Cross-Coupling

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The Selective Cross-Coupling of Secondary Alkyl Zinc Reagents to Five-Membered-Ring Heterocycles Using Pd-PEPPSI-IHept^{Cl}**

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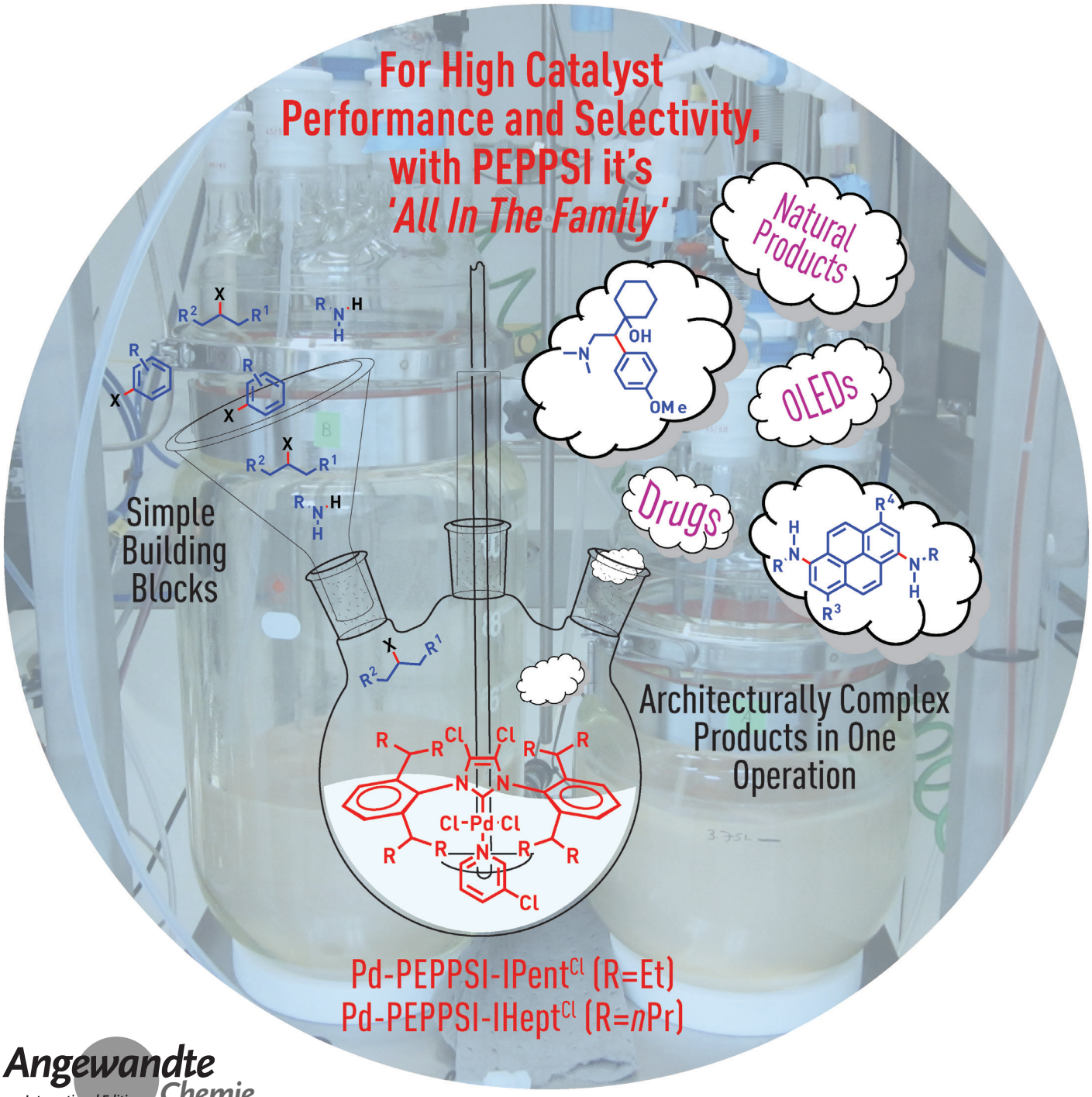


Abstract: *The ability to cross-couple secondary alkyl centers is fraught with a number of problems, including difficult reductive elimination, which often leads to β-hydride elimination. Whereas catalysts have been reported that provide decent selectivity for the expected (non-rearranged) cross-coupled product with aryl or heteroaryl oxidative-addition partners, none have shown reliable selectivity with five-membered-ring heterocycles. In this report, a new, rationally designed catalyst, Pd-PEPPSI-IHept^{Cl}, is demonstrated to be effective in selective cross-coupling reactions with secondary alkyl reagents across an impressive variety of furans, thiophenes, and benzo-fused derivatives (e.g., indoles, benzofurans), in most instances producing clean products with minimal, if any, migratory insertion for the first time.*

Within the last five years, interest in the development of methods for the construction of C(sp^2)–C(sp^3) bonds has been growing rapidly.[1] Many companies in the pharmaceutical sector have initiated programs to incorporate aromatic and heteroaromatic molecules that are decorated with branched alkyl chains (i.e., the carbon bound to the aromatic ring is secondary) into their medicinal-compound collections.[2] This move is to compensate, in part, for the relatively low success rates of polyaromatic, "flat" compounds (e.g., biaryls) as clinical candidates.[2] Branched, alkyl-substituted heterocycles are also being aggressively pursued in the development of new OLEDs (organic light-emitting diodes) for the visual-display, screen, and lighting industries.[3] Therefore, the construction of C(sp^2)–C(sp^3) bonds has become a heavily pursued area of synthetic chemistry to support the discovery, investigation, and manufacturing of these societally important compounds that collectively are worth tens of billions of dollars annually.[4]

One of the areas that is pursued most aggressively for C(sp^2)–C(sp^3) bond formation is palladium-catalyzed cross-coupling (see Figure 1 for general mechanistic considerations).[4a,b,g,5] Being a late transition metal, Pd is highly tolerant of reactive functional groups, such as esters, nitriles, and even alcohols, amines, and carboxylic acids.[6] This makes Pd catalysis particularly desirable because it can be used to assemble complex, densely functionalized targets in a highly convergent fashion. Recently, we have made advances in Pd-catalyzed C(sp^2)–C(sp^3) couplings involving six-membered-ring aromatic and heteroaromatic compounds.[5] Owing to the high interest in five-membered-ring heteroaromatic compounds in a number of sectors,[2,3] we were encouraged to attempt to couple 3-pentylzinc bromide (**11**) with a small selection of such compounds (**10**; Scheme 1) using our most selective catalyst to date,[5a] Pd-PEPPSI-IPent^{Cl} (**9**,[7] see Figure 2; PEPPSI = pyridine-enhanced precatalyst preparation, stabilization, and initiation). Unfortunately, despite all attempts with **9**, isomerization by migratory insertion (MI) extensively led to nearly exclusive formation of the isomeric product(s) (i.e., **B** and **C**) rather than the desired one (**A**) from direct reductive elimination (RE; see Figure 1 for key mechanistic interpretation). Poor selectivity was observed independent of whether oxidative addition occurred at the C2 (**12**) or C3 position (**13** or **14**) of the five-membered ring.

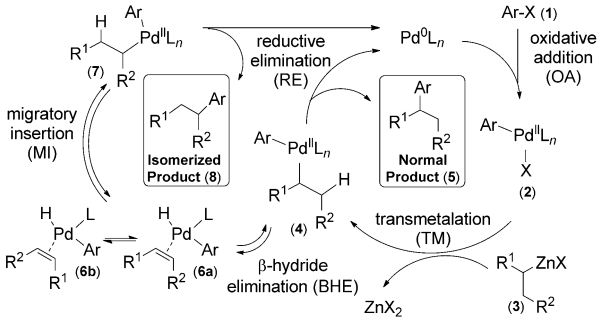
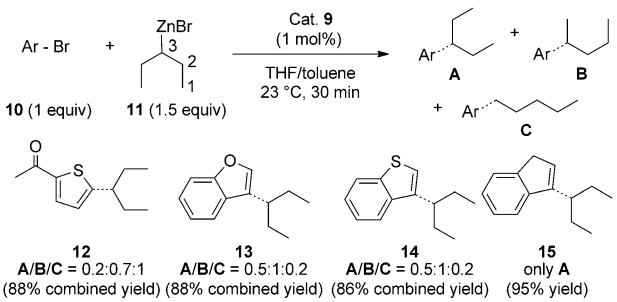


Figure 1. Desired reductive elimination (RE) and migratory insertion (MI) pathways for the Pd-mediated cross-coupling of a secondary alkyl zinc reagent to aromatic heterocycles. Ar = five- or six-membered heteroaromatic compound, R^1 and R^2 = alkyl groups.



Scheme 1. Cross-coupling of 3-pentylzinc bromide (**11**) to various five-membered-ring heterocycles. See Figure 2 for the structure of the PEPPSI precatalyst.

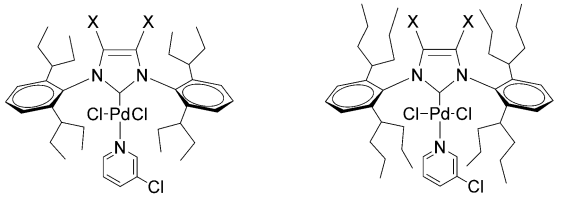


Figure 2. Pd-PEPPSI precatalysts used in this study.

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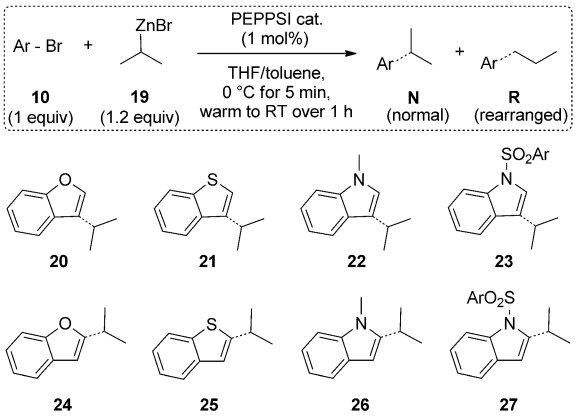
As **11** could be coupled with six-membered heteroaromatic compounds with complete selectivity using **9**,[5a] it would appear that the five- and six-membered-ring congeners are strikingly different in their reactivity, the former being much more difficult to cross-couple with any level of selectivity. This encouraged us to carry out a thorough sweep of the literature, and strikingly, we found that there are no reported scope studies for the general and selective coupling of secondary alkyl fragments to five-membered-ring heterocycles, including 5,6-fused systems where the site of oxidative addition is in the five-membered ring (i.e., at the C2 or C3 position of e.g., indole, benzofuran).[8] Given the high importance of such compounds, the dearth of published results speaks to the difficulty of this coupling. Herein, we disclose the first comprehensive report on the Pd-catalyzed cross-coupling of secondary alkyl organometallics to produce these highly prized products.

Given the surprising, but consistent poor preliminary results in Scheme 1 with the heterocyclic oxidative-addition partners, the first and easiest structural feature to investigate was the impact of bond angles, and thus possible size (steric) effects that are due to changes in the bond angles in the five- versus the six-membered ring. One might argue that with the smaller bond angles in the five-membered ring, there is a reduced steric footprint/influence in the transition state for β-hydride elimination (BHE), which we have demonstrated to be the key to mitigate migratory insertion (MI).[5a] When we submitted the indenyl analogue to the same transformation, the reaction proceeded well, cleanly providing the desired, non-rearranged isomer (**15A**). Given the direct physical comparison between the aromatic compounds leading to **13A** or **14A** with **15A**, it is difficult to implicate reduced steric effects into the rationale for the poor selectivity. The fact that MI is the primary reaction path taken whether the coupling is occurring at the C2 or C3 position of the five-membered ring also makes it challenging on first glance to implicate electronic or coordination effects. Concurrently, we investigated the electronic features of these heterocycles by computational studies, and the corresponding finding will be discussed below.

Moving forward, we hypothesized that if the ligand's bulk was brought further into the coordination sphere of Pd, we could make up for any lost steric impact of the five-membered ring. Furthermore, this might also override any unfavorable electronic features that the five-membered heterocycles impart on the critical steps of RE and BHE.[5a] To this end, two catalysts, Pd-PEPPSI-IHept[9] (**17**) and Pd-PEPPSI-IHept^{Cl} (**18**;[10] Figure 2), were applied to this cross-coupling along with **9** and its analogue Pd-PEPPSI-IPent (**16**),[5b,11] which is not chlorinated in the NHC core (Table 1). 2-Propylzinc bromide (**19**), while a seemingly simple substrate, is actually the most challenging secondary organometallic reagent to cross-couple selectively owing to the maximum number of hydrides that enable BHE, and thus MI, to occur.

When considering the data in Table 1, a number of trends become apparent. In most cases, IPent (**16**) and IHept (**17**) actually led to greater amounts of the MI product (i.e., **R**) than of the desired branched product (i.e., **N**), whereas their

Table 1: Comparison of several PEPPSI precatalysts for the cross-coupling of a variety of five-membered-ring heterocycles (**10**) and 2-propylzinc bromide (**19**).

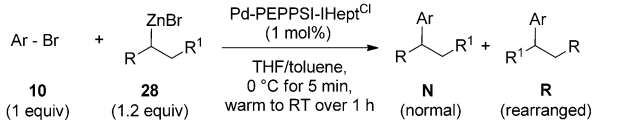


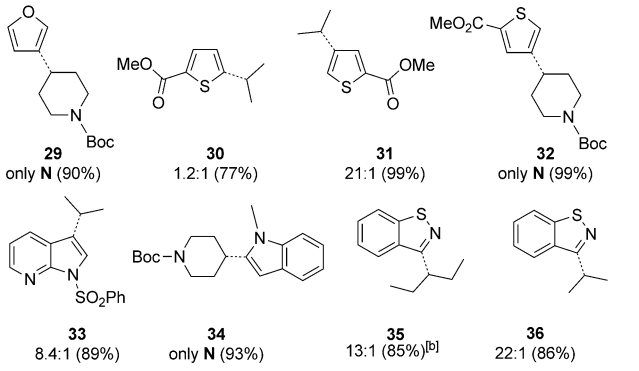
	Product	Normal (**N**) to rearranged (**R**) product ratio[a]			
		IPent (**16**)	IPent^{Cl} (**9**)	IHept (**17**)	IHept^{Cl} (**18**)
1	**20**	1:9.4	5.5:1	1:1.5	9:1
2	**21**	1:1	24:1	3:1	only **N**
3	**22**	2.7:1	20.7:1	9:1	only **N**
4	**23**	1:3	5:1	1.1:1	only **N**
5	**24**	1:9	3:1	1:3	6:1
6	**25**	1:18	1:1	1:8	2:1
7	**26**	1:6	23:1	7.2:1	only **N**
8	**27**	n.r.	1:2[b]	trace	1.3:1[c]

[a] Unless otherwise indicated, reactions proceeded to the coupled products will full conversion. [b] Reaction proceeded to 22% conversion. [c] Reaction proceeded to 17% conversion.

chlorinated analogues were much more selective. In the case of IHept^{Cl} (**18**), the branched product was always formed as the major one, and in many cases, **N** was the only isomer produced. Coupling at the C3 position in the five-membered ring (entries 1–4) is noticeably more selective than at the C2 position (entries 5–8) for all heteroaromatic compounds studied. Whereas it could be argued that steric effects influence the selectivity with N-substituted indoles (e.g., **27**), this would seem less likely for benzothiophene and benzofuran substrates. Certainly, the physical presence of the fused benzene ring is more noticeable at the C3 position, but the same trend is observed in its absence (see Table 2). A substrate survey revealed that this trend of greater intrinsic selectivity at the C3 than at the C2 position was also observed with simple five-membered heterocycles. With 2-propylzinc bromide, methyl 2-thiophenecarboxylate reacted with high selectivity at the C3 position (**31**), whereas no selectivity was observed at the C2 position (**30**). With a 4-piperidenylzinc derivative, both furan (**29**) and thiophene (**32**) electrophiles coupled with no visible MI, providing the desired products in excellent yield. Again, methylindole could be coupled with complete selectivity at the C2 position (**34**), whereas some interesting diheteroatom-containing structures reacted with 2-propyl- (**33** and **36**) and 3-pentylzinc bromide (**35**) with good to excellent selectivity. Collectively, these results suggest that there is a pronounced electronic effect that differentiates the C2 and C3 positions, assuming for now that there is no coordination to Pd.

Table 2: Cross-coupling of various five-membered heterocycles with secondary alkyl zinc bromides using the Pd-PEPPSI-IHept^{Cl} (**18**) catalyst.[a]





[a] The ratios below the product numbers are the **N**/**R** ratios, which were determined by ^{1}H NMR spectroscopy of the product mixture both prior to and following purification. The yield of isolated product after column chromatography on silica gel is given in parentheses. [b] The reaction was performed at 50 °C; the fraction of the minor, rearranged isomer contained some of the 1- and 2-pentyl isomers. Boc = *tert*-butyloxycarbonyl.

In an effort to understand the normal (**N**) to rearranged (**R**) selectivity, a series of calculations were carried out on compounds **20**–**27**. Whereas the coupling of **4** (see Figure 1) leading to the normal product (**5**) accesses only one irreversible transition state, the formation of the rearranged product requires accessing two β-hydride-elimination transition states [TS(**4**↔**6a**) and TS(**6b**↔**7**)] and the reductive-elimination transition state [TS(**7**↔**8**)] that leads from the linear alkyl species (**7**) to the rearranged product (**8**). Previous work[5] demonstrated that the first β-hydride elimination TS is the key one for formation of the rearranged product (**R**) as it is an irreversible step, and once accessed, the subsequent barriers are lower. Those computations[5] also demonstrated a good predictive ability for to the experimental **N**/**R** selectivities by computing the transition-state energy differences ($\Delta\Delta E^{\ddagger} = E\{TS(\mathbf{4}\leftrightarrow\mathbf{6a})\} - E\{TS(\mathbf{4}\leftrightarrow\mathbf{5})\}$). The convention implies that a positive value for $\Delta\Delta E^{\ddagger}$ gives a higher TS for the β-hydride elimination and thus favors the normal product (**5**) whereas a negative $\Delta\Delta E^{\ddagger}$ value suggests the formation of greater amounts of the rearranged product (**8**). Calculations were performed on the Pd-PEPPSI-IPent and Pd-PEPPSI-IPent^{Cl} catalysts,[12] and the experimental selectivities and the computed data were compared for substrates substituted at the C2 (Figure 3a) and the C3 position (Figure 3b; for more details, see the Supporting Information).[13]

One outlier aside, an excellent fit is indicated in Figure 3a, and the data again fit acceptably well in Figure 3b. The solid data points in both plots reside in the upper right part of the graphs, indicating that better selectivity was achieved with the Pd-PEPPSI-IPent^{Cl} (**9**) than with the Pd-PEPPSI-IPent (**16**)

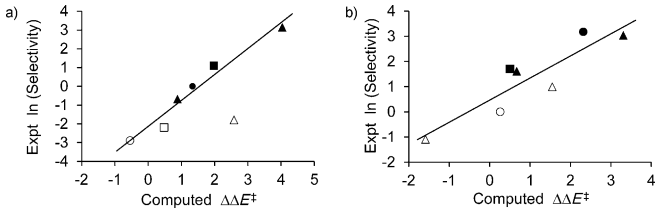


Figure 3. Experimental selectivity [ln(normal/rearranged)] versus the computed $\Delta\Delta E^{\ddagger}$ values, which are the TS energy differences in kcal mol^{-1} [TS(**4**↔**6a**) − TS(**4**↔**5**)] at a) the C2 position and b) the C3 position for substrates **20**–**27.** □: IPent, O heterocycle; ○: IPent, S heterocycle; △: IPent, N heterocycle; ■: IPent^{Cl}, O heterocycle; ●: IPent^{Cl}, S heterocycle; ▲: IPent^{Cl}, N heterocycle.

catalyst. Independently, the calculations are very predictive for both positions. Steric hindrance plays a much greater role in the β-hydride elimination TS [TS(**4**↔**6a**)] than in the reductive-elimination TS [TS(**4**↔**5**)]; therefore, increasing the steric bulk on the NHC (from IPent to IHept) and/or adding chloride substituents in the backbone, which push the large substituents towards the active site (i.e., in IPent^{Cl} and IHept^{Cl}),[5] leads to enhanced selectivity.

In summary, two new, rather bulky Pd NHC catalysts, Pd-PEPPSI-IHept (**17**) and Pd-PEPPSI-IHept^{Cl} (**18**),[10] have been reported, and their use in the selective cross-coupling of secondary alkyl zinc reagents to five-membered-ring heterocycles has been investigated. The selectivities that were achieved with Pd-PEPPSI-IHept^{Cl} (**18**) in this study,[10] both at the C2 and C3 positions of various heteroaromatic compounds, are without precedent. This catalyst provides a powerful approach in the pursuit of complex new compounds for the discovery and manufacture of new therapeutics and novel materials, including OLEDS.

Keywords: alkyl zinc reagents · cross-coupling · N-heterocyclic carbenes · palladium · transition-metal catalysis

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[12] The conformations of the 3-pentyl chains are computationally problematic, therefore, only the conformation of the X-ray structure was used.

[13] Calculations used the B3LYP/6-31*/LANL2TZ(F) method. Additional information is available in the Supporting Information.

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