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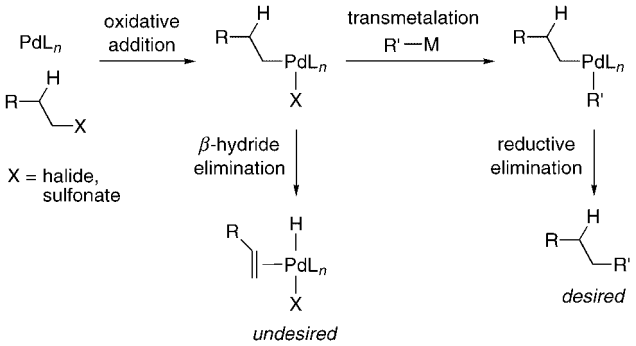
A Method for Palladium-Catalyzed Cross-Couplings of Simple Alkyl Chlorides: Suzuki Reactions Catalyzed by $[Pd_2(dba)_3]/PCy_3$**

Jan H. Kirchhoff, Chaoyang Dai, and Gregory C. Fu*

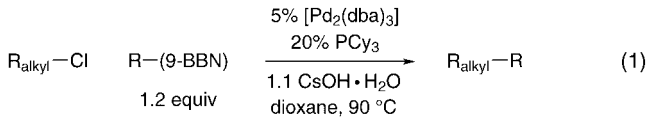
Palladium-catalyzed cross-couplings of organic electrophiles with main-group organometallic compounds serve as straightforward, powerful methods for carbon – carbon bond formation, and such processes are routinely used in fields ranging from materials science to natural product synthesis.[1] The overwhelming majority of studies of metal-catalyzed cross-couplings have employed a halide or sulfonate as the electrophile and a organometallic reagent as the nucleophile in which the carbon atoms to be coupled are all sp^2-hybridized (e.g., for the synthesis of biaryls). In contrast, reports of successful couplings of simple halides/sulfonates bound to sp^3-hybridized carbon atoms are very rare.[2] Two of the likely reasons that have hampered the utilization of these important families of electrophiles are: 1) slow oxidative addition of the alkyl halide/sulfonate to palladium, and 2) if oxidative addition has indeed taken place, β-hydride elimination of the resulting alkyl – palladium complex, in preference to cross-coupling (Scheme 1).



Scheme 1. Palladium-catalyzed cross-coupling of an alkyl halide/sulfonate.

It is critical to point out that three studies in particular have, however, described noteworthy progress in overcoming this considerable limitation in the scope of metal-catalyzed cross-coupling reactions. In a pioneering investigation in 1992, Suzuki et al. discovered that $[Pd(PPh_3)_4]$ can catalyze couplings of alkyl iodides with alkyl boranes at 60 °C in yields as high as 71 %.[3, 4] Furthermore, we established last year that $Pd(OAc)_2/PCy_3$ effects Suzuki reactions of alkyl bromides at room temperature.[5] Finally, in a series of reports beginning in 1995, Knochel et al. have demonstrated that a nickel-based catalyst can promote cross-couplings of alkyl bromides and iodides with organozinc reagents.[6] Although each of these studies represents an important development, even collectively they provide a solution to only a small subset of the coupling processes of interest.

Thus, there is still a very substantial need for the development of catalysts to cross-couple alkyl halides. Since there has been essentially no success to date in any palladium- or nickel-catalyzed coupling of simple alkyl chlorides, in contrast to iodides or bromides, they represent a particularly significant challenge.[2, 7] In view of our recent progress in developing mild conditions for Suzuki reactions of alkyl bromides,[5] we decided to determine if we might also be able to contribute to solving the problem of coupling alkyl chlorides. In this communication, we describe the advances that we have made toward this objective [Eq. (1); 9-BBN = 9-borabicyclo[3.3.1]-nonane].



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[**] dba = (*E*,*E*)-dibenzylideneacetone, Cy = cyclohexyl. We thank Dr. Matthew R. Netherton for helpful discussions and Johnson Matthey Inc. for supplying palladium compounds. Support has been provided by the Deutsche Akademie der Naturforscher Leopoldina (Leopoldina fellowship to J.H.K., BMBF-LPD 9901/8-48), Bristol-Myers Squibb, the National Institutes of Health (National Institute of General Medical Sciences, R01-GM62871), the Natural Sciences and Engineering Research Council of Canada (postdoctoral fellowship to C.D.), and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been provided in part by NSF CHE-9808061 and NSF DBI-9729592.

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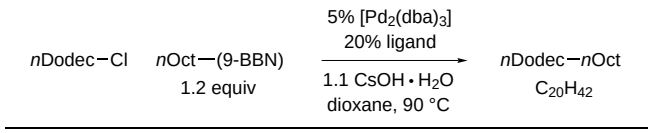
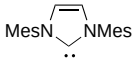
Lower reactivity for alkyl chlorides, as compared to bromides or iodides, is of course a recurring observation in organic chemistry that probably originates from the decreased leaving-group ability of the chloride ion[8] and/or the higher strength of the C–Cl bond (C–Cl: ≈79; C–Br: ≈66; C–I: ≈52 kcal mol^{-1}).[9] Not surprisingly, when we subjected an alkyl chloride (1-chlorododecane) to the conditions that have proved useful for the corresponding cross-coupling of an alkyl bromide with an alkyl borane (4% $Pd(OAc)_2$, 8% PCy_3, 1.2 $K_3PO_4 \cdot H_2O$, THF, room temperature), we obtained only very small amounts (<5% yield) of the desired product. However, through optimization and by increasing the reaction temperature, we have been able to perform the targeted coupling in good yield (Table 1, entry 1).

Table 1. Relative efficiency of various ligands in the palladium-catalyzed Suzuki cross-coupling of an alkyl chloride.



Entry	Ligand[a]	Yield of $C_{20}H_{42}$ [%][b]
1	PCy_3	77
2	P(cyclopentyl)$_3$	57
3	P*i*Pr$_3$	53
4	P*t*Bu$_3$	<2
5	P*n*Bu$_3$	5
6[c]	dcpe	<2
7	PPh_3	<2
8	P(*o*-tol)$_3$	<2
9	P(2-furyl)$_3$	4
10[c]	dppf	<2
11[c]	binap	<2
12	$AsPh_3$	<2
13	$P(OPh)_3$	<2
14		8

[a] dcpe = 1,2-bis(dicyclohexylphosphanyl)ethane, tol = tolyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Mes = mesityl. [b] Determined by GC versus a calibrated internal standard. [c] For bidentate ligands, 10% of the ligand was used.

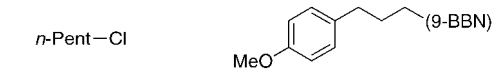
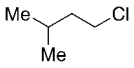
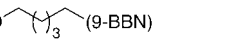
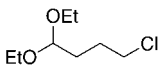
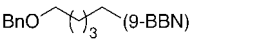
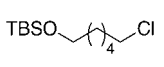
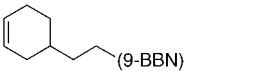
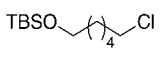
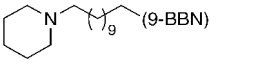
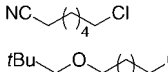
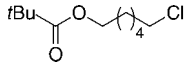
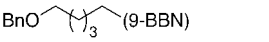
As we had determined for alkyl bromides, the efficiency of the Suzuki cross-coupling of alkyl chlorides is strongly dependent on the structure of the phosphane.[10] P(cyclopentyl)$_3$ and P*i*Pr$_3$, which are sterically and electronically similar to PCy_3, are, however, significantly less effective (Table 1, entries 2 and 3, respectively). For trialkyl phosphanes that are appreciably larger (P*t*Bu$_3$) or smaller (P*n*Bu$_3$) than PCy_3, essentially no coupling is observed (<5%; entries 4 and 5), which illustrates that the window of reactivity is relatively narrow. Furthermore, dcpe, a bidentate analogue of PCy_3, does not furnish the desired product (entry 6).

A wide array of triarylphosphanes, both monodentate (entries 7–9) and bidentate (entries 10 and 11), are also ineffective under these conditions. Finally, arsanes, phosphites, and N-heterocyclic carbenes provide virtually no activity (entries 12–14).

The conditions described in Equation (1) are the best that we have developed to date for Suzuki cross-couplings of alkyl chlorides. Thus, we have determined that a 2:1 phosphane:palladium ratio is optimal[11] and that $[Pd_2(dba)_3]$, $CsOH \cdot H_2O$, and dioxane are the palladium source, the activator, and the solvent of choice, respectively. $Pd(OAc)_2$, $K_3PO_4 \cdot H_2O$, and THF, which we employed in Suzuki reactions of alkyl bromides, furnish markedly lower activity.[12]

By using our optimized reaction conditions, we can perform Suzuki cross-couplings of an array of alkyl chlorides that possess β hydrogen atoms (Table 2). Thus, $[Pd_2(dba)_3]/PCy_3$ couples unfunctionalized substrates in good yield (83%; entry 1). Furthermore, the process is compatible with a variety of functional groups, including aryl, benzyl, and silyl

Table 2. Suzuki cross-couplings of alkyl chlorides [Eq. (1)].

Entry	R_{alkyl}–Cl	R–(9-BBN)[a]	Yield [%][b]
1	*n*-Dodec–Cl	*n*-Oct–(9-BBN)	83
2	*n*-Pent–Cl		82
3			74
4			70
5			72
6[c]			73
7		*n*-Oct–(9-BBN)	73
8[d]			65

[a] Prepared by hydroboration with 9-BBN of the corresponding alkene and used without purification. [b] Yield of isolated product, average of two runs. [c] 1.05 equiv of R–(9-BBN) was used. [d] KOH was used instead of $CsOH \cdot H_2O$.

ethers (entries 2–6), acetals (entry 4), olefins (entry 5), amines (entry 6), nitriles (entry 7), and esters (entry 8).[13] In the case of esters, we employ KOH, rather than $CsOH \cdot H_2O$,[14] to decrease the extent of hydrolysis.[15]

This report has introduced an important new class of substrates into the family of compounds that can be considered as potential partners in metal-catalyzed cross-coupling reactions. Until now, the limited progress that had been achieved in coupling alkyl halides had been restricted to iodides and bromides. In this study, we have described the first catalyst that is effective for reactions of alkyl chlorides; specifically, we have established that $[Pd_2(dba)_3]/PCy_3$ catalyzes the Suzuki cross-coupling of a range of chlorides that contain β hydrogen atoms with an array of alkyl-9-BBN derivatives. The conditions are compatible with a variety of functional groups, including potential ligands such as nitriles and amines. Current investigations are focused on discovering even more active catalysts, expanding the scope of suitable substrates, and developing additional coupling processes.

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Experimental Section

A vial equipped with a septum screw-cap and a stir bar was purged with argon. The olefin (1.20 mmol, 1.20 equiv) and then a solution of 9-BBN (0.50 M in THF; 2.40 mL, 1.20 mmol, 1.20 equiv) were introduced to the vial, and the resulting homogeneous solution was stirred for at least 6 hours at room temperature. After that time, the THF was removed under vacuum and replaced with dioxane (0.9 mL).[16] In air, a stir bar, $[Pd_2(dba)_3]$ (45.8 mg, 0.05 mmol, 5%), PCy_3 (56.0 mg, 0.20 mmol, 20%), and $CsOH \cdot H_2O$ (185 mg, 1.10 mmol, 1.10 equiv) were placed into a second vial, which was then capped with a septum screw-cap and purged with argon for 10 minutes. Dioxane (0.3 mL) was added by syringe, and then the solution of the alkyl-9-BBN was added through a cannula (the alkyl-9-BBN was transfered completely by rinsing the first vial with dioxane (2×0.3 mL)). The alkyl chloride (1.00 mmol, 1.00 equiv) was introduced to this homogeneous brown solution, and the resulting mixture was stirred vigorously under argon for 48 hours at 90 °C. At the conclusion of the coupling, the reaction mixture, which was now heterogeneous, was cooled to room temperature, diluted with Et_2O (5 mL), and filtered through a short plug of silica gel with Et_2O washings (30 mL). The solvent was evaporated, and the resulting yellow residue was purified by flash chromatography.

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[9] J. March, *Advanced Organic Chemistry*, Wiley, New York, **1992**, p. 24.

[10] If no phosphane is present, no coupling product is detected (< 2%).

[11] With a 1:1 phosphane:palladium ratio, the yield according to GC is ca. 70%; with a 1:2 phosphane:palladium ratio, ca. 60%.

[12] Each change in parameter leads to a change in yield of ≈15 – 25%.

[13] Lower yields are observed for reactions of more hindered substrates. To date, we have not been able to perform couplings of secondary alkyl chlorides or secondary alkyl boranes.

[14] When 1.0 equiv of $CsOH \cdot H_2O$ or KOH is added to *n*-octyl-9-BBN ($\delta(^{11}B) = 89$ ppm) in dioxane at 90 °C, ^{11}B NMR analysis indicates that a soluble [*n*-octyl-9-BBN(OH)]$^-$ "ate" complex is quickly formed ($\delta = -1$ for $CsOH \cdot H_2O$; $\delta = 18$ ppm for KOH (equilibrium between three- and four-coordinate boron; the four-coordinate adduct resonates at $\delta = -2$ ppm)). Presumably, this is the species that transfers the *n*-octyl group to palladium (Scheme 1). For ^{11}B NMR investigations of related systems, see: K. Matos, J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461 – 470. See also: R. Köster, G. Seidel, B. Wrackmeyer, *Chem. Ber.* **1992**, *125*, 617 – 625.

[15] Use of a less hindered (methyl) ester leads to a lower yield (≈55%).

[16] If desired, the synthesis of the alkyl-9-BBN can be conducted directly in dioxane by hydroborating the olefin with solid 9-BBN dimer, rather than a solution of 9-BBN in THF (both are commercially available).

Hydrogen Bonding Modulates the Selectivity of Enzymatic Oxidation by P450: Chameleon Oxidant Behavior by Compound I**

Samuël P. de Visser, François Ogliaro, Pankaz K. Sharma, and Sason Shaik*

Two of the important reactions of the enzyme cytochrome P450 are C–H hydroxylation and C=C epoxidation.[1–5] Different P450 isozymes give different ratios of these products with substrates which can undergo both hydroxylation and epoxidation.[1] Furthermore, mutation of a single amino acid away from the reaction center changes the ratio of the two products.[6] What are the factors that determine the oxidation regioselectivity? There may exist many answers[1–5] to this question and it is desirable to begin unraveling them step by step. Here we use model calculations of C–H hydroxylation and C=C epoxidation pathways, which show that the primary active species of the enzyme, compound I (Cpd I), behaves like a chameleon oxidant that changes its reactivity and selectivity patterns under the influence of hydrogen bonding and polarization effects, which mimic the protein environment.

To explore this issue, we used density functional calculations (see Methods Section) of a model Cpd I species that reacts with propene to give both allylic hydroxylation and C=C epoxidation. The reaction profiles were computed under different conditions, including effects of the environment such as polarization effect and NH ··· S hydrogen bonding of the type found in the crystal structures of P450 enzymes.[6, 7] Our model calculations, which focus on the electronic component of the environment, do not involve stereoelectronic effects

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