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Pd(0)-Catalyzed Diarylation of sp^3 C−H Bond in (2-Azaaryl)methanes

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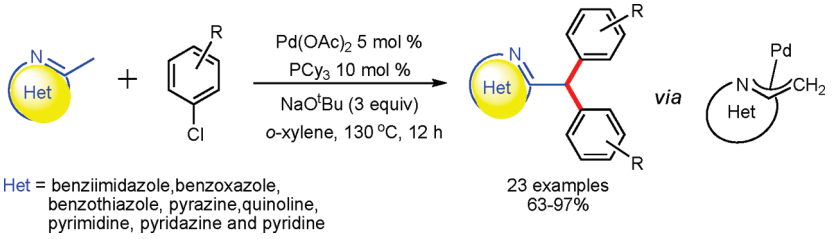
ABSTRACT



A highly efficient and selective palladium-catalyzed diarylation of (2-azaaryl)methanes at the methyl group is described. Aryl chlorides proved reactive enough. A palladium η^3-azaallyl intermediate has been identified on the basis of DFT studies.

Synthetic methods that utilize metal-catalyzed activation and subsequent functionalization of sp^2 and sp^3 C−H bonds have emerged as powerful tools to directly install important functional groups to construct complex structures.[1] In particular, palladium catalysts have been widely used to effectively achieve the functionalization of the C−H bonds of arenes and heteroarenes in both redox and redox-neutral settings.[2] These synthetic strategies have played increasingly important roles in natural product synthesis and drug discovery, and they have been extensively reviewed.[1b,c,2] In contrast, activation and functionalization of inert sp^3 C−H bonds still represent a huge challenge in organic synthesis.[3] Successful examples on functionalization of methyl groups are rather limited, and they took advantage of directing groups[4] and/or the relatively high acidity induced by highly withdrawing groups.[5] It is necessary to explore functionalization of methyl groups activated by other readily installed groups.

Acidity of methyl or other alkyl groups plays an important role in their arylation reactions. For example, palladium-catalyzed α-arylation of esters, ketones, and amides has become a powerful synthetic tool for the construction of $C(sp^3)-C(sp^2)$ bonds.[5a,b,6] Formation of enolates by deprotonation of α sp^3 C−H protons of carbonyl compounds should facilitate metalation. Much like in these carbonyl compounds, acidity of methyl protons in (2-azaaryl)methanes is enhanced by the azaaryl

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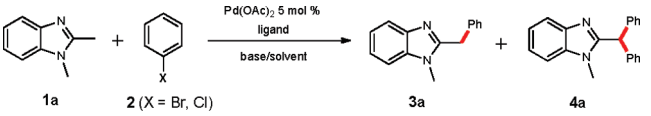
rings. Although the chemistry of azaallylic anions is well-known in organic synthesis,[7] well-established examples of metal-catalyzed α-arylation of (2-alkyl)azaarenes are rare.[8,9] We reason that both the acidity of these azaallylic protons and ligating ability of the nitrogen atom should facilitate a C−H cleavage process. We now report palladium-catalyzed efficient diarylation of (2-azaaryl)methanes, where a palladium η^3-azaallyl intermediate has been identified on the basis of DFT studies, and C−H activation likely proceeds via metalation-assisted intramolecular deprotonation.

Considering the significance of heteroaromatics in drug discovery and in material studies,[10] we have chosen benziimidazole **1a** as a substrate. We initiated our studies on the coupling between **1a** and PhBr using $Pd(OAc)_2$ (5 mol %) and a phosphine as a catalyst in the presence of a base (PhMe, 130 °C). When $P^tBu_3 \cdot HBF_4$ (10 mol %) was used together with KO^tBu, the coupling reaction occurred but was strongly influenced by the amount of PhBr and a base (entries 1−3). Both the monoarylation (minor) and the diarylation (major) products were detected even though an access of PhBr was used (entries 1 and 2). A good yield of the diarylation product **4a** could be isolated when 3 equiv of PhBr was used. Other milder bases (K_2CO_3 and Cs_2CO_3) turned out to be unfavorable for this reaction. The efficiency of this reaction was further improved when S-Phos was used. However, in most cases both coupled products were generated. We noted that essentially no coupling reaction between **1a** and PhBr or PhCl occurred when chelating phosphines (5 mol %) such as XantPhos and DPEphos were used (entries 10 and 11 and the Supporting Information). Gratifyingly, when PCy_3 was employed together with 3 equiv of PhBr, **4a** was obtained as the only product in 97% GC yield (entry 7). Importantly, under these optimized conditions, less reactive, readily available chlorobenzenes are efficient coupling partners, and **4a** was isolated as the only product in 95% yield (entries 8 and 9).

With the optimized conditions in hand, we further explored the scope of ArCl substrates in their coupling with 2-methylbenzimidazoles (Scheme 1). 2-Methylbenziimidazoles bearing *N*-alkyl and -aryl groups readily coupled with PhCl to give **4a**−**ad**. A broad scope of aryl halides bearing both electron-donating and -withdrawing groups has been established in their coupling with **1a**. These diarylation products were isolated in high yield and high selectivity. In addition, sterically hindered aryl bromides can also be applied. In particular, when mesityl bromide was used, monoarylation product **3m** was isolated in 81% yield.

Table 1. Optimization of Diarylation Conditions[a]



1a 2 (X = Br, Cl) 3a 4a

entry	**2** (equiv)	ligand	base	**3a**[d] (%)	**4a**[d] (%)
	PhBr				
1	3.0	$P^tBu_3 \cdot HBF_4$	KO^tBu[b]	15	49
2	1.0	$P^tBu_3 \cdot HBF_4$	KO^tBu	2.3	79
3	3.0	$P^tBu_3 \cdot HBF_4$	KO^tBu[c]	11	8
4	3.0	$P^tBu_3 \cdot HBF_4$	K_2CO_3	0	6
5	3.0	$P^tBu_3 \cdot HBF_4$	Cs_2CO_3	4	10
6	3.0	S-Phos	KO^tBu	1.5	91
7	3.0	PCy_3	KO^tBu	0	97
8	PhCl	PCy_3	KO^tBu	0	96 (94[e])
9[f]	3.0	PCy_3	NaO^tBu	0	99 (95[e])
10		Xantphos	KO^tBu	0	0
11		DPEphos	KO^tBu	0	0

[a] Reaction conditions: **1a** (1 mmol), $Pd(OAc)_2$ (5 mol %), 10 mol % of monodentate ligand or 5 mol % of bidentate ligand, base (3 equiv), PhMe (3 mL), 130 °C, 12 h, under N_2. [b] 1.5 equiv of base. [c] 1.0 equiv of base. [d] GC yield using 1,3,5-trimethoxybenzene as a standard. [e] Isolated yield. [f] *o*-Xylene (3 mL) was used.

Interestingly, although the diaylation product **4mb** was also isolated (12%), the second arylation occurred at the mesityl methyl group instead of at the 2-methylene position. The chemoselectivity of the second arylation is likely ascribed to the steric effect. Heteroaryl chlorides also proved applicable, and 3-chloropyridine coupled smoothly to give the diarylation product **4h**. In contrast, no coupling occurred for 2-chloropyridine, possibly because it oxidatively adds to Pd(0) to give an unreactive 2-pryidyl-bridged dinuclear palladium species.[11]

A broad scope of (2-azaaryl)methanes can be applied as given in Scheme 1. Condensed heteroaromatics such as 2-methylbenzoxazole, 2-methylthiazole, and 2-methylquinoline all underwent smooth coupling with PhCl, and the coupled products (**4n**, **4o**, and **4s**, respectively) were isolated in high yield. In addition, 4-methylpyrimidine, 3-methylpyridazine, and 2-methylpyrazine are also suitable substrates. It is noteworthy that in the case of 2-methylpyrazine a minor triarylation product **4rb** was also isolated (13%) in addition to the diarylation product (**4ra**, 81%). When 2-picoline was subjected to the standard conditions, a less clean reaction was obtained, and product **4t** was isolated in 63% yield. However, 4-picoline stood in sharp contrast, and essentially no coupled product (< 3%) was detected. Comparisons between reactivity of 2-picoline (63% yield) and 2-methylquinoline (95% yield) in phenylation reactions seem to suggest that a methyl group attached to a condensed azaarene undergoes coupling more readily. Indeed, more pronounced differences were revealed for the coupling of 1,2-dimethylimidazole with PhCl. Arylation occurred exclusively at the

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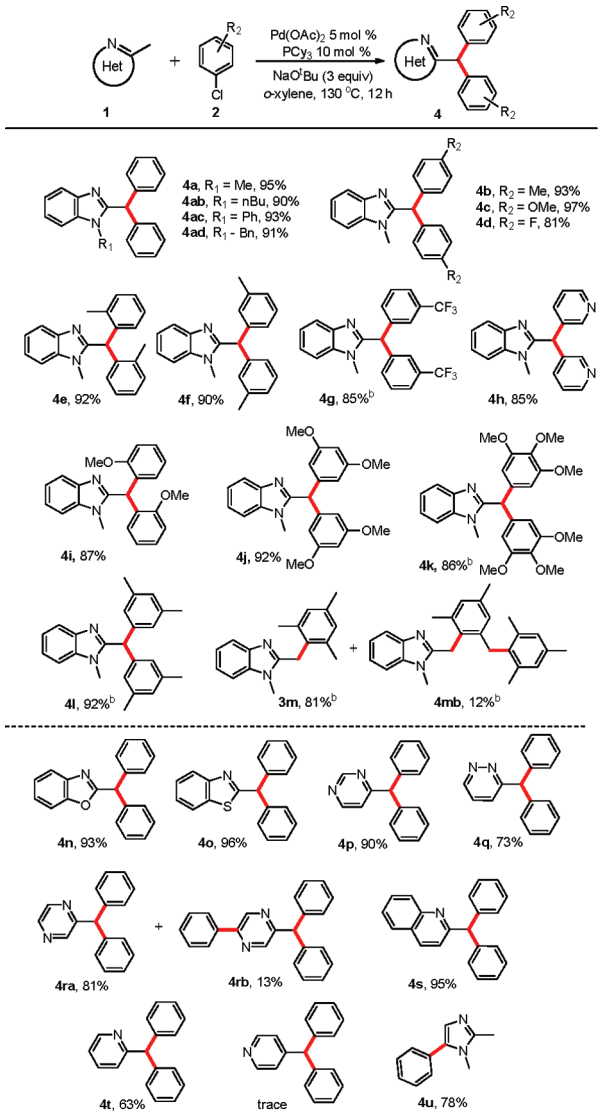
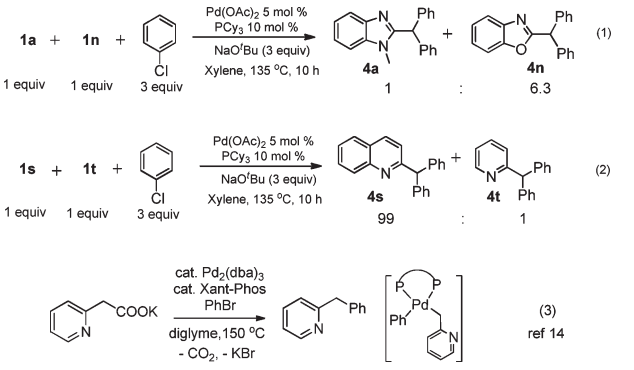
Scheme 1. Pd-Catalyzed Diarylation of (2-Azaaryl)methanes[a]



[a] Reaction conditions: **1** (1 mmol), **2** (3 mmol), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), NaO^tBu (3 equiv), and *o*-xylene (5 mL) under N_2, 130 °C, 12 h, isolated yield. [b] Aryl bromide (3 mmol) was used.

5-position, where activation of the sp^2 C−H bond took preference (**4u**). In addition, when the 4- and 5-positions of an imidazole are blocked as in 1,3-dimethyl-4,5-diphenylimidazole, no reaction occurred.

To gain insight into the mechanism of this coupling reaction, competition reactions have been carried out. The competition between 1,2-dimethylbenzimidazole and *N*-methylbenzoxazole in equimolar ratio revealed that the latter reacts preferentially with PhCl (eq 1). In another competition reaction, an equimolar amount of 2-picoline and 2-methylquinoline was allowed to react with PhCl (eq 2). As expected, 2-methylquinoline reacted in predominant preference, and products **4t** and **4s** were observed in a 1:99 ratio (GC). These results seem to suggest that four-membered palladacyclic intermediates are not likely involved because the nitrogen atom in 2-methylbenzimidazole and 2-picoline should offer stronger chelation assistance than that in the competitors. In addition, there is no direct correlation between the acidity and the reactivity of the heterocyclic substrate. For example, the more acidic 4-picoline (pK_a = 32.2[12]) gave essentially no desired product, while diarylation product **4t** was isolated in 63% yield for the less acidic 2-picoline (pK_a = 34[12]).[13] These results indicate that traditional acidity is not the only factor. We reason that the adjacent nitrogen atom in the heterocyclic substrate should play an important role possibly by formation of palladium η^3- or η^1-azaallyl intermediates. If η^1-azaallyl intermediates are involved, bidentate phosphines should be efficient ligands leading to Pd(P−P)Ar(η^1-azaallyl) intermediates, from which subsequent C−C reductive elimination can occur. Indeed, formation and reductive elimination of related Pd(Xantphos)(aryl)(2-picolyl) have been recently suggested in the decarboxylative C−C coupling between potassium 2-(2-pyridyl)acetate and PhBr (eq 3).[14] In our case, essentially no coupling was observed for chelating phosphines including Xant-Phos (Table 1), which suggests that η^3-azaallyl intermediates are more likely. The observed higher reactivity for a methyl group on a fused, condensed (2-azaaryl)methane is also consistent with this proposal since the formation of palladium η^3-azaallyl intermediate here resulted in only partial disruption of aromaticity in the azaarene.[15]



The KIE of this reaction was experimentally estimated by comparing the rates of the reactions of **1a** and **1a**-d_3 with mesityl bromide. A control experiment has shown that deuterium scrambling occurred among the methyl or methylene groups in **1a**, **1a**-d_3, and their coupled products when KO^tBu is present, indicating that KIE obtained from competition reactions is not applicable. Thus, the KIE was estimated to be 1.3 using **1a** and **1a**-d_3 in separate reactions

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(13) Competition reaction of 2-picoline and 4-picoline in equimolar ratio with PhCl (3 equiv) under the standard conditions revealed that only **4t** was obtained.

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with a large access of mesityl bromide. This small value suggests that the cleavage of the methyl C−H bond is not involved in the rate-determining step.

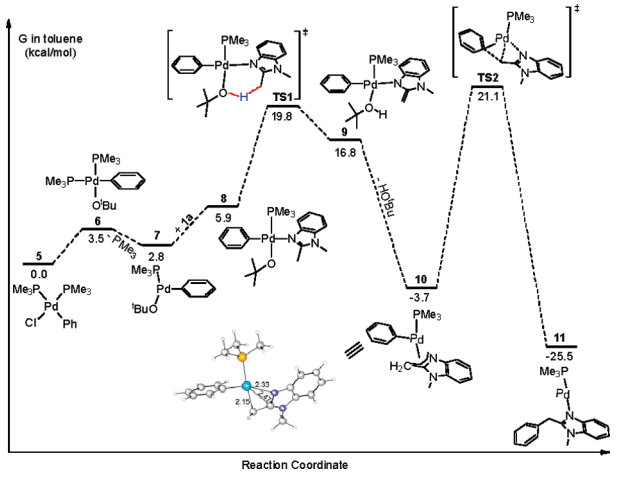

Figure 1. Proposed pathway of (2-azaaryl)methane arylation. PMe_3 was used to reduce the computational cost.

Theoretical studies at the DFT level were carried out to understand the mechanism of this coupling reaction (Figure 1). Starting from a model complex *cis*-Pd(Ph)Cl-$(PMe_3)_2$,[16] salt metathesis with KO^{t}Bu, affords the *tert*-butoxide complex in slight endogonicity. Subsequent substitution of the phosphine *trans* to phenyl group by an incoming **1a** should readily occur (ΔG = 2.4 kcal/mol). A transition state (**TS1**) was located for the C−H cleavage of intermediate **8** ($\Delta G^{\ddagger}$ = 13.9 kcal/mol). In this transition state, the O---H (1.182 Å) is nearly formed and the methyl C---H (1.464 Å) is substantially elongated. In addition, no Pd---C interaction was detected. This pathway of C−H activation is best described as metalation-assisted intramolecular deprotonation via a six-membered ring transition state. The resulting intermediate **9** can be described as an η^1-azaallyl (enaminate) complex. Subsequent slippage of the η^1 to the η^3-mode and extrusion of the *t*-BuOH to give **10** is highly energetically favorable. The trihapticity in **10** follows from the typical lengths of Pd−N (2.329 Å) and two Pd−C bonds (2.470 and 2.147 Å). An activation barrier of 24.8 kcal/mol was revealed for the C−C reduction elimination of this η^3-azaallylic species, and disruption of this trihapticity is necessary. Our estimated KIE value of 1.3 seems consistent with the DFT results, and the C−H cleavage is not involved in the date-determining step. An alternative C−H cleavage via σ-bond metathesis was also explored where no nitrogen precoordination is involved. This σ-bond metathesis process occurs with a significantly higher activation barrier ($\Delta G^{\ddagger}$ = 22.3 kcal/mol) and is therefore kinetically unfavorable (see the Supporting Information).[17]

In summary, we have developed palladium-catalyzed selective C−H cleavage and cross-coupling of (2-azaaryl)-methanes with aryl chlorides, and in most cases, diarylation products were observed. A broad scope of (2-azaaryl)-methanes has been defined. Theoretical studies indicated that the C−H activation may proceed via metalation-assisted intramolecular deprotonation to give a key palladium η^3-azaallylic intermediate, and this C−H cleavage process is not rate-determining. The wide scope, high selectivity, and the facile reaction conditions should make this synthetic method applicable to the synthesis of complex structures.

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Supporting Information Available. Experimental procedures, characterization of compounds, and optimized geometric data. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) The energy barrier for the oxidative addition of PhCl to Pd-$(PMe_3)_2$ was reported to be 29.3 kcal/mol. See: (a) Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2007**, *26*, 758. (b) Schoenebeck, F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2496.

(17) We cannot rule out the pathway of direct deprotonation followed by transmetalation to give *cis*-Pd$(PMe_3)_2$(Ph)(h^1-azaallyl) since the deprotonation of **1a** by KO^{t}Bu was estimated to be DG = 11.2 kcal/mol on the basis of DFT studies, so the corresponding DG‡ might be comparable to that in coordination-assisted intramolecular deprotonation. However, direct C−C reductive elimination of *cis*-Pd$(PMe_3)_2$(Ph)(h^1-azaallyl), if any, is unlikely because no coupling occurred when bidentate phosphines were used. Further studies are underway.