

Auxiliary-Assisted Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 Carbon–Hydrogen Bonds

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Abstract: We have developed a method for auxiliary-directed, palladium-catalyzed β -arylation and alkylation of sp^3 and sp^2 C–H bonds in carboxylic acid derivatives. The method employs a carboxylic acid 2-methylthioaniline- or 8-aminoquinoline amide substrate, aryl or alkyl iodide coupling partner, palladium acetate catalyst, and an inorganic base. By employing 2-methylthioaniline auxiliary, selective monoarylation of primary sp^3 C–H bonds can be achieved. If arylation of secondary sp^3 C–H bonds is desired, 8-aminoquinoline auxiliary may be used. For alkylation of sp^3 and sp^2 C–H bonds, 8-aminoquinoline auxiliary affords the best results. Some functional group tolerance is observed and amino- and hydroxy-acid derivatives can be functionalized. Preliminary mechanistic studies have been performed. A palladacycle intermediate has been isolated, characterized by X-ray crystallography, and its reactions have been studied.

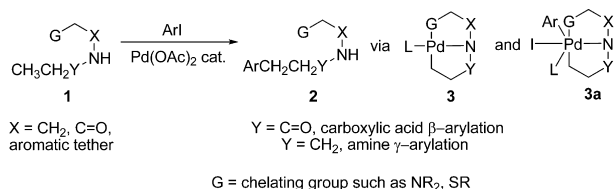
1. Introduction

In the past decade, transition-metal-catalyzed functionalization of carbon–hydrogen bonds has emerged as an efficient method for carbon–carbon and carbon–heteroatom bond formation.¹ Most of the developed methodology centers on the functionalization of sp^2 C–H bonds. Electron-rich heterocycles can be predictably and regioselectively arylated under palladium, rhodium, iridium, copper, and nickel catalysis.² Functionalization of directing-group-containing arenes has been extensively investigated. Palladium- and ruthenium-catalyzed arylation of imines, anilides, 2-arylpyridine derivatives, benzamides, benzoic acids, and nitroarenes has been demonstrated allowing short syntheses of the corresponding biaryls.³ These arylations are highly ortho-selective; however, in some cases, meta selectivity has been achieved.⁴

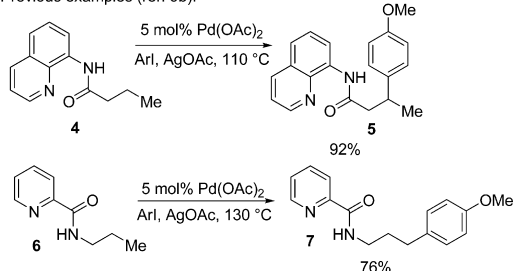
For both kinetic and thermodynamic reasons, metal-catalyzed functionalization of unactivated sp^3 C–H bonds is more difficult than that of sp^2 hybridized carbon–hydrogen bonds. The

activation of sp^2 C–H bonds is favored by precoordination of the arene π system to the transition metal as well as the subsequent formation of aryl-metal bond that is typically stronger than the corresponding alkyl-metal bond.⁵ In contrast, benzylic or α to heteroatom sp^3 carbon–hydrogen bonds undergo functionalization relatively easily, presumably due to weakness of those C–H bonds and proximity of aromatic system or electron lone pair. Consequently, transition-metal-catalyzed functionalization of activated sp^3 C–H bonds is quite common and many examples have been recently described in literature.⁶ On the other hand, catalytic functionalization of nonactivated, alkane sp^3 C–H bonds is rare. Most of the examples published so far report functionalization of sp^3 C–H bonds adjacent to quarternary centers which is the easiest case due to entropic considerations and impossibility of β -hydride elimination from the metalated intermediates.⁷ Notable exceptions include Ohno's synthesis of indoline derivatives from *N*-protected 2-bromo-

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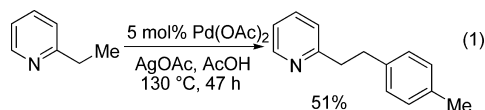
Scheme 1. Auxiliaries for sp^3 C–H Bond Arylation

Previous examples (ref. 9b):



nilines, Yu's 2-substituted pyridine alkylation, and β -arylation of carboxylic acid pentafluoroanilides.⁸

We reported in 2005 that 2-substituted pyridines are arylated by employing a combination of palladium acetate catalyst, stoichiometric silver acetate, and aryl iodide coupling partner.^{9a} While most examples involve arylation of sp^2 C–H bonds, *p*-tolylation of 2-ethylpyridine was also demonstrated in moderate yield (eq 1). Unfortunately, 2-ethylpyridine was the only substrate that underwent clean arylation of unactivated sp^3 C–H bonds. Other substrates afforded either a mixture of mono- and poly-arylation products or stilbene derivatives that can arise from β -hydride elimination from palladated intermediates.



We reasoned that the generality of the method could be improved by using pyridine or other chelating group as a removable auxiliary (Scheme 1). The reaction mechanism most likely involves cyclopalladation to afford **3** and step where Pd(II) is converted to a high-energy Pd(IV) species **3a** (Scheme 1). An additional chelating group should stabilize Pd(IV) species and facilitate the cyclometalation step. Additionally, β -hydride elimination should be retarded by saturating the coordination sites on palladium.

Depending on the attachment of the auxiliary, either β -arylation of carboxylic acids or γ -arylation of amines could be achieved. After the arylation, auxiliary could be removed by hydrolysis. We successfully demonstrated the concept and a preliminary account has been published.^{9b} Corey has used this methodology to arylate protected α -amino acid derivatives.^{10a} Chen has employed the arylation in context of celogentin total synthesis, demonstrating that C–H activation methodology is compatible with complex molecular environment.^{10b} Pyridine and quinoline auxiliary directed acetoxylation of sp^2 C–H bonds has been recently reported.¹¹

We report here a method for auxiliary-directed, palladium-catalyzed arylation and alkylation of unactivated sp^3 C–H bonds. Alkylation of sp^2 C–H bonds is also demonstrated. Arylation of sp^2 C–H bonds was not investigated since benzylamines and simple *N*-isopropyl benzamides can be arylated without the requirement of an auxiliary.¹² Mechanistic studies are also described.

2. Results

2.1. Auxiliary Optimization Studies. A successful auxiliary requires a nitrogen or sulfur coordinating group and a comparatively acidic NH group.¹³ The initial optimization experiments were directed toward using stoichiometric additives other than AgOAc to promote arylation. For the arylation of **8a**, a combination of inorganic base and a hydroxylic solvent was discovered to be successful.¹⁴ Subsequently, propionamides of a number of readily available auxiliaries were subjected to the optimized arylation conditions (Table 1). The conditions for the arylation involve heating substrate with iodobenzene in *tert*-amyl alcohol/water mixture in the presence of K_2CO_3 or K_3PO_4 base at 90–110 °C. 2-Methylthio-*N*-propionylaniline was efficiently arylated at 90 °C affording the monoarylation product predominately (entries 1 and 2). Better selectivity for the monophenylation was observed in mixed water/alcohol solvent. Increase of the coordinating group size from thiomethyl to thioisopropyl resulted in slight lowering of yield (entry 3). *tert*-Butyl derivative **8c** was shown to be inefficient and less than 20% conversion to the product was observed (entry 4). 2-Dimethylamino-*N*-propionylaniline **8d** was phenylated affording a reasonable conversion to the products. Use of the previously reported 8-aminoquinoline derivative resulted in formation of mono/diarylation product mixture (entry 6). Aliphatic auxiliaries such as 2-ethylthioethylamine and 2-dimethylaminoethylamine are not effective and the corresponding propionamides were arylated with low conversions (entries 7 and 8).

2.2. Arylation of Primary C–H Bonds: 2-Methylthioaniline Auxiliary. The optimization results show that the arylations are successful if commercially available 2-methylthioaniline and 8-aminoquinoline auxiliaries are employed (Table 1). Furthermore, 2-isopropylthioaniline and 2-dimethylaminoaniline auxiliaries are also efficient; however, these compounds are not commercially available. 2-Methylthioaniline auxiliary affords the best selectivity for monoarylation of primary carbon–hydrogen bonds (entry 2 vs entry 6, Table 1). Arylation scope by employing 2-methylthioaniline auxiliary is shown in

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- (13) See footnote 13, ref 9a.
- (14) See Supporting Information for optimization data.

Table 1. Auxiliary Optimization Studies^a

$\text{Auxiliary-NH} \xrightarrow[\text{PhI, K}_2\text{CO}_3]{5 \text{ mol\% Pd(OAc)}_2} \text{Auxiliary-NH} \begin{matrix} \text{---} \text{CH}_2\text{---} \text{CH}_2\text{---} \text{Ph} \\ \text{---} \text{CH}(\text{Ph})\text{---} \text{CH}_2\text{---} \end{matrix}$				
entry	amide	solvent, T	major product	NMR yield, %
1		<i>t</i> -Amyl-OH, 90 °C		55% 9a 22% 10a
2		<i>t</i> -Amyl-OH/H ₂ O 4/1, 90 °C		84% 9a 13% 10a
3		<i>t</i> -Amyl-OH/H ₂ O 4/1, 90 °C		59% 9b 8% 10b
4		<i>t</i> -Amyl-OH/H ₂ O 4/1, 90 °C		19% 9c
5		<i>t</i> -Amyl-OH/H ₂ O 4/1, 110 °C		61% 9d 6% 10d
6		<i>t</i> -Amyl-OH/H ₂ O 4/1, 110 °C		66% 9e 17% 10e
7 ^b		<i>t</i> -Amyl-OH/H ₂ O 4/1, 90 °C		45% 9f
8		<i>t</i> -Amyl-OH/H ₂ O 4/1, 90 °C		10% 9g

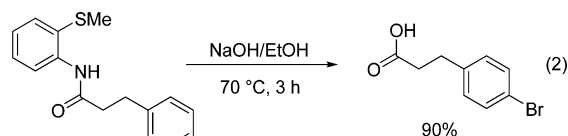
^a Amide (1 equiv), Pd(OAc)₂ (0.05 equiv), base (2.5 equiv), and PhI (3 equiv). Yields are NMR yields against dichloroethane internal standard. See the Supporting Information for details. ^b Base used - K₃PO₄.

Table 2. The arylation of propionyl derivative **8a** with *p*-bromiodobenzene is successful in *tert*-amyl alcohol/water mixture by employing K₂CO₃ base. Monoarylation product was obtained in 60% yield accompanied with 9% of diarylated species (entry 1). Reaction in acetonitrile is somewhat slower and afforded clean monoarylation (entry 2). 2-Methylbutyric acid amide was selectively arylated at β -position and the product was isolated in 60% yield (entry 3). Some functionality is tolerated on the amide.¹⁵

Thus, benzyl protected lactic acid derivative **11** was arylated with 4-iodo-*tert*-butylbenzene affording the product **11a** in 65% yield (entry 4). If **11** with 81% ee was employed in arylation, partial racemization was observed and **11a** was obtained with 75% ee. Phthaloyl protected alanine amide can be arylated by electron-rich 3,4-dimethyliodobenzene (entry 5) and electron-poor 4-chloriodobenzene (entry 6). In this case, highest conversion was obtained if toluene solvent and cesium acetate base were employed. Corey has reported

arylation of phthaloyl-protected amino acids by employing 8-aminoquinoline auxiliary, palladium acetate catalyst, and stoichiometric silver acetate.^{10a} However, clean β -monoarylation of methyl groups was elusive.

We also showed that directing group can be removed under base hydrolysis affording a phenylpropionic acid derivative (eq 2). Thus, *p*-bromophenylpropionic acid 2-methylthioanilide was heated with NaOH in ethanol to afford 90% of the hydrolysis product.



Secondary C–H bond arylation proceeds with a moderate yield even for a weak benzylic bond (entry 7) and requires the presence of catalytic pivalic acid additive employed by Larock and Fagnou.¹⁶ It has been suggested that pivalate anion acts as a catalytic proton shuttle between the substrate and inorganic base.^{16a} To efficiently arylate methylene groups one needs to employ another auxiliary as shown below.

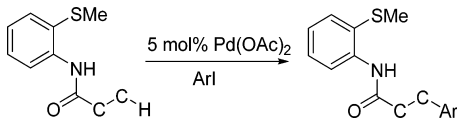
2.3. Arylation of Secondary C–H Bonds: 8-Aminoquinoline Auxiliary. Efficient arylation of secondary C–H bonds is possible by employing 8-aminoquinoline auxiliary. Optimal conditions involve heating substrate with aryl iodide and Cs₃PO₄ base in *tert*-amyl alcohol solvent. The arylation is highly selective for the β -position of the alkyl chain. Butyric acid derivative is arylated in good yield with both electron-rich and electron-poor aryl iodides (Table 3, entries 1 and 2).

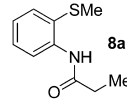
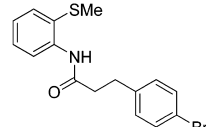
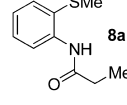
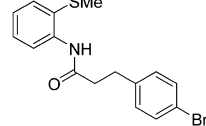
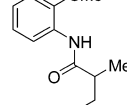
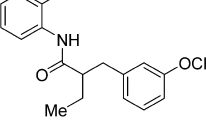
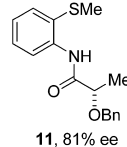
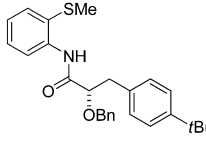
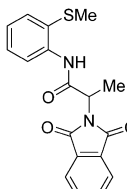
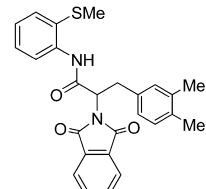
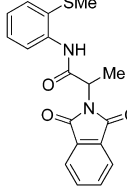
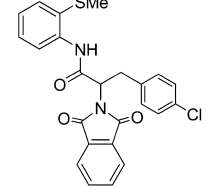
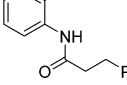
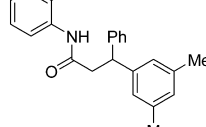
Cyclohexanecarboxylic acid amide can be arylated by *p*-methoxyiodobenzene and 3-bromiodobenzene affording diarylation products in reasonable yields. The diastereoselectivity depends on the aryl iodide. *p*-Methoxyphenylation affords about 4/1 isomer ratio (entry 3) or about 5/1 ratio if previously reported conditions^{9b} that use AgOAc are employed with all-*cis* isomer predominating in both cases. *m*-Bromophenylation results in the formation of all-*cis* isomer (entry 5). *m*-Methoxyphenylation of cyclopentanecarboxylic acid derivative affords monoarylation product *cis* isomer (entry 6). ω -Phthaloyl-protected amino group is compatible with the arylation conditions as shown in entry 7. 6-Aminohexanoic acid derivative is *p*-tolylated in good yield. Finally, alkenylation of sp² C–H bonds was shown to be successful (entry 8). 2-Methoxybenzoic acid amide was reacted with iodostyrene affording the product in good yield if AgOAc halide removing agent was employed.

2.4. Alkylation of C–H Bonds. The previously described conditions that involve use of AgOAc for iodide removal were not successful for C–H bond alkylation. Silver acetate reaction with alkyl iodides competes with the C-alkylation resulting in low catalytic turnover. The new conditions should

(15) While simple arylpropionic acids may be obtained by a condensation of acetic anhydride with an aromatic aldehyde followed by hydrogenation, aliphatic or aromatic ketones as well as aliphatic aldehydes are not generally suitable substrates for the Perkins reaction. Rosen, T. The Perkin Reaction. In: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 2, pp 395–408.

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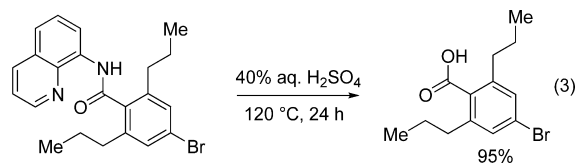
Table 2. Arylation of Primary C–H Bonds^a


entry	amide	solvent, T, base	major product	yield, %
1 ^b		<i>t</i> -Amyl-OH/H ₂ O 90 °C, K ₂ CO ₃		60
2		CH ₃ CN 90 °C, K ₂ CO ₃		54
3		<i>t</i> -Amyl-OH/H ₂ O 90 °C, K ₂ CO ₃		60
4		<i>t</i> -Amyl-OH 90 °C, K ₂ CO ₃		65
5		Toluene 110 °C, CsOAc		79
6		Toluene 110 °C, CsOAc		60
7		<i>t</i> -Amyl-OH 90 °C, K ₂ CO ₃ 20 mol% PivOH		47

^a Amide (1 equiv), Pd(OAc)₂ (0.05 equiv), base (2.5 equiv), and ArI (3–4 equiv) Yields are isolated yields. See the Supporting Information for details. ^b Diarylated product also isolated (9%). In all other cases, <5% diarylation was observed.

be successful since the competitive destruction of alkyl iodides is expected to be slower. It was determined that the optimal auxiliary for alkylation of C–H bonds is 8-aminoquinoline. Alkylation conditions involve heating of the substrate with alkyl iodide or benzyl bromide to 100–110 °C in *tert*-amyl alcohol in the presence of K₂CO₃ base and catalytic amount of pivalic acid (Table 4). β -Alkylation of propionic acid amide can be performed with branched (entry 1) or straight-chain primary alkyl iodides (entry 2). The yields are moderate. Benzoic acid derivatives, in contrast, can be alkylated in good yields by alkyl iodides (entry 3) and benzyl bromides (entries 4 and 5). Acid-catalyzed removal of the

directing group was also demonstrated affording the dialkylated benzoic acid in excellent yield (eq 3). Several examples of transition-metal-catalyzed sp² C–H bond alkylation have been reported.¹⁷

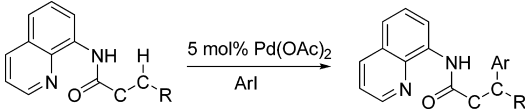
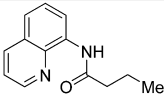
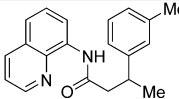
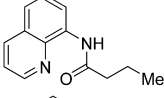
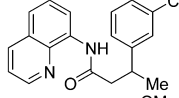
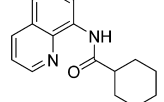
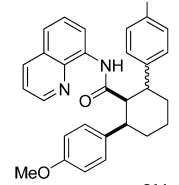
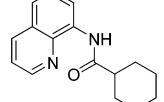
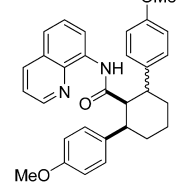
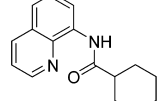
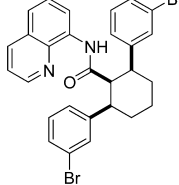
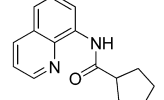
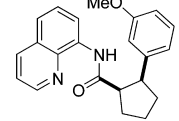
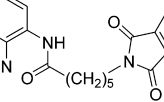
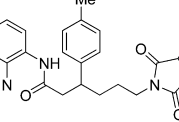
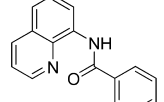
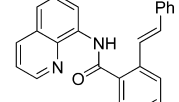


2.5. Mechanistic Considerations. 2.5.1. Synthesis of Palladium Complexes. Several complexes that are related to potential reaction intermediates were synthesized and characterized (Scheme 2). Reaction of 8-aminoquinoline pivalamide with palladium acetate in nitrile solvents afforded the corresponding acetonitrile and pivalonitrile complexes **13** and **14** in quantitative yields. Notably, the cyclometalated complexes are easily formed in high yields under conditions where catalytic reaction is successful (entry 2, Table 2). Nitrile ligands are labile and can be easily replaced by *tert*-butyl isonitrile to afford complex **15** in quantitative yield (Scheme 2). Complexes **13–15** were fully characterized by ¹H and ¹³C NMR as well as elemental analyses. Palladated methylene group signals appear in ¹H NMR spectra at 1.80–1.94 ppm (CDCl₃ solvent). The complexes exist as yellow-brownish, crystalline solids that are stable at room temperature in air. They are soluble in most common organic solvents except pentane.

The structure of the complex **13** was verified by single-crystal X-ray diffraction analysis. The ORTEP diagram of **13** is shown in Figure 1. Interestingly, **13** crystallizes in two different forms, orange blocks and yellow, thin plates. Both crystals were formed simultaneously upon slow diffusion of pentane into CH₂Cl₂ solution of **13** at –20 °C. Orange material is **13** that crystallizes in triclinic space group *P* $\bar{1}$, while the yellow plates is **13** that crystallizes in the orthorhombic space group *Cmca*. Structure shown in Figure 1 is the orange material that has two independent molecules in the asymmetric unit, one of which is depicted. The Pd(1)–N(1)–C(9)–C(8)–N(2) five-membered ring is planar within four degrees. The other ring, Pd(1)–N(2)–C(10)–C(11)–C(12), assumes a puckered geometry, with C(11) forming the flap of an envelope and N(2)–Pd(1)–C(12)–C(11) dihedral angle is 18.3(5)°. The N(2)–Pd(1)–C(12) angle is 83.3(2)°, showing distortion from an idealized square planar geometry at the palladium center. Several related crystallographically characterized palladium complexes that possess dianionic NNC ligands have been described in literature. Amino acid-derived (NNC)Pd complexes have been described by Beck.¹⁸ Espinet¹⁹ and an Italian group²⁰ have also reported several *ortho*-palladated species resulting from NNC ligands. Layh has shown that facile cyclometalation of sp³ C–H bonds is observed in a monoanionic (NN)Pd system, affording an interesting PdNSiC heterocycle.²¹

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Table 3. Arylation of Secondary C–H Bonds^a

				
entry	amide	solvent, T, base	major product	yield, %
1		<i>t</i> -Amyl-OH 90 °C, Cs ₃ PO ₄		79
2		<i>t</i> -Amyl-OH 90 °C, Cs ₃ PO ₄		81
3		<i>t</i> -Amyl-OH 90 °C, Cs ₃ PO ₄		63 all- <i>cis</i> 16 <i>cis</i> - <i>trans</i>
4		Neat 90 °C, AgOAc		69 all- <i>cis</i> 13 <i>cis</i> - <i>trans</i>
5		<i>t</i> -Amyl-OH 90 °C, Cs ₃ PO ₄		52 all- <i>cis</i> only
6		<i>t</i> -Amyl-OH 110 °C, Cs ₃ PO ₄		52
7		<i>t</i> -Amyl-OH 90 °C, Cs ₃ PO ₄		76
8		Neat 90 °C, AgOAc		64

^a Amide (1 equiv), Pd(OAc)₂ (0.05 equiv), base (1.5–3.3 equiv), and ArI (2–4 equiv) Yields are isolated yields. See the Supporting Information for details.

The reaction of **13** and **15** with bromine was investigated. If **13** was treated with Br₂ at –78 °C, an unstable product that decomposed in solution at –40 °C within minutes was obtained. Reaction of **15** with bromine at –78 °C in CH₂Cl₂ afforded a green solution, from which palladium(IV) dibromide **16** was isolated in 85% yield after recrystallization from dichloromethane-pentane at –20 °C (eq 4). Complex **16** decomposes at 0 °C within hours in solution and within days in solid state. Relative stability of **16** may be explained by strong binding of the isonitrile ligand to palladium. It is known that d⁶ octahedral complexes often require dissociation of one ligand to decompose by reductive elimination pathways.²² Interestingly, the signal

of palladated methylene group is shifted downfield compared with the corresponding signals for **13**–**15** and appears at 4.80 ppm in ¹H spectrum.

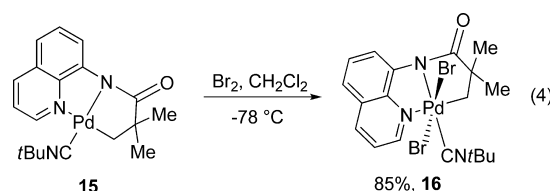
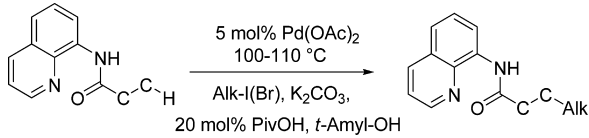
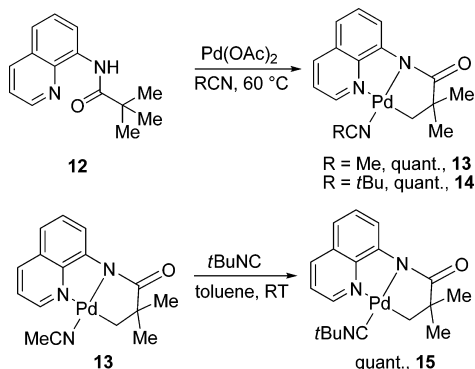


Table 4. Alkylation of C–H Bonds^a


entry	amide	AlkI(Br)	major product	yield, %
1		<i>i</i> -Butyl iodide		58
2		<i>n</i> -Octyl iodide		47
3		<i>n</i> -Propyl iodide		77
4				45
5		benzyl bromide		64

^a Amide (1 equiv), Pd(OAc)₂ (0.05 equiv), base (2.5–3.5 equiv), pivalic acid (0.2 equiv), and RI or RBr (3–4 equiv). Yields are isolated yields. See the Supporting Information for details.

Scheme 2. Synthesis of Nitrile and Isonitrile Complexes

The dibromide **16** was isolated as dark-green crystalline blocks. Its structure was verified by X-ray crystallographic

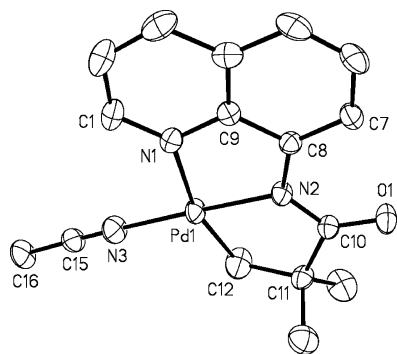


Figure 1. ORTEP view of **13**. Selected interatomic distances (Å) and angles (deg): Pd(1)–N(2) = 1.969(4), Pd(1)–C(12) = 2.012(6), Pd(1)–N(3) = 2.013(5), Pd(1)–N(1) = 2.124(5), N(2)–Pd(1)–C(12)–C(11) = 18.3(5), N(2)–Pd(1)–C(12) = 83.3(2).

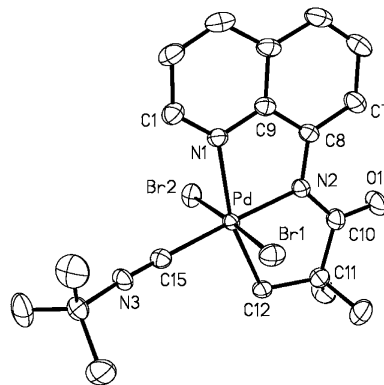


Figure 2. ORTEP view of **16**. Selected interatomic distances (Å) and angles (deg): Pd–N(2) = 1.981(3), Pd–C(15) = 1.993(4), Pd–C(12) = 2.072(3), Pd–N(1) = 2.171(3), Pd–Br(1) = 2.4411(5), Pd–Br(2) = 2.4690(5), N(1)–Pd–N(2)–C(8) = 2.0(2), Pd–N(2)–C(10)–C(11) = –5.5(4).

analysis. The five-membered Pd–N(2)–C(10)–C(11)–C(12) ring adopts an envelope conformation with C(11) forming the flap of the envelope (torsion angle Pd–N(2)–C(10)–C(11) = –5.5(4)°). An octahedral arrangement of ligands around Pd(IV) center is observed. The bromide ligands assume *trans* arrangement about the palladium center. While Pd(IV) complexes have been investigated quite extensively in recent years,²³ it appears that no alkylpalladium(IV) dibromides have been crystallographically characterized. Some Pd(IV) dibromides possessing polydentate nitrogen or sulfur ligands have been described.²⁴ It appears that the dianionic, tridentate NNC ligand stabilizes Pd(IV) oxidation state allowing for an efficient catalytic functionalization of C–H bonds and also for isolation of unusual and typically unstable high-valent Pd complexes. Unfortunately, attempts to replace the bromide substituent with an aryl or alkyl group have not been successful so far.

2.5.2. Mechanistic Studies. Upon dissolution of **13** in CD₃CO₂D, complete H/D exchange of the aliphatic hydrogens was observed within minutes at room temperature. The loss of alkyl hydrogen resonances in **13** with respect to time was measured by NMR at –35 °C in CD₂Cl₂ containing 40 equiv of CD₃CO₂D. First-order rate constant $k = 2.0 \times 10^{-4} \text{ s}^{-1}$ was obtained corresponding to $\Delta G^\ddagger = 18 \text{ kcal/mol}$.

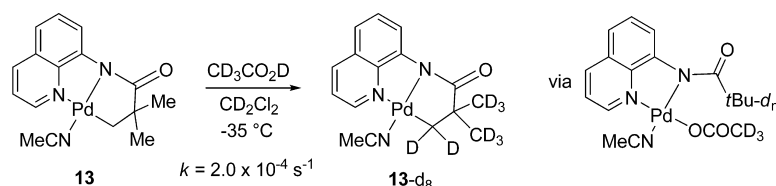
Complexes **13** and **15** were reacted with *p*-tolyl iodide and iodomethane, respectively, in acetone solvent at room temperature (Scheme 4). Following the treatment with HI to remove palladium, reaction mixture was either separated by preparative TLC (for arylation of **13**) or analyzed by ¹H NMR (for methylation of **15**). A mixture of mono- and disubstitution products was obtained in addition to the recovered unreacted amide. This result shows that monomeric palladated complexes are capable of reacting with alkyl and aryl halides and are thus competent intermediates in the catalytic cycle.

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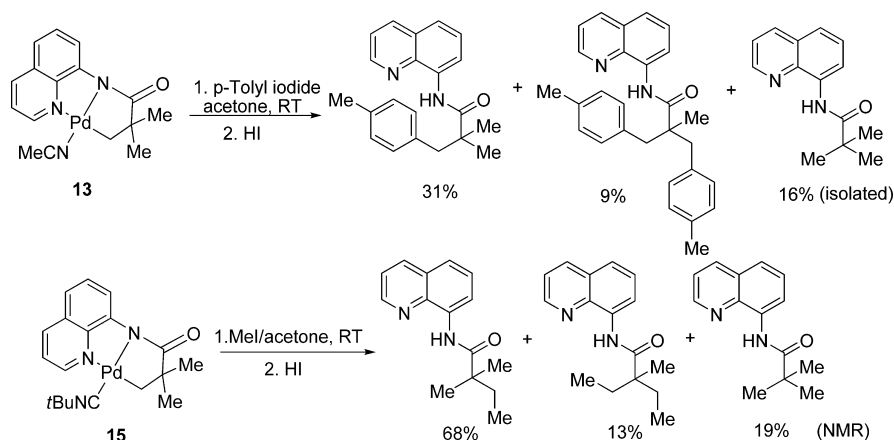
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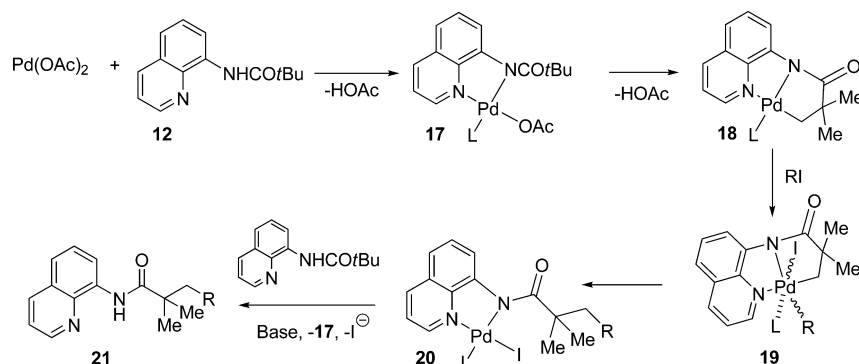
Scheme 3. H/D Exchange Studies



Scheme 4. Arylation and Alkylation of Palladated Intermediates



Scheme 5. Reaction Mechanism



Pivalonitrile exchange was studied in CD_2Cl_2 solution at -35°C by treatment of **14** with a large excess of CH_3CN . The first-order rate constant obtained by using 10 equiv of CH_3CN ($k_{\text{obs}} = 4.6 \times 10^{-5} \text{ s}^{-1}$) is about twice lower than the rate constant obtained using 20 equiv ($k_{\text{obs}} = 1.1 \times 10^{-4} \text{ s}^{-1}$). Thus it is clear that ligand displacement proceeds by an associative mechanism, consistent with the prevailing ligand substitution mechanism at square planar Pd(II) centers.

At this point a generalized mechanism for the auxiliary-directed arylation of C-H bonds can be proposed (Scheme 5). Palladium acetate reaction with 8-pivaloylaminoquinoline affords the palladium amide **17**. The next step involves a rapid cyclometalation of *tert*-butyl group resulting in the formation of **18**. We have shown that only amides possessing an NH group are reactive;^{9b} hence, formation of **17** is essential for the success of reaction. Oxidative addition of alkyl or aryl iodide to **18** produces **19**. However, intermediacy of Pd(III) can not be excluded²⁵ although formation of dimeric species is unlikely in strongly coordinating acetonitrile solvent. Reductive elimina-

tion followed by ligand exchange releases **21** and regenerates palladium amide.

3. Summary

We have developed a method for auxiliary-directed, palladium-catalyzed arylation and alkylation of sp^3 and sp^2 C-H bonds. Stoichiometric silver additives are not required in contrast with our previously reported procedure.^{9b} Instead, simple inorganic bases can be employed and some reactions can be performed in alcohol/water mixtures. By employing 2-methylthioaniline auxiliary, selective monoarylation of primary sp^3 C-H bonds can be achieved. If arylation of secondary sp^3 C-H bonds is desired, 8-aminoquinoline auxiliary may be used. For alkylation of sp^3 and sp^2 C-H bonds, 8-aminoquinoline auxiliary affords the best results. A cyclometalated reaction intermediate has been isolated, structurally characterized, and its conversion to a Pd(IV) species investigated. A general reaction mechanism has been proposed involving formation of palladium amide, cyclometalation, oxidative addition, and reductive elimination steps. Detailed mechanistic studies of separate catalytic steps will be reported in future.

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4. Experimental Section

General Procedure for Alkylation of C–H Bonds. A 2-dram screw-cap vial was charged with Pd(OAc)₂ (5 mol %), K₂CO₃ (2.5 equiv), substrate (1 equiv), pivalic acid (20 mol %), and alkyl iodide (3–4 equiv). The *tert*-amyl alcohol (0.7 mL) solvent was added and the resulting mixture was stirred and heated at 100–110 °C for 12–26 h. The conversion was monitored by GC. After completion of reaction, ethyl acetate was added to reaction mixture followed by extraction with water. Aqueous layer was washed once with ethyl acetate. Combined organic extracts were dried over MgSO₄. Filtration and evaporation under reduced pressure followed by purification by flash chromatography gave products.

***N*-(5-Methylhexanoyl)-8-aminoquinoline (Table 4, entry 1).** The general procedure was followed using *N*-propionyl-8-aminoquinoline (140 mg, 0.7 mmol), Pd(OAc)₂ (7.8 mg, 0.035 mmol), K₂CO₃ (242 mg, 1.75 mmol), pivalic acid (14 mg, 0.14 mmol), and 2-methyliodopropane (240 μL, 2.1 mmol). Resulting mixture was heated for 22 h at 110 °C. Flash chromatography (toluene/EtOAc 50/1 to 25/1) gave 104 mg (58%) of a colorless oil, R_f = 0.19 (toluene/EtOAc 50/1). ¹H NMR (300 MHz, CDCl₃, ppm) δ 9.82 (s, 1H) 8.83–8.78 (m, 2H) 8.17 (dd, 1H, *J* = 8.3, 1.7 Hz)

7.58–7.43 (m, 3H) 2.55 (t, 2H, *J* = 7.6 Hz) 1.89–1.77 (m, 2H) 1.63 (septet, 2H, *J* = 6.7 Hz) 1.37–1.28 (m, 2H) 0.92 (d, 6H, *J* = 6.7 Hz). ¹³C NMR (75 MHz, CDCl₃, ppm) δ 172.1, 148.3, 138.5, 136.5, 134.8, 128.1, 127.6, 121.7, 121.5, 116.6, 38.7, 28.1, 23.8, 22.7. Signal for one aliphatic carbon could not be detected. FT-IR (neat, cm^{−1}) ν 3353, 1687. Anal. Calcd for C₁₆H₂₀N₂O: C 74.97, H 7.86, N 10.93. Found: C 74.83, H 7.91, N 10.93.

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Supporting Information Available: Detailed experimental procedures, characterization data for new compounds, and X-ray crystallography data for **13** and **16**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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