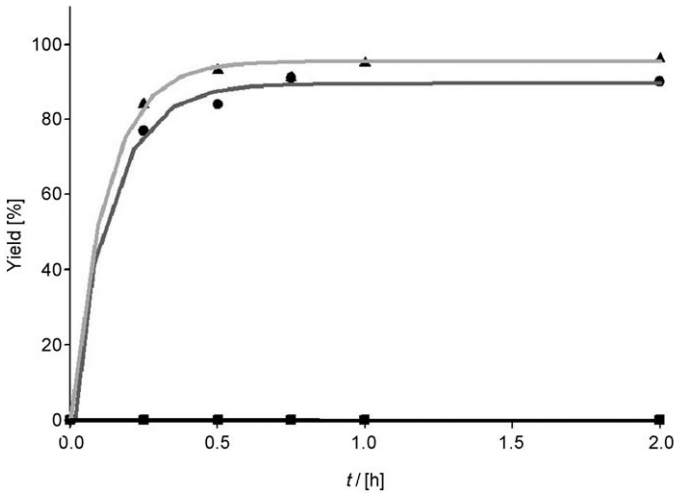


Figure 10. Rate of formation of **15** by using the Suzuki–Miyaura reaction with *t*BuOK in isopropanol with catalysts **1** (●), **4** (■), **5** (▲) and $PdCl_2$ (▼; control; hidden under ■). The relative rates (initial) are as follows: **1**: 2.8×10^{-5} mol L^{-1} s^{-1}; **4**: 0.0 mol L^{-1} s^{-1}; **5**: 2.9×10^{-5} mol L^{-1} s^{-1}. Conversion was determined by using GC/MS against a calibrated internal standard (undecane). All experiments were performed in triplicate. Control experiments with no catalyst showed no conversion.

that the pyridines attach to and detach from the NHC–Pd^0 complex in solution. This dissociation–association mechanism may also be responsible for slowing down the rate of palladium black formation, extending catalyst lifetime and in some cases producing higher reaction yields.

Experimental Section

See the Supporting Information for details of syntheses and characterisations.

CCDC-761243 (**1**), -761244 (**4**), -761245 (**8**), -761246 (**10**), -761247 (**11**) and -761248 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

This work was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Ontario Research and Development Challenge Fund (ORDCF). The authors graciously acknowledge the donation (in part) from Varian of a GCMS to evaluate the products of the transformations.

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Received: January 19, 2010
Revised: April 22, 2010
Published online: July 21, 2010

