Tetrahedron 65 (2009) 914–919

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Modified palladium-catalyzed regioselective *ortho*-arylation of sp^2 C–H bond substrates with a low catalyst loading

Fan Yang, Yangjie Wu *, Yanan Li, Biao Wang, Junli Zhang

Department of Chemistry, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, PR China

ARTICLE INFO

Article history:
Received 30 August 2008
Received in revised form 29 October 2008
Accepted 4 November 2008
Available online 7 November 2008

Keywords:
Palladium catalysis
Weak bases
Arylation
C–H activation

ABSTRACT

A novel and generally applicable system for *ortho*-arylation of a broad range of sp^2 C–H bond substrates such as arylated benzoxazoles, acylated anilines, and pyridines has been developed. The arylation was performed in trifluoroacetic acid (TFA) under air by using $PdCl_2$ as the catalyst with a low catalyst loading of 1 mol %. And it was found for the first time that the addition of weak base K_3PO_4 to the acidic solvent could remarkably enhance the reaction rate. The arylated products were isolated in moderate to good yields with high regioselectivity for the substrates containing a *meta*-substituent. This arylation is tolerant with various functional groups such as CH_3, CH_3O, CH_3CO, Br, and Cl.

1. Introduction

Transition-metal-catalyzed C–C and C–heteroatom bond formations via cleavage of C–H bonds are recently increasingly becoming facile and reliable protocols in organic synthesis due to their potential shortening of synthetic steps.[1] As a result, the development of such C–H activation would act as an attractive alternative to the traditional carbon–carbon couplings (such as Suzuki, Stille, and Negishi reaction) and thereby emerge as a fascinating area rich in opportunities and challenges.[2] To date, direct functionalization of C–H bond under palladium, ruthenium, or rhodium catalysis has been realized in arenes with a directing-group (such as the pyridine, imine, acetamine, carboxylic acid, and oxazoline)[3] and even certain free heterocycles.[4]

Compared to sp^3 C–H bonds, many efforts have been devoted to activate aromatic sp^2 C–H bonds, since the unsaturated aryl motif is a predominant feature in many pharmaceutically relevant and biologically active compounds.[4a,5] In particular, palladium-promoted regioselective direct arylation of sp^2 *ortho*-C–H bond has received the most attention. Sanford and co-workers have focused on the arylation of 2-arylpyridines and other nitrogen heterocycles with diphenyliodonium salts in AcOH or $AcOH/Ac_2O$ using 5 mol % of $Pd(OAc)_2$ as the catalyst.[3a] Subsequently, Daugulis and co-workers have demonstrated the $Pd(OAc)_2$-catalyzed direct arylation of benzoic acids in two different systems (AgOAc/HOAc and alkylphosphine ligand/Cs_2CO_3/DMF).[3b] In addition, Shi and co-workers showed that acetamine could direct highly regio- and chemo-selective *ortho*-arylation of acetanilides with trialkoxyarylsilanes through C–H functionalization.[3c] Recently, we have also reported $Pd(OAc)_2$-mediated benzoxazole directing regioselective *ortho*-arylation by coupling with aryl iodides using AgOAc as the additive for iodide removal.[6] However, the reported systems mostly employed $Pd(OAc)_2$ as the palladium source under the catalyst loadings of 5 mol % or even higher. Therefore, the more efficient catalytic system (such as lower catalyst loadings, new catalyst species, new additives) for such C–H activation is to be explored.

On the other hand, the utilized reaction conditions for functionalization of C–H bond are two different types of catalytic systems (ligand/base/aprotic polar solvent and additive/acidic solvent).[3,4] But what happens when a weak base is added to the acidic catalytic system? The question prompted us to investigate catalytic characteristics of the novel system involving a weak base and an additive in acidic solvent. Herein, we disclose that a low catalyst loading (1 mol %) of $PdCl_2$ is sufficient and generally applicable for the direct arylation of a wide range of sp^2 C–H bond substrates (e.g., arylated benzoxazole, acylated anilines, and pyridines), and discover for the first time that the weak bases enhance the reactivity greatly in trifluoroacetic acid (TFA).

2. Results and discussion

Under the base-free conditions, the arylation of 2-(3-methyl phenyl) benzoxazole (**1a**) with iodobenzene (**2a**) catalyzed by 1 mol % of $PdCl_2$ was explored and only a very low GC yield was

* Corresponding author. Tel./fax: +86 371 67766667.
E-mail address: wyj@zzu.edu.cn (Y. Wu).

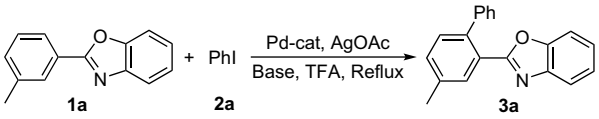
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.11.001

observed (Table 1, entry 1). However, gratifyingly, the addition of 2 equiv of KOAc to trifluoroacetic acid (TFA) solution produced **3a** in 35% GC yield (Table 1, entry 2). It indicated that the reactivity would be also dependent on other factors and the results for the screening of the reaction conditions with respect to bases and palladium sources are shown in Table 1. Under the catalyst loading of 1 mol %, various weak bases (such as NaOAc, $KF\cdot 2H_2O$, K_2HPO_4, CsF, and K_3PO_4) were examined in the arylation, and moderate to excellent yields were obtained (Table 1, entries 3–7). Notably, K_3PO_4 was shown to be the base of the best choice to give **3a** in the GC yield of 95% (Table 1, entry 7). However, when the loading of K_3PO_4 was decreased from 2 equiv (0.50 mmol) to 1.5 equiv (0.375 mmol), the reaction gave a moderate GC yield of 82% (Table 1, entry 8). Several other palladium species were checked for the arylation of **1a** with **2a**. $Pd(OAc)_2$ as the catalyst was also effective affording **3a** in 85% GC yield (Table 1, entry 9). Other palladium catalysts, $PdCl_2(PPh_3)_2$ and $PdCl_2(PhCN)_2$ provided **3a** in 72% and 54% GC yields, respectively (Table 1, entries 10–11).

Under the above optimized conditions, the scope of the diverse sp^2 C–H bond substrates and substituted aryl iodides was investigated. Initially, arylation of 2-arylbenzoxazoles were probed and the results are outlined in Table 2. The arylation could tolerate various functional groups such as CH_3O, Br, Cl, and CH_3CO. This would permit construction of more complicated structures through conventional Pd(0)/Pd(II) coupling processes. The electronic factor had a critical effect on the arylation. Electron-donating substituents would enhance the reactivity, while electron-withdrawing substituents would reduce the rate of the arylation (Table 2, entries 1–5). However, the reactions of aryl iodides bearing an *ortho*-substituent (either electron-donating or electron-withdrawing group) did not give the satisfactory results due to the *ortho*-effect (Table 2, entries 6 and 7). Even for the iodide containing an electron-donating substituent (CH_3), the arylated product could not be observed (Table 2, entry 6). The arylation of iodobenzene (**2a**) with 2-arylbenzoxazoles containing several functional groups was examined and moderate to good yields were obtained (Table 2, entries 8–11).

Subsequently, the catalytic protocol also allowed for efficient arylation of acylated anilines (Table 3). The arylation showed highly regioselectivity for acylated anilines containing a *meta*-substituent. The arylation of *N*-(3-methyl phenyl)-3,3-dimethylbutanamide (**4a**) with a series of aryl iodides proceeded smoothly to afford

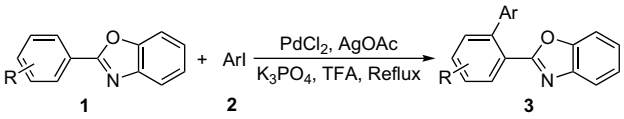
Table 1
Effect of bases and catalysts on the *ortho*-arylation of 2-(3-methyl phenyl) benzoxazole (**1a**) with iodobenzene (**2a**)[a]

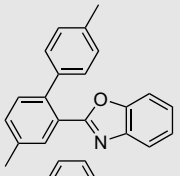
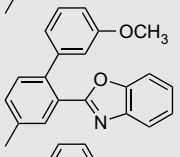
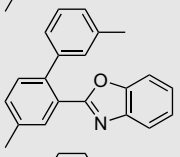
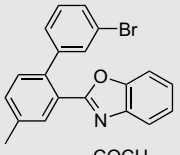
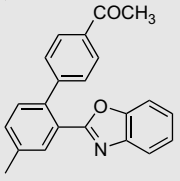
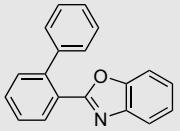
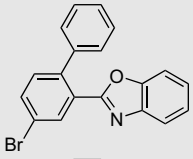
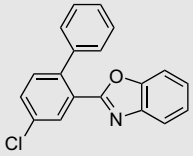
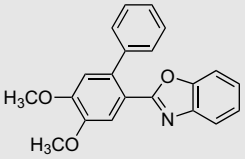


Entry	Catalyst	Base	Yield[b] (%)
1	$PdCl_2$	—	9
2	$PdCl_2$	KOAc	35
3	$PdCl_2$	NaOAc	24
4	$PdCl_2$	$KF\cdot 2H_2O$	53
5	$PdCl_2$	K_2HPO_4	39
6	$PdCl_2$	CsF	44
7	*$PdCl_2$*	*K_3PO_4*	*95 (88)*
8[c]	$PdCl_2$	K_3PO_4	82 (70)
9	$Pd(OAc)_2$	K_3PO_4	85 (72)
10	$PdCl_2(PPh_3)_2$	K_3PO_4	72
11	$PdCl_2(PhCN)_2$	K_3PO_4	54

[a] All the reactions were carried out in the presence of **1a** (0.25 mmol), **2a** (0.75 mmol), AgOAc (0.75 mmol), base (0.50 mmol), and catalyst (0.0025 mmol, 1 mol %) in TFA (0.6 mL) under reflux for 30 h.
[b] GC yield (isolated yield) based on the amount of **1a**.
[c] K_3PO_4 (0.375 mmol) was used.

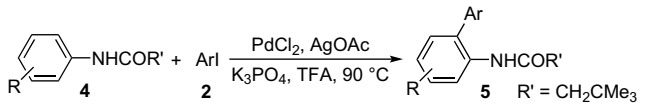
Table 2
$PdCl_2$-catalyzed *ortho*-arylation of 2-arylbenzoxazoles via C–H activation[a]

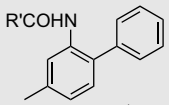
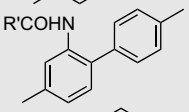
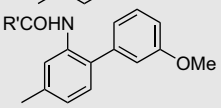
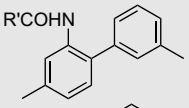
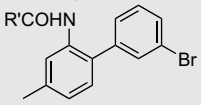
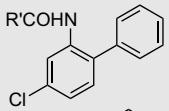
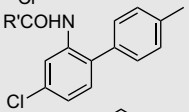
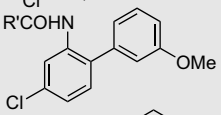
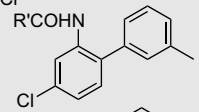
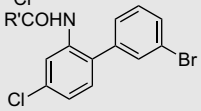
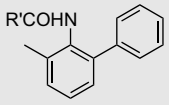
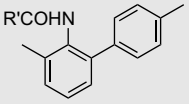
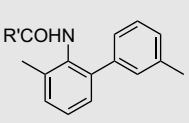


Entry	R (**1**)	Ar (**2**)	Product	Time (h)	Yield[b] (%)
1	3-Me (**1a**)	4-Me-C_6H_4 (**2b**)		40	91 (**3b**)
2	**1a**	3-MeO-C_6H_4 (**2c**)		100	90 (**3c**)
3	**1a**	3-Me-C_6H_4 (**2d**)		64	92 (**3d**)
4	**1a**	3-Br-C_6H_4 (**2e**)		96	84 (**3e**)
5	**1a**	4-MeCO-C_6H_4 (**2f**)		96	25 (**3f**)
6	**1a**	2-Me-C_6H_4 (**2g**)	—	—	—
7	**1a**	2-Cl-C_6H_4 (**2h**)	—	—	—
8	H (**1b**)	C_6H_5 (**2a**)		53	60 (**3g**)
9	3-Br (**1c**)	**2a**		120	82 (**3h**)
10	3-Cl (**1d**)	**2a**		110	87 (**3i**)
11	3,4-MeO (**1e**)	**2a**		120	72 (**3j**)

[a] All the reactions were carried out in the presence of **1** (0.25 mmol), **2** (0.75 mmol), AgOAc (0.75 mmol), K_3PO_4 (0.50 mmol), and $PdCl_2$ (0.0025 mmol, 1 mol %) in TFA (0.6 mL) under reflux.
[b] Yields are given for isolated products.

Table 3
$PdCl_2$-catalyzed *ortho*-arylation of acylated anilines via C–H activation[a]



Entry	R (**4**)	Ar (**2**)	Product	Time (h)	Yield[b] (%)
1	3-Me (**4a**)	C_6H_5 (**2a**)		18	90 (**5a**)
2	**4a**	4-Me-C_6H_4 (**2b**)		50	82 (**5b**)
3	**4a**	3-MeO-C_6H_4 (**2c**)		45	87 (**5c**)
4	**4a**	3-Me-C_6H_4 (**2d**)		35	82 (**5d**)
5	**4a**	3-Br-C_6H_4 (**2e**)		88	80 (**5e**)
6	**4a**	2-Me-C_6H_4 (**2g**)	—	—	—
7	3-Cl (**4b**)	**2a**		60	69 (**5f**)
8	**4b**	**2b**		120	66 (**5g**)
9	**4b**	**2c**		125	86 (**5h**)
10	**4b**	**2d**		58	67 (**5i**)
11	**4b**	**2e**		100	60 (**5j**)
12	2-Me (**4c**)	**2a**		32	85 (**5k**)
13	**4c**	**2b**		29	86 (**5l**)
14	**4c**	**2d**		48	81 (**5m**)

[a] All the reactions were carried out in the presence of **4** (0.25 mmol), **2** (0.75 mmol), AgOAc (0.75 mmol), K_3PO_4 (0.50 mmol), and $PdCl_2$ (0.0025 mmol, 1 mol %) in TFA (0.6 mL) at 90 °C.
[b] Yields are given for isolated products.

corresponding products in moderate to good yields (Table 3, entries 1–5). The *ortho*-effect also had great influence for the iodide bearing *ortho*-substituent (**2g**) and the arylation did not occur (Table 3, entry 6). In the case of a moderate electron-withdrawing group (Cl) substituted acylated aniline (**4b**), the desired products were also obtained in moderate to good yields after a prolonged time (Table 3, entries 7–11). Results for the reaction of *N*-(2-methyl phenyl)-3,3-dimethylbutanamide (**4c**) with several aryl iodides were similar to those of **4a** and good yields were observed (Table 3, entries 12–14).

In addition, the catalytic system was successfully applied to arylation of 2-arylpyridine (Table 4). The reactions of 2-phenylprydine with several aryl iodides were carried out efficiently and diarylated products were obtained in moderate to good yields (Table 4, entries 1–5). Functional groups such as CH_3O and Br could be tolerated in the arylation. However, for *ortho*-substituted iodide, even containing an electron-donating group (CH_3), the product was not observed (Table 4, entry 6).

3. Conclusion

In summary, we have developed an efficient system for the direct arylation of several sp^2 C–H bond substrates such as arylated benzoxazole, acylated anilines, and pyridines through C–H activation process. Remarkable features of the arylation are high efficiency using $PdCl_2$ as the catalyst with a low loading of 1 mol %, the arylated regioselectivity of the less sterically hindered *ortho*-C–H bond, and the unexpected enhancement of the arylation rate that the base K_3PO_4 displays in an acidic solvent (TFA). The reaction can be compatible to several functional groups such as CH_3, CH_3O, and CH_3CO, as well as Br and Cl substituents, which would permit to be functionalized further to construct more complicated structures. The arylation of iodides bearing *ortho*-substituent did not occur due to the *ortho*-effect. Current efforts are focused on the mechanistic studies and synthetic application of this efficient methodology.

4. Experimental

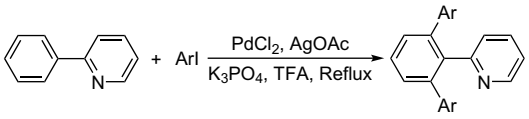
4.1. General methods

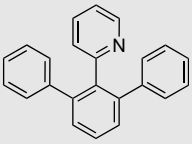
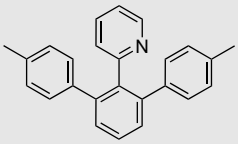
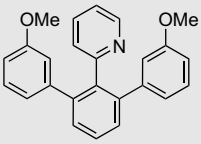
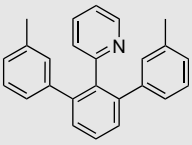
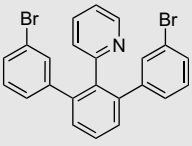
^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard. Melting points were measured using a WC-1 microscopic apparatus and are uncorrected. GC analysis was performed on Agilent 4890D gas chromatograph. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. High-resolution mass spectra were measured on a Waters Q-Tof MicroTM spectrometer. 2-Arylbenzoxazoles (**1**),[7] AgOAc,[8] and acylated anilines (**4**)[9] were prepared by following the previously published procedures. CH_2Cl_2 (analytical grade) was stored over molecular sieves and used without further purification. Ethyl acetate and hexane (analytical grade) were used for column chromatography without purification. The other chemicals were bought from commercial sources and used as received unless otherwise noted.

4.2. General procedure for arylation of C–H bond

Substrate (0.25 mmol), aryl iodide (0.75 mmol), $PdCl_2$ (0.0025 mmol, 1 mol %), K_3PO_4 (0.50 mmol), and silver acetate (0.75 mmol) were dissolved in trifluoroacetic acid (0.6 mL) in a 5 mL vial under air and heated at a specific temperature. The reaction process was monitored by GC analysis. After the reaction was complete, the mixture was diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite, and washed multiple times with CH_2Cl_2. The combined organic solutions were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

Table 4
$PdCl_2$-catalyzed *ortho*-arylation of 2-phenylpyridine via C–H activation[a]



Entry	Ar (**2**)	Product	Time (h)	Yield[b] (%)
1	C_6H_5 (**2a**)		75	78 (**7a**)
2	4-Me-C_6H_4 (**2b**)		45	75 (**7b**)
3	3-MeO-C_6H_4 (**2c**)		76	74 (**7c**)
4	3-Me-C_6H_4 (**2d**)		72	72 (**7d**)
5	3-Br-C_6H_4 (**2e**)		95	54 (**7e**)
6	2-Me-C_6H_4 (**2g**)	—	—	—

[a] All the reactions were carried out in the presence of 2-phenylpyridine **6** (0.25 mmol), **2** (0.75 mmol), AgOAc (0.75 mmol), K_3PO_4 (0.50 mmol), and $PdCl_2$ (0.0025 mmol, 1 mol %) in TFA (0.6 mL) under reflux.
[b] Yields are given for isolated products.

*4.2.1. 2-(2-Phenyl-5-methyl phenyl)benzoxazole (**3a**)[6]*

White solid, mp 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.22–7.31 (m, 8H), 7.36–7.38 (m, 2H), 7.71 (d, J=8.00 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.88, 109.49, 118.90, 123.29, 123.85, 124.80, 126.03, 127.03, 127.78, 130.07, 130.39, 130.85, 136.41, 138.61, 139.84, 140.45, 149.63, 163.11.

*4.2.2. 2-[2-(4-Methyl phenyl)-5-methyl phenyl]benzoxazole (**3b**)[6]*

White solid, mp 111–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.45 (s, 3H), 7.07–7.12 (m, 2H), 7.12–7.18 (m, 2H), 7.20–7.31 (m, 3H), 7.31–7.37 (m, 2H), 7.68–7.74 (m, 1H), 7.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.95, 21.22, 110.61, 120.04, 124.29, 124.84, 125.95, 128.72, 128.87, 131.17, 131.56, 131.88, 136.76, 137.21, 137.95, 139.64, 141.73, 150.78, 164.32.

*4.2.3. 2-[2-(3-Methoxyl phenyl)-5-methyl phenyl]-benzoxazole (**3c**)[6]*

White solid, mp 169–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.66 (s, 3H), 6.80–6.91 (m, 3H), 7.14–7.23 (m, 1H), 7.23–7.32 (m, 3H), 7.35–7.40 (m, 2H), 7.16 (dd, J=7.60, 1.84 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.97, 55.17, 110.58, 113.05, 114.16, 120.00, 121.46, 124.33, 124.92, 126.04, 129.08, 130.97, 131.44, 131.85, 137.57, 139.46, 141.66, 142.28, 150.78, 159.35, 164.12.

*4.2.4. 2-[2-(3-Methyl phenyl)-5-methyl phenyl]benzoxazole (**3d**)*

White solid, mp 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.45 (s, 3H), 7.00 (d, J=7.02 Hz, 1H), 7.05–7.20 (m, 3H), 7.21–7.28 (m, 3H), 7.32–7.36 (m, 2H), 7.72 (d, J=7.68 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.02, 21.54, 110.60, 120.05, 124.34, 124.91, 125.98, 126.11, 127.91, 127.97, 129.54, 131.18, 131.51, 131.90, 137.38, 137.72, 139.79, 140.85, 141.74, 150.79, 164.29; HRMS (positive ESI) calcd for $C_{21}H_{17}NO$: 300.1388 (M^++H); found: 300.1390.

*4.2.5. 2-[2-(3-Bromo phenyl)-5-methyl phenyl]benzoxazole (**3e**)[6]*

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.08–7.15 (m, 2H), 7.23–7.31 (m, 4H), 7.35–7.40 (m, 1H), 7.40–7.46 (m, 1H), 7.49–7.53 (m, 1H), 7.67–7.73 (m, 1H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.01, 110.56, 120.10, 122.09, 124.45, 125.08, 125.84, 127.77, 129.43, 130.13, 131.08, 131.44, 131.84, 131.93, 138.00, 138.11, 141.60, 143.09, 150.68, 163.50.

*4.2.6. 2-[2-(4-Acetyl phenyl)-5-methyl phenyl]benzoxazole (**3f**)[6]*

White solid, mp 169–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.61 (s, 3H), 7.26–7.32 (m, 3H), 7.32–7.39 (m, 3H), 7.39–7.44 (m, 1H), 7.70 (d, J=7.80 Hz, 1H), 7.91 (d, J=7.80 Hz, 2H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.98, 26.64, 110.54, 120.09, 124.44, 125.07, 125.84, 128.18, 129.13, 130.92, 131.52, 131.92, 135.68, 138.31, 138.36, 141.54, 145.97, 150.62, 163.45, 197.88.

*4.2.7. 2-(2-Phenyl phenyl)benzoxazole (**3g**)[6]*

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15–7.35 (m, 8H), 7.45–7.51 (m, 2H), 7.51–7.59 (m, 1H), 7.70 (d, J=7.60 Hz, 1H), 8.11 (dd, J=7.30, 1.80 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.58, 120.13, 124.37, 124.97, 126.33, 127.32, 127.59, 128.18, 128.86, 131.04, 131.20, 141.02, 141.74, 142.50, 150.77, 163.91.

*4.2.8. 2-(2-Phenyl-5-bromo phenyl)benzoxazole (**3h**)[6]*

White solid, mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.29 (m, 4H), 7.29–7.38 (m, 5H), 7.67–7.74 (m, 2H), 8.29 (d, J=2.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.59, 120.23, 121.45, 124.51, 125.28, 127.59, 127.89, 128.21, 128.65, 132.69, 133.53, 133.87, 139.84, 141.26, 141.45, 150.68, 162.26.

*4.2.9. 2-(2-Phenyl-5-chloro phenyl)benzoxazole (**3i**)[6]*

White solid, mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.28 (m, 4H), 7.28–7.35 (m, 4H), 7.39–7.43 (m, 1H), 7.54 (dd, J=8.00, 2.16 Hz, 1H), 7.71 (d, J=7.32 Hz, 1H), 8.14 (d, J=2.16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.59, 120.23, 124.52, 125.28, 127.57, 127.61, 128.19, 128.72, 130.66, 130.94, 132.49, 133.62, 139.83, 140.82, 141.43, 150.68, 162.39.

*4.2.10. 2-(2-Phenyl-4,5-dimethoxyl phenyl)benzoxazole (**3j**)[6]*

White solid, mp 129–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.02 (s, 3H), 6.93 (s, 1H), 7.20–7.24 (m, 2H), 7.27–7.31 (m, 3H), 7.32–7.36 (m, 3H), 7.67 (s, 1H), 7.68–7.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.09, 56.25, 110.39, 113.01, 113.83, 118.13, 119.66, 124.25, 124.61, 127.12, 128.04, 128.94, 136.20, 141.09, 141.58, 148.24, 150.59, 150.92, 163.90.

*4.2.11. N-(2-Phenyl-5-methyl phenyl)-3,3-dimethyl-butanamide (**5a**)*

White solid, mp 99–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H), 2.03 (s, 2H), 2.40 (s, 3H), 6.98 (d, J=7.70 Hz, 1H), 7.06 (s, 1H), 7.12 (d, J=7.70 Hz, 1H), 7.31–7.36 (m, 2H), 7.38–7.42 (m, 1H), 7.43–7.49 (2H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.47, 29.68, 31.21, 51.86, 121.61, 124.83, 127.78, 128.98, 129.24, 129.37, 129.73, 134.58, 138.17, 138.44, 169.97; HRMS (positive ESI) calcd for $C_{19}H_{23}NO$: 304.1677 (M^++Na); found: 304.1618.

*4.2.12. N-[2-(4-Methyl phenyl)-5-methyl phenyl]-3,3-dimethylbutanamide (**5b**)*

White solid, mp 67–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 9H), 1.94 (s, 2H), 2.29 (s, 3H), 2.32 (s, 3H), 6.86 (d, J=7.54 Hz, 1H), 6.98–7.04 (m, 2H), 7.15 (m, 4H), 8.08 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.13, 21.39, 29.65, 31.17, 51.73, 121.51, 124.76, 129.15, 129.61, 129.74, 134.59, 135.06, 137.48, 138.10, 169.93; HRMS (positive ESI) calcd for $C_{20}H_{25}NO$: 318.1834 (M^++Na); found: 318.1820.

*4.2.13. N-[2-(3-Methoxyl phenyl)-5-methyl phenyl]-3,3-dimethylbutanamide (**5c**)*

White solid, mp 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 9H), 1.96 (s, 2H), 2.32 (s, 3H), 3.74 (s, 3H), 6.77–6.92 (m, 4H), 7.04 (d, J=7.74 Hz, 2H), 7.26–7.32 (m, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.45, 29.66, 31.17, 51.85, 55.24, 113.38, 114.85, 121.43, 121.47, 124.68, 129.00, 129.54, 129.95, 134.59, 138.45, 139.53, 159.98, 169.93; HRMS (positive ESI) calcd for $C_{20}H_{25}NO_2$: 334.1783 (M^++Na); found: 334.1765.

*4.2.14. N-[2-(3-Methyl phenyl)-5-methyl phenyl]-3,3-dimethylbutanamide (**5d**)*

White solid, mp 74–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 9H), 1.95 (s, 2H), 2.31 (s, 6H), 6.88 (d, J=7.60 Hz, 1H), 7.00–7.15 (m, 5H), 7.20–7.30 (m, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.36, 21.42, 29.66, 31.18, 51.85, 121.44, 124.72, 126.30, 128.47, 128.81, 129.27, 129.64, 130.07, 134.57, 138.04, 138.22, 138.65, 169.93; HRMS (positive ESI) calcd for $C_{20}H_{25}NO$: 318.1834 (M^++Na); found: 318.1828.

*4.2.15. N-[2-(3-Bromo phenyl)-5-methyl phenyl]-3,3-dimethylbutanamide (**5e**)*

White solid, mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 9H), 1.98 (s, 2H), 2.31 (s, 3H), 6.85–6.93 (m, 2H), 6.90 (d, J=7.72 Hz, 1H), 7.16–7.28 (m, 2H), 7.40–7.47 (m, 2H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.43, 29.71, 31.23, 51.70, 122.30, 122.94, 125.17, 127.99, 128.10, 129.65, 130.40, 130.80, 132.35, 134.37, 138.99, 140.36, 170.07; HRMS (positive ESI) calcd for $C_{19}H_{22}BrNO$: 382.0782 (M^++Na); found: 382.0772.

*4.2.16. N-(2-Phenyl-5-chloro phenyl)-3,3-dimethylbutanamide (**5f**)*

White solid, mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H), 2.02 (s, 2H), 7.09–7.15 (m, 3H), 7.28–7.33 (m, 2H), 7.41–7.51 (m, 3H), 8.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.60, 31.16, 51.76, 120.78, 123.87, 128.30, 129.14, 129.18, 130.02, 130.68, 134.00, 135.83, 137.04, 169.89; HRMS (positive ESI) calcd for $C_{18}H_{20}ClNO$: 324.1131 (M^++Na); found: 324.1137.

*4.2.17. N-[2-(4-Methyl phenyl)-5-chloro phenyl]-3,3-dimethylbutanamide (**5g**)*

White solid, mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H), 2.01 (s, 2H), 2.40 (s, 3H), 7.05–7.09 (m, 2H), 7.09–7.14 (m, 1H), 7.18 (d, J=7.91 Hz, 2H), 7.26 (d, J=7.91 Hz, 2H), 8.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.98, 29.64, 31.24, 51.78, 120.55, 123.80, 129.00, 129.88, 130.76, 133.80, 133.96, 135.88, 138.19, 169.92; HRMS (positive ESI) calcd for $C_{19}H_{22}ClNO$: 338.1288 (M^++Na); found: 338.1240.

*4.2.18. N-[2-(3-Methoxyl phenyl)-5-chloro phenyl]-3,3-dimethylbutanamide (**5h**)*

White solid, mp 67–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H), 2.04 (s, 2H), 3.83 (s, 3H), 6.82–6.85 (m, 1H), 6.86–6.91 (m, 1H), 6.95–6.98 (m, 1H), 7.08–7.19 (m, 3H), 7.40 (t, J=7.94 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.64, 31.23, 51.85, 55.31, 113.81, 114.79, 120.55, 121.23, 123.78, 129.74, 130.26, 130.57, 134.08, 135.84, 138.37, 160.15, 169.96; HRMS (positive ESI) calcd for $C_{19}H_{22}ClNO_2$: 354.1237 (M^++Na); found: 354.1242.

*4.2.19. N-[2-(3-Methyl phenyl)-5-chloro phenyl]-3,3-dimethylbutanamide (**5i**)*

White solid, mp 46–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H), 2.03 (s, 2H), 2.40 (s, 3H), 7.07–7.15 (m, 5H), 7.22–7.27 (m, 1H), 7.34–7.40 (m, 1H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.39, 29.66, 31.26, 51.90, 120.51, 123.78, 126.14, 129.06, 129.08, 129.90, 129.98, 130.66, 133.92, 135.86, 136.93, 139.03, 169.92; HRMS (positive ESI) calcd for $C_{19}H_{22}ClNO$: 338.1288 (M^++Na); found: 338.1257.

*4.2.20. N-[2-(3-Bromo phenyl)-5-chloro phenyl]-3,3-dimethylbutanamide (**5j**)*

White solid, mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (s, 9H), 2.06 (s, 2H), 7.00 (s, 1H), 7.12–7.14 (m, 2H), 7.24–7.28 (m, 1H), 7.33–7.39 (m, 1H), 7.47–7.50 (m, 1H), 7.57 (d, J=7.84 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.68, 31.30, 51.75, 121.32, 123.21, 124.23, 127.83, 128.69, 130.67, 131.42, 132.22, 134.62, 135.66, 139.16, 170.04; HRMS (positive ESI) calcd for $C_{18}H_{19}BrClNO$: 402.0236 (M^++Na); found: 402.0224.

*4.2.21. N-(2-Phenyl-6-methyl phenyl)-3,3-dimethyl-butanamide (**5k**)*

White solid, mp 174–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H), 2.05 (s, 2H), 2.30 (s, 3H), 6.60 (s, 1H), 7.08–7.16 (m, 1H), 7.21–7.26 (m, 2H), 7.27–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.16, 29.86, 30.88, 50.20, 127.09, 127.31, 127.84, 128.35, 128.94, 130.12, 132.83, 136.56, 139.49, 139.80, 170.57; HRMS (positive ESI) calcd for $C_{19}H_{23}NO$: 304.1677 (M^++Na); found: 304.1660.

*4.2.22. N-[2-(4-Methyl phenyl)-6-methyl phenyl]-3,3-dimethylbutanamide (**5l**)*

White solid, mp 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H), 2.06 (s, 2H), 2.29 (s, 3H), 2.38 (s, 3H), 6.59 (s, 1H), 7.09–7.14 (m, 1H), 7.15–7.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.17, 21.11, 29.71, 30.86, 50.15, 126.99, 127.82, 128.77, 128.99, 129.88, 132.82, 136.43, 136.71, 136.96, 139.23, 170.54; HRMS (positive ESI) calcd for $C_{20}H_{25}NO$: 318.1834 (M^++Na); found: 318.1827.

*4.2.23. N-[2-(3-Methyl phenyl)-6-methyl phenyl]-3,3-dimethylbutanamide (**5m**)*

White solid, mp 83–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H), 2.05 (s, 2H), 2.28 (s, 3H), 2.35 (s, 3H), 6.68 (s, 1H), 7.05–7.16 (m, 4H), 7.18–7.28 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.12, 21.37, 29.68, 30.80, 50.12, 125.93, 126.93, 127.74, 128.00, 128.19, 129.61, 129.94, 132.79, 136.43, 137.88, 139.42, 139.65, 170.51; HRMS (positive ESI) calcd for $C_{20}H_{25}NO$: 318.1834 (M^++Na); found: 318.1837.

*4.2.24. 2-(2,6-Diphenyl phenyl)pyridine (**7a**)*[10]

White solid, mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84–6.91 (m, 2H), 7.05–7.12 (m, 4H), 7.12–7.19 (m, 6H), 7.28 (td, J=7.60, 1.72 Hz, 1H), 7.42–7.45 (m, 2H), 7.45–7.55 (m, 1H), 7.28–7.32 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.95, 126.33, 126.86, 127.71, 128.26, 129.54, 129.68, 134.96, 138.51, 141.62, 141.88, 148.56, 158.95.

*4.2.25. 2-[2,6-Di(4-methylphenyl)phenyl]pyridine (**7b**)*[11]

White solid, mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 6H), 6.80–6.91 (m, 10H), 7.20 (td, J=7.72, 1.62 Hz, 1H), 7.29–7.34 (m, 2H), 7.36–7.42 (m, 1H), 8.24 (d, J=4.80 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.08, 120.84, 126.83, 128.17, 128.39, 129.37, 129.51, 135.00, 135.81, 138.33, 138.69, 141.77, 148.42, 159.18.

*4.2.26. 2-[2,6-Di(3-methoxylphenyl)phenyl]pyridine (**7c**)*

White solid, mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 6H), 6.80–7.04 (m, 10H), 7.29 (td, J=7.72, 1.47 Hz, 1H), 7.39–7.44 (m, 2H), 7.46–7.52 (m, 1H), 8.30–8.32 (m, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 21.36, 120.84, 126.73, 126.85, 127.03, 127.49, 128.17, 129.39, 130.60, 134.90, 137.24, 138.48, 141.54, 141.92, 148.40, 159.16; HRMS (positive ESI) calcd for $C_{25}H_{21}NO_2$: 368.1651 (M^++H); found: 368.1648.

*4.2.27. 2-[2,6-Di(3-methylphenyl)phenyl]pyridine (**7d**)*

White solid, mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 6H), 6.80–7.04 (m, 10H), 7.29 (td, *J*=7.62, 1.65 Hz, 1H), 7.39–7.44 (m, 2H), 7.46–7.52 (m, 1H), 8.29–8.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.19, 120.70, 126.59, 126.71, 126.89, 127.34, 128.01, 129.22, 130.46, 134.75, 137.06, 138.33, 141.40, 141.80, 148.21, 159.03; HRMS (positive ESI) calcd for $C_{25}H_{21}N$: 336.1752 (M^++H); found: 336.1747.

*4.2.28. 2-[2,6-Di(3-bromophenyl)phenyl]pyridine (**7e**)*

White solid, mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83–6.90 (m, 1H), 6.93–7.04 (m, 5H), 7.24–7.32 (m, 4H), 7.37 (td, *J*=7.68, 1.70 Hz, 1H), 7.40–7.45 (m, 2H), 7.48–7.55 (m, 1H), 8.33–8.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.46, 121.86, 126.72, 128.28, 128.52, 129.20, 129.55, 129.79, 132.59, 135.39, 138.47, 140.47, 143.36, 148.78, 158.02; HRMS (positive ESI) calcd for $C_{23}H_{15}Br_2N$: 463.9649 (M^++H); found: 463.9642.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 20772114) and the Innovation Fund for Outstanding Scholar of Henan Province (No. 0621001100) for financial support of this research.

References and notes

1. (a) Bergman, R. G. *Nature* **2007**, *446*, 391; (b) Ellman, J. A. *Science* **2007**, *316*, 1131; (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67; (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.
2. For recent representative reviews, see: (a) Herrerıas, C. I.; Yao, X.-Q.; Li, Z.-P.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546; (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.
3. For selected examples on C–H bonds functionalization with a directing-group, see: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330; (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879; (c) Yang, S.-D.; Li, B.-J.; Wan, X.-B.; Shi, Z.-J. *J. Am. Chem. Soc.* **2007**, *129*, 6066; (d) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112; (e) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783; (f) Denmark, S. E.; Kallemeyn, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15958; (g) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048; (h) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858; (i) Zhang, Y.-H.; Feng, J.-Q.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900; (j) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869.
4. For selected examples on C–H bonds functionalization of free arenes, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050; (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972; (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581; (d) Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236; (e) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074; (f) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332; (g) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449; (h) Murphy, J. M.; Liao, X.-B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.
5. (a) Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1873; (b) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485; (c) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.
6. Yang, F.; Wu, Y.-J.; Zhu, Z.-W.; Zhang, J.-L.; Li, Y.-N. *Tetrahedron* **2008**, *64*, 6782.
7. Yoshifuji, M.; Nagase, R.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 873.
8. Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211.
9. Ranu, B. C.; Dey, S. S.; Hajra, A. *Green Chem.* **2003**, *5*, 44.
10. Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439.
11. Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.