JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

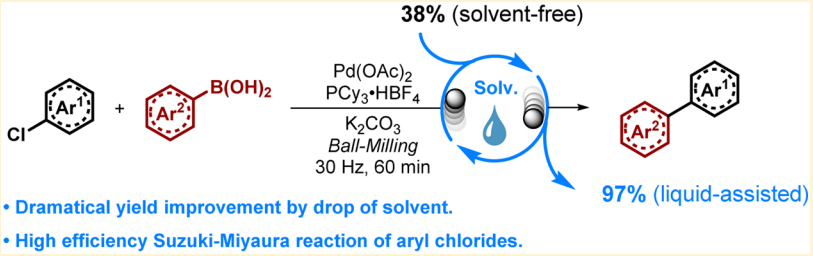
Liquid-Assisted Grinding Accelerating: Suzuki–Miyaura Reaction of Aryl Chlorides under High-Speed Ball-Milling Conditions

Zhi-Jiang Jiang,[†] Zhen-Hua Li,[*,‡] Jing-Bo Yu,[†] and Wei-Ke Su[*,†]

[†]National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P. R. China

[‡]Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China

Supporting Information

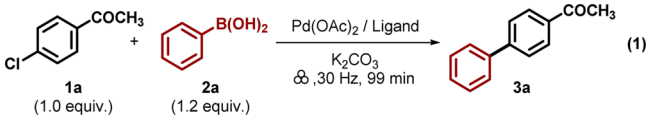


ABSTRACT: The effect of liquid-assisted grinding has been studied using mechanical Suzuki–Miyaura reaction of aryl chlorides as the model reaction. Catalytic systems of Davephos and PCy_3 are tested respectively showing strong influences from different liquids. Unexpected improvement of yield over 55% is observed using alcohols as additives, which is explained by *in situ* formed alkoxides and their participation in oxidative addition. Further expansion of substrates using $Pd(OAc)_2/PCy_3$/MeOH system gives desired products in good to high yields.

High-speed ball-milling (HSBM) promoted mechanical organic reaction has been extensively studied during the past decades, showing its unusual features of high efficiency, excellent chemo-selectivity, and sometimes unique reactivity.[1] Although previous research of this field mainly emphasized on its advantage of totally solvent-free characterization during the reaction procedures from the aspect of green chemistry, introducing small amount of liquid during the grinding, which is called liquid-assisted grinding (LAG),[2] has attracted considerable attention from the community, and shows its potential in chemo-selectivity control,[3] and yield improvement.[4] To unveil the relationship, Mack et. al. showed the diyne/enyne selectivity depended on solvents' polarity,[3b] while Halasz and Užarević reported the correlation of reaction rate with solvents' donor number.[4a] However, the detailed mechanism of solvent molecule's participation is still unclear for those cases.

During our continuous research interest toward fast organic synthesis under HSBM conditions,[5] the unusual features of LAG have attracted our attention. As the small amount of liquid has a strong influence on reaction outcomes, we envision LAG could also be used to facilitate the procedure of transition-metal catalyzed reactions by applying the solvent molecules as ligands. Suzuki–Miyaura reaction as one of the most powerful tools for C–C bond construction has been successfully studied under HSBM conditions using aryl bromides as substrates.[6] Also, the reaction has even been used as a model for mechanochemical parameter investigation,[6d,e] which proves better to understand the ball-milling process. Despite the ligand-free and extremely fast manner of these reactions, the coupling of aryl chlorides remains a challenge, where the only successful case was reported by Cravotto,[7] using hexamethylene diisocyanate cross-linked chitosan/Pd(II) to give moderate to high yields. Thus, this reaction is chosen as the model for the LAG examination to further improve the utility. Herein, we wish to uncover our preliminary result of LAG promoted highly efficient mechanical Suzuki–Miyaura reaction of aryl chlorides.

At the commencement, *p*-chloroacetophenone **1a** and phenylboronic acid **2a** were chosen as model substrates for primary reaction optimization (eq 1). Considering the inert



nature of aryl chlorides, bidentate ligand Davephos was first used to establish the model reaction.[8] Although, the primary attempts gave low yield after 60 min grinding, the following optimization of mechanochemical parameters improved the yield to 55% (see Table S1 in the Supporting Information for more details). Several simpler ligands were then examined, including dppf, dppe, dppp, dppb, PCy_3,[9] and PPh_3 (Table 1).

Received: August 8, 2016
Published: October 1, 2016

DOI: 10.1021/acs.joc.6b01938
J. Org. Chem. 2016, 81, 10049–10055

Table 1. Examination of Ligands[a]

no.	ligand (mol%)	time/min[b]	%yield[c]
1		120	n.d.
2	Davephos (10)	90	55
3	dppf (10)	120	9
4	dppe (10)	120	n.d.
5	dppp (10)	120	n.d.
6	dppb (10)	120	n.d.
7	PCy_3 (20)	120	21
8	PPh_3 (20)	120	n.d.

[a]Reaction conditions unless specified otherwise: **1a** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), ligand (5 mol% for bidentate ligand or 10 mol% for monodentate ligand), and K_2CO_3 (5.0 equiv) were placed in a 25 mL stainless-steel vessel with two stainless-steel balls (ø = 1.4 cm). Ball milling conditions: 60 min at 30 Hz. [b]5 min pause followed after every 30 min grinding. [c]Yield based on **1a**, average of three runs.

Accordingly, PCy_3 gave a better result, which has been involved in aryl chlorides activation previously.[10] Bis-triphenylphospite bidentate ligands with inappropriate steric hindrance failed in cleaving C−Cl bond (Table 1, entries 3−6). A similar result was also found by using monodentate PPh_3 as the ligand. Further optimization of reaction system involving catalytic system loading and ratio based on PCy_3 system led to an improvement in yield for both Davephos and PCy_3 system (see Table S2 in the Supporting Information). Then we turned our focus on the LAG effect of this reaction by adding liquid to the system.

Initially, we hypothesized that the solvents commonly used in Suzuki−Miyaura reaction may lead to good result in mechanochemistry environment.[11] Thus, examination using THF, dioxane, DMF, and CH_3CN as additives (η = 0.045 μL/mg)[12] was performed under the optimal conditions (Table 2, entries 2−5). In the case of THF and dioxane, positive effects were observed. However, erosion of yields was found in the combination of Davephos/DMF and PCy_3/CH_3CN, respectively. The strong fluctuation of yields implicates the phenomenon of solvent-dependence may also present in the solvent-less environment. Thus, further examination of LAG additives was performed to have a glance at the inner pattern.

First, aprotic solvents were tested considering the potential dechlorination of aryl chlorides by protic solvents as alcohols.[13] Inert low-polarity alkanes as *n*-hexane and *n*-heptane gave moderate positive-effect for both ligands, and similar results were also obtained in the cases of dichloromethane and chloroform (Table 2, entries 6−9). Liner ethers did not show positive-effect as their cyclic analogues (Table 2, entries 10−12), while ethyl ether gave unexpected positive result when combined with PCy_3. High-polarity solvent also led to unpredictable results (Table 2, entries 13−15). Ethyl acetate gave the most effective result for Davephos in the aprotic solvent test, while only small promotion was found in the PCy_3 system. The reactions with acetone show retard with Davephos, while a moderate improvement for PCy_3. However, dual negative effect was found when using DMSO as additive, which may be caused by undesired coordination to the metal center.[14]

Frustrated by the results above, protic solvents, such as methanol, ethanol, and H_2O, were then tested (Table 2, entries 16−18). To our surprise, strong positive-effect was found in both Davephos and PCy_3 systems using alcohols as assisted liquid, which afforded product in nearly quantitative yields. For

Table 2. Examination of LAG Additives[a]

no.	solv.	Davephos %yield[b]	%dev.[c]	PCy3 %yield[b]	%dev.[c]
1	neat	66		38	
2	THF	87	+19	56	+18
3	dioxane	90	+23	47	+9
4	DMF	85	+18	37	−4
5	CH_3CN	60	−6	48	+10
6	*n*-hexane	83	+17	55	+17
7	*n*-heptane	80	+14	59	+21
8	CH_2Cl_2	79	+13	59	+21
9	$CHCl_3$	68	+2	54	+17
10	Et_2O	60	−6	67	+29
11	$(CH_2OMe)_2$	56	−10	42	+4
12	PEG-600	62	−4	37	−1
13	EtOAc	94	+28	47	+9
14	acetone	47	−19	52	+14
15	DMSO	51	−15	31	−7
16	MeOH	98	+32	97	+59
17	EtOH	99	+33	94	+56
18	H_2O	88	+21	87	+49
19	*n*-PrOH	89	+23	95	+57
20	*i*-PrOH	68(92)[d]	+2	77(90)[d]	+39
21	*n*-BuOH	90	+14	91	+53
22	*t*-BuOH	67(87)[d]	+1	42(71)[d]	+4
23	$(CH_2OH)_2$	72	+6	65	+27

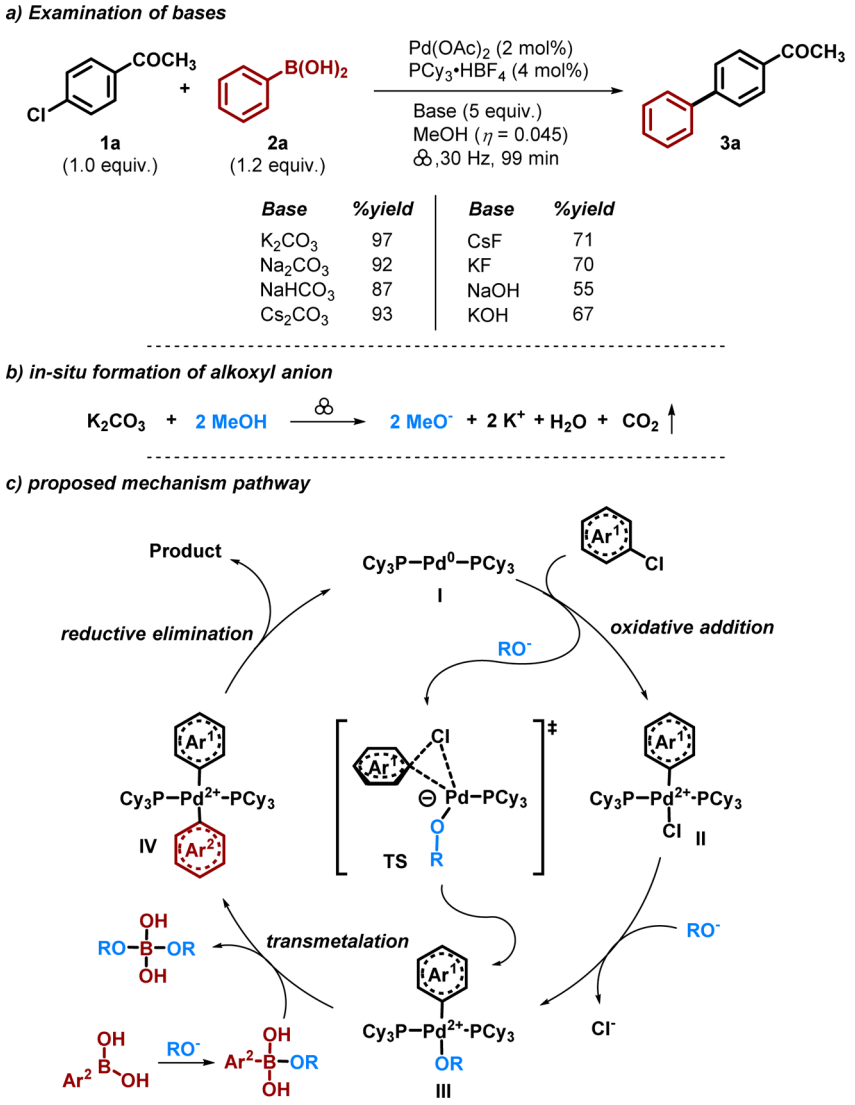
[a]Reaction conditions unless specified otherwise: **1a** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.05 equiv), Davephos (0.05 equiv) or $PCy_3 \cdot HBF_4$ (0.1 equiv), K_2CO_3 (5.0 equiv), and LAG additive (η = 0.045 μL/mg) were placed in a 25 mL stainless-steel vessel with two stainless-steel balls (ø = 1.4 cm). Ball milling conditions: 60 min at 30 Hz. [b]Yield based on **1a**, average of three runs. [c]Deviation of yield from neat conditions. [d]120 min at 30 Hz.

the latter, over 55% improvement of yields were found using methanol and ethanol. H_2O also elevated the yields to 88% and 87% for each system. Inspired by the results, alcohols with a different degree of steric hindrance were then screened (Table 2, entries 19−22). Linear alcohols as *n*-PrOH and *n*-BuOH also gave high yields, but the results with branched alcohols depraved with the increase of steric hindrance as expected. It is noteworthy that the Davephos system seemed to be more sensitive to hindrance, where *i*-PrOH and *t*-BuOH gave similar results. Prolonging the grinding time led these reactions to moderate or good yields implicating the steric hindrance has influenced the reaction rate. Besides, ethylene glycol was also tested, which gave moderate positive effect (Table 2, entry 23).

Further attempts were paid to explain the unexpected role of alcohols in $Pd(OAc)_2/PCy_3$ system. Based on the result of base screening (Scheme 1a), carbonates gave better result than common used CsF and KF. Thus, we envision the alcohols may react with carbonates and transform to alkoxides by releasing CO_2 during the grinding process (Scheme 1b). Further results by replacing the alcohol/base combination by potassium or sodium methoxide as base provided support for the hypothesis, which gave relative yields of 95% and 88%, respectively. From the aspect of the classic mechanism of Suzuki−Miyaura reaction (Scheme 1c),[15] alkoxides usually participate in the steps of ligand exchange and boronic acid activation. While in this mechanical Suzuki−Miyaura reaction presented, it is clear that the steric hindrance of alcohols has a strong influence on the reaction rate (Table 2, entries 20,22), which is mainly controlled by the rate of oxidative addition of C−Cl bond (**I** to **II**) as the rate-determining step. Thus, based on previous

DOI: 10.1021/acs.joc.6b01938
J. Org. Chem. 2016, 81, 10049−10055

Scheme 1. Mechanism Studies



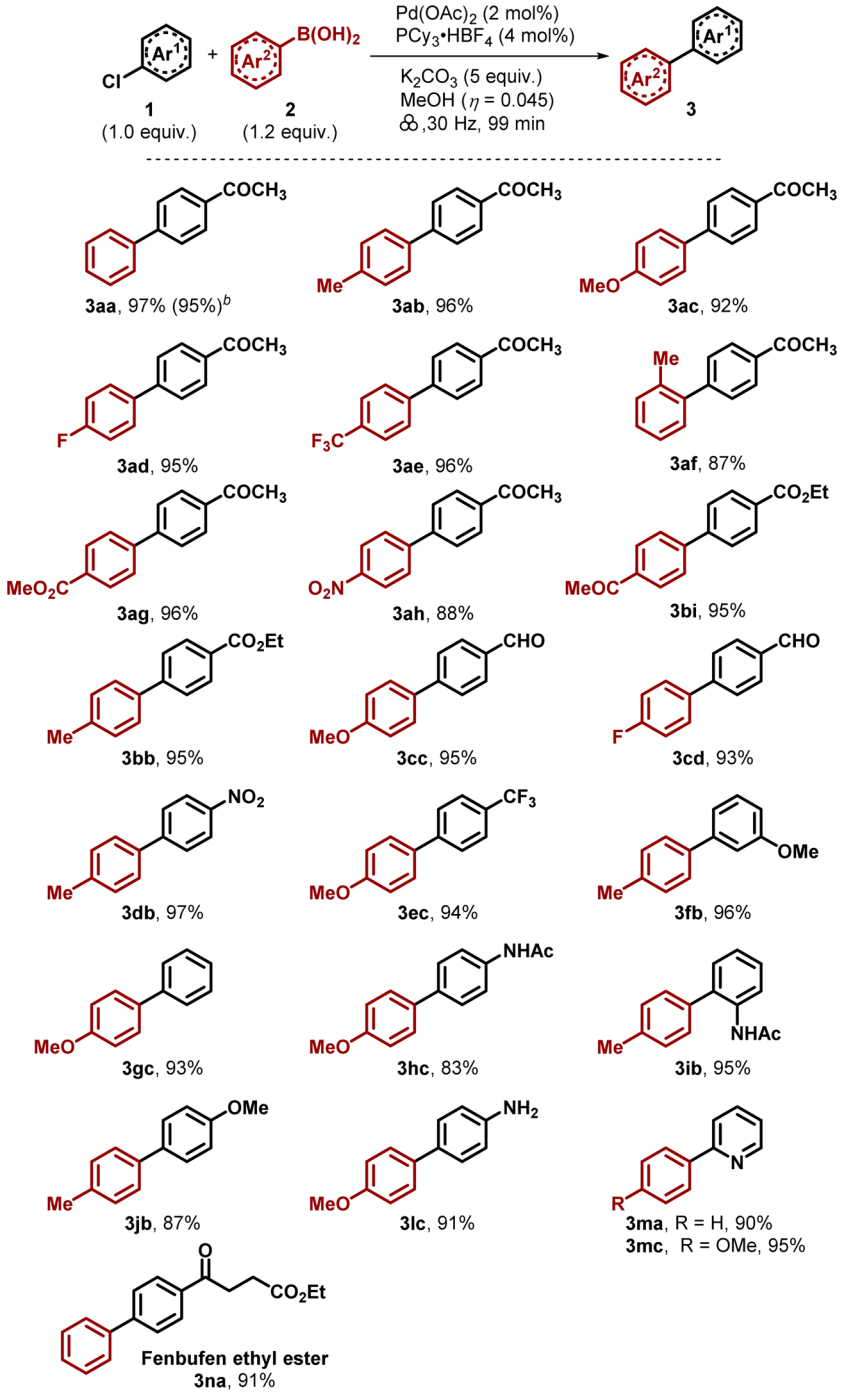
mechanism study,[11] we proposed that a fast synergic oxidative addition occurred under HSBM condition though **TS**, which gave intermediate **III** from **I** directly.

Finally, after a simple test to reduce of the amount of catalyst loading,[16] the substrates scope was then examined using 2 mol % of $Pd(OAc)_2/PCy_3$ with methanol (η = 0.045 μL/mg), which was summarized in Table 3. First, several aryl boronic acids were tested, showing both electron-rich and -deficient species **2a**–**i** worked well during the 99 min grinding. A slight drop in yields was observed using steric **2f** and strong electron withdrawing **2h** as coupling partner, where both reactions gave acceptable yields of 87% and 88%, respectively. Next, several activated aryl chlorides were explored, and all the substrates **1b**–**f** tested gave yields over 90%. Unsubstituted chlorobenzene **1g** also afforded high yield in this sealed environment, without significant loss by volatilization. Afterward, unactivated aryl chlorides bearing electron-donating substitutions were also examined. Accordingly, acetylamino group at *para*-position gave moderate yield, while the directing effect of this group helped the *ortho*-substituted analogue to afford higher yield. To our surprise, unprotected *p*-chloroaniline gave C–C bond coupling product **3lc** sorely, where no trace of C–N bond formation was detected. Besides, the reaction protocol could also be used in the synthesis of Fenbufen ethyl ester **3na** with a high yield of 91%. Scaling up of model reaction to gram level still gave good yield of 95%, which was obtained using 0.5 mol % catalytic system with 2.5 equiv of K_2CO_3.[17] Finally, the protocol was compared with the solvent-based reaction using methanol, dioxane, and dioxane (5% methanol) as solvent. Surprisingly, no conversion of acetophenone was detected after 6 h stirring under room temperature. Further elevating of reaction temperature for the reaction of dioxane and dioxane (5% methanol) gave 61% and 63% after 6 h refluxing, while the methanol solvated reaction only gave less than 10% product under similar conditions.

In summary, we have disclosed a study about LAG accelerated high-efficiency aryl chlorides participated Suzuki–Miyaura reaction under HSBM condition. The result implicates the LAG effect does not only provide substoichiometric solvent-environment, but may also participate in the formation of mechanically induced transition species. Thus, this technique may have the potential to induce higher catalytic activity for existing systems under HSBM conditions. Expansion of substrate scope showed the system built in this work could be applied to both activated and unactivated aryl chlorides with good to high yields.

DOI: 10.1021/acs.joc.6b01938
J. Org. Chem. 2016, 81, 10049–10055

Table 3. Examination of Substrate Scope[a]



[a]Reaction conditions unless specified otherwise: **1a** (1.0 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (2 mol%), $PCy_3{\cdot}HBF_4$ (4 mol%), K_2CO_3 (5.0 equiv), and MeOH (η = 0.045 μL/mg) were placed in a 25 mL stainless-steel vessel with two stainless-steel balls (ø = 1.4 cm). Ball milling conditions: 99 min at 30 Hz. Yield based on **1**, average of two runs. [b]**1a** (10.0 mmol), **2a** (12.0 mmol), $Pd(OAc)_2$ (0.5 mol%), $PCy_3{\cdot}HBF_4$ (1.0 mol%), K_2CO_3 (2.5 equiv), and MeOH (η = 0.045 μL/mg) were placed in a 50 mL stainless-steel vessel with two stainless-steel balls (ø = 1.4 cm). Ball milling conditions: 120 min at 30 Hz.

EXPERIMENTAL SECTION

General Information. All reagents were obtained from commercial suppliers and used without further purification, unless otherwise indicated. The mechanochemical reactions were performed using a commercial Mix-Miller with maximum grinding frequency of 30 Hz. TLC (thin-layer chromatography) analysis was performed using precoated glass plates. Melting points (mp) were obtained on a digital melting point apparatus and uncorrected. NMR spectra were recorded with 400 and 500 MHz spectrometer for ^1H and 126 MHz for ^{13}C, TMS was used as internal standard. Mass spectra were measured with a HRMS-ESI-Q-TOF and a low resolution MS instrument using ESI ionization. The optimization experiments were tracked with TLC every 30 min grinding, while substrate scope examination were grinding without interruption.

General Procedure for the Synthesis of Biaryls. A mixture of substrate **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (2 mol%), $PCy_3{\cdot}HBF_4$ (4 mol%), K_2CO_3 (5.0 equiv), and MeOH (η = 0.045 μL/mg)

DOI: 10.1021/acs.joc.6b01938
J. Org. Chem. 2016, 81, 10049−10055

were added to the 25 mL screw-capped stainless steel vessel, along with two stainless steel balls (ø = 1.4 cm). After that, the vessel was placed in the mixer mill, and the contents were ball milled at 30 Hz for 99 min. At the end of the reaction, small portion (3 mL) ethyl acetate was added into the vessel and grinding for another 2 min at 30 Hz, which was filtered and washed with HCl (1 M). Then, after the washing by brine, the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel (eluents: *n*-hexane/ethyl acetate = 10:1) to give the desired product.

General Procedure for Comparison Experiment in Solvent Environment. In an oven-dried 10 mL Schlenk tube, phenylboronic acid (1.2 mmol), $Pd(OAc)_2$ (2 mol%), $PCy_3{\cdot}HBF_4$ (4 mol%), K_2CO_3 (5.0 equiv) were weighed. The tube was then sealed, evacuated, and refilled with Ar for three times. Then solvent (5 mL) and acetophenone (1.0 mmol) were added. The mixture was then stirred at specified temperature or r.t. for 3 h. At the end of the reaction, the mixture was filtered and washed with HCl (1 M). Then, after the washing by brine, the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel (eluents: *n*-hexane/ethyl acetate = 10:1) to give the desired product.

1-([1,1′-Biphenyl]-4-yl)ethan-1-one (**3aa**).[18] White solid (190.3 mg, 97% yield); mp 120.2−121.1 °C (lit.[18] 119−120 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.64−7.59 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 2.64 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.7, 145.7, 139.9, 135.9, 128.9, 128.9, 128.2, 127.2, 127.2, 26.6; MS (ESI): $C_{14}H_{12}O$ ([M+H]$^+$): calcd. 197.1, found: 197.2.

1-(4′-Methyl-[1,1′-biphenyl]-4-yl)ethan-1-one (**3ab**).[19] White crystal (201.7 mg, 96% yield); mp 118.9−120.6 °C (lit.[19] 119−120 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2 H), 2.65 (s, 3H), 2.42 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.7, 145.7, 138.2, 137.0, 135.6, 129.7, 128.9, 127.1, 126.9, 26.6, 21.1; MS (ESI): $C_{15}H_{15}O$ ([M+H]$^+$): calcd. 211.1, found: 211.1.

1-(4′-Methoxy-[1,1′-biphenyl]-4-yl)ethan-1-one (**3ac**).[18] White crystal (208.4 mg, 92% yield),154.6−156.4 °C (lit.[18] 155−156 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.02 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.66 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.59 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.02 (dt, *J* = 8.5, 2.0 Hz, 2H), 3.88 (s, 3H), 2.65 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.6, 159.9, 145.3, 135.3, 132.2, 128.9, 128.3, 126.6, 114.4, 55.3, 26.6; MS (ESI):$C_{15}H_{15}O_2$ ([M + H]$^+$): calcd. 227.1, Found: 227.1.

1-(4′-Fluoro-[1,1′-biphenyl]-4-yl)ethan-1-one (**3ad**).[20] White crystal (203.1 mg, 95% yield); mp 102.5−104.0 °C (lit.[20] 108.7−110.4 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.60−7.54 (m, 2H), 7.15 (m, 2H), 2.64 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.6, 163.0 (d, *J* = 249.5 Hz), 144.7, 136.0 (d, *J* = 3.3 Hz), 135.9, 129.0, 128.9, 127.1, 115.9 (d, *J* = 21.5 Hz), 26.6; MS (ESI): $C_{14}H_{12}FO$ ([M+H]$^+$): calcd.215.1, found: 215.1.

1-(4′-(Trifluoromethyl)-[1,1′-biphenyl]-4-yl)ethan-1-one (**3ae**).[21] White crystal (254.1 mg, 95% yield); mp 122.2−122.9 (lit.[21] 120.6−121.4 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.08 (dt, *J* = 9.0, 1.5 Hz, 2H), 7.75 (s, 4H), 7.71 (d, *J* = 8.5, 1.5 Hz, 2H), 2.67 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.5, 144.2, 143.4, 136.6, 130.2 (q, *J* = 32.4 Hz), 129.0, 127.6, 127.5, 125.9 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.5 Hz), 26.7; MS (ESI): $C_{15}H_{12}F_3O$ ([M+H]$^+$): calcd. 265.1, found: 265.1.

1-(2′-Methyl-[1,1′-biphenyl]-4-yl)ethan-1-one (**3af**).[19] Colorless oil (183.2 mg, 87% yield); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 6.0 Hz, 2H), 7.31−7.15 (m, 4H), 2.64 (s, 3H), 2.27 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.8, 147.0, 140.8, 135.6, 135.2, 130.5, 129.5, 129.5, 128.2, 127.9, 125.9, 26.6, 20.4; MS (ESI): $C_{15}H_{15}O$ ([M+H]$^+$): calcd. 211.1, found: 211.1.

Methyl 4′-Acetyl-[1,1′-biphenyl]-4-carboxylate (**3ag**).[22] White solid (243.9 mg, 96% yield); mp 164.8−165.7 (lit.[22] 164.5−166.0 °C);^{1}H NMR (500 MHz, chloroform-*d*) δ 8.15 (dt, *J* = 8.5, 2.0 Hz, 2H), 8.07 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.76−7.69 (m, 4H), 3.97 (s, 3H), 2.67 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.5, 166.8, 144.4, 144.2, 136.5, 130.2, 129.8, 129.0, 127.4, 127.2, 52.2, 26.7; MS (ESI): $C_{16}H_{15}O_3$ ([M+H]$^+$): calcd. 255.1, found: 255.1.

1-(4′-Nitro-[1,1′-biphenyl]-4-yl)ethan-1-one (**3ah**).[22] Yellow solid (212.1 mg, 88% yield); mp 150.2−152.1 (lit.[22] 145.5−146.5 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.35 (dt, J = 9.0, 2.5 Hz, 2H), 8.10 (dt, J = 8.0, 2.0 Hz, 2H), 8.00 (dt, J = 6.5, 3.0 Hz, 2H), 7.74 (dt, J = 9.0, 1.5 Hz, 2H), 2.68 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.6, 147.6, 146.2, 143.1, 137.0, 129.1, 128.1, 127.6, 124.2, 26.7; MS (ESI): $C_{14}H_{12}NO_3$ ([M+H]$^+$): calcd. 242.1, found: 242.0.

Ethyl 4′-Acetyl-[1,1′-biphenyl]-4-carboxylate (**3bi**).[23] White solid (254.1 mg, 95% yield); mp 105.9−107.5 (lit.[23] 106.7−107.7 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.16 (dt, J = 8.5, 2.0 Hz, 2H), 8.07 (dt, J = 8.5, 2.0 Hz, 2H), 7.75−7.69 (m, 4H), 4.43 (q, *J* = 7.0 Hz, 2H), 2.67 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H); ^{13}C{H} NMR (126 MHz, $CDCl_3$) δ 197.6, 166.3, 144.5, 144.1, 136.5, 130.2, 129.0, 127.4, 127.2, 61.1, 26.7, 14.4; $C_{17}H_{17}O_3$ ([M+H]$^+$): calcd. 269.1, found: 269.2.

Ethyl 4′-Methyl-[1,1′-biphenyl]-4-carboxylate (**3bb**).[24] White solid (288.2 mg, 95% yield); mp 70.7−72.5 °C (lit.[23] 75−76 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.11 (dt, *J* = 8.5, 1.5 Hz, 2H), 7.66 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.54 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.41 (q, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 166.6, 145.5, 138.1, 137.2, 130.0, 129.6, 129.0, 127.1, 126.8, 60.9, 21.2, 14.4; MS (ESI): $C_{16}H_{17}O_2$ ([M+H]$^+$): calcd. 241.1, found: 241.2.

4′-Methoxyl-[1,1′-biphenyl]-4-carbaldehyde (**3cc**).[18] White solid (201.5 mg, 95% yield); mp 104.5−105.4 °C (lit.[18] 104−105 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 10.1 (s, 1H), 7.94 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.73 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.61 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.03 (dt, *J* = 8.5, 2.0 Hz, 2H), 3.89 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 191.8, 160.2, 146.8, 134.7, 132.1, 130.3, 128.5, 127.1, 114.5, 55.4; MS (ESI): $C_{14}H_{13}O_2$ ([M+H]$^+$): calcd. 213.1, found: 213.1.

4′-Fluoro-[1,1′-biphenyl]-4-carbaldehyde (**3 cd**).[25] White crystal (186.8 mg, 95% yield); mp 78.4−79.4 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 10.1 (s, 1H), 7.97 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.65−7.57 (m, 2H), 7.19 (tt, *J* = 9.0, 3.0 Hz, 2H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 191.8, 163.1 (d, *J* = 248.2 Hz), 146.1, 135.8 (d, *J* = 3.3 Hz), 135.2, 130.4, 129.0 (d, *J* = 8.3 Hz), 127.5, 116.0 (d, *J* = 21.8 Hz); MS (ESI): $C_{13}H_{10}FO$ ([M+H]$^+$): calcd. 201.1, found: 201.1.

4-Methyl-4′-nitro-1,1′-biphenyl (**3db**).[26] Yellow solid (207.1 mg, 97% yield); mp 138.1−138.8 °C (lit.[24] 134−135 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.30 (dt, *J* = 9.0, 2.5 Hz, 2H), 7.74 (dt, *J* = 8.5, 2.5 Hz, 2H), 7.55 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.32 (dt, *J* = 7.5 Hz, 2H), 2.44 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 147.6, 146.9, 139.1, 135.9, 129.9, 127.5, 127.2, 124.1, 21.2; MS (ESI): $C_{13}H_{11}NO_2$ ([M+H]$^+$): calcd. 214.1, found: 214.1.

4-Methoxy-4′-(trifluoromethyl)-1,1′-biphenyl (**3ec**).[24] Colorless oil (237.1 mg, 94% yield); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.5, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.30−7.25 (m, 2H), 6.96 (dt, *J* = 9.0, 3.0 Hz, 2H), ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 159.2, 141.2 (q, *J* = 2.1 Hz), 132.3, 131.3, 130.1 (q, *J* = 1.6 Hz), 128.6 (q, *J* = 28.2 Hz), 126.1 (q, *J* = 5.4 Hz), 124.3 (q, *J* = 274.4 Hz), 113.2, 55.2; MS (ESI): $C_{14}H_{12}F_3O$ ([M+H]$^+$): calcd. 253.1, found: 253.0.

3-Methoxy-4′-methyl-1,1′-biphenyl (**3fb**).[24] Colorless oil (190.4 mg, 96% yield); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.52 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.20 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H), 7.14 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.90 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 3.89 (s, 3H), 2.43 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 159.9, 142.7, 138.2, 137.2, 129.7, 129.4, 127.0, 119.5, 112.7, 112.4, 55.2, 21.1; MS (ESI): $C_{14}H_{15}O$ ([M+H]$^+$): calcd. 198.1, found: 199.2.

4-Methoxy-1,1′-biphenyl (**3gc**).[18] White solid (171.3 mg, 93% yield); mp 86.2−87.4 °C (lit.[18] 87−88 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.60−7.53 (m, 4H), 7.46−7.41 (m, 2H), 7.35−7.30 (m, 1H), 7.00 (dt, *J* = 9.0, 3.0 Hz, 2H), 3.87 (s, 3H); ^{13}C{H} NMR

DOI: 10.1021/acs.joc.6b01938
J. Org. Chem. 2016, 81, 10049−10055

(126 MHz, chloroform-*d*) δ 159.2, 140.9, 133.8, 128.7, 128.2, 126.7, 126.7, 114.2, 55.4; MS (ESI): $C_{13}H_{13}O$ ([M+H]$^+$): calcd. 185.1, found: 185.1.

N-(4′-Methoxy-[1,1′-biphenyl]-4-yl)acetamide (**3hc**). White solid (200.5 mg, 83% yield); mp 206.8−207.6 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.56 (d, *J* = 8.5, 2H), 7.54−7.49 (m, 4H), 6.98 (d, *J* = 8.5, 2H), 7.23 (br, 1H), 3.86 (s, 3H), 2.22 (s, 3H); ^{13}C{H} NMR (126 MHz, DMSO-d_6) δ 168.2, 158.5, 138.1, 134.4, 132.2, 127.2, 126.3, 119.3, 114.3, 55.1, 24.0; HRMS (ESI): $C_{15}H_{15}NNaO_2$ ([M+Na]$^+$): calcd. 264.0995, found: 264.1004.

N-(4′-Methyl-[1,1′-biphenyl]-2-yl)acetamide (**3ib**).[27] Yellow solid (214.3 mg, 95% yield); mp 105.2−106.1 °C (lit.[25] 103 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.29 (d, *J* = 8.0 Hz, 1H), 7.39−7.34 (m, 1H), 7.33−7.22 (m, 4H), 7.18 (t, *J* = 7.0 Hz, 2H), 2.44 (s, 3H), 2.04 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 168.2, 137.8, 135.1, 134.8, 132.1, 130.1, 129.8, 129.1, 128.2, 124.3, 121.5, 24.6, 21.2; MS (ESI): $C_{15}H_{16}NO$ ([M+H]$^+$): calcd. 226.1, found: 226.0.

4-Methoxy-4′-methyl-1,1′-biphenyl (**3jb**).[28] White solid (172.5 mg, 87% yield); mp 110.1−111.9 °C (lit.[26] 107.9−108.1 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.53 (dt, *J* = 9.5, 3.0 Hz, 2H), 7.47 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.25 (dt, *J* = 9.0, 3.0, 2H), 3.87 (s, 3H), 2.40 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 159.0, 138.0, 136.3, 133.8, 129.4, 128.0, 126.6, 114.2, 55.3, 21.1; MS (ESI): $C_{14}H_{15}O$ ([M+H]$^+$): calcd. 199.1, found: 199.1.

4′-Methoxyl-[1,1′-biphenyl]-4-amine (**3lc**).[29] White solid (182.1 mg, 91% yield); mp 144.9−145.3 °C (lit.[27] 145 °C) ; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.47 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.38 (dt, *J* = 8.5, 2.5 Hz, 2H), 6.96 (dt, *J* = 8.5, 3.0 Hz, 2H), 7.26 (dt, *J* = 8.5, 2.5, 2H), 3.85 (s, 3H), 3.71 (br, 2H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 158.4, 145.3, 133.9, 131.4, 127.6, 127.4, 115.4, 114.1, 55.3; MS (ESI): $C_{13}H_{14}N$ ([M+H]$^+$): calcd. 184.1, found: 184.1.

2-Phenylpyridine (**3ma**).[30] Colorless oil (139.3 mg, 90% yield); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.72 (dt, *J* = 5.0, 1.0 Hz, 1H), 8.04−7.98 (m, 2H), 7.80−7.72 (m, 2H), 7.53−7.47 (m, 2H), 7.46−7.40 (m, 1H), 7.27−7.21 (m, 1H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 157.5, 149.6, 139.4, 136.8, 129.0, 128.7, 127.0, 122.1, 120.6; MS (ESI): $C_{11}H_{10}N$ ([M+H]$^+$): calcd. 156.1, found: 156.2.

2-(4-Methoxyphenyl)pyridine (**3mc**).[28] White solid (176.5 mg, 95% yield); mp 52.9−54.4 °C (lit.[26] 53.2−53.9 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.67 (dq, *J* = 5.0, 1.0 Hz, 1H), 7.97 (dt, *J* = 9.0, 3.0 Hz, 2H), 7.76−7.66 (m, 2H), 7.21−7.15 (m, 1H), 7.01 (dt, *J* = 8.5, 3.0 Hz, 2H), 3.88 (s, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 160.5, 157.1, 149.4, 136.7, 131.9, 128.2, 121.4, 119.9, 114.2, 55.4; MS (ESI): $C_{12}H_{12}NO$ ([M+H]$^+$): calcd. 186.1, found: 186.2.

Ethyl 4-([1,1′-Biphenyl]-4-yl)-4-oxobutanoate (**3na**).[31] White solid (254.7 mg, 91% yield); mp 81.5−82.3 °C (lit.[31] 80.6−82.1 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.08 (dt, *J* = 8.5, 3.0 Hz, 2H), 7.71 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.67−7.63 (m, 2H), 7.52−7.46 (m, 2H), 7.42 (tt, *J* = 7.5, 1.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.37 (t, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C{H} NMR (126 MHz, chloroform-*d*) δ 197.7, 172.9, 145.9, 139.8, 135.3, 128.9, 128.6, 128.2, 127.2, 127.2, 60.7, 33.4, 28.4, 14.2; MS (ESI): $C_{18}H_{19}O_3$ ([M+H]$^+$): calcd. 283.1, found: 283.1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01938.

Reaction optimization studies and ^{1}H and ^{13}C NMR data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: lizhenhua@zjut.edu.cn.

*E-mail: pharmlab@zjut.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Special Program for Key Basic Research of the Ministry of Science and Technology of China (No. 2014CB460608) and the National Natural Science Foundation of China (Nos. 21376221, 21406201, and 21506190) for financial support. We also thank Prof. Yi-Yi Weng, Dr. Wei Shi, and Dr. Feng-Fan Liu at Zhejiang University of Technology for helpful discussion, and Mr. Chao Zhang and Miss Qiao-Ling Shao for technical assistance.

■ REFERENCES

(1) (a) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. *Chem. Soc. Rev.* **2012**, *41*, 413−447. (b) Wang, G.-W. *Chem. Soc. Rev.* **2013**, *42*, 7668−7700. (c) James, S. L.; Friščić, T. *Chem. Soc. Rev.* **2013**, *42*, 7494−7496. (d) Hernández, J. G.; Friščić, T. *Tetrahedron Lett.* **2015**, *56*, 4253−4265. (d1) Tan, D.; Loots, L.; Friščić, T. *Chem. Commun.* **2016**, *52*, 7760−7781.

(2) (a) Friščić, T.; Childs, S. L.; Rizvi, S. A. A.; Jones, W. *CrystEngComm* **2009**, *11*, 418−426. (b) Bowmaker, G. A. *Chem. Commun.* **2013**, *49*, 334−348.

(3) (a) Shearouse, W. C.; Mack, J. *Green Chem.* **2012**, *14*, 2771−2775. (b) Chen, L.; Regan, M.; Mack, J. *ACS Catal.* **2016**, *6*, 868−872.

(4) (a) Tireli, M.; Kulcsár, M. J.; Cindro, N.; Gracin, D.; Biliškov, N.; Borovina, M.; Ćurić, M.; Halasz, I.; Užarević, K. *Chem. Commun.* **2015**, *51*, 8058−8061. (b) Lou, S.-J.; Mao, Y.-J.; Xu, D.-Q.; He, J.-Q.; Chen, Q.; Xu, Z.-Y. *ACS Catal.* **2016**, *6*, 3890−3894.

(5) (a) Su, W.; Yu, J.; Li, Z.; Jiang, Z. *J. Org. Chem.* **2011**, *76*, 9144−9150. (b) Yu, J.; Li, Z.; Jia, K.; Jiang, Z.; Liu, M.; Su, W. *Tetrahedron Lett.* **2013**, *54*, 2006−2009. (c) Zhu, X.; Zhang, Q.; Su, W. *RSC Adv.* **2014**, *4*, 22775−22778. (d) Li, Z.; Jiang, Z.; Su, W. *Green Chem.* **2015**, *17*, 2330−2334. (e) Jia, K.-Y.; Yu, J.-B.; Jiang, Z.-J.; Su, W.-K. *J. Org. Chem.* **2016**, *81*, 6049−6055.

(6) (a) Nielsen, S. F.; Peters, D.; Axelsson, O. *Synth. Commun.* **2000**, *30*, 3501−3509. (b) Klingensmith, L. M.; Leadbeater, N. E. *Tetrahedron Lett.* **2003**, *44*, 765−768. (c) Schneider, F.; Ondruschka, B. *ChemSusChem* **2008**, *1*, 622−625. (d) Schneider, F.; Stolle, A.; Ondruschka, B.; Hopf, H. *Org. Process Res. Dev.* **2009**, *13*, 44−48. (e) Schneider, F.; Szuppa, T.; Stolle, A.; Ondruschka, B.; Hopf, H. *Green Chem.* **2009**, *11*, 1894−1899. (f) Bernhardt, F.; Trotzki, R.; Szuppa, T.; Stolle, A.; Ondruschka, B. *Beilstein J. Org. Chem.* **2010**, *6*, 1.

(7) Cravotto, G.; Garella, D.; Tagliapietra, S.; Stolle, A.; Schüßler, S.; Leonhardt, S. E. S.; Ondruschka, B. *New J. Chem.* **2012**, *36*, 1304−1307.

(8) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.

(9) PCy_3·HBF_4 was used as stable PCy_3 source with the presence of K_2CO_3 as Brønsted base, for more details see: Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555−1564.

(10) (a) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575−5578. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(11) Proutiere, F.; Schoenebeck, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8192−8195.

(12) η represents the mass ratio of liquid additive used (volume) to the mass of other materials including reagents and solid grinding auxiliary, for more details see: ref 2a. The usage of η = 0.045 μL/mg based on optimization using dioxane as additive.

(13) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619−1620.

(14) Diao, T.; White, P.; Guzei, I.; Stahl, S. S. *Inorg. Chem.* **2012**, *51*, 11898−11909.

DOI: 10.1021/acs.joc.6b01938
J. Org. Chem. 2016, 81, 10049−10055

(15) (a) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. - Eur. J.* **2011**, *17*, 2492−2503. (b) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116−2119. (c) Schmidt, A. F.; Kurokhtina, A. A.; Larina, E. V. *Russ. J. Gen. Chem.* **2011**, *81*, 1573−1574. (d) Thomas, A. A.; Denmark, S. E. *Science* **2016**, *352*, 329−332.
(16) Further optimization showed the usage of catalytic system could be reduce to 2 mol%, which grinding time was prolonging to 99 min. Although similar yields were obtained using 1 mol% catlaytic system, the reproductivity was poor affording yields between 77 and 97%. For more details, see Table S3 in Supporting Information.
(17) It seemed increasing the filling degree of grinding stock led to better mixing, which gave good reporductivity when catalytic system and K_2CO_3 usage were reduced to 0.5 mol% and 2.5 equiv., respectively.
(18) Zhang, G. *Synthesis* **2005**, *2005*, 537−542.
(19) Solodenko, W.; Mennecke, K.; Vogt, C.; Gruhl, S.; Kirschning, A. *Synthesis* **2006**, *2006*, 1873−1881.
(20) Kienle, M.; Knochel, P. *Org. Lett.* **2010**, *12*, 2702−2705.
(21) Prastaro, A.; Ceci, P.; Chiancone, E.; Boffi, A.; Cirilli, R.; Colone, M.; Fabrizi, G.; Stringaro, A.; Cacchi, S. *Green Chem.* **2009**, *11*, 1929−1932.
(22) Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729−3732.
(23) Chen, Y.-H.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 7648−7651.
(24) Rao, M. L.N.; Jadhav, D. N.; Banerjee, D. *Tetrahedron* **2008**, *64*, 5762−5772.
(25) Lipshutz, B. H.; Frieman, B. A.; Lee, C.-T.; Lower, A.; Nihan, D. M.; Taft, B. R. *Chem. - Asian J.* **2006**, *1*, 417−429.
(26) Zhou, W.-J.; Wang, K.-H.; Wang, J.-X.; Huang, D.-F. *Eur. J. Org. Chem.* **2010**, *2010*, 416−419.
(27) Grieve, W. S. M.; Hey, D. H. *J. Chem. Soc.* **1932**, 1888−1894.
(28) Parmentier, M.; Gros, P.; Fort, Y. *Tetrahedron* **2005**, *61*, 3261−3269.
(29) Razler, T. M.; Hsiao, Y.; Qian, F.; Fu, R.; Khan, R. K.; Doubleday, W. *J. Org. Chem.* **2009**, *74*, 1381−1384.
(30) Liu, W.; Zhu, Y.; Li, C.-J. *Synthesis* **2016**, *48*, 1616−1621.
(31) Cohen, S. G.; Crossley, J. *J. Am. Chem. Soc.* **1964**, *86*, 4999−5003.

DOI: 10.1021/acs.joc.6b01938
J. Org. Chem. 2016, 81, 10049−10055