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Pd-PEPPSI-IHept^{Cl}: A General Purpose, Highly Reactive Catalyst for the Selective Coupling of Secondary Alkyl Organozincs.

Bruce Atwater,[a] Nalin Chandrasoma,[a] David Mitchell,[c] Michael J. Rodriguez,[c] and Michael G. Organ*[a,b]

Abstract: *Pd-PEPPSI-IHept^{Cl}*, a new, very bulky yet flexible Pd-NHC complex has been evaluated in the cross-coupling of secondary alkylzinc reactants with a wide variety of oxidative addition partners in high yields and excellent selectivity. The desired, direct reductive elimination branched products were obtained with no sign of migratory insertion across electron-rich and electron poor aromatics and all forms of heteroaromatics (5- and 6-membered). Impressively, there is no impact of substituents at the site of reductive elimination (i.e., ortho or even di-ortho), which has not yet been demonstrated by another catalyst system to date.

After decades of targeting structurally simplified molecules that are more straightforward to prepare as potential leads in the pharmaceutical industry, the current trend is to move back toward compounds that are more architecturally complex or more 'natural product-like'. There are many reasons for this including better on-target specificity, reduced toxicity, and improved phamacokinetic properties of potential drug candidates.[1] This movement in the pharmaceutical industry has created challenges for synthetic chemists leading to invigorated interest in the development of reactions that generate tertiary and quaternary carbon centres.[2] In particular there is increasing interest in the preparation such centres where at least one of the substituents is an aryl or heteroaryl moiety.[3] Interestingly, a similar trend in materials science has also been developing over the last few years where organic light-emitting diodes (OLEDs), for example, now contain more complex alkyl chains to better solubilize the typically crystalline aromatic cores and to fine-tune their electronic properties.[4] Here cross-coupling presents a very direct route to these motifs of increasing sp^3 character.

In the last few years there has been growing interest in the development of catalysts that can effectively generate connections between sp^2 and sp^3 centres.[3] On the surface of it, the reaction seems straightforward enough as the mechanism is believed to be very similar to the well-known analogous coupling of two sp^2 centres that leads, for example, to biaryls. The key difference is that there is no possibility of forming constitutional isomers with these type of products. However, with alkyl centres

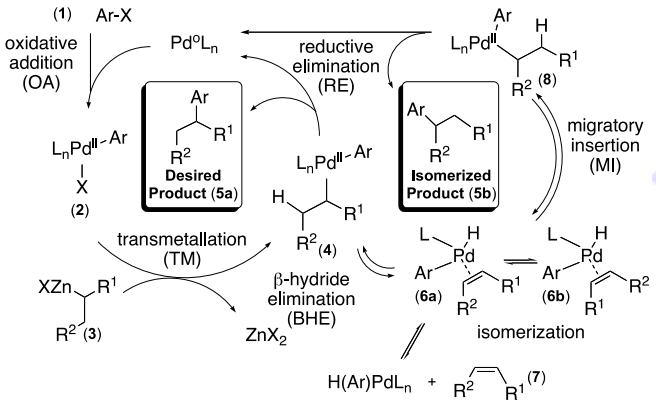

Figure 1. Mechanism of cross-coupling of secondary metal alkyls.

there is the possibility of forming elimination products at various stages in the catalytic cycle (Figure 1). Agostic interactions between the electron poor metal centre and the electron rich adjacent C-H bonds can progress along the reaction coordinate toward beta hydride elimination (BHE) (i.e., from intermediate **4** to **6a**). Dissociation of the resultant olefin (**7**) at this stage can drain off all the alkyl starting material into the undesired corresponding unsaturated byproduct and, because the reaction conditions are typically basic, the metal hydride can be readily reduced rendering this destructive pathway catalytic. If the resultant olefin reinserts into the metal hydride with the same regiochemistry (i.e., **4** → **6a** → **4**) the event is essentially of no consequence. However, if the olefin rotates, or dissociates and subsequently re-associates about the metal hydride bond with alternate regiochemistry, and reinsertion now occurs, the isomeric metal alkyl results in a process known as migratory insertion (MI) (i.e., **4** → **6a** → **6b** → **8**).

We,[5] and others,[3] have been investigating the cross-coupling of secondary metal alkyls to aryl- and heteroaryl-motifs with the intention of producing single products with the desired connectivity (i.e., **5a** with no MI). During the course of these investigations it was found that good, and in a limited number of cases, outstanding selectivity for the desired branched products could be achieved with 6-membered ring aryl and heteroaryl oxidative addition partners.[5c] The key is to favour RE at the cost of the undesired BHE. We have shown by computation that if BHE occurs the opportunity now exists to form a more stable metal alkyl.[5b] That is, if R^1 is an alkyl group and R^2 = H, the equilibrium will be driven to the formation of **8**. If that transpires, the fate of the reaction is determined as the barrier to RE from the lower energy metal alkyl is also greatly reduced and this will drain the reaction in the direction of the undesired isomer (**5b**).

There is an electronic contribution to this selectivity whereby a more electron-poor metal centre will have a lower reduction

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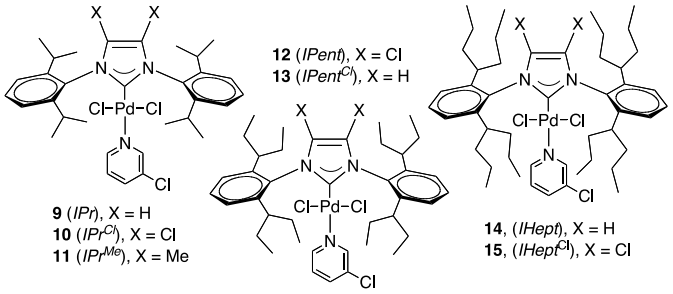


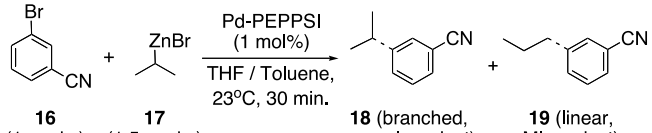
Figure 2. *Pd-PEPPSI* pre-catalysts used in this study.

potential and thus the RE pathway becomes more likely relative to BHE. Indeed, oxidative addition (OA) partners of similar size and pattern of substituents on the ring will have improved selectivity for the electron-poor compound (e.g., p-chlorobenzonitrile) relative to an electron-rich one (e.g., p-chloroanisole).[5b] However, we believe sterics play a greater role because the more sterically sensitive BHE transition state involves a 4-membered ring intermediate whereas RE goes through a 3-membered ring structure. Here the structure of the ancillary on the metal plays a crucial role as an ideal ligand platform will offer the opportunity to systematically vary the steric topology about the metal centre to discourage BHE.

To illustrate this importance of sterics, *Pd-PEPPSI-IPr* catalyst (**9**) (Figure 2) was used to couple 3-bromocyanobenzene (**16**) and isopropylzinc bromide (**17**) and no selectivity was achieved (1:1, branched to linear), however both the (relatively) electron-rich *IPr^Me* (**10**) and electron-poor *IPr^Cl* (**11**) derivatives exhibited similar and vastly improved selectivity (relative to **9**) of ~15:1 (Table 1). Here either substituent pushes the N-aryl moiety inward toward Pd to a similar extent, which we propose is essential in mitigating BHE. These steric impacts are seen again with *IPent* (**12**) that had improved selectivity relative to *IPr* (10:1), which jumped again to 56:1 with the NHC chlorinated core (**13**).

Employing **13** broadly in the coupling of secondary alkyl zinc reagents to 6-membered ring heterocycles led to excellent selectivity for the desired RE product.[5b] Shockingly however,

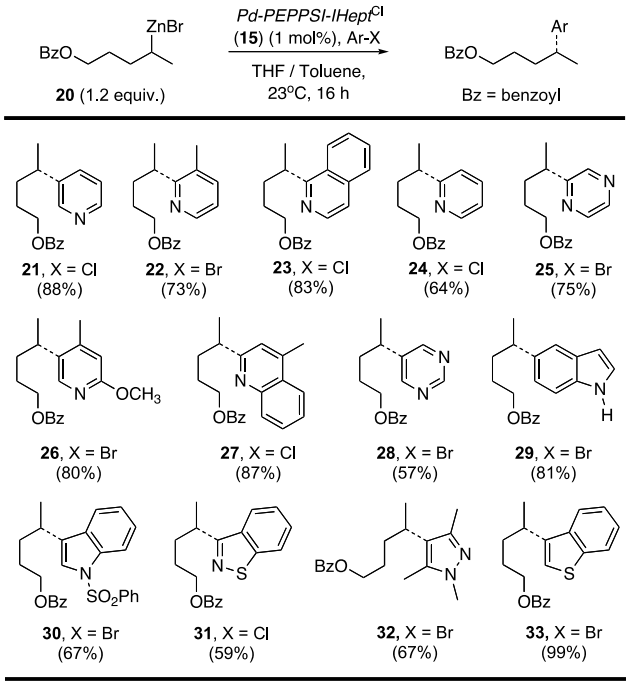
Table 1. Coupling of 3-bromobenzonitrile with isopropylzinc bromide.



16 (1 equiv.) **17** (1.5 equiv.) **18** (branched, normal product) **19** (linear, MI product)

Enrty[a]	*Pd-PEPPSI*	Conv. of **16**	**18** : **19**
1	**9**	99%	1 : 1
2	**10**	99%	14.7 : 1
3	**11**	99%	15 : 1
4	**12**	99%	10 : 1
5	**13**	99%	56 : 1
6	**15**	99%	only **18**

Table 2. Coupling of 5-benzyloxy-2-pentylzinc bromide ether.[a]



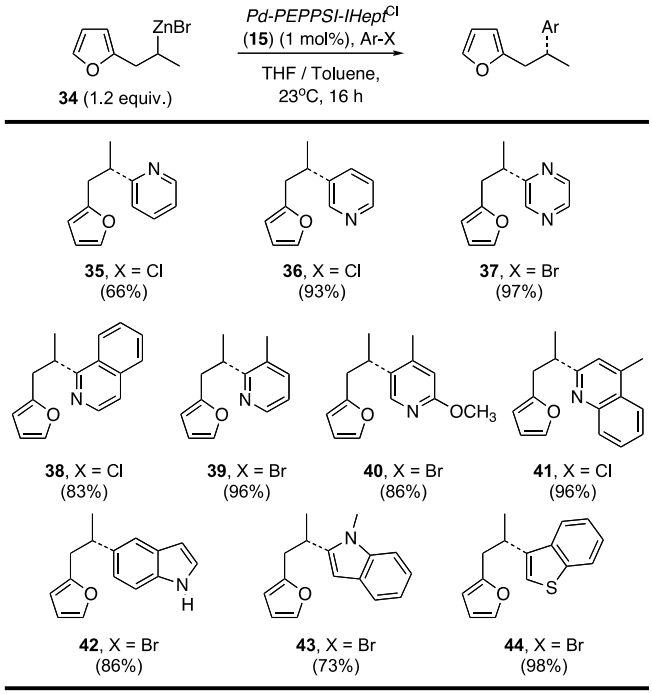
[a] Yields are reported on compounds purified by silica gel chromatography. Reactions were performed in duplicate and average yields are reported.

when 5-membered ring aromatics, such as pyrroles, furans, indoles, etc., were examined with **13** in otherwise identical couplings, no selectivity was observed for RE and the products of MI dominated.[5a] While we attribute these effects mostly to the now electron-rich aromatic core, relative to heterocycles such as pyridines and pyrimidines, we felt that the propensity for BHE could be overcome with carefully engineered sterics that can force the pathway toward RE. To this end we have developed *Pd-PEPPSI-IHept^Cl* (**15**) as a general-purpose catalyst for the selective cross-coupling of secondary alkylzinc reagents.

Reagent **20** was suitable to examine the generality of **15** against 5- and 6-memberd ring heterocycle OA partners (Table 2). Strikingly, there was impressive selectivity across all substrates, with no MI products detectable in the analysis of the crude reaction mixtures. It would appear that the bulky isoheptyl chains, in combination with the chlorines on the back of the NHC core are sufficient to force the pathway in the direction of RE, thus completely eliminating the possibility of BHE from occurring.

Next the complexity of zinc reagents that could be coupled was examined to see just how far the reactivity of **15** could be pushed, while maintaining selectivity for the desired product isomer. To this end we examined substrates that have activated β-hydrides, where if BHE did occur it would lead to conjugated systems. Reactant **34**, possessing a benzylic hydride underwent smooth coupling with both 5- and 6-membered ring heterocycle partners, again with no sign of the products of MI (Table 3). Reagent **46** nicely demonstrates the often underappreciated property of zinc metal centres, which is that they react with very high chemoselectivity[6] (Table 4). The ester moiety in **46** tolerates the zinc centre, but would not be able to withstand the presence of a lithio or magnesium centre, for example. Again,

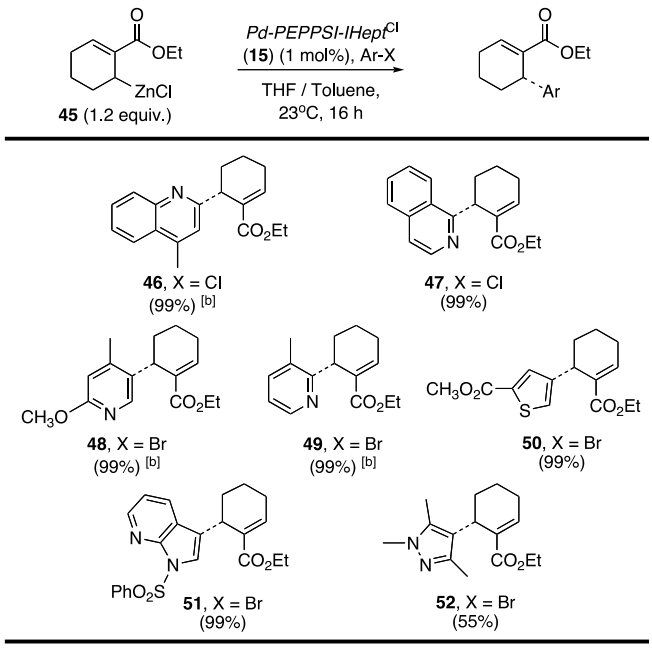
Table 3. Coupling of 1-furan-2-propylzinc bromide.[a]



[a] Yields are reported on compounds purified by silica gel chromatography. Reactions were performed in duplicate and average yields are reported.

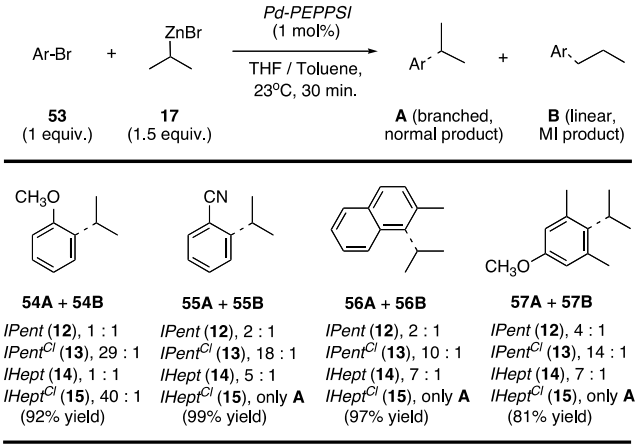
the coupling reaction employing **15** proceeded in high yields and with no MI.

Table 4. Coupling of ethyl (cyclohex-6-enyl-1-zinc bromide)-1-carboxylate (**46**).[a]



[a] Yields are reported on compounds purified by silica gel chromatography. Reactions were performed in duplicate and average yields are reported. [b] Reduced starting materials could not be separated fully from the cross-coupled product, thus yields are estimated by a combination of product mass and NMR spectroscopy (conversion to product is quantitative).

Table 5. Coupling of ortho substituted aryls with isopropylzinc bromide.[a]



[a] Yields are reported on compounds purified by silica gel chromatography. Reactions were performed in duplicate and average yields are reported.

In the final evaluation of just how adept **15** is at driving RE in the face of obstacles, we revisited the impact of ortho substituents on selectivity (Table 5). The presence of even a single group dramatically reduces the relative rate of RE that completely compromises the ability of *IPent* (**12**) to be at all selective (e.g., compounds **54** and **55**). Increasing the size of the N-aryl substituents improved selectivity (e.g., catalyst **12** vs **14)**, but chlorinating the NHC core has a much greater impact (e.g., catalyst **12** vs **13** and catalyst **14** vs. **15**). Remarkably, and without precedent, **15** was able to couple bis-ortho flanked centres (compounds **56** and **57**) with complete selectivity for RE.

In summary, *Pd-PEPPSI-IHept*^{Cl} (**15**)[7] has been demonstrated to be the first generally applicable, fully selective catalyst for the cross-coupling of secondary alkylzinc reagents. The substrate scope includes zincs that are predisposed to BHE, yet the high rate of RE precludes any of this undesired side reaction from occurring. The coupling and selectivity seems fully insensitive to the nature of the OA partner as electron-rich examples all couple with equal efficacy to their electron-poor counterparts, as do both 6- and 5-membered ring heterocycles. Most impressively, even intensively hindered 2,6-disubstituted OA partners cleanly yield the desired isomers in all cases.

Acknowledgements

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Keywords: cross-couple • *PEPPSI* • selective • secondary alkylzinc • Palladium

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[7] *Pd-PEPPSI-IHept*^{Cl} was obtained from Total Synthesis Ltd., Toronto, Ontario, Canada (http://totalsynthesis.ca/)

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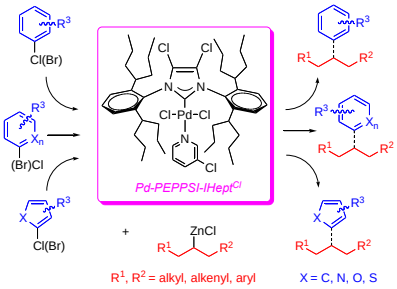
Pd-PEPPSI-IHept^{Cl} has emerged as a '*one-catalyst-fits-all*' candidate for the selective coupling of secondary alkyl-zinc reagents with a wide selection of aromatic and 5- and 6-membered ring heteroaromatic oxidative addition partners. Impressively, hindered 2,6-disubstituted oxidative addition partners couple with no migratory insertion, verifying the high rate of reductive elimination with this catalyst.



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