Heterogeneous & Homogeneous & Bio- & Nano-
CHEMCATCHEM
CATALYSIS

Accepted Article

Title: Palladium-Catalyzed Direct Monoarylation of Aryl C-H Bond with Iodoarenes

Authors: Li Su, Dong-Dong Guo, Bin Li, Shi-Huan Guo, Gao-Fei Pan, Ya-Ru Gao, and Yong-Qiang Wang

To be cited as: *ChemCatChem* 10.1002/cctc.201700138

Link to VoR: http://dx.doi.org/10.1002/cctc.201700138

A Journal of
ChemPubSoc Europe

WILEY-VCH

www.chemcatchem.org

Palladium-Catalyzed Direct Monoarylation of Aryl C-H Bond with Iodoarenes

Li Su, Dong-Dong Guo, Bin Li, Shi-Huan Guo, Gao-Fei Pan, Ya-Ru Gao, Yong-Qiang Wang[a]*

Abstract: Transition-metal-catalyzed direct arylation of nonactivated aryl C-H bond with iodoarenes has now emerged as an important method for the construction of biaryls. Generally, the direct arylation reaction proceeds in the presence of stoichiometric silver additives; moreover, diarylation product is often unavoidable when there are two identical aromatic C–H bonds in the substrate. We herein disclose an efficient $Pd(OAc)_2$/TFA/O_2 catalysis system that could promote direct arylation reactions of a variety of aromatic C−H bonds with diverse iodoarenes under silver-free conditions. The coupling reaction possesses complete monoarylation selectivity. The approach provides a straightforward, facile, and economical route to biaryls.

Introduction

The biaryl motif is a key structural component of diverse natural products, functional materials, and pharmaceuticals active compounds.[1] As a result, the development of efficient method for aryl-aryl bond construction has been attracting significant attentions from the synthesis community.[2] Over the past decade, transition-metal-catalyzed direct arylations of nonactivated aryl C-H bonds have been greatly studied due to their synthesis efficiency and minimization of atomic waste compared to traditionally cross-couplings of organometallic aryls with aryl halides.[3-5] In 2005, Daugulis and Zaitsev reported a pioneering palladium-catalyzed direct coupling of aromatic C-H bond of anilides with iodoarenes in the presence of AgOAc (1 equiv).[6] Since then, the powerful Pd^{II}/Ag^{I}/ArI reaction system and its modifications have been successfully used in various aryl C-H bond direct arylation.[7,8] Despite these considerable advances, the method suffers from two major drawbacks: i) the requirement for stoichiometric silver additives in order to scavenge iodide. Nevertheless, due to their good oxidizability and catalytic activity, the silver(I) species sometimes cause undesired side reactions.[9] Moreover, silver salts are expensive, thereby increasing the overall cost of the process; ii) the challenge of the monoarylations. Currently, the diarylation products can be obtained unavoidably when there are two identical aromatic C–H bonds in the substrate. For example, in the directing-group-assisted arylation of *ortho* aromatic C-H bonds,[6,10] high selective monoarylation is achieved only when one *ortho* substituent is present, or there is a substituent at an arene *meta* position to protect one of *ortho* C-H bond by steric hindrance. In spite of its products being interesting structures in organic materials, the diarylation still is a limitation in the synthesis of diverse polyaryl molecules.

Recently, Larrosa et al. demonstrated that the role of silver salt in several Pd-catalyzed C-H arylation processes of iodoarenes is only iodide scavenger through the formation and precipitation of the insoluble AgI salts, thereby keeping catalytic active Pd^{II} from forming inactive PdI_2.[11] Meanwhile, they developed an elegant KOAc/NMe_4Cl combination to replace silver salt and successfully applied it in a range of C-H arylations of iodoarenes.[11,12] Inspired by the research, we envisioned that trifluoroacetic acid (TFA) might also take place of silver salt in the process. The idea was based on following considerations that i) TFA and $Pd(OAc)_2$ can facilitate the generation of more electropositive $[PdO_2CCF_3]^+$ species, which, compared with $[PdOAc]^+$, is easier to form phenyl-Pd complexes through electrophilic substitution of C-H bonds at *ortho* position[13] and ii) although the induction of TFA could not completely prevent the formation of PdI_2, the high concentration of TFA could push the equilibrium between PdI_2 and $Pd(TFA)_2$ to favor the latter, thus keeping enough active Pd^{II} to catalyze the coupling reaction. Furthermore, because of no induction of other metal ion in the reaction system, the approach is favourable, compared to previous methods, to the recovery of noble metal palladium in amplified preparation.

Results and Discussion

Given the good directing capacity of pyridine and the importance of pyridine-containing biaryls in medicinal chemistry,[14] we initially evaluated the Pd^{II}/TFA-promoted arylation strategy with 2-phenylpyridine (**1a**) and iodobenzene (**2a**) as the model substrate (Table 1). First, the solvent screening was performed with $Pd(OAc)_2$ (10 mol%) as catalyst and TFA (5 equiv.) as additive (entries 1-6). Gratifyingly, acetic acid and anisole[15] were competent to the transformation, and mixed solvent, acetic acid / anisole (1:1) gave the best yield (55%)(entry 6). It should be noteworthy that the reaction possessed complete monoarylation selectivity without diarylation product observed in spite of **1a** having two identical aromatic C–H bonds at *ortho* position of pyridine group. To our surprise, the atmosphere of the reaction clearly affected the transformation, and O_2 atmosphere provided much better result than air or Ar (entries 6-8). At present the detail of the O_2 function in the reaction is unclear, and studies on related mechanism are ongoing. Increasing the amount of TFA gave improved yields (entries 9-13), with 8.0 equiv. of TFA affording the best yield (95%) (entry 11). Using other palladium sources, $Pd(TFA)_2$ provided the moderate yield (entry 13); the lower yield indicated

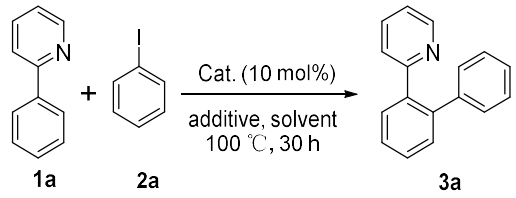
[a] Li Su, Dong-Dong Guo, Bin Li, Shi-Huan Guo, Gao-Fei Pan, Ya-Ru Gao, Yong-Qiang Wang*

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science
Northwest University
Xi'an 710069 (PR. China)
E-mail: wangyq@nwu.edu.cn

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

10.1002/cctc.201700138

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

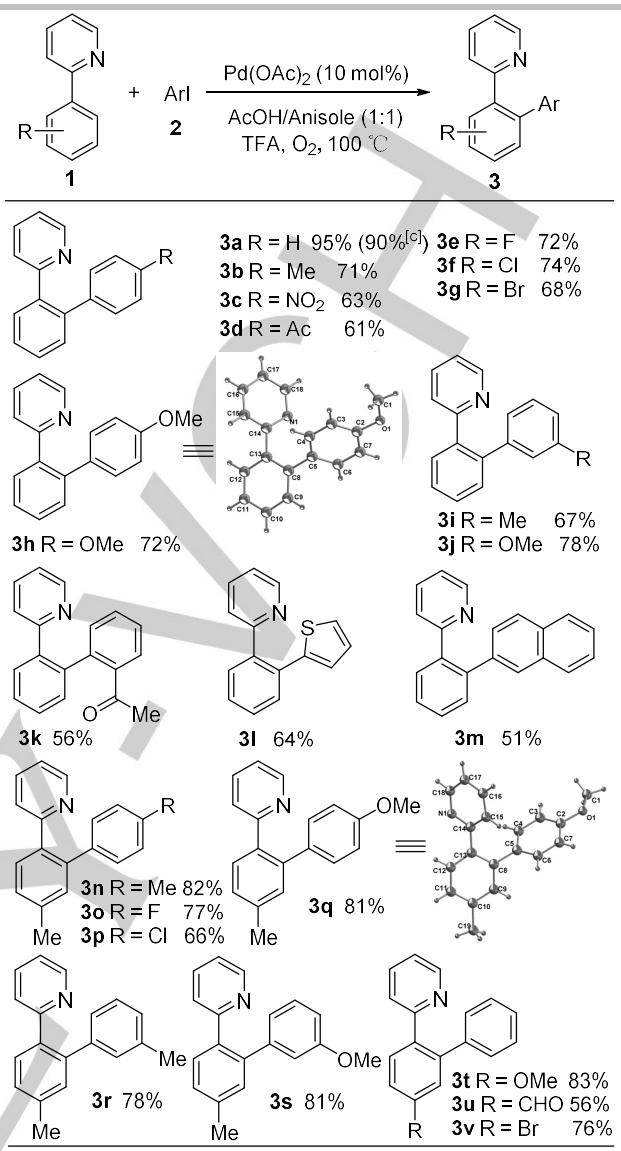
entry	catalyst	additive (equiv)	solvent	yield (%)[b]
1	$Pd(OAc)_2$	TFA (5)	DMSO	0
2	$Pd(OAc)_2$	TFA (5)	1,4-diioxane	32
3	$Pd(OAc)_2$	TFA (5)	DMF	0
4	$Pd(OAc)_2$	TFA (5)	anisole	43
5	$Pd(OAc)_2$	TFA (5)	acetic acid	45
6	$Pd(OAc)_2$	TFA (5)	acetic acid / anisole (1:1)	55
7[c]	$Pd(OAc)_2$	TFA (5)	acetic acid / anisole (1:1)	80
8[d]	$Pd(OAc)_2$	TFA (5)	acetic acid / anisole (1:1)	48
9[c]	$Pd(OAc)_2$	TFA (1)	acetic acid / anisole (1:1)	18
10[c]	$Pd(OAc)_2$	TFA (3)	acetic acid / anisole (1:1)	45
11[c]	$Pd(OAc)_2$	TFA (8)	acetic acid / anisole (1:1)	95
12[c]	$Pd(OAc)_2$	TFA(10)	acetic acid / anisole (1:1)	93
13[c]	$Pd(TFA)_2$	TFA (8)	acetic acid / anisole (1:1)	50
14[c]	$PdCl_2$	TFA (8)	acetic acid / anisole (1:1)	<10
15[c]	$Pd(OH)_2$	TFA (8)	acetic acid / anisole (1:1)	<10
16[c]	$Pd(PPh_3)_2Cl_2$	TFA (8)	acetic acid / anisole (1:1)	<10
17[c,e]	PdI_2	-	acetic acid / anisole (1:1)	0
18[c,e]	PdI_2	TFA (8)	acetic acid / anisole (1:1)	15

[a] Reaction conditions: **1a** (0.323 mmol, 50 mg), $Pd(OAc)_2$ (0.032 mmol, 7 mg), **2a** (0.485 mmol, 99 mg), TFA, solvent (1 mL), under air, 100 °C, 30 h. [b] Isolated yield. [c] Under O_2 (1 atm). [d] Under Ar (1 atm). [e] 72 h.

that the fresh $[PdO_2CCF_3]^+$ generated *in situ* had better catalytic activity. $Pd(OH)_2$, $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ could not promote the reaction effectively (entries 14-16). As our assumption above, PdI_2 did not work for the reaction (entry 17). Nevertheless, when TFA (8 equiv.) was introduced into the PdI_2 reaction system, the desired **3a** was produced albeit only in 15% yield (entry 18). These results demonstrated our assumption that TFA are able to regenerate catalytically active Pd^{II} *in situ*.

With the optimal reaction conditions in hand, we moved on to explore the substrate scope of the 2-arylpyridines and iodoarenes. The results were summarized in Scheme 1. We first examined the substituent effect of iodobenzene with **1a** as a partner. A broad range of substituent groups with diverse steric and electronic properties (ether, alkyl, halide, acetyl and nitro groups) at the *ortho*-, *meta*- or *para*-positions of the benzene ring were compatible with this procedure, affording the corresponding products in 56–95% yields, with complete monoarylation selectivity (**3b-3k**). It is noteworthy that halides (F, Cl and Br) were tolerated under our reaction conditions (**3e-3g**). These were synthetically interesting results, because such substituents could be versatile handles for further transformations. Interestingly, other aromatic substrates, such as 2-iodothiophene and 2- iodonaphthalene also were suitable substrates for the reaction to give the corresponding products (**3l 3m**) with three different aromatic rings in good yields. Then, different substituted 2-arylpyridines at *para*-position, which also possess two identical aromatic C–H bonds at *ortho* position of pyridine group, were examined with iodobenzene as its partner. Delightedly, all reactions afforded the desired products in good yields. And the complete monoarylation selectivity was highlighted again. The molecular structures of compounds **3h** and **3q** were confirmed by X-ray crystallographic analysis.

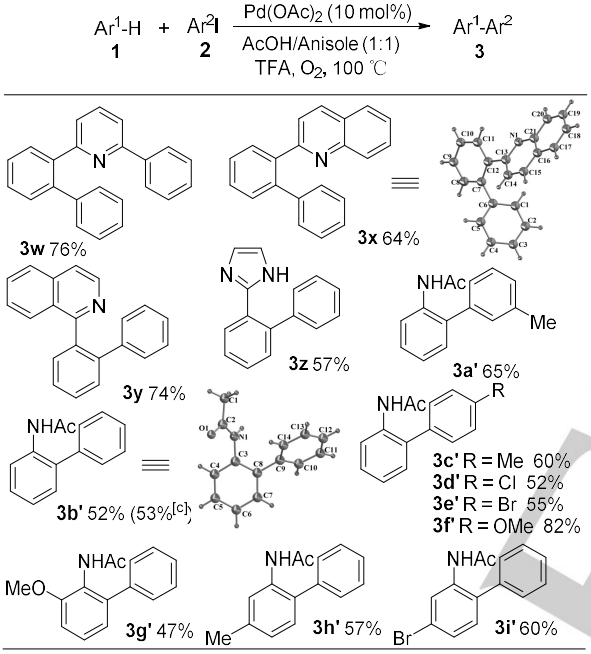
Next, we estimated the combination of $Pd(OAc)_2$/TFA/O_2 might be a general catalysis system for the direct arylations of aryl C-H



[a] Reaction conditions: **1** (0.323 mmol), $Pd(OAc)_2$ (0.032 mmol), **2** (0.485 mmol), TFA (2.584 mmol), AcOH / anisole (1:1) (1 mL), under O_2 (1 atm), 100 ℃, 20-40 h. [b] Isolated yield. [c] **1a** (8 mmol) was used.

Scheme 1. Substrate Scope of 2-Arylpyridines and Iodoarenes[a,b]

bond with iodoarenes. Therefore, a wide variety of direct C-H arylation reactions with iodoarenes were investigated (Scheme 2). Changing pyridine directing group to phenyl substituted pyridine (**1w**), quinoline (**1x**), isoquinoline (**1y**) and imidazole (**1z**) did not affect the efficiency of the direct C-H arylation reaction. They all underwent smooth reactions furnishing the desired products in good yields (**3w-3z**). Finally, we were pleased to find that the catalysis system could be readily extended to the direct arylation of acetylaniline. Iodoarenes having various substitutes (Me, OMe, Cl and Br) successfully coupled with acetylaniline, providing the corresponding diaryls (**3a'-3i'**) in 47-82% yields. It is worthwhile to note that all these direct C-H arylation reactions were complete monoarylation selectivity without diarylation product detected. The molecular structures of compounds **3x** and **3b'** were confirmed by X-ray crystallographic analysis.

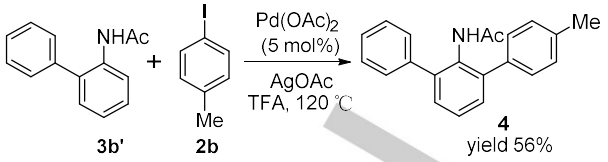


[a] Reaction conditions: **1** (0.323 mmol), $Pd(OAc)_2$ (0.032 mmol), **2** (0.485 mmol), TFA (2.584 mmol), AcOH / anisole (1:1) (1 mL), under O_2 (1 atm), 100 ℃, 20-40 h. [b] Isolated yield. [c] Acetylaniline (**1b'**,10 mmol) was used.

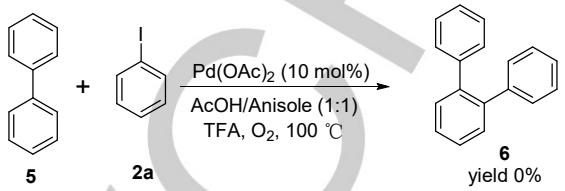
Scheme 2. Scope of Various Arenes and Iodoarenes[a,b]

We further demonstrated the scalability of this protocol to prepare 1.66 g of **3a** (Scheme 1, 90% yield) and 1.12 g of **3b'** (Scheme 2, 53% yield) under the standard conditions, respectively. The synthetic potential of the monoarylation products can be exploited through the second *otho*-C-H arylation. The monoarylation product **3b'** reacted with 4-iodotoluene using $Pd(OAc)_2$ (5 mol %) as the catalyst, AgOAc as the oxidant and TFA as solvent to produce compound **4** in 56% yield[6] (Scheme 3).

To gain insight into the reaction mechanism, biphenyl (**5**) was used as the substrate to react with iodobenzene (**2a**) under the standard conditions (Scheme 4). The reaction didn't happen at



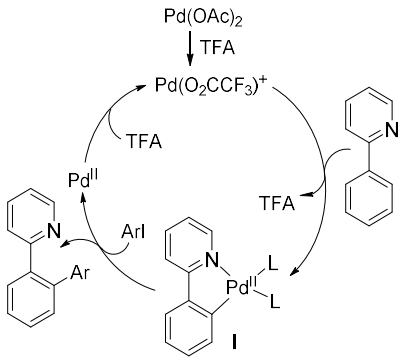
Scheme 3. The reaction of the second arylation



Scheme 4. The reaction of biphenyl with iodobenzene

all, demonstrating that nitrogen atom of the pyridyl very likely participated in the reaction. We next wondered if there were radicals involving in the reaction. When the radical scavenging reagent TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was introduced into the standard reaction system of **1a** with **2a**, the reaction proceeded normally, showing low possibility of radical process.

Based on above results and literature reports,[4a,16] a plausible mechanism was proposed as scheme 5. $Pd(OAc)_2$ is treated with TFA to obtain active $Pd(O_2CCF_3)^+$,[13] which affords the five-membered palladacycle species **I** through coordination of nitrogen of pyridyl and subsequent *ortho*-position C-H bond activation. Then, oxidative addition of aryl iodide to Pd^{II} species **I** affords Pd^{IV} species, following reductive elimination to generate the desired product; however, a transmetalation process between two palladium centers is also possible. Currently, we think the excellent monoarylation selectivity lies in the mild reaction condition and steric hindrance of aryl restricting the formation of favorable five-membered palladacycle intermediate on the other side.



Scheme 5. Proposed Reaction Mechanism

Conclusions

In summary, we have developed an efficient $Pd(OAc)_2$/TFA/O_2 catalysis system that could promote direct arylations of a variety of arenes including arylpyridine, benzoquinoline, benzoisoquinoline, 2-phenylimidazole and acetylaniline with diverse substituted iodoarenes under silver-free conditions. The coupling reactions possess complete monoarylation selectivity. The approach provides a straightforward, facile, and economical route to biaryls under mild reaction conditions. Detailed mechanistic investigations and the applications of the reaction are currently underway.

Experimental Section

General Information

All commercial reagents and solvents were used as received without further purification. Reactions were followed with TLC (0.254 mm silica gel 60-F plates). Visualization was accomplished with UV light. Flash chromatographies were carried out on silica gel 200-300 mesh. Melting points (m. p.) were measured on electrothermal digital melting point apparatus and were uncorrected. ^{1}HNMR and ^{13}CNMR spectra were recorded at 400 MHz using $CDCl_3$ as solvent. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm) or tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, Infrared (IR) data were recorded as films on potassium bromide plates on a Bruker Tensor 27 FT-IR spectrometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}).High resolution mass spectra were acquired on a Bruker Daltonics MicroTof-QII mass spectrometer. X-ray crystal structure analyses were measured on Bruker Smart APEXIICCD instrument using Mo-Kα radiation. The structures were solved and refined using the SHELXTL software package.

General procedure for the preparation of 3

A sealed tube containing the 2-phenyl pyridine **1** (0.32 mmol), $Pd(OAc)_2$ (10%, 0.032 mmol, 7 mg), was evacuation and filled with dioxygen gas using an oxygen containing balloon. Then acetic acid / anisole (1:1, 1 mL), Iodobenzene (0.48 mmol, 98 mg) and trifluoroacetate (TFA) (2.58 mmol, 0.2 mL) were sequentially added to the system via syringe under an oxygen atmosphere. The mixture was heated to 100 ℃ for 20-40 h. Then the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO3 (3 × 2 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography afforded the product **3**.

Chemical Characterisation

2-(Biphenyl-2-yl)pyridine (3a)[5h] Prepared according to general procedure to afford as white solid (70 mg, 95% yield), R_f = 0.32 (EtOAc/hexanes = 1:4); m. p. = 87-90 ℃. IR (KBr): 3057, 1732, 1583, 1425, 1288, 989, 748, 696 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$) δ 8.64-8.62 (m, 1H), 7.71-7.69 (m, 1H), 7.48-7.23 (m, 3H), 7.39-7.34 (m, 1H), 7.25-7.21 (m, 3H), 7.18-7.19 (m, 2H), 7.10-7.07 (m, 1H), 6.88 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 149.5, 141.4, 140.6 139.5, 135.2, 130.5 (2C), 129.7, 128.6, 128.1, 127.7, 126.7, 125.4, 121.4. HRMS (ESI) m/z calcd for $C_{17}H_{14}N$ $[M + H]^+$ 232.1121, found 232.1129.

2-[2-(4-Methylphenyl)]phenylpyridine (3b)[5h] Prepared according to general procedure to afford as colourless oil (56 mg, 71% yield), R_f = 0.30 (EtOAc/hexanes = 1:8). IR (KBr): 3018, 2924, 1911, 1585, 1460, 1149, 1022, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.65 (d, *J* = 4.0 Hz, 1H), 7.71 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.45-7.48 (m, 3H), 7.39-7.32 (m, 1H), 7.16-7.01 (m, 5H), 6.91 (d, *J* = 8.0 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.4, 149.5, 140.6, 139.4, 138.4, 136.4, 135.3, 130.6, 130.5, 129.6, 128.9, 128.6, 127.5, 125.5, 121.3, 21.2. HRMS (ESI) m/z calcd for $C_{18}H_{16}N$ $[M + H]^+$ 246.1277, found 246.1275.

2-[2-(4-Nitrobenzene)]phenylpyridine (3c)[5b] Prepared according to general procedure to afford as light green solid (56 mg, 63% yield), R_f = 0.30 (EtOAc/hexanes = 1:10); m. p. = 107-108 ℃. IR (KBr): 3049, 1925, 1595, 1516, 1344, 1103, 1014, 852, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.66-8.58 (m, 1H), 8.17-8.09 (m, 2H), 7.77-7.69 (m, 1H), 7.62-7.46 (m, 4H), 7.38-7.32 (m, 2H), 7.27-7.14 (m, 1H), 7.10-6.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.5, 149.6, 148.4, 146.6, 139.7, 138.4, 135.9, 130.8, 130.4, 130.3, 128.9, 128.9, 125.0, 123.3, 121.9. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}N_2O_2$ $[M + H]^+$ 277.0972, found 277.0967.

1-(2'-(Pyridin-2-yl)-[1,1'-biphenyl]-4-yl)ethanone (3d)[11] Prepared according to general procedure to afford as light yellow solid (53 mg, 61% yield), R_f = 0.30 (EtOAc/hexanes = 1:10); m. p. = 101-103 ℃. IR (KBr): 3041, 2920, 1938, 1672, 1581, 1743, 1354, 1269, 1113, 957, 841, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65-7.58 (m, 1H), 7.45-7.39 (m, 2H), 7.36-7.32 (m, 2H), 7.20-7.15 (m, 2H), 7.05 (m, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 158.8, 149.6, 146.5, 139.6, 139.5, 135.6, 135.3, 130.7, 130.4, 129.9, 128.7, 128.4, 128.2, 125.3, 121.7, 26.7. HRMS (ESI) m/z calcd for $C_{19}H_{16}NO$ $[M + H]^+$ 274.1226, found 274.1217.

2-[2-(4-Fluorobenzene)]phenylpyridine (3e)[5e] Prepared according to general procedure to afford as white solid (57 mg, 72% yield), R_f = 0.30 (EtOAc/hexanes= 1:8); m. p. = 102-105 ℃. IR (KBr): 3006, 2924, 1900, 1728, 1583, 1456, 1423, 1217, 1092, 839, 750, 557 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (s, 1H), 7.73-7.60 (m, 1H), 7.50-7.35 (m, 4H), 7.16-7.05 (m, 3H), 6.97-6.81 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.9 (J_{C-F} = 224.0 Hz), 159.1, 149.5, 139.5, 137.3, 135.4, 131.2 (J_{C-F} = 8.0 Hz), 130.5, 130.4, 128.6, 127.8, 125.3, 121.5, 115.1, 114.9. HRMS (ESI) m/z calcd for $C_{17}H_{13}FN$ $[M + H]^+$ 250.1027, found 250.1026.

2-[2-(4-Chlorophenyl)]phenylpyridine (3f)[5h] Prepared according to general procedure to afford as light yellow solid (63 mg, 74% yield), R_f = 0.30 (EtOAc/hexanes = 1:10); m. p. = 98-100 ℃. IR (KBr): 3053, 1913, 1583, 1454, 1279, 1090, 997, 754, 557, 517 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.74-8.59 (m, 1H), 7.79-7.67 (m, 1H), 7.56-7.42 (m, 4H), 7.28-7.21 (m, 2H), 7.19-7.08 (m, 3H), 6.99-6.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.0, 149.6, 139.8, 139.5, 139.3, 135.5, 132.8, 131.0, 130.6, 130.4, 128.7, 128.3, 128.0, 125.3, 121.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}ClN$ $[M + H]^+$ 266.0731, found 266.0724.

2-[2-(4-Bromobenzene)]phenylpyridine (3g)[5e] Prepared according to general procedure to afford as white solid (67 mg, 68% yield), R_f = 0.30 (EtOAc/hexanes = 1:3); m. p. = 97-99 ℃. IR (KBr): 3053, 1915, 1581, 1454, 1279, 1153, 997, 754, 557 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (d, *J* = 4.0 Hz, 1H), 7.73-7.63 (m, 1H), 7.49-7.33 (m, 6H), 7.17-7.08 (m, 1H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.0, 149.6, 140.3, 139.5, 139.3, 135.5, 131.3, 131.2, 130.6, 130.3, 128.7, 128.01, 125.3, 121.6, 121.1. HRMS (ESI) m/z calcd for $C_{17}H_{13}BrN$ $[M + H]^+$ 310.0226, found 310.0217.

2-[2-(4-Methoxyphenyl)]phenylpyridine (3h)[5h] Prepared according to general procedure to afford as light yellow solid (59 mg, 70% yield), R_f = 0.30 (EtOAc/hexanes = 1:5); m. p. = 63-64 ℃. IR (KBr): 3008, 2927, 1606, 1512, 1427, 1240, 1028, 758, 561 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.64 (d, *J* = 4.0 Hz, 1H), 7.68-7.63 (m, 1H), 7.47-7.37 (m, 4H), 7.13-7.04 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.5, 158.5, 149.5, 140.2, 139.4, 135.3, 133.7, 130.8, 130.5, 130.5, 128.5, 127.3, 125.4, 121.3, 113.5, 55.2. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}NO$ $[M + H]^+$ 262.1226, found 262.1221.

CCDC 1526791 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

2-[2-(3-Methylphenyl)]phenylpyridine (3i)[5h] Prepared according to general procedure to afford as white solid (53 mg, 67% yield), R_f = 0.30 (EtOAc/hexanes = 1:15); m. p. = 103-105 ℃. IR (KBr): 3057, 2920, 1583, 1425, 1271, 1086, 984, 758, 700, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.68-8.56 (m, 1H), 7.75-7.66 (m, 1H), 7.51-7.42 (m, 3H), 7.42-7.35 (m, 1H), 7.14-7.08 (m, 2H), 7.07-7.01 (m, 2H), 6.96-6.88 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.3, 149.4, 141.2, 140.7, 139.42, 137.7, 135.2, 130.5, 130.5, 130.4, 128.5, 127.9, 127.6, 127.5, 126.9, 1*25.4, 121.3, 21.4.* HRMS (ESI) *m/z* calcd for $C_{18}H_{16}N$ $[M + H]^+$ 246.1277, found 246.1270.

2-[2-(3-Methoxyphenyl)]phenylpyridine (3j)[5h] Prepared according to general procedure to afford as light yellow solid (65 mg, 78% yield), R_f = 0.30 (EtOAc/hexanes = 1:10); m. p. = 78-79 ℃. IR (KBr): 3059, 2925, 1515, 1462, 1292, 1213, 1047, 864, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.78-8.59 (m, 1H), 7.80-7.71 (m, 1H), 7.51 (s, 3H), 7.47-7.39 (m, 1H), 7.24-7.10 (m, 2H), 7.02-6.94 (m, 1H), 6.87-6.78 (m, 2H), 6.74 (s, 1H), 3.67 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.2, 149.4, 142.7, 140.5, 139.5, 135.3, 130.5, 130.4, 129.1, 128.6, 127.8, 125.4, 122.2, 121.4, 114.9, 112.9, 55.1. HRMS (ESI) m/z calcd for $C_{18}H_{16}N$ $[M + H]^+$ 262.1226, found 262.1217.

1-(2'-(Pyridin-2-yl)-[1,1'-biphenyl]-2-yl)ethan-1-one (3k) Prepared according to general procedure to afford as brown solid (49 mg, 56% yield), R_f = 0.30 (EtOAc/hexanes = 1:4); m. p. = 99-100 ℃. IR (KBr): 3051, 2924, 1936, 1680, 1577, 1429, 1352, 1250, 1012, 953, 756, 594, 511 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.62-8.56 (m, 1H), 7.80-7.73 (m1H), 7.58-7.48 (m, 3H), 7.45-7.33 (m, 4H), 7.23-7.18 (m, 1H), 7.15-7.10 (m, 1H), 7.01-6.96 (m, 1H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 202.4, 158.3, 149.4, 140.6, 140.3, 139.7, 139.5, 135.5, 131.6, 130.8, 130.4(2C), 128.6, 128.3, 128.1, 127.1, 124.9, 121.5, 29.4. HRMS (ESI) m/z calcd for $C_{19}H_{16}NO$ $[M + H]^+$ 274.1226, found 274.1215.

2-(2-(Thiophene-2-yl)phenyl)pyridine (3l)[17] Prepared according to general procedure to afford as light yellow oil (49 mg, 64% yield), R_f = 0.30 (EtOAc/hexanes = 1:30), IR (KBr): 3060, 2924, 1923, 1585, 1462, 1259, 1151, 1022, 795, 754, 492 cm-1. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.65 (d, *J* = 4.0 Hz, 1H), 7.65-7.47 (m, 3H), 7.46-7.37 (m, 2H), 7.25-7.04 (m, 3H), 6.99-6.79 (m, 1H), 6.69 (d, *J* = 3.2 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.3, 149.5, 142.9, 139.9, 135.5, 133.1, 130.7, 130.5, 128.5, 128.1, 127.1, 127.0, 125.7, 125.0, 121.8. HRMS (ESI) *m/z* calcd for $C_{15}H_{12}NS$ $[M + H]^+$ 238.0685, found 238.0673.

2-(2-(Naphthalen-2-yl)phenyl)pyridine (3m)[5n] Prepared according to general procedure to afford as colourless oil (46 mg, 51% yield), R_f = 0.30 (EtOAc/hexanes = 1:15), IR (KBr): 3055, 2924, 1921, 1585, 1462, 1219, 1022, 822, 754, 621, 478 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.67-8.58 (m, 1H), 7.74-7.68 (m, 4H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.54-7.46 (m, 3H), 7.45-7.37 (m, 2H), 7.28-7.21 (m, 1H), 7.15 (m, 1H), 7.03 (dd, *J* = 8.0 Hz, 4.0Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.2, 149.6, 140.5, 139.7, 139.1, 135.4, 133.4, 132.2, 130.9, 130.7, 128.7, 128.3(2C), 128.1, 127.9, 127.7, 127.4, 126.1, 125.9, 125.5, 121.4. HRMS (ESI) m/z calcd for $C_{21}H_{16}N$ $[M + H]^+$ 282.1277, found 282.1261.

2-(4'-Methyl-4-methylbiphenyl-2-yl)pyridine (3n) Prepared according to general procedure to afford as light yellow solid (70 mg 82% yield), R_f = 0.30 (EtOAc/hexanes = 1:10); m. p. = 69-75 ℃. IR (KBr): 2918, 1726, 1587, 1458, 1219, 1045, 785, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.66-8.57 (m, 1H), 7.64-7.55 (m, 1H), 7.38-7.33 (m, 1H), 7.26-7.17 (m, 2H), 7.09-7.00 (m, 5H), 6.90-6.82 (m, 1H), 2.42 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.3, 149.2, 140.4, 138.5, 138.4, 136.5, 136.3, 135.3, 131.3, 130.5, 129.6, 128.8, 128.2, 125.5, 121.2, 21.3, 21.2. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N$ $[M + H]^+$ 260.1434, found 260.1424.

2-(4'-Fluoro-4-methylbiphenyl-2-yl)pyridine (3o) Prepared according to general procedure to afford as white solid (65 mg, 77% yield), R_f = 0.30 (EtOAc/hexanes = 1:8); m. p. = 103-104 ℃. IR (KBr): 3055, 2922, 1587, 1506, 1417, 1217, 1092, 987, 833, 744, 550 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$) *δ* 8.66 (s, 1H), 7.69-7.57 (m, 1H), 7.48-7.39 (m, 1H), 7.35-7.30 (m, 1H), 7.20-7.12 (m, 3H), 7.12-6.74 (m, 4H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.9 ($J_{C\text{-}F}$ = 250.0 Hz), 159.2 ($J_{C\text{-}F}$ = 8.3 Hz),149.5, 139.4, 138.5, 137.5, 135.3, 131.2, 131.1, 130.5, 128.5, 125.3, 121.3, 115.1, 114.9, 21.2. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}FN$ $[M + H]^+$ 264.1183, found 264.1171.

2-(4'-Chloro-4-methylbiphenyl-2-yl)pyridine (3p) Prepared according to general procedure to afford as yellow solid (59 mg, 66% yield), R_f = 0.30 (EtOAc/hexanes = 1:8) ; m. p. = 103-104 ℃. IR (KBr): 2924, 1907, 1587, 1462, 1257, 1092, 829, 752, 582, 474 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.70-8.62 (m, 1H), 7.72-7.55 (m, 1H), 7.51-7.39 (m, 1H), 7.36-7.30 (m, 1H), 7.28-7.20 (m, 3H), 7.18-7.09 (m, 3H), 6.97-6.89 (m, 1H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.0, 149.5, 140.0, 139.2, 138.5, 136.7, 135.5, 132.7, 131.1, 131.0, 130.6, 128.7, 128.3, 125.3, 121.4, 21.3. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}ClN$ $[M + H]^+$ 280.0888, found 280.0877.

2-(4'-Methoxy-4-methylbiphenyl-2-yl)pyridine (3q)[5h] Prepared according to general procedure to afford as white solid (71 mg, 81% yield), R_f = 0.30 (EtOAc/hexanes = 1:5); m. p. = 92-94 ℃. IR (KBr): 2999, 2914, 2035, 1915, 1610, 1460, 1429, 1246, 1142, 1026, 837, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.63 (s, 1H), 7.66-7.53 (m, 1H), 7.41-7.31 (m, 1H), 7.26-7.19 (m, 2H), 7.11-6.99 (m, 3H), 6.91-6.82 (m, 1H), 6.81-6.71 (m, 2H), 3.76 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 154.7, 153.7, 144.7, 135.3, 133.6, 131.9, 130.5, 129.1, 126.5, 126.0, 125.8, 123.4, 120.7, 116.4, 108.8, 50.5, 16.5. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}NO$ $[M + H]^+$ 276.1383, found 276.1370. CCDC 1526790 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

2-(3'-Methyl-5-methylbiphenyl-2-yl)pyridine (3r) Prepared according to general procedure to afford as colourless oil (47 mg, 78% yield), R_f = 0.30 (EtOAc/hexanes = 1:10), IR (KBr): 2924, 1716, 1585, 1462, 1290, 1142, 787, 596, 519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.72-8.63 (m, 1H) 7.72-7.62 (m, 1H), 7.45-7.37 (m, 1H), 7.34-7.28 (m, 2H,) 7.17-7.07 (m, 4H), 7.00-6.89 (m, 2H), 2.49 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.3, 149.3, 141.4, 140.56, 138.3, 137.7, 136.7, 135.1, 131.2, 130.5, 130.4, 128.3, 127.9, 127.4, 126.9, 125.4, 121.1, 21.4, 21.3. HRMS (ESI) *m/ z*calcd for $C_{19}H_{18}N$ $[M + H]^+$ 260.1434, found 260.1422.

2-(3'-Methoxy-5-methylbiphenyl-2-yl)pyridine (3s)[5h] Prepared according to general procedure to afford as light yellow oil (71 mg, 81% yield), R_f = 0.30 (EtOAc/hexanes = 1:5), IR (KBr): 2925, 1921, 1732, 1581, 1462, 1225, 1041, 785, 536 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (s, 1H), 7.59 (s, 1H), 7.36 (s, 1H), 7.26 (s, 2H), 7.20-7.01 (m, 2H), 6.93-6.83 (m, 1H), 6.82-6.72 (m, 2H), 6.68 (s, 1H), 3.62 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 154.6, 154.5, 144.6, 138.1, 135.6, 133.6, 132.0, 130.5, 126.3, 125.7, 124.3, 123.8, 120.7, 117.4, 116.5, 110.1, 108.1, 50.4, 16.5. HRMS(ESI) *m/z* calcd for $C_{19}H_{18}ON$ $[M + H]^+$ 276.1383, found 276.1370.

2-(5-Methoxybiphenyl-2-yl)pyridine (3t)[5h] Prepared according to general procedure to afford as light yellow solid (70 mg, 83% yield), R_f = 0.30 (EtOAc/hexanes = 1:10); m. p. = 68-69 ℃. IR (KBr): 3057, 2933, 1720, 1597, 1464, 1319, 1215, 1038, 987, 860, 791, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.70-8.60 (m, 1H), 7.76-7.68 (m, 1H), 7.42-7.35 (m, 1H), 7.31-7.27 (m, 3H), 7.25-7.20 (m, 2H), 7.13-7.05 (m, 2H), 7.01 (s, 1H), 6.89-6.81 (m, 1H), 3.93 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.6, 158.9, 149.4, 142.0, 141.4, 135.1, 132.3, 131.9, 129.6, 128.1, 126.9, 125.4, 120.9, 115.7, 113.3, 55.4. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}ON$ $[M + H]^+$ 262.1226, found 262.1213.

6-(Pyridin-2-yl)-[1,1'-biphenyl]-3-carbaldehyde (3u)[5b] Prepared according to general procedure to afford as yellow solid (46 mg, 56% yield), R_f = 0.30 (EtOAc/hexanes = 1:25); m. p. = 84-85 ℃. IR (KBr): 3055, 2924, 2723, 1697, 1585, 1462, 1261, 1178, 1026, 839, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.72 (s, 1H), 8.19-7.98 (m, 2H), 7.97-7.87 (m, 1H), 7.54-7.42 (m, 1H), 7.31 (s, 3H), 7.23 (s, 3H), 7.01-6.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 157.9, 149.7, 145.0, 141.5, 140.0, 136.2, 135.5, 132.0, 131.5, 129.6, 128.6, 128.3, 127.4, 125.4, 122.2. HRMS (ESI) *m/z* calcd for $C_{18}H_{14}ON$ $[M + H]^+$ 260.1070, found 260.1062.

2-(5-Bromobiphenyl-2-yl)pyridine (3v) Prepared according to general procedure to afford as yellow solid (75 mg, 76% yield), R_f = 0.30 (EtOAc/hexanes = 1:25); m. p. = 132-135 ℃. IR (KBr): 3035, 2924, 1647, 1581, 1460, 1288, 1086, 1011, 829, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 -8.64 (m, 1H), 7.63 (s, 3H), 7.46-7.37 (m, 1H), 7.31-7.26 (m, 3H), 7.21-7.13 (m, 3H), 6.92-6.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 149.6, 142.5, 131.0, 138.3, 135.4, 133.2, 132.1, 130.6, 129.5, 128.3, 127.3, 125.3, 122.6, 121.7. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}BrN$ $[M + H]^+$ 310.0226, found 310.0221.

2-([1,1'-Biphenyl]-2-yl)-6-phenylpyridine (3w)[24] Prepared according to general procedure to afford as white solid (75 mg, 76% yield), R_f = 0.30 (EtOAc/hexanes = 1:100); m. p. = 84-85 ℃. IR (KBr): 3051, 2922, 1930, 1564, 1439, 1254, 1169, 987, 754, 694 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ 7.92-7.84 (m, 3H), 7.63-7.54 (m, 5H), 7.52-7.43 (m, 3H), 7.36-7.30 (m, 5H), 7.12-7.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 156.8, 141.9, 1410, 139.7, 139.6, 136.3, 130.8, 130.7, 129.8, 128.8, 128.6 (2C), 128.1, 127.7, 127.1, 126.6, 123.3, 118.1. HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N$ $[M + H]^+$ 308.1434, found 308.1426.

2-([1,1'-Biphenyl]-2-yl)quinoline (3x)[21] Prepared according to general procedure to afford as white solid (57.6 mg, 64% yield), R_f = 0.30 (EtOAc/hexanes = 1:50); m. p. = 100-101 ℃. IR (KBr): 3059, 2925, 2480, 1954, 1676, 1599, 1500, 1311, 1217, 1072, 1034, 947, 768, 519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.19 (m, 1H), 7.91-7.85 (m, 1H), 7.82-7.77 (m, 1H), 7.76-7.70 (m, 2H), 7.55-7.49 (m, 4H), 7.23 (s, 5H), 6.99-6.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 148.3, 141.2, 140.8, 139.8, 134.8, 130.9, 130.6, 129.9, 129.6, 129.4, 129.0 128.2, 127.9, 127.5, 126.9, 126.6, 126.4, 123.6. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}N$ $[M + H]^+$ 282.1277, found 282.1262. CCDC 1526795 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

1-([1,1'-Biphenyl]-2-yl)isoquinoline (3y) Prepared according to general procedure to afford as white solid (67 mg, 74% yield), R_f = 0.30 (EtOAc/hexanes = 1:15); m. p. = 86-89 ℃. IR (KBr): 3049, 2924, 1552, 1379, 1263, 1071, 1024, 746, 698, 521 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.62-8.53 (m, 1H), 7.80-7.73 (m, 1H), 7.67-7.53 (m, 7H), 7.39-7.33 (m, 1H), 7.16-7.10 (m, 2H), 7.09-6.99 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 142.0, 141.6, 141.1, 138.2, 136.0 130.7, 130.0, 129.8, 129.1, 128.8, 127.7, 127.5, 127.3(2C), 126.8, 126.6, 126.5, 119.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}N$ $[M + H]^+$ 282.1277, found 282.1265.

2-(Biphenyl-2-yl)-imidazole (3z)[22] Prepared according to general procedure to afford as brown solid (42 mg, 57% yield), R_f = 0.30 ($EtOAc/CH_2Cl_2$ = 1:20); m. p. = 217-219 ℃. IR (KBr): 3026, 2908, 1572, 1427, 1298 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0, 1.6 Hz, 1H), 7.46-7.39 (m, 5H), 7.30-7.33 (m, 3H), 6.91 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 141.1, 139.2, 130.6, 129.5, 129.2(2C), 128.9 (2C), 128.8, 128.6, 128.0, 127.9. HRMS (ESI) *m/z* calcd for $C_{15}H_{13}N_2$ $[M + H]^+$ 221.1073, found 221.1072.

N-(3'-Methyl-[1,1'-biphenyl]-2-yl)acetamide (3a')[20] Prepared according to general procedure to afford as brown oil (47 mg, 65% yield), R_f = 0.3 (EtOAc/hexanes = 1:5). IR (KBr): 3267, 2924, 1522, 1444, 1038, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.1 Hz, 1H), 7.39-7.32 (m, 2H), 7.26-7.11 (m, 6H), 2.41 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 138.7, 138.0, 134.7, 132.2, 130.0 (2C), 128.9, 128.7, 128.3, 126.2, 124.3, 121.5, 24.7, 21.5. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}ON$ $[M + H]^+$ 226.1226, found 226.1223.

N-(Biphenyl-2-yl)acetamide (3b')[23] Prepared according to general procedure to afford as green solid (35 mg, 52% yield), R_f = 0.30 (EtOAc/hexanes = 1:4); m. p. = 83-85 ℃. IR (KBr): 3282, 3028, 2920, 1955, 1655, 1527, 1431, 1298, 1007, 742, 519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.42-7.33 (m, 4H), 7.26-7.14 (m, 3H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 138.2, 134.7, 132.3, 130.1, 129.2, 129.1, 128.4, 128.0, 124.4, 121.8, 24.6. HRMS (ESI) *m/z* calcd for $C_{14}H_{14}ON$ $[M + H]^+$ 212.1070, found 212.1076. CCDC 1526796 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

N-(4'-Methyl-[1,1'-biphenyl]-2-yl)acetamide (3c')[18] Prepared according to general procedure to afford as brown solid (43 mg, 60% yield), R_f = 0.30 (EtOAc/hexanes = 1:4), m. p. = 99-102 ℃. IR (KBr): 3340, 2922, 1909, 1520, 1441, 1009, 754, 519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.2 Hz, 1H), 7.37-7.14 (m, 8H), 2.42 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 137.8, 135.1, 134.8, 132.1, 130.1, 129.8, 129.1, 128.3, 124.4, 121.6, 24.7, 21.3. HRMS (ESI) *m/z* calcd for C15H16ON $[M + H]^+$ 226.1226, found 226.1217.

N-(4'-Chloro-[1,1'-biphenyl]-2-yl)acetamide (3d')[20] Prepared according to general procedure to afford as brown white solid (41 mg, 52% yield), R_f = 0.3 (CH_2Cl_2), m. p. = 121-122 ℃. IR (KBr): 3276, 2924, 1651, 1284, 1007, 760, 602 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.3 Hz, 2H), 7.33-7.28 (m, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.12-7.10 (m, 2H), 6.95 (s, 1H), 1.96 (s, 3H). ^{13}C NMR (100 MHz $CDCl_3$) δ 168.4, 136.6, 134.6, 134.1, 131.4, 130.6, 130.0, 129.3, 128.8, 124.7, 122.3, 24.6. HRMS (ESI) *m/z* calcd for $C_{14}H_{13}ClON$ $[M + H]^+$ 246.0680, found 246.0689.

N-(4'-Bromo-[1,1'-biphenyl]-2-yl)acetamide (3e')[19] Prepared according to general procedure to afford as brown solid (51 mg, 55% yield), R_f = 0.3 (CH_2Cl_2), m. p. = 135-136 ℃. IR (KBr): 3265, 2922, 1651, 1286, 1003, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.1 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.41-7.34 (m 1H), 7.30-7.15 (m 4H), 7.05 (s 1H), 2.04 (s 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 137.1, 134.5, 132.3, 130.4, 130.0, 128.8, 124.8, 122.4, 122.3, 100.0, 24.6. HRMS (ESI) *m/z* calcd for $C_{14}H_{13}BrON$ $[M + H]^+$ 290.0175, found 290.0166.

N-(4'-Methoxy-[1,1'-biphenyl]-2-yl)acetamide (3f')[20] Prepared according to general procedure to afford as brown solid (63 mg, 82% yield), R_f = 0.3 (CH_2Cl_2/CH_3OH = 100:1), m. p. = 128-129 ℃. IR (KBr): 3350, 2920, 1516, 1240, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.2 Hz, 1H), 7.37-7.27 (m, 3H), 7.25-7.11 (m, 3H), 7.01 (d, J = 8.6 Hz 2H), 3.87 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 159.3, 134.9, 131.9, 130.4, 130.2, 130.2, 128.1, 124.3, 121.6, 114.5, 55.4, 24.7. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}ClO_2N$ $[M + H]^+$ 242.1176, Found 242.1174.

N-(3-Methoxy-[1,1'-biphenyl]-2-yl)acetamide (3g')[20] Prepared according to general procedure to afford as colourless oil (36.2 mg, 47% yield), R_f = 0.3 (EtOAc/hexanes = 1:2), IR (KBr): 3249, 2924, 1660, 1468, 1261, 1018, 760, 521 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 6H), 6.94 (d, J = 7.9 Hz, 2H), 6.69 (s, 1H), 3.86 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 155.1, 141.1, 139.5, 128.63, 128.2, 128.1, 127.3, 122.9, 122.4, 110.5, 55.8, 23.2. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}NO_2$ $[M + H]^+$ 242.1176, Found 242.1174.

N-(4-Methyl-[1,1'-biphenyl]-2-yl)acetamide (3h')[25] Prepared according to general procedure to afford as brown solid (41.0 mg, 57% yield), R_f = 0.3 (CH_2Cl_2/CH_3OH = 100:1), m. p. = 135-137 ℃. IR (KBr): 3230, 2922,

1655, 1296, 1028, 698, 609 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.42-7.32 (m, 3H), 7.13 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 2.40 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 138.5, 138.2, 134.4, 129.9, 129.6, 129.3, 129.1, 127.8, 125.3, 122.3, 24.6, 21.5. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}NO$ $[M + H]^+$ 226.1226, Found 226.1229.

N-(4-Bromo-[1,1'-biphenyl]-2-yl)acetamide (3i')[26] Prepared according to general procedure to afford as brown solid (55.4 mg, 60% yield), R_f = 0.3 (EtOAc/hexanes = 1:4), m. p. = 105-108 ℃. IR (KBr): 3261, 2922, 1657, 1284, 1007, 698, 598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.52-7.41 (m, 3H), 7.37-7.27 (m, 3H), 7.15 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 137.1, 135.9, 131.2, 130.7, 129.3, 129.1, 128.4, 127.3, 124.1, 122.1, 24.7. HRMS (ESI) *m/z* calcd for $C_{14}H_{12}BrNO$ $[M + H]^+$ 290.0175, Found 290.0163.

N-(4-methyl-[1,1':3',1''-terphenyl]-2'-yl)acetamide (4). The solution of 4-Iodotoluene (1.0 mmol), *N*-([1,1'-biphenyl]-2-yl)acetamide (0.5 mmol), palladium acetate (0.025 mmol), silver acetate (1.0 mmol) in TFA (2 mL) in a dram screw-cap vial was heated at 120 ℃ for 12 h. The reaction was generally stopped when no more precipitate was formed. The reaction mixture was diluted with touene (5 mL), and the solution was decanted and the precipitate was washed with toluene (2 × 5 mL). Combined organic solutions were evaporated under reduced pressure. Product was isolated by flash chromatography on silica gel. to afford **4** as white solid (80.0 mg, 56% yield), R_f = 0.3 (CH_2Cl_2/CH_3OH = 100:1), m. p. = 171-175℃. IR (KBr): 3242, 2922, 1653, 1365, 1018, 804, 507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 5 H), 7.28-7.26 (m, 2H), 7.24-7.12 (m, 5H), 6.54 (s, 1H), 2.31 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 140.9, 140.8, 139.9, 137.0, 136.8, 131.2, 130.1, 129.8, 129.0, 128.8, 128.6, 128.2, 127.8, 127.3, 22.9, 21.3. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO^+$ $[M + H]^+$ 302.1539, Found 302.1547.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (NSFC-21572178, 21272185).

Keywords: Palladium-catalysis • Arylation • Iodoarenes • C–H Activation • Biaryls

[1] (a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; (b) D. Hurst, U. Umejiego, D. Lynch, H. Seltzman, S. Hyatt, M. Roche, S. McAllister, D. Fleischer, A. Kapur, M. Abood, S. Shi, J. Jones, D. Lewis, P. Reggio, *J. Med. Chem.* **2006**, *49*, 5969; (c) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651.

[2] For representative reviews of C-H arylation, see: (a) D. Alberico, M. E.Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; (b) F. Kakiuchi, T. Kochi, *Synthesis*. **2008**, 3013; (c) G. P. McGlacken, L. Bateman, *Chem. Soc. Rev*. **2009**, *38*, 2447; (d) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121,* 5196*; Angew. Chem., Int. Ed*. **2009**, *48*, 5094; (e) O. Daugulis, *Top. Curr. Chem.* **2010**, *292*, 57; (f) G. P. Chiusoli, M. Catellani, M. Costa, E. Motti, N. D. Ca', G. Maestri, *Coord. Chem. Rev*. **2010**, *254*, 456.

[3] Recent reviews on traditionally cross-couplings: see: (a) A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854*; Angew. Chem., Int. Ed.* **2011**, *50*, 6722; (b) E.-i. Negishi, *Angew. Chem.* **2011**,*123,* 6870*; Angew. Chem., Int. Ed.* **2011**, *50*, 6738.

[4] Selected reviews on direct arylation reactions: (a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; (b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; (c) J. Wencel-Delord, T. Drçge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; (d) L. McMurray, F. O'Hara, *J.* M. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; (e) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; (f) J. Yamaguchi, A. Yamaguchi, D. K. Itami, *Angew. Chem,* **2012**, *124,* 9092*; Angew. Chem., Int. Ed.* **2012**, *51*, 8960; (g) D. Y. K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452; (h) G. Rouquet, N. Chatani, *Angew. Chem.* **2013**, *125,* 11942*; Angew. Chem., Int. Ed.* **2013**, *52*, 11726; (i) I. Hussain, T. Singh, *Adv. Synth. Catal.* **2014**, *356*, 1661; (j) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107; (k) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W.Krska, *Chem. Soc. Rev.* **2016**, *45*, 546; (l) H. M. L.Davies, D. Morton, *J. Org. Chem.* **2016**, *81*, 343; (m) M. Seki, *Org. Process Res. Dev.* **2016**, *20*, 867.

[5] Selected recent direct arylation examples: (a) N. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234; (b) W.-Y. Yu, W. N. Sit, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 3174; (c) P. B. Arockiam, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Angew. Chem.* **2010***, 122, 6779; Angew. Chem., Int. Ed.* **2010**, *49*, 6629; (d) B. Yu, X. Yan, S. Wang, N. Tang, C. Xi, *Organometallics* **2010**, *29*, 3222; (e) Q. Shuai, L. Yang, X. Guo, O. Basl, C.-J. Li, *J. Am. Chem. Soc.* **2010**, *132*, 12212; (f) N. Luo, Z. Yu, *Chem. Eur. J.* **2010**, *16*, 787; (g) C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Commun.* **2010**, *46*, 677; (h) W. Li, Z. Yin, X. Jiang, P. Sun, *J. Org. Chem.* **2011**, *76*, 8543; (i) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566; (j) H. Li,; W. Wei, Y. Xu, C. Zhang, X. Wan, *Chem. Commun.,* **2011**, *47*, 1497; (l) P. B. Arockiam, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem.* **2013**, *15*, 67; (m) J. S. Sun Ho, L. C. M. C.Castro, Y. Aihara, M. Tobisu, N. Chatani, *Asian J. Org. Chem.* **2014**, *3*, 48; (n) G. M.Reddy, N. S. S. Rao, P. Satyanarayana, H. Maheswaran, *RSC Adv.* **2015**, *5*, 105347; (o) S. Rajkumar, S. Karthik, T. Gandhi, *J. Org. Chem.* **2015**, *80*, 5532; (p) L.Huang, D. J.Weix, *Org. Lett.*, **2016**, *18*, 5432; (q) P. Nareddy, F. Jordan, S. E. Brenner-Moyer, M. Szostak, *ACS Catal.* **2016**, *6*, 4755. (r) X. Li, J. Pan, S. Song, N. Jiao, *Chem. Sci.* **2016**, *7*, 5384.

[6] O. Daugulis, V. G. Zaitsev, *Angew. Chem* **2005***,117,* 4114*; Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

[7] Selected reviews: (a) M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**, *108*, 3132; (b) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*, 3149; (c) M. Alvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174; (d) Y. Yamamoto, *Chem. Rev.* **2008**, *108* 3199. (e) J.-M. Weibel, A. Blanc, P. Pale, Silver in Organic Chemistry, ed. M. Hamata, Wiley, New Jersey, 2010.

[8] Selected recent examples: (a) H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879; (b) V. S. Thirunavukkarasu, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2008***, 120, 9604; Angew. Chem., Int. Ed.* **2008**, *47*, 9462; (c) R. B. Bedford, R. L. Webster, C. J. Mitchell, *Org. Biomol. Chem.* **2009**, *7*, 4853; (d) M. P. Huestis, K. Fagnou, *Org. Lett.* **2009**, *11*, 1357; (e) T. Nishikata, A. R. Abela, B. H. Lipshutz, *Angew. Chem,* **2010,** *122*, 793**.** *Angew. Chem., Int. Ed.* **2010**, *49*, 781. (f) S. A. Ohnmacht, A. J. Culshaw, M. F. Greaney, *Org. Lett.* **2010**, *12*, 224; (g) O. René, K. Fagnou, *Org. Lett.* **2010**, *12*, 2116; (h) G.-W. Wang, T.-T. Yuan, D.-D. Li, *Angew. Chem* **2011***, 123,* 1416*; Angew. Chem., Int. Ed.* **2011**, *50*, 1380; (i) W. Li, Z Xu, P. Sun, X. Jiang, M. Fang, *Org. Lett.* **2011**, *13*, 1286; (j) J. Cornella, M. Righi, I. Larrosa, *Angew. Chem,* **2011**, *123,* 9601*; Angew. Chem., Int. Ed.* **2011** *50*, 9429; (k) F. Chen, Q.-Q. Min, X. Zhang, *J. Org. Chem.* **2012**, *77*, 2992. (l) C. Arroniz, A. Ironmonger, Rassias, I. Larrosa, *Org. Lett.* **2013** 15, 910; (m) J.-C. Wan, J.-M. Huang, Y.-H. Jhan, J.-C. Hsieh, *Org. Lett* **2013**, *15*, 2742; (n) P. Ricci, K. Kraemer, X. C. Cambeiro, I. Larrosa, *J. Am. Chem. Soc.* **2013**, *135*, 13258; (o) S. Islam, I. Larrosa, *Chem. Eur. J.* **2013**, *19*, 15093; (p) J. Luo, S. Preciado, I. Larrosa, *J. Am. Chem. Soc.* **2014**, *136*, 4109; (q) L. C. M. Castro, N. Chatani, *Chem. Eur. J.* **2014**, *20*, 4548; (r) D. Santrač, S. Cella, W. Wang, L. Ackermann, *Eur. J. Org. Chem.* **2016**, 5429–5436.

[9] (a) C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155. (b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; (c) G. Rassias, N. G. Stevenson, N. R. Curtis, J. M. Northall, M. Gray, J. C. Prodger, A. J. Walker, *Org. Process Res. Dev.* **2010**, *14*, 92; (d) M. Vellakkaran, M. M. S. Andappanb, N. Kommu, *Green Chem.* **2014**, *16*, 2788.

[10] Selected recent examples: (a) F. Yang, Y. Wu, Y. Li, B. Wang, J. Zhang, *Tetrahedron* **2009**, *65*, 914; (b) D.-D. Li, T.-T. Yuan, G.-W. Wang, *J. Org. Chem.* **2012**, *77*, 3341; (c) R. Feng, J. Yao, Z. Liang, Z. Liu, Y. Zhang, *J. Org. Chem.* **2013**, *78*, 3688; (d) Y. Jaiswal, Y. Kumar, R.

Thakur, J. Pal, R. Subramanian, A. Kumar, *J. Org. Chem.*, **2016**, *81*, 12499.

[11] C. Arroniz, J. G. Denis, A. Ironmonger, G. Rassias, I. Larrosa, *Chem. Sci.* **2014**, *5*, 3509.

[12] Another successful example avoiding silver salts for specific substrates (naphthylamides) via bidentate-chelation assistance: L. Huang, Q. Li, C. Wang, C. Qi, *J. Org. Chem.***2013**, *78*, 3030.

[13] (a) W. Lu, Y. Yamaoka, Y. Taniguchi, T. Kitamura, K. Takaki, Y. J. Fujiwara, *J. Organomet. Chem.* 1999, 580, 290; (b) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992.

[14] (a) A. R. Dick, M. Sanford, *Tetrahedron* **2006**, *62*, 2439; (b) J. Bouffard, K. Itami, *Top. Curr. Chem.* **2010**, *292*, 231; (c) L. Ackermann, R. Vicente, *Top. Curr. Chem.* **2010**, *292*, 211; (d) E. Beck, M. Guant, *Top. Curr. Chem.* **2010**, *292*, 85; (f) S. Oi, S. Fukita. Y. Inoue, *Chem. Commun.* **1998**, 2439; (g) L. Ackermann, A. Althammer, R. Born, *Tetrahedron* **2008**, *64*, 6115; (h) D. A. Colby, A. S. Tsai, R. G. Bergman, A. J. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814.

.

[15] Anisole is a good solvent for the reaction, which likely because anisole possesses great solubility for the substrate and high boiling point (155℃).

[16] (a) V. S. Thirunavukkarasu, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2008**, *120*, 9604; *Angew. Chem., Int. Rd.* **2008**, *47*, 9462; (b) W. Li, Z. Yin, X. Jiang, P. Sun, *J. Org. Chem.* **2011**, *76*, 8543

[17] L.-Y. Liao. K. M. Liu, X. F. Duan, *J. Org. Chem.* **2015**, *80*, 9856.

[18] Z. J. Jiang, Z. H. Li, J. B. Yu, W. K. Su, *J. Org. Chem.* **2016**, *81*, 10049.

[19] J. Hubrich, T. Himmler, L. Rodefeld, L. Ackermann, *Adv. Synth. Catal.* **2015**, 357, 474.

[20] S. Yang, B. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 6066.

[21] D. Kalyani, N. R. Deprez. L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330.

[22] B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, *125*, 10580.

[23] P. Gao, L. Liu, Z. Shi, Y. Yuan, *Org. Biomol. Chem.* **2016**, *14*, 7109.

[24] J. Feng, G. Lu, M. Lv, C. Cai, *Synlett.* **2013**, *24*, 2153.

[25] J. Kim, Y. Moon, Lee, S. *Chem. Commun.* **2014**, *50*, 3227.

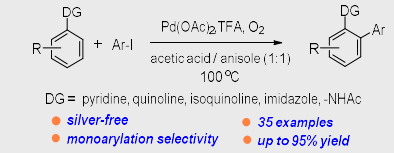
[26] R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun.* **2014**, *50*, 2442.

10.1002/cctc.201700138

WILEY-VCH

FULL PAPER

Text for Table of Contents



*Li Su, Dong-Dong Guo, Bin Li, Shi-Huan Guo, Gao-Fei Pan, Ya-Ru Gao, Yong-Qiang Wang**

Page No. – Page No.

Palladium-Catalyzed Direct Monoarylation of Aryl C-H Bond with Iodoarenes

Biaryls synthesis: An efficient $Pd(OAc)_2$/TFA/O_2 catalysis system that could promote direct arylation reactions of a variety of aromatic C−H bonds with diverse iodoarenes under silver-free conditions has been developed. The approach possesses complete monoarylation selectivity, and provides a straightforward, facile, and economical route to biaryls.