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Pd-Catalyzed Alkylation of (Iso)quinolines and Arenes: 2-Acylpyridine Compounds as Alkylation Reagents

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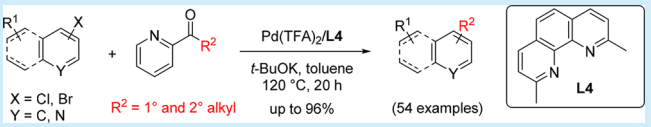
Supporting Information

ABSTRACT: The first Pd-catalyzed alkylation of (iso)-quinolines and arenes is reported. The readily available and bench-stable 2-acylpyridine compounds were used as an alkylation reagent to form the structurally versatile alkylated (iso)quinolines and arenes. The method affords a convenient pathway for the introduction of alkyl groups into organic molecules.

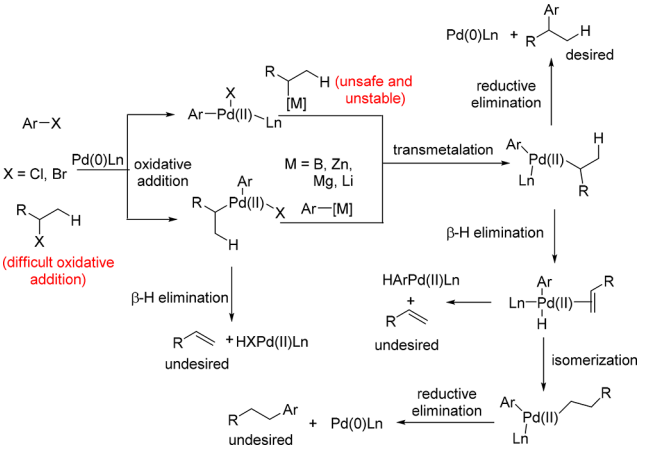


Transition-metal-catalyzed cross-coupling reactions, in particular, palladium-mediated couplings, have been extensively used for $C(sp^2)-C(sp^2)$ bond formation in synthetic organic chemistry and materials science during the past several decades.[1] In recent years, $C(sp^3)$ nucleophiles and electrophiles have been investigated in Pd-catalyzed cross-coupling reactions to build the $C(sp^2)-C(sp^3)$ bond.[2] However, the newly developed catalytic methods for forging the $C(sp^2)-C(sp^3)$ bond still remain a challenge in organic synthesis. The core challenge in Pd-catalyzed alkylation is to choose the suitable alkylation cross-coupling partners: the alkyl organometallic species are substantially less stable than an aryl organometallic species;[3] the oxidative addition of alkyl halides is considerably more difficult than that of aryl halides.[4] Furthermore, the [Pd(II)]-alkyl intermediates are prone to β-H elimination and isomerization, which can compete with the formation of the desired product (Scheme 1).[3,4]

To overcome these pitfalls, great progress has been made in reducing the undesired byproduct[5] as well as in addressing the problems in the handling and preparation of the cross-coupling partner.[6] However, the alkylation of (iso)quinolines and arenes without using organometallic species have been rather limited until now.[7]

Recently, reductive cross-coupling of two electrophiles has attracted considerable attention for synthetic alkylated (iso)-quinolines and arenes.[8−11] Although the strategy avoids employing stoichiometric organometallic partner, most nickel-catalyzed reductive cross-coupling reactions extensively require stoichiometric metal powder reductants (Scheme 2, eq 1). Coupling via C−H functionalization has also emerged as a powerful tool for formation of alkylated (iso)quinolines and arenes,[12] but the strategy often relies on the use of directing groups and is limited to specific C−H bonds. Fortunately, using aryl ketones as an alkylation reagent has been reported in several studies. In 2009, a novel route to the synthesis of diarylmethanes via a Pd-catalyzed α-arylation of benzyl ketones was reported (Scheme 2, eq 2).[13] In 2013, Zhang[14] also reported the synthesis of diarylmethanes by using aryl methyl ketones with aryl bromides (Scheme 2, eq 3). Unfortunately, their methods for the introduction of the primary and secondary alkyl chains onto (iso)quinolines and arenes are limited. As part of our ongoing efforts in the development novel methods for Pd-catalyzed cross-coupling reactions,[15] we herein report a Pd-catalyzed alkylation of (iso)quinolines and arenes with 2-acylpyridine compounds (Scheme 2, eq 4).

Scheme 1. Pd-Catalyzed Cross-Coupling Reactions Involving $C(sp^3)$ Nucleophiles and Electrophiles



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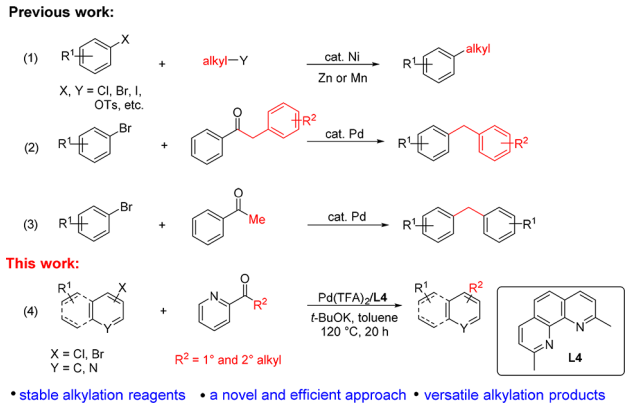
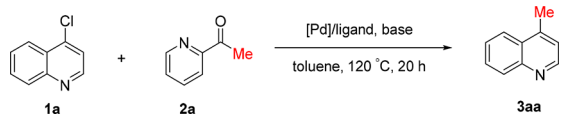
Scheme 2. Transition-Metal-Catalyzed Cross-Coupling Reactions for C(sp^2)−C(sp^3) Bond Formation



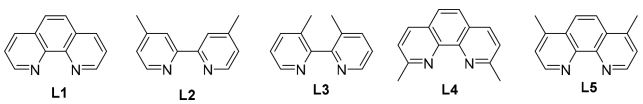
Herein, we began our investigations on the cross-coupling of 4-chloroquinoline **1a** and 2-acetylpyridine **2a** (Table 1). To our delight, in the presence of 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, and 2.5 equiv of *t*-BuOK under argon at 120 °C, the 4-methylquinoline **3aa** was obtained, albeit in a moderate yield of 43% (entry 1). Then various palladium sources were screened (entries 2−5); $Pd(TFA)_2$ was found to be the most effective catalyst, giving **3aa** in 72% yield (entry 5). Next, the base screening indicates that strong base is critical for the enolization of 2-acetylpyridine and *t*-BuOK was the most effective base (entries 5−11). Following this, changing the solvent from toluene to another one, such as H_2O, THF, CH_3CN, DMF, DMA, and DMSO, the reaction yield diminished drastically (see Table S1 for details). Subsequent ligand screening revealed that 2,9-dimethyl-1,10-phenanthroline **L4** was the most effective for the current reaction, giving the product in 88% yield. Other ligands gave inferior results (entries 12−17). Moreover, a lower yield was obtained at a lower reaction temperature (entry 18).

Table 1. Optimization of Reaction Conditions[a]



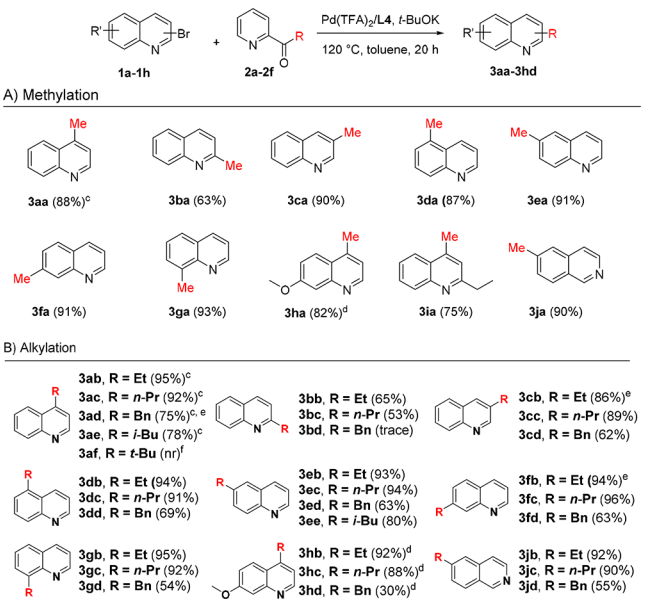
entry	[Pd]	ligand	base	yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	*t*-BuOK	43
2	$Pd(dba)_2$	PPh_3	*t*-BuOK	65
3	$Pd(acac)_2$	PPh_3	*t*-BuOK	65
4	$PdCl_2$	PPh_3	*t*-BuOK	nr[d]
5	$Pd(TFA)_2$	PPh_3	*t*-BuOK	72
6	$Pd(TFA)_2$	PPh_3	KOH	32
7	$Pd(TFA)_2$	PPh_3	*t*-BuONa	43
8	$Pd(TFA)_2$	PPh_3	NaOH	40
9	$Pd(TFA)_2$	PPh_3	Cs_2CO_3	nr
10	$Pd(TFA)_2$	PPh_3	K_2CO_3	nr
11	$Pd(TFA)_2$	PPh_3	K_3PO_4	nr
12	$Pd(TFA)_2$	*t*-Bu_3P	*t*-BuOK	72
13	$Pd(TFA)_2$	**L1**	*t*-BuOK	80
14	$Pd(TFA)_2$	**L2**	*t*-BuOK	73
15	$Pd(TFA)_2$	**L3**	*t*-BuOK	76
16	$Pd(TFA)_2$	**L4**	*t*-BuOK	88
17	$Pd(TFA)_2$	**L5**	*t*-BuOK	83
18[c]	$Pd(TFA)_2$	**L4**	*t*-BuOK	78

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 equiv), [Pd] (5 mol %), ligand (10 mol %), base (2.5 equiv), solvent (2 mL), 120 °C, 20 h, Ar. [b]Yield of isolated product. [c]Reaction performed in 100 °C. [d]nr = no reaction.



With the optimal reaction conditions in hand, the substrate scope of the methylation of various quinoline halides was studied (Scheme 3, part A). The results indicate that the methylation reaction at any position of quinoline proceed smoothly to give the desired products in 63−93% yields (**3aa**−**ga**). Substrates possessing an electron-donating group at the C-7 and C-2 positions afforded the target products **3ha** and **3ia** in 82% and 75% yields, respectively. 6-Bromoisoquinoline was also compatible with the cross-coupling reaction to give the desired **3ja** in 90% yield.

Scheme 3. Pd-Catalyzed Alkylation Reactions of Quinoline Halides and 2-Acylpyridine Compounds[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (2.0 equiv), $Pd(TFA)_2$ (5 mol %), **L4** (10 mol %), *t*-BuOK (2.5 equiv), toluene (2 mL), 120 °C, 20 h, Ar. [b]Isolated yields. [c]4-Chloroquinoline was used. [d]4-Chloro-7-methoxyquinoline was used. [e]**2d** (2.0 equiv), $Pd(TFA)_2$ (10 mol %), **L4** (20 mol %), and 2.5 equiv of *t*-BuOK were used. [f]nr = no reaction.

To establish the scope of this protocol, various quinoline halides **1a**−**i** were reacted with 2-acylpyridines **2b**−**e** under the optimized conditions to give the desired products in good to excellent yields (Scheme 3, Part B). It was found that variously substituted substrates **2**, such as ethyl, *n*-propyl, and benzyl, could be used as an effective substituent group for the alkylation reaction. The effect of various groups on the quinoline ring was also investigated, and a strong dependence on the position of the substituents was observed. Substrates **2** with ethyl, *n*-propyl groups at the C-3, C-4, C-5, C-6, C-7, and C-8 positions worked well to give the desired products in excellent yields (**3ab**, **3cb**−**gb**, **3ac**, and **3cc**−**gc**), whereas substrates with an ethyl or *n*-propyl group at the C-2 position only gave the target molecule in moderate yield (**3bb**, **3bc**). Benzyl substituent substrates gave the desired benzylated

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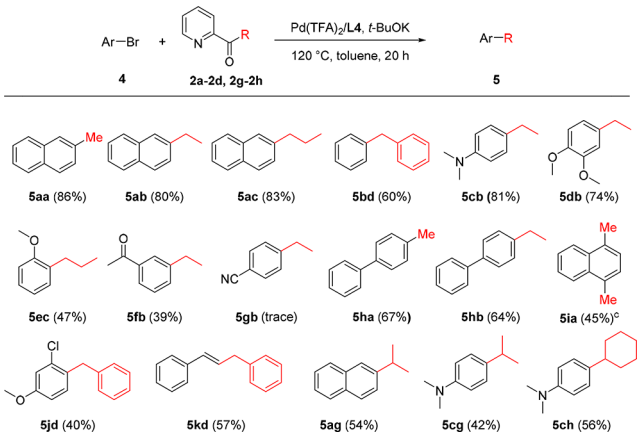
products in 55−75% yields (**3ad**, **3cd**−**gd**). However, the cross-coupling reaction of 2-bromoquinoline **1b** with 2-phenyl-1-(pyridin-2-yl)ethan-1-one **2d** resulted in a trace amount of the desired product. To confirm whether the rearrangement of the carbon skeleton will take place or not, isobutyl group substituents **2e** were used, and ^{1}H NMR analysis of the reaction mixture showed that no rearrangement byproducts **3ae**, **3ee** were observed. 4-Chloro-7-methoxyquinoline **1h** and 6-bromoisoquinoline **1j** worked well under the optimal reaction conditions. When 2,2-dimethyl-1-(pyridin-2-yl)-propan-1-one was used as an alkylation reagent, no desired product **3af** was detected.

We then examined this alkylation process using aryl bromides as the cross-coupling partners (Scheme 4). As

Scheme 4. Pd-Catalyzed Alkylation Reactions of Aryl Bromides and 2-Acylpyridine Compounds[a,b]

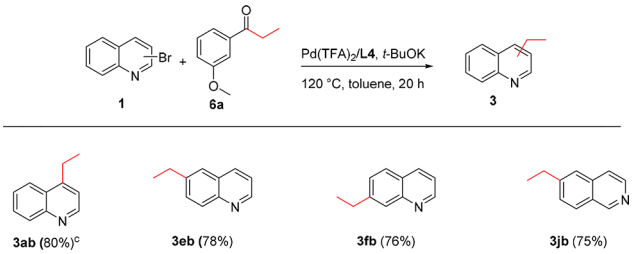


[a]Reaction conditions: **4** (0.5 mmol), **2** (2.0 equiv), $Pd(TFA)_2$ (5 mol %), **L4** (10 mol %), *t*-BuOK (2.5 equiv),toluene (2 mL), 120 °C, 20 h, Ar. [b]Isolated yields. [c]**2a** (4.0 equiv) and *t*-BuOK (5.0 equiv) were used.

expected, a variety of aryl bromides **4** reacted with 2-acylpyridine compounds **2** to furnish the desired products in moderate to good yield (**5aa**−**ch**). In principle, electron-withdrawing and electron-donating substituents (such as amide, methoxy, and ketone) were all well-tolerated under the standard reaction conditions (**5cb**−**fb**), albeit with a diminished yield when using electron-withdrawing substituent substrates. When a nitrile-containing substrate was used, the desired product **5gb** was obtained in a trace amount. The alkylation of 4-bromo-1,1′-biphenyl proceeded smoothly to give **5ha** and **5hb** in good yield. The alkylation method is also applicable to the dimethylation of 1,4-dibromonaphthalene to obtain the desired 1,4-dimethynapthalene **5ia** in 45% yield. When 1-bromo-2-chloro-4-methoxybenzene **4j** was used, the coupling occurred exclusively at the bromine-substituted carbon to get the desired product **5jd**. No chloride displacement product was detected in the reaction. When 2-bromovinylbenzene was used as substrate, **5kd** was obtained in 57% yield. Importantly, ^{1}H NMR analysis of isopropyl products **5ag**, **5cg** showed that no isomerization took place. Cyclohexyl could also be introduced into arene, and the desired **5ch** was obtained in 56% yield.

Next, in order to expand the utility of this reaction, we investigated a variety of ketone derivatives (such as 1-(pyridin-3-yl)ethan-1-one, 1-(pyridin-4-yl)ethan-1-one, acetophenone, and so on) as the cross-coupling partners to obtain the corresponding alkylated products (see Table S2 for details). Unfortunately, only *m*-methoxypropiophenone provided the desired product in good yield. We next extended Pd-catalyzed ethylation of quinoline halides **1a**, **1e**, and **1f** with *m*-methoxypropiophenone **6a**. Reaction at the C4, C6, or C7 position of quinoline halides and the C6 position of isoquinoline bromine **1j** could obtain good yields (**3ab**, **3eb**, **3fb**, and **3jb**) (Scheme 5).

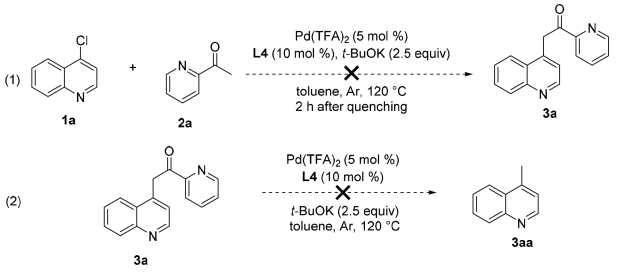
Scheme 5. Pd-Catalyzed Alkylation Reactions of Quinoline Halides and *m*-Methoxypropiophenone[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **6a** (2 equiv), $Pd(TFA)_2$ (5 mol %), **L4** (10 mol %), *t*-BuOK (2.5 equiv), toluene (2 mL), 120 °C, 20 h, Ar. [b]Isolated yields. [c]4-Chloroquinoline was used.

To obtain insight into the reaction mechanism, an array of control experiments were carried out. To our surprise, α-arylation product **3a** was not obtained by quenching the reaction after 2 h (Scheme 6, eq 1). Then a further experiment

Scheme 6. Control Reactions for Exploring the Mechanism



was studied where α-arylation product **3a** as the raw material was added to reaction mixture, and 4-methyquinoline **3aa** was not observed (Scheme 6, eq 2), which indicated that **3a** was not the intermediate in this transformation. Next, the picolinic acid was isolated from the reaction mixture of 4-chloroquinoline and 1-(pyridin-2-yl)butan-1-one. When $H_2{}^{18}O$ was added in the reaction, the ^{18}O-labeled picolinic acid was detected by HRMS spectrum, which suggested that H_2O might be involved in the C−C bond cleavage process. On the basis of the above results and related reports,[14,16] a reaction pathway for the alkylation of (iso)quinolines and arenes was proposed (see Scheme S3 for details).

In summary, we have developed a novel and highly efficient approach for the preparation of alkylated (iso)quinolines and arenes using Pd-catalyzed cross coupling of (iso)quinoline halides and arene halides with abundant and readily available 2-acylpyridine compounds. The alkylation of (iso)quinolines and arenes proceeds smoothly to give the corresponding products in moderate to excellent yields with no rearrangement byproducts. The current method, which displays a broad

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substrate scope, has opened the door for the well-established primary and secondary alkylation of (iso)quinolines and arenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02498.

Experimental procedures and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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