JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

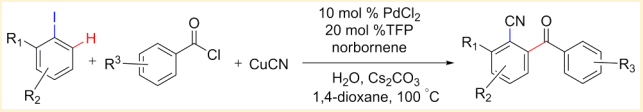
Palladium-Catalyzed Sequential Acylation/Cyanation of Aryl Iodides: A Regiospecific Synthesis of 2-Cyanoaryl Ketones

Shanfei Pan, Feifei Wu, Ruicheng Yu, and Wanzhi Chen*

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

Supporting Information

ABSTRACT: A palladium-catalyzed, norbornene-mediated acylation/cyanation reaction of iodobenzene was developed by the use of acyl chlorides as acylation reagents and cuprous cyanide. The reaction gave the 2-cyanoaryl ketones efficiently by using readily available starting materials.



INTRODUCTION

Palladium-catalyzed coupling reactions, including Heck, Suzuki, and Sonogashira couplings using commercially available organic halides or pseudohalides as the substrates, have become the classical protocols for C−C bond formations in pharmaceutical and material science.[1,2] The protocol allows one C−C bond formation through one C-halide bond. Although sequential double couplings of dihaloarene may result in difunctionalization of arenes, the availability of the starting materials is limited.[3] Transition-metal-catalyzed direct C−H bond functionalization represents one of the most promising procedures to produce C−C or C−heteroatom bonds.[4] The combination of C−halide and C−H activation would result in simultaneous double functionalization. Such step-economic transformations are urgently needed.[5]

The Catellani reaction allows the introduction of two different groups in one pot from aryl halides leading to polysubstituted aromatic compounds and fused aromatic rings using palladium/norbornene as a catalyst.[6] The method has been employed for the synthesis of cyclic or acyclic benzonitriles, helical alkenes, annulated indole derivatives, diaryl derivatives, etc.[7] The Catellani reaction is usually limited to ortho-alkylation and arylation. Recently, palladium-catalyzed ortho C−H amination of aryl iodides was reported, providing amination products exclusively at the ortho-position instead of ipso.[8] Such a synthetic strategy has been extended to tandem C−H amination and C−I alkenylation,[9a,b] arylation,[9c] borylation,[9d] alkynylation,[9e,f] etc. for the synthesis of polysubstituted aromatic compounds. Most recently, palladium/norbornene-catalyzed ortho-acylation of aryl iodides was reported leading to diaryl ketones and aryl alkyl ketones.[10]

Aryl ketones are very important compounds widely used in pharmaceutical, fragrance, dye, and agrochemical industries.[11] Traditional synthetic methods of aryl ketones rely primarily on Friedel−Crafts acylation in the presence of Lewis acids or Brønsted acid[12] or the reaction of activated carboxylic acid derivatives with organometallic reagents.[13] Although transition-metal-catalyzed direct C−H bond activation/acylation of aromatic compounds offers an atom economic and environmentally friendly alternative strategy to aromatic ketones, the regioselective acylation is limited due to the directing groups.[14,15]

We have recently reported the synthesis of 2-alkynylanilines through palladium/norbornene-catalyzed tandem C−H amination and C−I alkynylation.[9f] As a continuation, herein we report a palladium/norbornene-catalyzed sequential acylation/cyanation reaction of aryl iodide with acyl chlorides and cuprous cyanide, which selectively leads to a series of aromatic ketones in moderate to good yields.

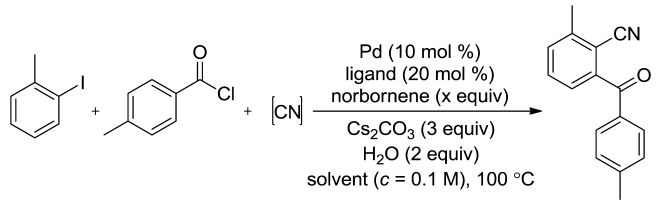
RESULTS AND DISCUSSION

The three-component reaction of 2-iodotoluene (**1a**), 4-methyl-benzoyl chloride (**2a**), and potassium ferrocyanide [$K_4Fe(CN)_6{\cdot}3H_2O$] was initially chosen as the model reaction to optimize the reaction conditions. The combination of palladium chloride/tri(2-furyl)phosphine (TFP)/norbornene was used as the catalyst in the presence of Cs_2CO_3 in toluene at 100 °C. The selected results are summarized in Table 1. The desired product **3a** was obtained in 26% yield (Table 1, entry 1). Further investigation of various solvents revealed that the yield was slightly improved when toluene was replaced by 1,4-dioxane (entry 2). More polar solvents such as DMF and CH_3CN were found to be ineffective for this reaction (entries 3 and 4). The effect of other monodentate phosphine ligands was examined. Only a trace amount of product was detected when PPh_3 and $(3\text{-}ClPh)_3P$ were employed, and $(C_6F_5)_3P$ was totally inactive (entries 7−9). Different palladium catalysts, including Pd(II) and Pd(0) catalysts, were surveyed, and it was found that $Pd(OAc)_2$, $[Pd(C_3H_5)Cl]_2$, and $Pd_2(dba)_3{\cdot}CHCl_3$ cannot catalyze this reaction (entries 10 and 12). In addition, the variation of the amount of norbornene did not show a significant influence on the formation of the target product. Finally, we screened a series of cyanation reagents, including CuCN, TMSCN, and $Zn(CN)_2$. The yield of the target product was dramatically increased to 72% when CuCN was used (entry 13). Surprisingly, employment of TMSCN and $Zn(CN)_2$ did not result in any cyanation products (entries 14 and 15). We

Received: November 27, 2015
Published: January 25, 2016

DOI: 10.1021/acs.joc.5b02710
J. Org. Chem. 2016, 81, 1558−1564

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	[Pd]	ligand	solvent	[CN]	x	yield (%)
1	$PdCl_2$	TFP	toluene	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	26
2	$PdCl_2$	TFP	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	30
3	$PdCl_2$	TFP	DMF	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	trace
4	$PdCl_2$	TFP	CH_3CN	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	trace
5	$PdCl_2$	TFP	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	1	13
6	$PdCl_2$	TFP	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	3	32
7	$PdCl_2$	PPh_3	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	trace
8	$PdCl_2$	$(3\text{-}ClC_6H_4)_3P$	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	trace
9	$PdCl_2$	$(C_6F_5)_3P$	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	N.D.
10	$Pd(OAc)_2$	TFP	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	trace
11	$[Pd(C_3H_5)Cl]_2$	TFP	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	trace
12	$Pd_2(dba)_3{\cdot}CHCl_3$	TFP	dioxane	$K_4Fe(CN)_6{\cdot}3H_2O$[b]	2	trace
13	$PdCl_2$	TFP	dioxane	CuCN[c]	2	72
14	$PdCl_2$	TFP	dioxane	TMSCN[d]	2	N.D.
15	$PdCl_2$	TFP	dioxane	$Zn(CN)_2$[e]	2	N.D.
16	$PdCl_2$	TFP	dioxane	CuCN[f]	2	N.D.
17	$PdCl_2$	TFP	dioxane	CuCN[g]	2	N.D.
18	$PdCl_2$	TFP	dioxane	CuCN[h]	2	56
19	$PdCl_2$	TFP	dioxane	CuCN[i]	2	trace
20	$PdCl_2$	TFP	dioxane	CuCN[j]	2	N.D.
21	–	TFP	dioxane	CuCN	2	N.D.

[a] **1a** (0.3 mmol, 1.0 equiv), **2a** (0.9 mmol, 3.0 equiv), CuCN (0.36 mmol, 1.2 equiv), Pd (10 mol %), ligand (20 mol %), norbornene (0.6 mmol, 2.0 equiv), Cs_2CO_3 (0.9 mmol, 3.0 equiv), H_2O (0.6 mmol, 2.0 equiv), solvent (3.0 mL), 100 °C, 12 h. [b] 4 equiv. [c] 1.2 equiv. [d] TMSCN (2 equiv), CsF (3 equiv). [e] $Zn(CN)_2$ (2 equiv). [f] Without H_2O. [g] 80 °C. [h] 120 °C. [i] K_2CO_3 (3.0 equiv). [j] Na_2CO_3 (3.0 equiv).

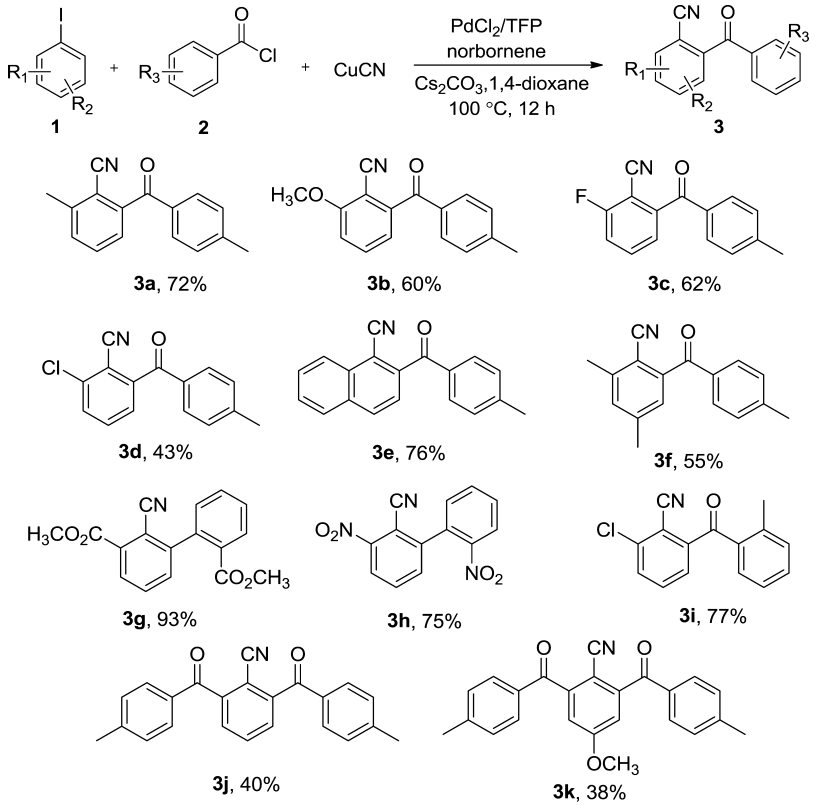
found that water is essential to the acylation reaction, and no desired product was observed when the reaction was conducted in strictly anhydrous dioxane (entry 16). The reaction did not occur below 80 °C, and higher temperature than 100 °C resulted in decrease of the yield (entries 17 and 18). The screening of bases showed that K_2CO_3 and Na_2CO_3 are not effective (entries 19–20). Further investigation revealed that none of the product was detected without palladium catalyst (entry 21).

Under the optimized reaction conditions, the scope of aryl iodides was examined (Table 2). Generally, aryl iodides containing electron-donating and electron-withdrawing groups were both tolerated under the reaction conditions, providing the corresponding diaryl ketones **3a**–**3k** in moderate to good yields (Table 2). The inherent electronic nature of aryl iodides plays an important effect on this reaction. Aryl iodides **1a** and **1b**, bearing electronic-donating ortho-substitutents, reacted smoothly, giving **3a** and **3b** in ca. 70% yields. However, when 2-chloroiodobenzene was reacted with 4-methylbenzoyl chloride **2a** and CuCN, low yield of the desired product **3d** was obtained under the standard conditions. Notably, the substrate **1c** containing a *ortho*-fluoride substitutent could work well in this transformation, and the corresponding product **3c** was isolated in 62% yield. 1-Iodonaphthalene also worked well, providing the diaryl ketone **3e** in good yield (76%). When aryl iodides with strong electron-withdrawing groups were employed in the reaction, the desired products could not be obtained at all. Instead, the cross-coupling products of two molecules of aryl iodides were isolated. Homocoupling products, diethyl 2′-cyano-[1,1′-biphenyl]-2,3′-dicarboxylate **3g** and 2′,3-dinitro-[1,1′-biphenyl]-2-carbonitrile **3h** were isolated in 93% and 75% yields, respectively. This result might indicate that the reaction is strongly influenced by the substituents of iodobenzene. Aryl iodides with strong electron-withdrawing groups are more reactive than acid anhydrous with respect to oxidative addition toward palladium. For aryl iodides without ortho-substituents, diketones **3j** and **3k** were obtained in ca. 40% yields under the standard conditions. Unlike 2-iodotoluene, the reaction of 3-iodotoluene with 4-methylbenzoyl chloride and CuCN gave a complicated mixture. Under the similar conditions, 2-bromotoluene and 2-chlorotoluene were not reactive probably because C–Br bond and C–Cl bonds are more inert than a C–I bond.

The scope of this reaction with a number of functionalized benzoyl chlorides **2** was subsequently explored. Ortho-, para-, and meta-substituted benzoyl chlorides were all good coupling partners in these reactions, and target ketones were afforded in moderate to good yields (Table 3, **4a**–**4p**). Generally, benzoyl chlorides with ortho-substituted groups work better in this reaction than the ones with para-substituted groups.[16] The reactions of 2-methylbenzoyl chloride and 3-methylbenzoyl chloride with 2-iodotoluene yielded the corresponding ketons **4b** and **4c** almost quantitatively. Similarly, 2-methoxybenzoyl chloride also afforded **4d** in 86% yield. The structure of **4d** was

DOI: 10.1021/acs.joc.5b02710
J. Org. Chem. 2016, 81, 1558–1564

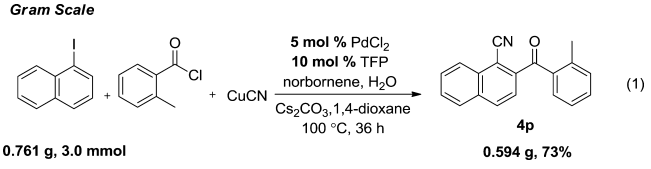
Table 2. Substrate Scope of Aryl Iodide[a]



[a]Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (3.0 equiv), CuCN (1.2 equiv), $PdCl_2$ (10 mol %), TFP (20 mol %), norbornene (2.0 equiv), Cs_2CO_3 (3.0 equiv), H_2O (2.0 equiv), 1,4-dioxane (3.0 mL), 100 °C, 12 h.

confirmed by X-ray single-crystal diffraction, and the molecular structure is given in the Supporting Information. For benzoyl chlorides bearing electron-withdrawing ortho-substituents, the yields of the corresponding products **4f** and **4h** are much lower. Benzoyl chlorides having either electron-donating or electron-withdrawing para-substituents showed relatively lower activities than unsubstituted benzoyl chloride, and their corresponding products **4e**, **4g**, and **4i** were obtained in moderate yields. When 2,4,6-trimethylbenzoyl chloride was applied, **4m** was obtained in 64% yield, illustrating that the steric hindrance did not play a critical role in the reaction. 2-Furoyl chloride is not a suitable substrate, and no desired furoyl derivatives were obtained. The acetylation reaction was not successful in the cases of acetyl chloride or cyclohexanecarbonyl chloride. However, we were able to isolate 2-acetyl-6-methylbenzonitrile **4q** in 27% yield when acetic anhydride was applied under anhydrous conditions.

It is noteworthy that this sequential acylation/cyanation can be performed on the gram scale, and the loading of palladium catalyst can be lowered to 5 mol % (eq 1). We used 1-



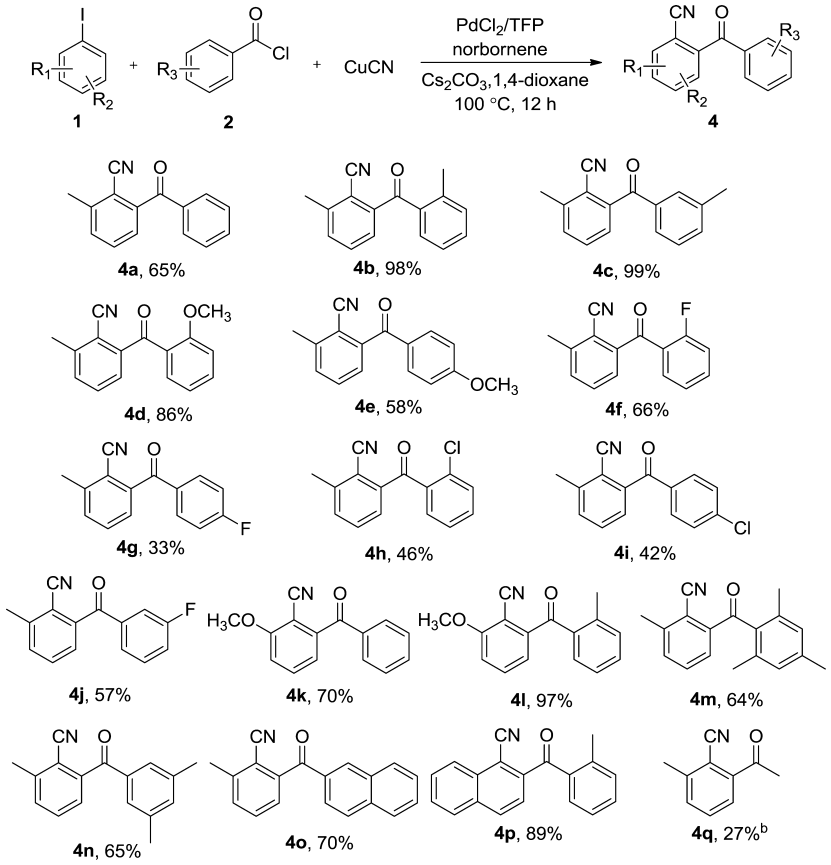
iodonaphthalene and 2-methylbenzoyl chloride as the substrates. The reaction of 1-iodonaphthalene (3 mmol, 0.761 g) and 2-methylbenzoyl chloride (9 mmol, 1.386 g) was performed in the presence of 0.15 mmol of palladium, 0.3 mmol of ligand, 6 mmol of H_2O, and 9 mmol of Cs_2CO_3 at 100 °C. The desired product **4p** was isolated in 73% yield within 36 h.

To gain mechanistic insights of this reaction, two control experiments were performed, and the conversion was calculated according to the isolated products (Chart 1, eqs 2–6). When benzoic anhydride was employed other than benzoyl chloride under anhydrous conditions, **4a** was isolated in up to 70% yield (Chart 1, eq 2). When benzoyl chloride and CuCN were replaced by benzoyl cyanide, the reaction did not occur under the standard reaction conditions (Chart 1, eq 3). Further addition of CuCN did not initiate the reaction of 2-iodotoluene (Chart 1, eq 4). We also found that benzoylation of 2-iodotuluene and benzonitrile with benzoyl chloride was not successful under the present reaction conditions (Chart 1, eqs 5 and 6). In the reaction of 2-iodotoluene with benzoyl chlorides, only a trace amount of expected 3-methylphenylphenone was observed, and a significant amount of di(*o*-tolyl) ether, 2-(*o*-tolyl)bicyclo[2.2.1]hept-2-ene, and 5,9-dimethyl-1,2,3,4,4*a*,12*b*-hexahydro-1,4-methanotriphenylene were formed. These experiments may indicate that the acylation/cyanation product is not formed via acylation of benzonitrile.

Based on the above experimental results and previous reports,[6−10] a plausible mechanism is proposed in Scheme 1. The reaction is initiated by oxidative addition of substrate **1** to Pd(0) complex to generate aryl−Pd(II) complex **I**. A five-membered palladacycle intermediate **III** would be produced through norbornene insertion to the C−Pd bond and subsequent intramolecular C−H activation reaction via intermediate **II**. This palladacycle undergoes oxidative addition with acid anhydride, in situ generated from hydrolysis of

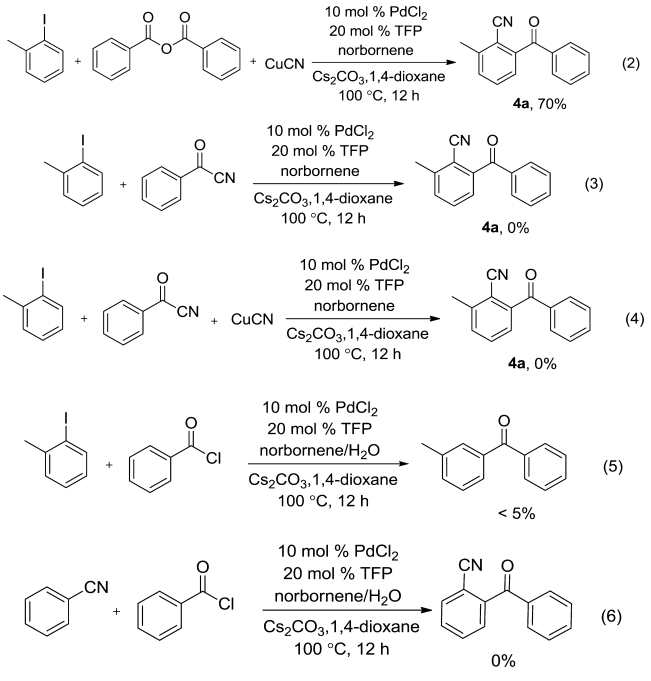
DOI: 10.1021/acs.joc.5b02710
J. Org. Chem. 2016, 81, 1558−1564

Table 3. Substrates Scope of Benzoyl Chloride[a]



[a]Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (3.0 equiv), CuCN (1.2 equiv), $PdCl_2$ (10 mol %), TFP (20 mol %), norbornene (2.0 equiv), Cs_2CO_3 (3.0 equiv), H_2O (2.0 equiv), 1,4-dioxane (3 mL), 100 °C, 12 h. [b]Acetic anhydride (5 equiv).

Chart 1. Control Experiments (eqs 2–6)



benzoyl chloride. The palladium(IV) species **IV** undergoes a reductive elimination to give species **V**. After de-insertion of norbornene from **V**, a new aryl-Pd(II) species is formed with norbornene exclusion. At last, intermediate **VII**, formed by the transmetalation of species **VI** with CuCN, yields the desired product **3** or **4** and regenerates Pd(0) catalyst after reductive elimination.

CONCLUSION

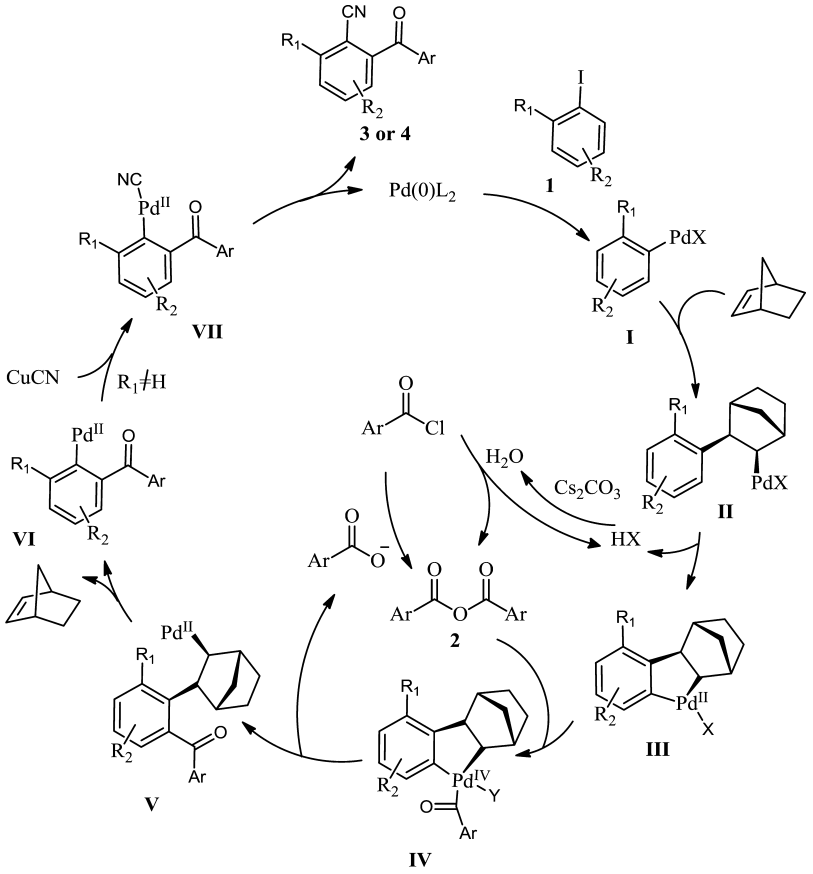
In conclusion, a palladium-catalyzed site-selective C–H bond acylation/C–I acyanation of aryl iodides with commercially available benzoyl choloride was reported. The reaction provides a straightforward and practical way to prepare a series of *ortho*-cyano aryl ketones in good to high yields. The development of further applications of this transformation is in progress in our laboratory.

EXPERIMENTAL SECTION

General Procedure for the Sequential Acylation/Cyanation Reaction between Aryl Iodides 1, Acyl Chlorides 2, and CuCN. A 25 mL of Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with aryl iodide (0.3 mmol, 1.0 equiv), benzoyl chloride (126 mg, 0.9 mmol, 3.0 equiv), CuCN (32.2 mg, 0.36 mmol, 1.1 equiv), $PdCl_2$ (5.3 mg, 0.03 mmol, 10 mol %), TFP (13.9 mg, 0.06 mmol, 20 mol %), Cs_2CO_3 (293 mg, 0.9 mmol, 3.0 equiv), norbornene (56 mg, 0.6 mmol, 2.0 equiv), H_2O (10.8 mg, 0.6 mmol, 2.0 equiv), and 1,4-dioxane (3.0 mL). The resulting light-yellow suspension was stirred at room temperature for 5 min under N_2 and then heated to 100 °C overnight. Upon completion of the reaction as monitored by TLC, the reaction was allowed to cool to room temperature, diluted with ethyl acetate (5 mL) and water (15 mL), and extracted with ethyl acetate (10 mL × 3). The organic phase was collected and washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated.

DOI: 10.1021/acs.joc.5b02710
J. Org. Chem. 2016, 81, 1558–1564

Scheme 1. Possible Catalytic Cycle



The crude residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding products.

*2-Methyl-6-(4-methylbenzoyl)benzonitrile (**3a**).* Light-yellow oil (50 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 2.64 (s, 3H), 7.29 (d, J = 7.6 Hz, 2H), 7.41 (dd, J = 0.8, 7.6 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 21.8, 111.8, 116.1, 127.0, 129.4, 130.6, 131.6, 132.3, 133.5, 142.5, 143.7, 144.9, 193.9. HR MS (TOF MS, EI+) m/z calcd for $C_{16}H_{13}NO$: 235.0997; found: 235.0993.

*2-Methoxy-6-(4-methylbenzoyl)benzonitrile (**3b**).* Light-yellow solid (45 mg, 60% yield); melting point: 101−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.99 (s, 3H), 7.12−7.16 (m, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.59−7.63 (m, 1H), 7.72 (d, J = 8.4 Hz, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 21.8, 56.5, 100.7, 113.3, 114.3, 121.3, 129.4, 130.5, 133.4, 133.5, 143.9, 145.1, 162.1, 193.4. HR MS (TOF MS, EI+) m/z calcd for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0944.

*2-Fluoro-6-(4-methylbenzoyl)benzonitrile (**3c**).* Yellow oil (44 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.31 (d, J = 7.6 Hz, 2H), 7.39−7.44 (m, 2H), 7.67−7.73 (m, 3H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 21.9, 101.0 (d, $^2J_{C-F}$ = 16.2 Hz), 111.9, 118.6 (d, $^2J_{C-F}$ = 19.5 Hz), 125.5 (d, $^3J_{C-F}$ = 3.9 Hz), 129.6, 130.5, 132.9, 134.1 (d, $^3J_{C-F}$ = 8.8 Hz), 143.6, 145.5, 164.0 (d, $^1J_{C-F}$ = 260.0 Hz), 192.1 (d, $^4J_{C-F}$ = 1.9 Hz). HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{10}FNO$: 239.0746; found: 239.0748.

*2-Chloro-6-(4-methylbenzoyl)benzonitrile (**3d**).* White solid (33 mg, 43% yield); melting point: 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.51 (dd, J = 1.2, 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.68−7.72 (m, 3H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 21.9, 112.4, 114.0, 127.5, 129.6, 130.6, 131.8, 132.8, 132.9, 138.8, 144.4, 145.6, 192.4. HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{10}ClNO$: 255.0451; found: 255.0455.

*2-(4-Methylbenzoyl)-1-naphthonitrile (**3e**).* Light-yellow oil (62 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.69−7.79 (m, 4H), 7.99 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 21.9, 109.3, 115.8, 124.9, 126.1, 128.7, 128.8, 129.5, 130.7, 132.5, 132.6, 133.5, 133.6, 142.4, 145.2, 194.2. HR MS (TOF MS, EI+) m/z calcd for $C_{19}H_{13}NO$: 271.0997; found: 271.0994.

*2,4-Dimethyl-6-(4-methylbenzoyl)benzonitrile (**3f**).* Yellow oil (41 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.44 (s, 3H), 2.59 (s, 3H), 7.21 (s, 1H), 7.28 (s, 1H), 7.30 (d, J = 0.8 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 20.7, 21.7, 21.8, 108.8, 116.4, 127.7, 129.4, 130.5, 132.9, 133.7, 142.6, 142.7, 143.4, 144.9, 194.2. HR MS (TOF MS, EI+) m/z calcd for $C_{17}H_{15}NO$: 249.1154; found: 249.1156.

*Dimethyl 2′-cyano-[1,1′-biphenyl]-2,3′-dicarboxylate (**3g**).* Yellow oil (41 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 4.00 (s, 3H), 7.31 (dd, J = 1.2, 7.6 Hz, 1H), 7.52−7.58 (m, 2H), 7.62−7.70 (m, 2H), 7.12−7.15 (m, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 52.2, 52.9, 112.4, 116.1, 129.1, 129.3, 129.7, 130.9, 131.0, 131.5, 132.4, 132.6, 133.1, 139.5, 148.4, 164.9, 166.6. HR MS (TOF MS, EI+) m/z calcd for $C_{17}H_{13}NO_4$: 295.0845; found: 295.0841.

*2′,3-Dinitro-[1,1′-biphenyl]-2-carbonitrile (**3h**).* Yellow solid (30 mg, 75% yield); melting point: 188−190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, J = 1.4, 7.8 Hz, 1H), 7.69−7.76 (m, 2H), 7.80−7.89 (m, 2H), 8.30 (dd, J = 1.0, 8.2 Hz, 1H), 8.37 (dd, J = 1.2, 8.4 Hz, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 107.6, 113.3, 124.8, 125.6, 131.0, 131.8, 131.9, 133.1, 134.1, 134.2, 146.2, 147.4, 149.3. HR MS (TOF MS, EI+) m/z calcd for $C_{13}H_7N_3O_4$: 269.0437; found:269.0432.

*2-Chloro-6-(2-methylbenzoyl)benzonitrile (**3i**).* Yellow solid (59 mg, 77% yield); melting point: 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H), 7.23−7.31 (m, 2H), 7.35 (d, J = 7.6, 1H), 7.45−7.50 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.70 (dd, J = 1.2, 8.0 Hz, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.9, 112.5, 113.9, 125.6,

DOI: 10.1021/acs.joc.5b02710
J. Org. Chem. 2016, 81, 1558−1564

128.6, 130.8, 132.0, 132.4, 132.5, 132.8, 135.7, 139.3, 139.6, 144.4, 194.5. HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{10}ClNO$: 255.0451; found: 255.0456.

*2,6-Bis(4-methylbenzoyl)benzonitrile (**3j**).* Light-yellow solid (41 mg, 40% yield); melting point: 164−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 6H), 7.31 (d, J = 8.0 Hz, 4H), 7.71−7.79 (m, 7H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 21.9, 110.0, 114.7, 129.6, 130.6, 131.5, 133.1, 143.9, 145.5, 193.2. HR MS (TOF MS, EI+) m/z calcd for $C_{23}H_{17}NO_2$: 339.1259; found:339.1263.

*4-Methoxy-2,6-bis(4-methylbenzoyl)benzonitrile (**3k**).* White solid (42 mg, 38% yield); melting point: 166−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 6H), 3.91 (s, 3H), 7.18 (s, 2H), 7.30 (d, J = 8.0 Hz, 4H), 7.75 (d, J = 8.0 Hz, 4H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 21.9, 56.2, 101.3, 114.9, 116.2, 129.6, 130.6, 132.9, 145.6, 145.8, 161.6, 193.1. HR MS (TOF MS, EI+) m/z calcd for $C_{24}H_{19}NO_3$: 369.1365; found: 369.1362.

*2-Benzoyl-6-methylbenzonitrile (**4a**).* Light-yellow oil (43 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 7.43 (dd, J = 1.2, 7.2 Hz, 1H), 7.48−7.58 (m, 4H), 7.62−7.66 (m, 1H), 7.81 (m, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 111.8, 116.0, 127.2, 128.6, 130.4, 131.6, 132.6, 133.8, 136.1, 142.1, 143.8, 194.2. HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{11}NO$: 221.0841; found: 221.0843.

*2-Methyl-6-(2-methylbenzoyl)benzonitrile (**4b**).* Yellow oil (69 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 2.62 (s, 3H), 7.21 (t, J = 7.4 Hz, 1H), 7.27−7.31 (m, 2H), 7.35−7.37 (m, 1H), 7.42 (td, J = 7.6, 1.6 Hz, 1H), 7.48−7.52 (m, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.7, 20.9, 111.9, 116.1, 125.4, 128.3, 130.5, 131.6, 131.7, 131.9, 133.2, 136.6, 139.1, 142.4, 144.1, 196.1. HR MS (TOF MS, EI+) m/z calcd for $C_{16}H_{13}NO$: 235.0997; found: 235.0994.

*2-Methyl-6-(3-methylbenzoyl)benzonitrile (**4c**).* Orange yellow oil (70 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.64 (s, 3H), 7.35−7.45 (m, 3H), 7.50−7.58 (m, 3H), 7.66 (s, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 21.4, 111.8, 116.1, 127.1, 127.8, 128.5, 130.7, 131.6, 132.5, 134.7, 136.1, 138.6, 142.3, 143.7, 194.4. HR MS (TOF MS, EI+) m/z calcd for $C_{16}H_{13}NO$: 235.0997; found: 235.0992.

*2-(2-Methoxybenzoyl)-6-methylbenzonitrile (**4d**).* Light-yellow oil (65 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 3.65 (s, 3H), 6,97 (d, J = 8.4 Hz, 1H), 7.05−7.09 (m, 1H), 7.39−7.58 (m, 5H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 55.6, 111.1, 111.7, 116.3, 120.9, 127.3, 127.6, 131.1, 131.5, 132.7, 134.0, 143.0, 143.5, 158.5, 194.0. HR MS (TOF MS, EI+) m/z calcd for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0948.

*2-(4-Methoxybenzoyl)-6-methylbenzonitrile (**4e**).* Yellow oil (43 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (s, 3H), 3.89 (s, 3H), 6.94−6.98 (m, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.79−7.83 (m, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 20.8, 55.6, 111.7, 113.9, 116.1, 126.7, 128.9, 131.6, 132.0, 132.9, 142.9, 143.6, 164.2, 192.9. HR MS (TOF MS, EI+) m/z calcd for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0949.

*2-(2-Fluorobenzoyl)-6-methylbenzonitrile (**4f**).* Light-yellow oil (47 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 7.12−7.17 (m, 1H), 7.31 (td, J = 1.2, 7.6 Hz, 1H), 7.46−7.48 (m, 1H), 7.52−7,55 (m, 2H), 7.57−7.63 (m, 1H), 7.73 (td, J = 1.6, 7.6 Hz, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 111.2, 116.0, 116.5 (d, $^2J_{C-F}$ = 21.7 Hz), 124.7 (d, $^3J_{C-F}$ = 3.8 Hz), 125.6 (d, $^2J_{C-F}$ = 13.2 Hz), 127.6 (d, $^4J_{C-F}$ = 2.1 Hz), 131.5 (d, $^4J_{C-F}$ = 2.0 Hz), 131.8, 133.4, 135.0 (d, $^3J_{C-F}$ = 8.4 Hz), 142.0, 143.9, 161.0 (d, $^1J_{C-F}$ = 253.1 Hz), 191.2. HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{10}FNO$: 239.0746; found: 239.0745.

*2-(4-Fluorobenzoyl)-6-methylbenzonitrile (**4g**).* Yellow oil (24 mg, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 7.15−7.20 (m, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.52−7.60 (m, 2H), 7.84−7.88 (m, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 111.8, 115.9 (d, $^2J_{C-F}$ = 22.2 Hz), 115.9, 126.9, 131.7, 132.5 (d, $^3J_{C-F}$ = 3.0 Hz), 132.6, 133.0 (d, $^3J_{C-F}$ = 9.9 Hz), 141.9, 143.9, 166.2 (d, $^1J_{C-F}$ = 255.9 Hz), 192.7. HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{10}FNO$: 239.0746; found: 239.0746.

*2-(2-Chlorobenzoyl)-6-methylbenzonitrile (**4h**).* Light-yellow solid (35 mg, 46% yield); melting point: 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H), 7.39−7.57 (m, 7H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.9, 111.7, 116.0, 127.1, 128.8, 130.4, 130.4, 131.8, 132.2, 132.5, 134.1, 137.3, 140.4, 144.6, 193.2; HR MS (TOF MS, EI +) m/z calcd for $C_{15}H_{10}ClNO$: 255.0451; found: 255.0448.

*2-(4-Chlorobenzoyl)-6-methylbenzonitrile (**4i**).* Light-yellow solid (32 mg, 42% yield); melting point: 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 7.41 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.52−7.59 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 111.8, 115.9, 127.0, 129.1, 131.7, 132.7, 134.4, 140.5, 141.6, 144.0, 193.0. HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{10}ClNO$: 255.0451; found: 255.0450.

*2-(3-Fluorobenzoyl)-6-methylbenzonitrile (**4j**).* Light-yellow oil (40 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H), 7.32−7.37 (m, 1H), 7.42−7.60 (m, 6H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 111.9, 115.9, 116.8 (d, $^2J_{C-F}$ = 22.7 Hz), 120.9 (d, $^2J_{C-F}$ = 20.9 Hz), 126.3 (d, $^4J_{C-F}$ = 2.5 Hz), 127.2, 130.3 (d, $^3J_{C-F}$ = 6.4 Hz), 131.7, 132.9, 138.1 (d, $^3J_{C-F}$ = 6.4 Hz), 141.4, 144.1, 162.7 (d, $^1J_{C-F}$ = 247.5 Hz), 192.9 (d, $^4J_{C-F}$ = 3.2 Hz). HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{10}FNO$: 239.0746; found: 239.0749.

*2-Benzoyl-6-methoxybenzonitrile (**4k**).* Yellow oil (49 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (s, 3H), 7.15−7.18 (m, 2H), 7.47−7.51 (m, 2H), 7.60−7.65 (m, 2H), 7.81−7.83 (m, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 56.5, 100.8, 113.5, 114.2, 121.4, 128.6, 130.4, 133.5, 133.9, 135.9, 143.5, 162.1, 193.7. HR MS (TOF MS, EI+) m/z calcd for $C_{15}H_{11}NO_2$: 237.0790; found: 237.0788.

*2-Methoxy-6-(2-methylbenzoyl)benzonitrile (**4l**).* Yellow oil (73 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.99 (s, 3H), 7.12 (dd, J = 0.8, 7.6 Hz, 1H), 7.17 (dd, J = 0.4, 8.4 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.30−7.33 (m, 2H), 7.44 (td, J = 1.2, 7.2 Hz, 1H), 7.56−7.60 (m, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.8, 56.5, 100.8, 114.2, 122.5, 125.4, 130.7, 131.8, 132.0, 133.5, 136.5, 139.2, 143.8, 162.4, 195.6. HR MS (TOF MS, EI+) m/z calcd for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0946.

*2-Methyl-6-(2,4,6-trimethylbenzoyl)benzonitrile (**4m**).* White solid (50 mg, 64% yield); melting point: 192−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 6H), 2.33 (s, 3H), 2.67 (s, 3H), 6.90 (s, 2H), 7.35 (dd, J = 0.6, 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.54 (dd, J = 0.6, 7.6 Hz, 2H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 19.6, 20.9, 21.2, 111.2, 116.4, 128.7, 129.1, 132.0, 134.4, 134.8, 135.8, 139.5, 140.4, 145.1, 198.1. HR MS (TOF MS, EI+) m/z calcd for $C_{18}H_{17}NO$: 263.1310; found: 263.1311.

*2-(3,5-Dimethylbenzoyl)-6-methylbenzonitrile (**4n**).* Light-yellow oil (48 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (d, J = 4.0 Hz, 6H), 2.65 (s, 3H), 7.26 (s, 1H), 7.39−7.40 (m, 3H), 7.49−7.57 (m, 2H): ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 20.8, 21.2, 111.8, 116.0, 127.0, 128.2, 131.5, 132.3, 135.6, 136.2, 138.3, 142.6, 143.7, 194.6. HR MS (TOF MS, EI+) m/z calcd for $C_{17}H_{15}NO$: 249.1154; found: 249.1158.

*2-(2-Naphthoyl)-6-methylbenzonitrile (**4o**).* Light-yellow solid (57 mg, 70% yield); melting point: 184−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H), 7.48−7.65 (m, 5H), 7.88−8.01 (m, 4H), 8.20 (s, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.9, 111.9, 116.1, 125.1, 127.0, 127.2, 127.9, 128.8, 129.1, 129.7, 131.6, 132.2, 132.5, 133.1, 133.4, 135.9, 142.4, 143.9, 194.2. HR MS (TOF MS, EI+) m/z calcd for $C_{19}H_{13}NO$: 271.0997; found: 271.0998.

*2-(2-Methylbenzoyl)-1-naphthonitrile (**4p**).* Yellow oil (72 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H), 7.22−7.25 (m, 1H), 7.32−7.37 (m, 2H), 7.45−7.49 (m, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.69−7.79 (m, 2H), 7.98 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.9, 109.9, 115.6, 125.5, 126.4, 128.6, 129.1, 130.9, 131.8, 132.2, 132.6, 133.9, 136.6, 139.3, 142.2, 196.3. HR MS (TOF MS, EI+) m/z calcd for $C_{19}H_{13}NO$: 271.0997; found: 271.0997.

*2-Acetyl-6-methylbenzonitrile (**4q**).*[17] White solid (13 mg, 27% yield); melting point: 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 2.68 (s, 3H), 7.52 (d, J = 7.2 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 7.2 Hz, 1H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 20.9, 28.0, 110.8, 116.8, 127.1, 131.9, 133.8, 140.6, 144.6, 196.7.

DOI: 10.1021/acs.joc.5b02710
J. Org. Chem. 2016, 81, 1558−1564

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02710.

Crystallographic data for **4d** (CIF)

Spectra of ^{1}H NMR, ^{13}C NMR for new products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chenwzz@zju.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial supports from National Natural Science Foundation of China (nos. 21572203 and J1210042) and Zhejiang Provincial Natural Science Foundation of China (no. LZ16B020001) are gratefully acknowledged.

■ REFERENCES

(1) (a) Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062. (b) Leenders, S. H. A. M.; Gramage-Doria, R.; Bruin, B.; Reek, J. N. H. *Chem. Soc. Rev.* **2015**, *44*, 433. (c) Gandeepan, P.; Cheng, C.-H. *Chem. - Asian J.* **2015**, *10*, 824. (d) Denmark, S. E.; Ambrosi, A. *Org. Process Res. Dev.* **2015**, *19*, 982.

(2) (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Seidel, G.; Fürstner, A. *Chem. Commun.* **2012**, *48*, 2055. (c) de Vries, J. G. *Top. Organomet. Chem.* **2012**, *42*, 1.

(3) Zhang, X.; Liu, A.; Chen, W. *Org. Lett.* **2008**, *10*, 3849.

(4) (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (b) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937.

(5) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.

(6) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (b) Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157. (c) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. (d) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759. (e) Maestri, G.; Della Cá, N.; Catellani, M. *Chem. Commun.* **2009**, 4892. (f) Della Cá, N.; Maestri, G.; Malacria, M.; Derat, E.; Catellani, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 12257. (g) Motti, E.; Della Cá, N.; Xu, D.; Piersimoni, A.; Bedogni, E.; Zhou, Z.-M.; Catellani, M. *Org. Lett.* **2012**, *14*, 5792.

(7) (a) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045. (b) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (c) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436. (d) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (e) Gericke, K. M.; Chai, D. I.; Bieler, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1447. (f) Martins, A.; Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 5186. (g) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990. (h) Wu, X.; Zhou, P.; Wang, L.; Xu, P.; Liang, Y. *Chem. Commun.* **2014**, *50*, 3882. (i) Zhang, H.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 10174. (j) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334. (k) Dong, Z.; Wang, J.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 5887.

(8) Dong, Z.; Dong, G.-B. *J. Am. Chem. Soc.* **2013**, *135*, 18350.

(9) (a) Chen, Z.-Y.; Ye, C.-Q.; Zhu, H.; Zeng, X.-P.; Yuan, J.-J. *Chem. - Eur. J.* **2014**, *20*, 4237. (b) Zhou, P.-X.; Ye, Y.- Y.; Ma, J.-W.; Zheng, L.; Tang, Q.; Qiu, Y.-F.; Song, B.; Qiu, Z.-H.; Xu, P.-F.; Liang, Y.-M. *J. Org. Chem.* **2014**, *79*, 6627. (c) Ye, C.; Zhu, H.; Chen, Z. *J. Org. Chem.* **2014**, *79*, 8900. (d) Shi, H.; Babinski, D. J.; Ritter, T. *J. Am. Chem. Soc.* **2015**, *137*, 3775. (e) Sun, F.; Gu, Z. *Org. Lett.* **2015**, *17*, 2222. (f) Pan, S.; Ma, X.; Zhong, D.; Chen, W.; Liu, M.; Wu, H. *Adv. Synth. Catal.* **2015**, *357*, 3052.

(10) (a) Dong, Z.; Wang, J.; Ren, Z.; Dong, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 12664. (b) Huang, Y.; Zhu, R.; Zhao, K.; Gu, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 12669. (c) Zhou, P.-X.; Ye, Y.-Y.; Liu, C.; Zhao, L.-B.; Hou, J.-Y.; Chen, D.-Q.; Tang, Q.; Wang, A.-Q.; Zhang, J.-Y.; Huang, Q.-X.; Xu, P.-F.; Liang, Y.-M. *ACS Catal.* **2015**, *5*, 4927.

(11) (a) Romines, K. R.; Freeman, G. A.; Schaller, L. T.; Cowan, J. R.; Gonzales, S. S.; Tidwell, J. H.; Andrews, C. W.; Stammers, D. K.; Hazen, R. J.; Ferris, R. G.; Short, S. A.; Chan, J. H.; Boone, L. R. *J. Med. Chem.* **2006**, *49*, 727. (b) Neumann, H.; Brennführer, A.; Beller, M. *Chem. - Eur. J.* **2008**, *14*, 3645. (c) Lampe, J. W.; Biggers, C. K.; Defauw, J. M.; Foglesong, R. J.; Hall, S. E.; Heerding, J. M.; Hollinshead, S. P.; Hu, H.; Hughes, P. F.; Jagdmann, G. E.; Johnson, M. G.; Lai, Y.-S.; Lowden, C. T.; Lynch, M. P.; Mendoza, J. S.; Murphy, M. M.; Wilson, J. W.; Ballas, L. M.; Carter, K.; Darges, J. W.; Davis, J. E.; Hubbard, F. R.; Stamper, M. L. *J. Med. Chem.* **2002**, *45*, 2624. (d) Deng, Y.; Chin, Y.-W.; Chai, H.; Keller, W. J.; Kinghorn, A. D. *J. Nat. Prod.* **2007**, *70*, 2049. (e) Harrington, P. J.; Lodewijk, E. *Org. Process Res. Dev.* **1997**, *1*, 72.

(12) (a) Sartori, G.; Maggi, R. *Chem. Rev.* **2006**, *106*, 1077. (b) Chevallier, F.; Blin, T.; Nagaradja, E.; Lassagne, F.; Roisnel, T.; Halauko, Y. S.; Matulis, V. E.; Ivashkevich, O. A.; Mongin, F. *Org. Biomol. Chem.* **2012**, *10*, 4878.

(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(14) (a) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (b) Sharma, S.; Park, J.; Park, E.; Kim, A.; Kim, M.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Adv. Synth. Catal.* **2013**, *355*, 332. (c) Lu, J.; Zhang, H.; Chen, X.; Liu, H.; Jiang, Y.; Fu, H. *Adv. Synth. Catal.* **2013**, *355*, 529. (d) Park, J.; Park, E.; Kim, A.; Lee, Y.; Chi, K.-W.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2011**, *13*, 4390. (e) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6293. (f) Pi, C.; Cui, X.; Liu, X.; Guo, M.; Zhang, H.; Wu, Y. *Org. Lett.* **2014**, *16*, 5164.

(15) Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455.

(16) (a) Grainger, R.; Cornella, J.; Blakemore, D. C.; Larrosa, L.; Campanera, J. M. *Chem. - Eur. J.* **2014**, *20*, 16680. (b) Konovalov, A. I.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 13410.

(17) Mangas-Sánchez, J.; Busto, E.; Gotor-Fernández, V.; Gotor, V. *Org. Lett.* **2012**, *14*, 1444.

DOI: 10.1021/acs.joc.5b02710
J. Org. Chem. 2016, 81, 1558−1564