Homogeneous Catalysis

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# Pd-PEPPSI-IPent$^{Cl}$: A Highly Effective Catalyst for the Selective Cross-Coupling of Secondary Organozinc Reagents**

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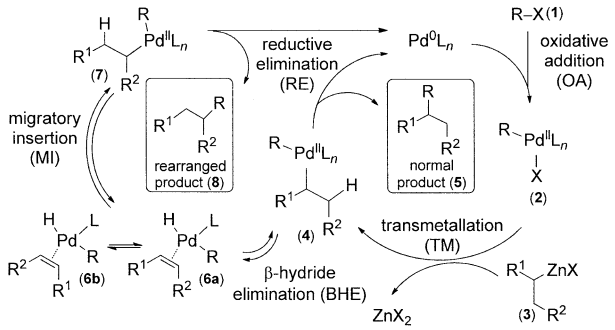
Molecules with architectural complexity, especially those possessing high alkyl content, have been avoided in the pharmaceutical sector owing to the challenges associated with their synthesis.[1] Consequently, medicinal chemistry efforts have focused primarily on developing drug candidates that are relatively flat (e.g., biaryls), and can be prepared readily using cross-coupling methodology.[1] However, such compounds are prone to promiscuous protein binding and side effects.[2] Consequently, there is new interest in the pursuit of molecules with increased alkyl composition resulting in more three-dimensional topology to improve target specificity.[2] The cross-coupling of alkyl nucleophiles can figure prominently in this approach and the mechanism is detailed in Scheme 1.[3,4]




***Scheme 1.*** Cross-coupling mechanism with alkylzinc nucleophiles.

Problematically, the Pd$^{II}$ center in transmetallation (TM) intermediate **4** can readily undergo β-hydride elimination (BHE) resulting in the formation of olefin by-products. Also, an electron-rich oxidative addition (OA) partner will slow reductive elimination (RE), leading to more BHE. Energetically, the metal-alkyl complex (**4** or **7**) is favored over the olefin-coordinated metal hydride (**6**; see below). With primary organometallic compounds (e.g., Scheme 1, $R^1 = H$) reinsertion into the olefin favors reformation of the primary metal-alkyl (i.e., **4**) for steric and electronic reasons. The same would be true if the starting organometallic compound were secondary (e.g., $R^1 = CH_3$, $R^2 = H$), however this migratory insertion (MI) leads to the undesired isomer (**8**) rather than the expected one (**5**) after RE. To avoid formation of this undesired isomer, the barrier to RE, relative to BHE, must be lower (see below). We envisioned that this could be accomplished by designing a catalyst that increases the steric bulk around the Pd center while, at the same time, reduces the electron density on it.[4a] This increased ligand bulk would increase the strain in the TM intermediate (e.g., **4**) and favor RE, which would relieve the strain, and a more easily reduced metal would drive the same step electronically. To examine this, we have created a series of new Pd-PEPPSI precatalysts, including Pd-PEPPSI-IPr$^{Cl}$ (**12**), Pd-PEPPSI-IPr$^{Me}$ (**13**), Pd-PEPPSI-IPr$^{Quino}$ (**14**), and Pd-PEPPSI-IPent$^{Cl}$ (**16**), and evaluated them in alkyl cross-coupling (Table 1).

To establish a baseline of inherent selectivity by minimizing substrate interactions, *para*-substituted derivatives were first coupled (Table 1; entries 1–10). These results indeed demonstrate that ligand sterics are important as the catalyst featuring IPent[5] (**15**) showed much higher selectivity than that with IPr[6] (**11**). There is a general trend that electron-withdrawing groups (EWGs) on the OA partner improve selectivity for the branched (normal) product (e.g., entry 1 vs. 6, and 2 vs. 7). When the substituent on **9** was positioned closer to Br, and thus Pd in intermediate **4**, immediate effects on selectivity were observed. When Pd-PEPPSI-IPr (**11**) was used, a *meta* group tipped the balance towards BHE, as the linear product (**8**) was favored (e.g., entry 11). When there was a substituent at the *ortho* position, the rearranged product (**8**) now dominated with Pd-PEPPSI-IPr (**11**; entry 21), thus indicating that the rate of RE, relative to BHE, has been profoundly impacted. However, the reaction catalyzed by Pd-PEPPSI-IPent (**15**) shows that ligand bulk helps to counteract the negative effects of substrate hindrance as the branched product remained dominant (e.g., entries 15 and 25), so selectivity is primarily under catalyst control with **15**.

When substituents were placed on the backbone of the IPr NHC the preference for BHE versus RE, seen with **11** was completely reversed (see catalysts **12**, **13**, and **14**) for *meta*-substituted coupling partners. For example, for catalysts **12**, **13**, and **14** (entries 12–14), the selectivity for the branched product **5** was a sharp improvement on that seen for catalyst **11** (entry 11). An even more dramatic change was observed in the selectivity obtained with *ortho*-substituted aryl halides, e.g., entry 21 versus entries 22–24. When catalyst **16** having a ligand with the bulkier *N*-phenyl NHC substituent and

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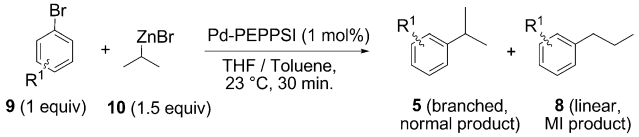
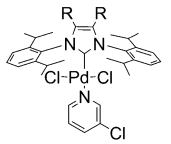
***Table 1:*** Control study coupling aryl bromides (**9**) to isopropylzinc bromide (**10**) using Pd-PEPPSI precatalysts **11**–**16**.[a,b]



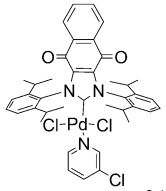

**9** (1 equiv) **10** (1.5 equiv) **5** (branched, normal product) **8** (linear, MI product)

| Entry | Ar–Br | Cat. | **5**/**8** | Prod. | Yield [%] | $\Delta\Delta E^{\ddagger}$[c] |
|---|---|---|---|---|---|---|
| 1 | 4-$CO_2CH_3$ | **11** | 5.0:1 | **a** | 99 | 1.3 |
| 2 | 4-$CO_2CH_3$ | **15** | 40:1 | **a** | 98[d] | |
| 3 | 4-$CO_2CH_3$ | **16** | 56:1 | **a** | 94 | |
| 4 | 4-CHO | **15** | 39:1 | **b** | 78[d] | |
| 5 | 4-CHO | **16** | 59:1 | **b** | 92 | |
| 6 | 4-$OCH_3$ | **11** | 2.5:1 | **c** | 89[d] | 1.2 |
| 7 | 4-$OCH_3$ | **15** | 33:1 | **c** | 95[d] | |
| 8 | 4-$OCH_3$ | **16** | 46:1 | **c** | 79 | |
| 9 | 4-CN | **15** | 27:1 | **d** | 92[d] | |
| 10 | 4-CN | **16** | 59:1 | **d** | 92 | |
| 11 | 3-CN | **11** | 1:1.4 | **e** | 82[d] | −0.9 |
| 12 | 3-CN | **12** | 15:1 | **e** | 81 | 2.0 |
| 13 | 3-CN | **13** | 15:1 | **e** | 79 | 2.5 |
| 14 | 3-CN | **14** | 13:1 | **e** | 78 | 1.6 |
| 15 | 3-CN | **15** | 11:1 | **e** | 66[d] | |
| 16 | 3-CN | **16** | 61:1 | **e** | 81 | |
| 17 | 3-CHO | **15** | 22:1 | **f** | 71[d] | |
| 18 | 3-CHO | **16** | 48:1 | **f** | 84 | |
| 19 | 3-$OCH_3$ | **15** | 34:1 | **g** | 57[d] | |
| 20 | 3-$OCH_3$ | **16** | 39:1 | **g** | 66 | |
| 21 | 2-CN | **11** | 1:6.6 | **h** | 38 | −1.8 |
| 22 | 2-CN | **12** | 4.3:1 | **h** | 72 | 1.0 |
| 23 | 2-CN | **13** | 5.2:1 | **h** | 66 | 1.6 |
| 24 | 2-CN | **14** | 8.5:1 | **h** | 70 | 1.1 |
| 25 | 2-CN | **15** | 2.4:1 | **h** | 80[d] | |
| 26 | 2-CN | **16** | 28:1 | **h** | 76 | |
| 27 | 2-$OCH_3$ | **15** | 1.9:1 | **i** | 46[d] | |
| 28 | 2-$OCH_3$ | **16** | 23:1 | **i** | 54 | |

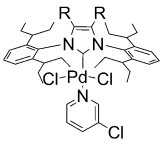
[a] Ratio determined by $^1$H NMR spectroscopy after purification. [b] Yields of the isolated mixtures of *i*Pr and *n*Pr products, averaged over two runs. [c] $\Delta\Delta E^{\ddagger}$ is the DFT selectivity (see text). [d] These entries have been reported previously, see Ref. [4g].




**11**, R = H, (Pd-PEPPSI-IPr)
**12**, R = Cl, (Pd-PEPPSI-IPr$^{Cl}$)
**13**, R = Me, (Pd-PEPPSI-IPr$^{Me}$)




**14**, (Pd-PEPPSI-IPr$^{Quino}$)




**15**, R = H, (Pd-PEPPSI-IPent)
**16**, R = Cl, (Pd-PEPPSI-IPent$^{Cl}$)

chlorines on the NHC backbone (IPent$^{Cl}$) was used, selectivity for the non-rearranged 'normal' product was now near optimal for the *meta*-substituted aryl halides (entry 16) and still excellent (approximately 28:1) for the *ortho* case (entry 26). When we examined the scope of this transformation using Pd-PEPPSI-IPent$^{Cl}$ (**16**) to prepare compounds of biological and medicinal interest, it became clear that this catalyst shows very high reactivity, broad functional group tolerance, and most importantly, virtually exclusive selectivity for the desired, non-rearranged product (Scheme 2).

In an effort to understand the selectivity demonstrated in this study, density functional theory (DFT) calculations were performed.[7] Figure 1 depicts the potential energy surface (PES) for the selectivity associated with formation of the normal (**5**) and rearranged products (**8**) for catalysts **11** and

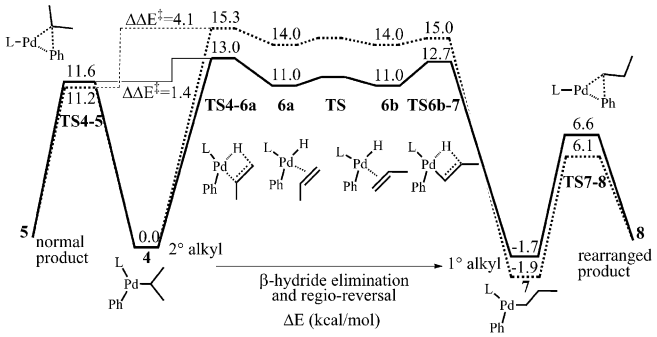


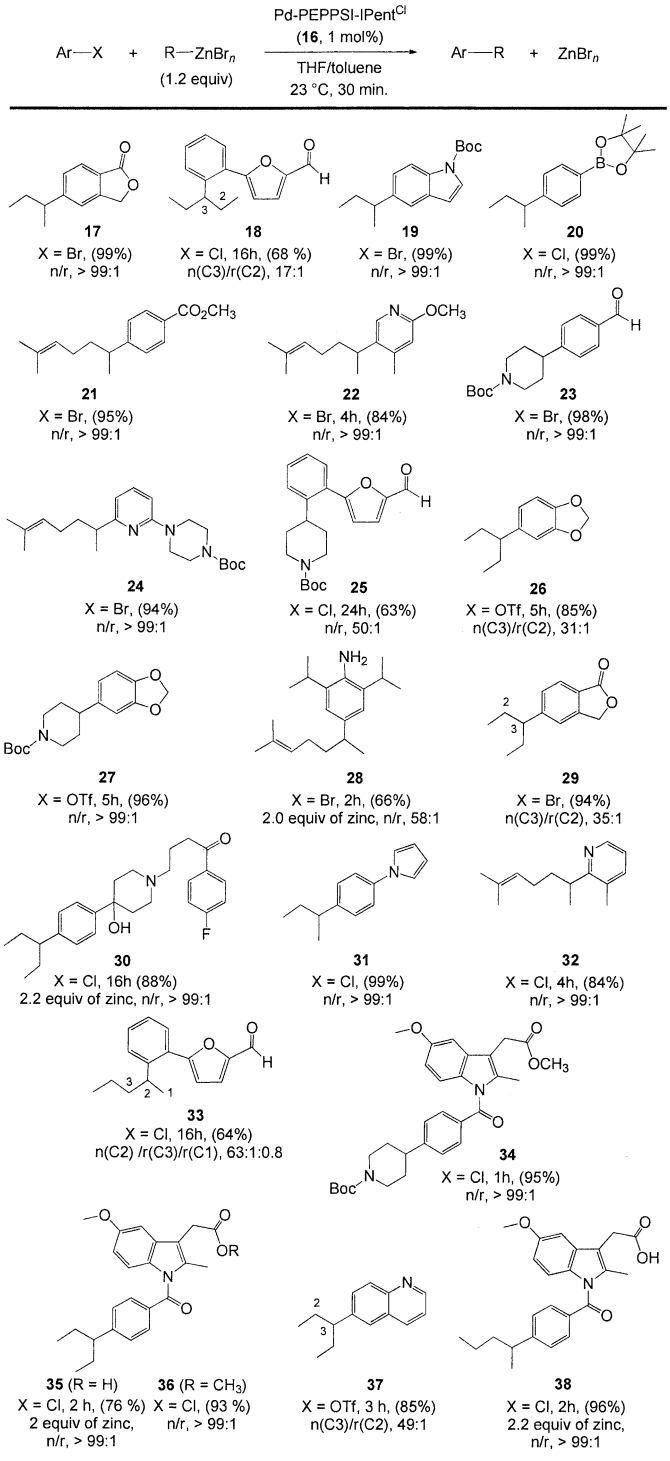

***Figure 1.*** The DFT potential energy surface for RE versus BHE for the coupling of Ph–X and isopropylzinc halide with precatalysts **11** (——) and **12** (•••••). L = NHC ligand.

**12**.[8] Figure 1 illustrates that from the intermediate species (**4**), which was formed from an isopropyl zinc reagent, RE can lead directly to the normal product (**5**). This pathway competes with BHE to form an olefin-hydrido complex (**6a**), which through reinsertion of the olefin into the hydride with opposite regiochemistry (MI) leads to linear alkyl **7** that can reductively eliminate to form isomer **8**.

On looking at the shape of the PES, it can be seen that the selectivity between normal (**5**) and rearranged (**8**) products is decided at transition states (TSs) **TS4**→**5** and **TS4**→**6a**, directly leading from the intermediate **4**. If BHE and reinsertion occurs to form the linear intermediate (**7**), RE of the linear chain (**TS7**→**8**) has a lower barrier and is significantly faster than BHE. This feature on the PES differs from the cationic $Pd^{II}$ olefin polymerization process, wherein BHE from primary or secondary alkyls is much faster than olefin insertion into the Pd–alkyl bond.[9] This polymerization surface leads to a Curtin–Hammett regime where the analogous Pd-alkyl complexes **4** and **7** are in equilibrium and the selectivity is defined by the relative height of the two TSs for insertion into the respective metal alkyls.[9] In the case of the coupling reactions in this work, **TS4**→**6a** was always found to be slightly higher than **TS6b**→**7** whereas the RE of the primary alkyl group (**TS7**→**8**) always has a substantially lower energy TS. Thus, the relative heights of **TS4**→**5** (associated rate constant $k_5$ leading to product **5**) and **TS4**→**6a** ($k_8$ leading to product **8**) define the selectivity for this transformation.

Based on an Eyring expression,[10] the relative rate constants (i.e., selectivity) for the formation of **5** versus **8** can be expressed as: $\ln\{k_5/k_8\} = \Delta\Delta E^{\ddagger}/RT$, where $\Delta\Delta E^{\ddagger} = \Delta E^{\ddagger}{}_8 - \Delta E^{\ddagger}{}_5$.[11] In the example shown in Figure 1 for Pd-PEPPSI-IPr (**11**), the normal product is favored over the rearranged product by 1.4 kcal mol$^{-1}$ (a positive $\Delta\Delta E^{\ddagger}$ implies a selectivity for the normal product). Upon introduction of the chlorides onto the NHC backbone, as in Pd-PEPPSI-IPr$^{Cl}$ (**12**), this energy difference increases significantly to 4.1 kcal mol$^{-1}$. To get a direct comparison to




***Scheme 2.*** Scope study for C($sp^2$)–C($sp^3$) couplings using Pd-PEPPSI-IPent$^{Cl}$. The ratio was determined by $^1$H NMR spectroscopy after purification; isomers were inseparable. The yields of the isolated products include that of the rearranged isomer, where relevant, averaged over two runs. A ratio of >99:1 means that minor isomers are not observed at all. n = normal product, r = rearranged product.

experiment, the selectivities for Pd-PEPPSI-IPr (**11**), Pd-PEPPSI-IPr$^{Cl}$ (**12**), Pd-PEPPSI-IPr$^{Me}$ (**13**), and Pd-PEPPSI-IPr$^{Quino}$ (**14**) were computed for a variety of aryl groups coupling to *i*PrZnX (Table 1, entries 1, 6, 11–14, 21–24); agreement between theory and experiment is excellent (Figure 2a). In the examples shown in Table 1, entries 11 and 21, the rearranged product was favored and in these cases, the BHE TS is lower in energy than the RE TS, and the greatest experimental selectivities toward the normal product (entries 12 and 13) corresponded to the largest computed $\Delta\Delta E^{\ddagger}$ (2.0–2.5 kcal mol$^{-1}$).

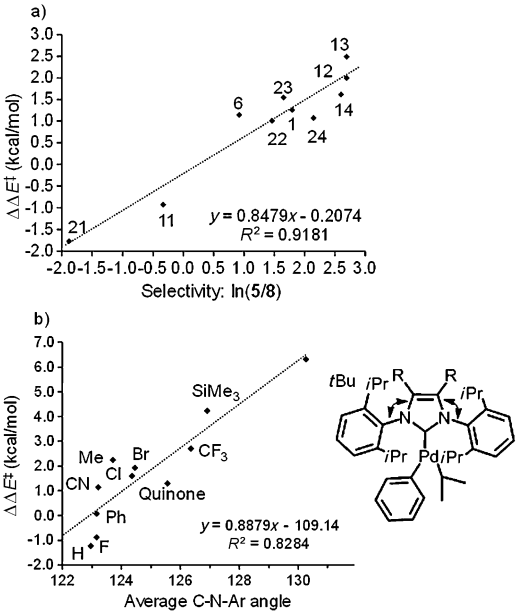



***Figure 2.*** a) A comparison of the computed difference in energy ($\Delta\Delta E^{\ddagger}$) between RE and BHE (ordinate) versus the log of the experimental selectivity (abscissa) for catalysts **13**–**16**, shown in Table 1. Each number on the graph corresponds to a table entry. b) A comparison of the computed $\Delta\Delta E^{\ddagger}$ value between RE and BHE (ordinate) versus the average of the two computed C-N-aryl bond angles (see arrows on structure) of the NHC (abscissa) for a set of related IPr-based NHC catalysts for the reaction shown in Table 1 with bromobenzene. Each group on the graph corresponds to the R groups on the NHC backbone.

As the calculations accurately predicted the selectivity with different catalysts and aryl groups, we examined other catalysts, including virtual ones, based on the IPr NHC core[8] (Figure 2b). From an electronic perspective the data are interesting in that we expected the ligand with hydrogen substituents on the NHC backbone (i.e., in catalyst **11**) to provide intermediate results, yet it is at the extreme. Comparatively higher $\Delta\Delta E^{\ddagger}$ values of 2.2 and 2.7 kcal mol$^{-1}$ were obtained for the ligands with electron-donating $CH_3$ and electron-withdrawing $CF_3$ groups, respectively. The most compelling trend is that as the groups on the NHC backbone become bulkier, the $\Delta\Delta E^{\ddagger}$ value gets larger with very high selectivity predicted for ligands with *t*Bu and TMS sustituents (Figure 2b). It would seem there is a strong steric component in that a larger group on the backbone prevents isomerization. This fact can be rationalized if one considers that the selectivity is a function of the difference between the barriers for RE, having a three-center TS (e.g., **TS4**→**5**), and BHE, having a four-center TS (e.g., **TS4**→**6a**). Thus, if larger groups

are on the NHC backbone, they act to push the aryl groups towards the active site, thus destabilizing the four-center TS of BHE to a greater extent than the three-center TS of RE, and therefore increasing selectivity towards the non-rearranged product.

A series of Pd-PEPPSI complexes have been created with various substitution patterns on the NHC backbone that have demonstrated extraordinary selectivity in the Negishi cross-coupling of secondary zinc nucleophiles. Whether the substituents render the metal center more electron rich (e.g., **13**) or poor (e.g., **12**, **14**), selectivity for the normal, non-rearranged product is favored. Computational studies reveal that the relative barrier difference between RE and BHE correlate very well with observed selectivities. Further, it would appear that the effect imparted by the NHC substituents is primarily steric in origin.[12] This analysis has led to the creation of Pd-PEPPSI-IPent$^{Cl}$ (**16**) that has shown unprecedented selectivity, leading to virtually one single (desired) isomer for reactions of a wide selection of alkylzincs and highly functionalized (hetero)aromatic halides.

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[12] Tolman electronic parameter (TEP) analysis failed to yield consistent trends between selectivity and electronic ligand effects. For complete TEP analysis, see the Supporting Information.

  