Facile synthesis of mono-, bis- and tris-aryl-substituted aniline derivatives in aqueous DMF

Chun Liu,* Xiaoxiao Song, Qijian Ni, and Jieshan Qiu

State Key Lab of Fine Chemicals, Dalian University of Technology, Dalian 116024, P R China
E-mail: chunliu70@yahoo.com

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.906

Abstract

A facile, efficient and general protocol for synthesizing a series of mono-, bis- and tris-aryl-substituted aniline derivatives is described *via* the $Pd(OAc)_2$-catalyzed aerobic and ligand-free Suzuki reaction of mono-, di- and tribromoanilines with aryl boronic acids in aqueous *N*,*N*-dimethylformamide (DMF). This is the first example to prepare 2,6-bisaryl-4-nitroanilines and 2,6-bisarylanilines *via* a palladium-catalyzed ligand-free Suzuki reaction.

Keywords: aryl-substituted aniline; Suzuki reaction; palladium; ligand-free; aqueous

Introduction

Mono-, bis- and tris-aryl-substituted aniline derivatives have been extensively used in the synthesis of dyes, pharmaceuticals, ferromagnetic materials, and especially organometallic complexes,[1-4] because the amino group can react easily with aldehydes or ketones to afford the products with strong electronic donor properties and versatile structures, which have excellent coordinative ability to metals after further modification. Over the past decade, complexes synthesized from aniline derivatives have been a focus in organometallic chemistry and catalysis, such as *N*-heterocyclic carbene ligands (NHC) and β-diketiminate (*nacnac*) ligands.[5-10]

So far, several approaches to the construction of mono-, bis- and tris-aryl-substituted aniline derivatives have been developed, such as nitration followed by reduction,[11-12] or *via* the palladium-catalyzed Suzuki reaction promoted by an oxygen and/or moisture sensitive ligand.[13-18] In 1995, Miura *et al.* reported $Pd(PPh_3)_4$ as catalyst for the Suzuki reaction to synthesize mono-, di-, and triphenylanilines.[13] Later, Paul *et al.* demonstrated a silica supported ligand-free palladium catalyst for the Suzuki reaction to provide 2,4,6-triphenylaniline.[15] In 2004, Zuideveld *et al.* described a protocol to afford 2,6-bisarylanilines *via* the $Pd(PPh_3)_4$-catalyzed Suzuki reaction in toluene/ethanol/H_2O.[6] Meinhard *et al.* in 2007 reported a method to prepare 2,6-bisarylanilines using $Pd(PPh_3)_4$ in benzene.[4] Pisano reported the preparation of 2,6-

diphenylaniline product with $Pd(PPh_3)_4$ in refluxing DME under N_2 to obtain 81% yield in 2 h.[18] In 2010, Frech *et al*. presented the preparation of 2,4,6-triphenylaniline in a Pd-pincer complex mediated system.[17] However, these methods are always combined with complex ligands, high palladium loadings, long reaction times, harsh conditions or low yields.

In recent years, many protocols have been developed to synthesize 4-arylanilines *via* the palladium-catalyzed Suzuki reaction either in the presence of a ligand or under ligand-free conditions.[19-21] In 2004, Thiot *et al.* prepared ionic gel-stabilized palladium nanoparticles to catalyze the cross-coupling of 4-bromoaniline with phenyl boronic acid in MeCN/H_2O at 85°C for 6.5 h under argon.[19] In 2010, Singh *et al*. reported the same reaction in aqueous DMF at 110°C.[20] Zhang described a ligand-free protocol in 2005 to afford 4-phenylaniline in PEG/H_2O at the presence of 1 mol% $Pd(OAc)_2$ at 50°C.[21] However, a general and facile protocol for the palladium-catalyzed ligand-free Suzuki reaction for synthesizing mono-, bis- and tris-aryl-substituted aniline derivatives has not been reported.

The palladium-catalyzed Suzuki coupling reaction has been extensively used in the synthesis of herbicides, natural products, advanced materials, and pharmaceuticals.[22-30] Recently, this transformation has been performed successfully without any additional ligand under mild conditions.[31-37] For example, systems of 10% Pd/C-*i*-PrOH,[31] $Pd(OAc)_2$-ethylene glycol monomethyl ether/H_2O[32] and $Pd(OAc)_2$-acetone/H_2O[33] have been developed. For the past few years, we have been involved in the development of the palladium-catalyzed ligand-free Suzuki reaction and have reported several effective ligand-free protocols, such as $Pd(OAc)_2$-*i*-PrOH/H_2O[34], $Pd(OAc)_2$-PEG400[35,36] and $PdCl_2$-DMF/H_2O[37], which could perform the Suzuki reaction efficiently under aerobic and mild conditions. In the present paper, we report a facile and general approach for the synthesis of mono-, bis- and tris-aryl-substituted aniline derivatives *via* the $Pd(OAc)_2$-catalyzed aerobic and ligand-free Suzuki reaction of mono-, di- and tribromoanilines with aryl boronic acids in aqueous DMF.

Results and Discussion

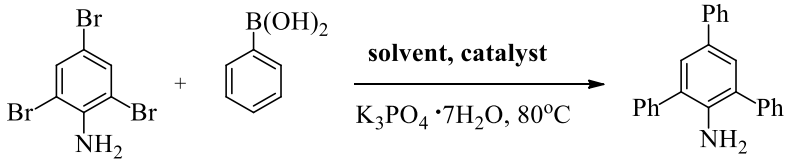
Investigation of reaction conditions

In our concept, solvents play a crucial role in the palladium-catalyzed ligand-free Suzuki reaction. Thus, we first studied the effects of different solvents on the model cross-coupling of 2,4,6-tribromoaniline with phenyl boronic acid under air at 80°C. The results are shown in Table 1 (Table 1, entries 1-5). We tested a series of typical solvents which were commonly used in the palladium-catalyzed ligand-free Suzuki reaction. To our surprise, PEG400 exhibited a rather poor catalytic activity under the reaction conditions (Table 1, entry 1), although the $Pd(OAc)_2$/PEG400 catalytic system could catalyze the Suzuki coupling of aryl chlorides efficiently at room temperature.[35,36] However, reactions carried out in aqueous media demonstrated high efficiency. For example, the reaction could finish in*i*-PrOH/H_2O in 60 min (Table 1, entry 2), and a quantitative yield of 2,4,6-triphenylaniline was obtained in DMF/H_2O

within 30 min (Table 1, entry 4). The results revealed that DMF/H_2O (2/1) was the preferred solvent to activate this catalytic system.

The next investigation was to optimize the palladium species. As shown in Table 1, the reaction catalyzed by $Pd(OAc)_2$ resulted in a quantitative yield in 30 min (Table 1, entry 4), while only 2% and 5% yields were obtained using $Pd_2(dba)_3$ and 5% Pd/C, respectively (Table 1, entries 7 and 8). This was consistent with our reported results.[37-39] Hence, $Pd(OAc)_2$ is the best choice.

Table 1. Effects of solvents and palladium species on the Suzuki reaction of 2,4,6-tribromoaniline with phenyl boronic acid[a]

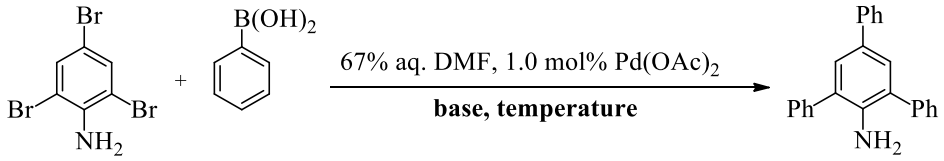


Entry	Solvent (V/V)	Catalyst (mol%)	Time / min	Yield / %[b]
1	PEG400	$Pd(OAc)_2$ (1.0)	60	10[c]
2	*i*-PrOH/H_2O (2/1)	$Pd(OAc)_2$ (1.0)	60	97
3	DMF/H_2O (3/1)	$Pd(OAc)_2$ (1.0)	60	86
4	**DMF/H_2O (2/1)**	**$Pd(OAc)_2$ (1.0)**	**30**	**99**
5	DMF/H_2O (1/1)	$Pd(OAc)_2$ (1.0)	60	75
6	DMF/H_2O (2/1)	$PdCl_2$ (1.0)	60	91[c]
7	DMF/H_2O (2/1)	$Pd_2(dba)_3$ (1.0)	60	2[c]
8	DMF/H_2O (2/1)	5% Pd/C (1.0)	60	5[c]

[a] Reaction conditions: 2,4,6-tribromoaniline (0.25 mmol), phenyl boronic acid (1.125 mmol), $K_3PO_4·7H_2O$ (1.25 mmol), solvent (4 mL), 80 °C, in air. The reaction was monitored by TLC.
[b] Isolated yields. [c] HPLC yield.

Further investigation was carried out to study the influences of the bases. The results are summarized in Table 2. $K_3PO_4·7H_2O$, K_2CO_3 and Na_2CO_3 exhibited high reactivity, and $K_3PO_4·7H_2O$ was the best one in terms of rate (Table 2, entries 4, 5 and 7). Some other inorganic bases, such as KOH, $LiOH·H_2O$ also gave good yields (Table 2, entries 2 and 3). NaOH, Li_2CO_3 and KF resulted in moderate yields (Table 2, entries 1, 6 and 8). While the organic bases such as CH_3COONa and CH_3ONa provided relatively low reactivity (Table 2, entries 9 and 10). The results demonstrated that $K_3PO_4·7H_2O$ was the optimum base. Temperature was the last factor which was investigated. From Table 2, it is clear that the higher the temperature was, the better the result was obtained. Therefore, 80°C is the optimal temperature (Table 2, entry 7).

Table 2. Effects of bases and temperature on the Suzuki reaction of 2,4,6-tribromoaniline with phenyl boronic acid[a]



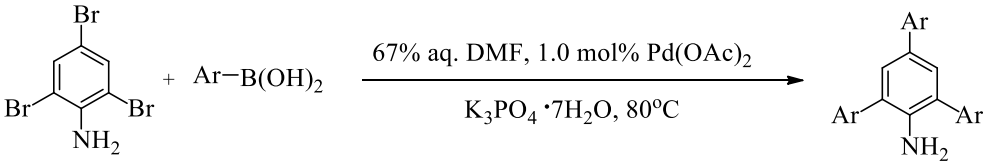
Entry	Base	Temperature / °C	Time / min	Yield / %[b]
1	NaOH	80	60	59[c]
2	KOH	80	60	76[c]
3	$LiOH·H_2O$	80	60	88[c]
4	K_2CO_3	80	60	99
5	Na_2CO_3	80	60	99[c]
6	Li_2CO_3	80	60	48[c]
7	**$K_3PO_4·7H_2O$**	**80**	**30**	**99**
8	KF	80	60	61[c]
9	CH_3COONa	80	60	9[c]
10	CH_3ONa	80	60	36[c]
11	$K_3PO_4·7H_2O$	50	60	64[c]
12	$K_3PO_4·7H_2O$	60	60	87[c]
13	$K_3PO_4·7H_2O$	70	60	98[c]

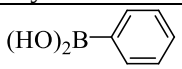
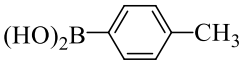
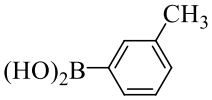
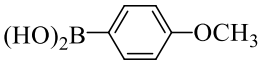
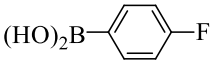
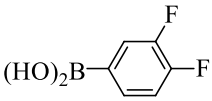
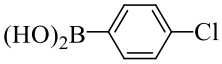
[a] Reaction conditions: 2,4,6-tribromoaniline (0.25 mmol), phenyl boronic acid (1.125 mmol), base (1.25 mmol), $Pd(OAc)_2$ (1.0 mol%), DMF/H_2O (2.7 mL/1.3 mL), in air. The reaction was monitored by TLC. [b] Isolated yields. [c] HPLC yield.

Scope and limitation of substrates

To evaluate the scope and limitations of this procedure, the cross-couplings of 2,4,6-tribromoaniline with a series of aryl boronic acids were examined under optimized reaction conditions. As shown in Table 3, aryl boronic acids bearing electron-rich groups afforded good to excellent yields (Table 3, entries 2-4). To the best of our knowledge, the present method is the most effective protocol for the synthesis of such products.[8] Apparently, electronic effects did not affect the yields in this methodology (Table 3, entries 5-7).

Table 3. The Suzuki reaction of 2,4,6-tribromoaniline with aryl boronic acids[a]

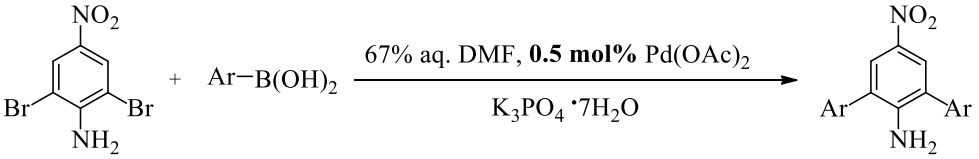


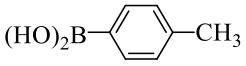
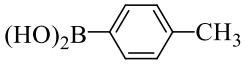
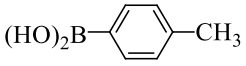
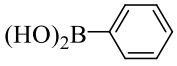
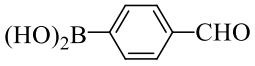
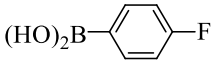
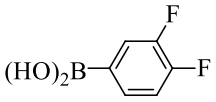
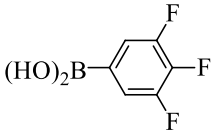
Entry	Aryl boronic acid	Time / min	Yield / %[b]
1		30	99
2		55	86
3		40	98
4		80	82
5		40	93
6		15	87
7		35	98

[a] Reaction conditions: 2,4,6-tribromoaniline (0.25 mmol), aryl boronic acid (1.125 mmol), $K_3PO_4 \cdot 7H_2O$ (1.25 mmol), $Pd(OAc)_2$ (1.0 mol%), DMF/H_2O (2.7 mL/1.3 mL), 80 °C, in air. The reaction was monitored by TLC. [b] Isolated yields

We further investigated the Suzuki reaction of 2,6-dibromo-4-nitroaniline with aryl boronic acids. The results are shown in Table 4. Control experiments were carried out to reveal the effect of temperature on the cross-coupling of 2,6-dibromo-4-nitroaniline with 4-methylphenyl boronic acid (Table 4, entries 1-3). Obviously, the reaction at 80°C was much better than those at 50°C and 25°C. Aryl boronic acids bearing either electron-rich or electron-deficient groups demonstrated high reactivity and afforded the corresponding products in high yields in the presence of 0.5 mol% $Pd(OAc)_2$ (Table 4, entries 3 and 5). Cross-couplings involving mono-, di- and trifluorophenyl boronic acids were all completed in short reaction times (Table 4, entries 6-8). To the best of our knowledge, the present method is the first example for the synthesis of 2,6-bisaryl-4-nitroanilines in the absence of a ligand. Moreover, this is the fastest and most efficient protocol compared to the reported approaches, which were associated with phosphines, harsh conditions and long reaction times.[4]

Table 4. The Suzuki reaction of 2,6-dibromo-4-nitroaniline with aryl boronic acids [a]

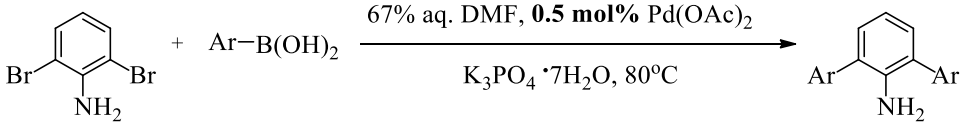


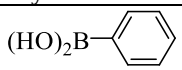
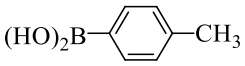
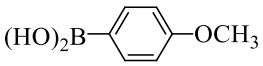
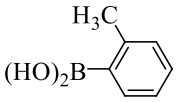
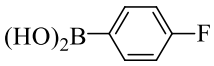
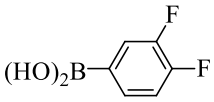
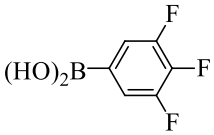
Entry	Aryl boronic acid	Temperature / °C	Time / min	Yield / %[b]
1		25	60	19
2		50	60	94
3		80	15	99
4		80	60	94
5		80	60	98
6		80	20	99
7		80	25	97
8		80	20	75

[a] Reaction conditions: 2,6-dibromo-4-nitroaniline (0.25 mmol), aryl boronic acid (0.75 mmol), $K_3PO_4·7H_2O$ (0.75 mmol), $Pd(OAc)_2$ (0.5 mol%), DMF/H_2O (2.7 mL/1.3 mL), in air. The reaction was monitored by TLC. [b] Isolated yields.

Further investigation was carried out to study the Suzuki reaction of 2,6-dibromoaniline with aryl boronic acids (see Table 5). The results indicated that 4-methylphenyl boronic acid coupled more efficiently than 4-methoxyphenyl boronic acid, resulted in 96% and 62% yields, respectively (Table 5, entries 2 and 3). The reason why 4-methoxyl boronic acid showed much lower activity than 4-methyl boronic acid might be due to the 4-MeO's negative inductive effect, resulting in a decrease of the nucleophilicity of 4-methoxyphenyl boronic acid. As far as we know, 2,6-bisarylaniline derivatives are very important intermediates to prepare *N*,*N*-bidentate ligands.[5-6] The present protocol is the simplest and most efficient method to construct these intermediates compared with the previous reports.[5-6] To our delight, fluoro-substituted phenyl boronic acids all gave good to excellent yields (Table 5, entries 5-7).

Table 5. The Suzuki reaction of 2, 6-dibromoaniline with aryl boronic acids[a]

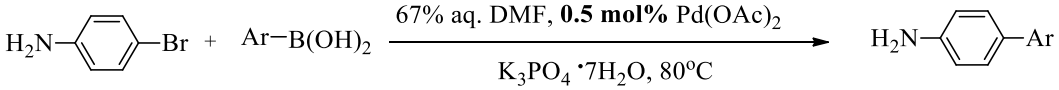


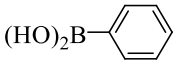
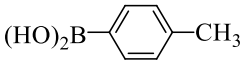
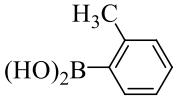
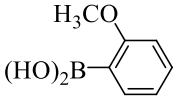
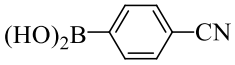
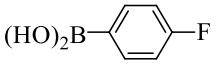
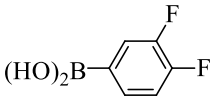
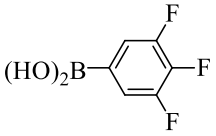
Entry	Aryl boronic acid	Time / min	Yield / %[b]
1		80	96
2		45	96
3		60	62
4		120	66
5		60	96
6		65	96
7		20	88

[a] Reaction conditions: 2,6-dibromoaniline (0.5 mmol), aryl boronic acid (1.5 mmol), $K_3PO_4 \cdot 7H_2O$ (1.5 mmol), $Pd(OAc)_2$ (0.5 mol%), DMF/H_2O (2.7 mL/1.3 mL), 80 °C, in air. The reaction was monitored by TLC. [b] Isolated yields.

To further extend the scope of this methodology, we tried to carry out the Suzuki coupling of 4-bromoaniline with a series of aryl boronic acids. As shown in Table 6, aryl boronic acids bearing electron-rich groups or ortho-substituted groups, such as 4-methyl, 2-methyl, 2-methoxyl, and mono-, di-, trifluroro groups, coupled with 4-bromoaniline resulting in excellent yields (Table 6, entries 2-4, 6-8). Compared with the results in Table 5, it was clear that the steric hindrance did not affect the yields (Table 6, entries 3 and 4). The coupling also proceeded readily with electron deficient boronic acids, *e.g.* 4-cyanophenylboronic acid, to afford the product in 62% yield (Table 6, entry 5). Unfortunately, this protocol could not activate chlorinated anilines.

Table 6. The Suzuki reaction of 4-bromoaniline with aryl boronic acids[a]



Entry	Aryl boronic acid	Time / min	Yield / %[b]
1		20	99
2		20	99
3		50	98
4		120	94
5		120	62
6		25	97
7		40	93
8		30	92

[a] Reaction conditions: 4-bromoaniline (0.5 mmol), aryl boronic acid (0.75 mmol), $K_3PO_4 \cdot 7H_2O$ (1.0 mmol), $Pd(OAc)_2$ (0.5 mol%), DMF/H_2O (2.7 mL/1.3 mL), 80 °C, in air. The reaction was monitored by TLC.
[b] Isolated yields.

Conclusions

In summary, we have developed a facile and general protocol to synthesize mono-, bis- and tris-aryl-substituted aniline derivatives *via* the $Pd(OAc)_2$-catalyzed ligand-free Suzuki reaction in 67% aqueous DMF under air. It is noteworthy that a wide range of substrates including mono-, di- and tribromoanilines could perform the Suzuki reaction with aryl boronic acids smoothly resulting in good to excellent yields.

Further study including the synthesis and catalytic activity of NHC and *nacnac* ligands prepared from aryl-substituted anilines described in this paper are currently under investigation in our laboratory.

Experimental Section

General. All the reactions were carried out under air. All aryl halides and aryl boronic acids were purchased from Alfa Aesar, Avocado and used without purification. ^{1}H NMR spectra were recorded on a Varian Inova 400 spectrometer. Chemical shifts are reported in ppm relative to TMS. Mass spectroscopy data of the products were collected on a MS-EI instrument. HPLC yields were recorded on a Waters Alliance 2695-2996-2475 High Performance Liquid Chromatography. Other products were isolated by chromatography on a short silica gel (200-300 mesh) column using petroleum ether (60-90 °C), unless otherwise noted. Compounds described in the literature were characterised by comparison of their ^{1}H NMR spectra with reported data.
The HPLC measurement was carried out using an XBridge C18 (2.1×150mm, 5μm) column. Mobile phase consisted of H_2O (including 0.3% HOAc and 0.3% $N(CH_2CH_3)_3$) and MeOH, the gradient elution was adopted, the volume ratio of H_2O to MeOH was 30:70 at the beginning to 0:100 at the end, the flow rate was 0.3 mL/min. A variable wavelength UV detector at 246 nm was used. The value of time of retention was 14.2 min.

Typical experimental procedure for the Suzuki reaction of bromoanilines with aryl boronic acids

Procedure 1. A mixture of 2,4,6-tribromoaniline (0.25 mmol), aryl boronic acid (1.125 mmol), $K_3PO_4 \cdot 7H_2O$ (1.25 mmol), $Pd(OAc)_2$ (1.0 mol%), DMF (2.7 mL) and distilled water (1.3 mL) was stirred at 80°C under air for the indicated time. The mixture was added to brine (15 mL) and extracted three times with ethyl acetate (3×15 mL). The solvent was concentrated under vacuum and the product was isolated by chromatography on a short silica gel (200-300 mesh) column.
Procedure 2. A mixture of 2,6-dibromo-4-nitroaniline (0.25 mmol), aryl boronic acid (0.75 mmol), $K_3PO_4 \cdot 7H_2O$ (0.75 mmol), $Pd(OAc)_2$ (0.5 mol%), DMF (2.7 mL) and distilled water (1.3 mL) was stirred at 80°C under air for the indicated time. The mixture was added to brine (15 mL) and extracted three times with ethyl acetate (3×15 mL). The solvent was concentrated under vacuum and the product was isolated by chromatography on a short silica gel (200-300 mesh) column.
Procedure 3. A mixture of 2,6-dibromoaniline (0.5 mmol), aryl boronic acid (1.5 mmol), $K_3PO_4 \cdot 7H_2O$ (1.5 mmol), $Pd(OAc)_2$ (0.5 mol%), DMF (2.7 mL) and distilled water (1.3 mL) was stirred at 80°C under air for the indicated time. The mixture was added to brine (15 mL) and extracted three times with ethyl acetate (3×15 mL). The solvent was concentrated under vacuum and the product was isolated by chromatography on a short silica gel (200-300 mesh) column.
Procedure 4. A mixture of 4-bromoaniline (0.5 mmol), aryl boronic acid (0.75 mmol), $K_3PO_4 \cdot 7H_2O$ (1.0 mmol), $Pd(OAc)_2$ (0.5 mol%), DMF (2.7 mL) and distilled water (1.3 mL) was stirred at 80°C under air for the indicated time. The mixture was added to brine (15 mL) and extracted three times with ethyl acetate (3×15 mL). The solvent was concentrated under vacuum and the product was isolated by chromatography on a short silica gel (200-300 mesh) column.

2,4,6-Tris(4-methylphenyl)aniline (Table 3, entry 2). Prepared by procedure 1, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 86% yield. ^{1}H NMR: δ 7.49-7.46 (m, 6H, Ph), 7.38 (s, 2H, Ph), 7.29 (d, *c* 8.0 Hz, 4H, Ph), 7.20 (d, *J* 8.0 Hz, 2H, Ph), 2.41 (s, 6H, 2×C*H*$_3$), 2.37 (s, 3H, C*H*$_3$), ppm; ^{13}C NMR: δ 140.07 (Ph), 138.16 (Ph), 137.13 (2×Ph), 136.81 (2×Ph), 136.01 (Ph), 131.22 (Ph), 129.65 (4×Ph), 129.47 (2×Ph), 129.30 (4×Ph), 128.40 (2×Ph), 128.13 (2×Ph), 126.34 (2×Ph), 21.19 (2×*C*H$_3$), 21.11 (*C*H$_3$); MS (EI) *m/z*: calculated value: 363.1987, found value: 363.1990 (M^+); mp 113.1-114.0 °C.

2,4,6-Tris(3-methylphenyl)aniline (Table 3, entry 3). Prepared by procedure 1, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 98% yield. ^{1}H NMR: δ 7.41-7.35 (m, 10H, Ph), 7.27 (t, *J* 7.4 Hz, 1H, Ph), 7.21-7.17 (m, 2H, Ph), 7.07 (d, *J* 7.2 Hz, 1H, Ph), 3.91 (s, 2H, N*H*$_2$), 2.41 (s, 6H, 2×C*H*$_3$), 2.37 (s, 3H, C*H*$_3$), ppm; ^{13}C NMR: δ 140.99 (Ph), 140.07 (Ph), 139.77 (2×Ph), 138.70 (2×Ph), 138.31 (Ph), 131.39 (Ph), 130.22 (2×Ph), 128.94 (2×Ph), 128.75 (Ph), 128.66 (Ph), 128.39 (2×Ph), 128.29 (2×Ph), 127.36 (Ph), 127.26 (Ph), 126.48 (2×Ph), 123.67 (2×Ph), 21.70 (*C*H$_3$), 21.65 (2×*C*H$_3$) ppm; MS (EI) *m/z*: calculated value: 363.1987, found value: 363.1990 (M^+); mp 96.8-97.4 °C.

2,4,6-Tris(4-methoxylphenyl)aniline (Table 3, entry 4). Prepared by procedure 1, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 82% yield. ^{1}H NMR: δ 7.52-7.47 (m, 6H, Ph), 7.31 (s, 2H, Ph), 7.01 (d, *J* 8.8 Hz, 4H, Ph), 6.93 (d, *J* 8.8 Hz, 2H, Ph), 3.87 (s, 6H, 2×OC*H*$_3$), 3.85 (s, 2H, N*H*$_2$), 3.83 (s, 3H, OC*H*$_3$), ppm; ^{13}C NMR: δ 158.92 (2×Ph), 158.47 (Ph), 140.19 (Ph), 133.68 (Ph), 132.02 (2×Ph), 130.81 (Ph), 130.49 (4×Ph), 128.00 (2×Ph), 127.80 (2×Ph), 127.45 (2×Ph), 114.30 (4×Ph), 114.14 (2×Ph), 55.36 (3×O*C*H$_3$) ppm; MS (EI) *m/z*: calculated value: 411.1834, found value: 411.1844 (M^+); mp 154.0-154.8 °C.

2,4,6-Tris(4-fluorophenyl)aniline (Table 3, entry 5). Prepared by procedure 1, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 93% yield. H NMR: δ 7.53-7.49 (m, 6H, Ph), 7.30 (s, 2H, Ph), 7.17 (t, *J* 8.8 Hz, 4H, Ph), 7.08 (t, *J* 8.8 Hz, 2H, Ph), 3.81 (s, 2H, N*H*$_2$), ppm; ^{13}C NMR: δ 162.40 (d, J_{CF} = 245 Hz, 2×Ph), 162.15 (d, J_{CF} = 244 Hz, Ph), 140.52 (Ph), 136.92 (d, J_{CCCCF} = 3 Hz, Ph), 135.40 (d, J_{CCCCF} = 2 Hz, 2×Ph), 131.15 (d, J_{CCCF} = 8 Hz, 4×Ph), 130.44 (Ph), 128.52 (2×Ph), 128.03 (d, J_{CCCF} = 8 Hz, 2×Ph), 127.57 (2×Ph), 116.08 (d, J_{CCF} = 21 Hz, 4×Ph), 115.71 (d, J_{CCF} = 21 Hz, 2×Ph), ppm; MS (EI) *m/z*: calculated value: 375.1235, found value: 375.1241 (M^+); mp 127.6-129.4°C.

2,4,6-Tris(3,4-difluorophenyl)aniline (Table 3, entry 6). Prepared by procedure 1, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 87% yield. ^{1}H NMR: δ 7.38-7.16 (m, 11H, Ph), 3.87 (s, 2H, N*H*$_2$), ppm; ^{13}C NMR: δ 150.55 (dd, *J* 248, 12 Hz, 3×Ph), 149.96 (dd, *J* 248, 12 Hz, 2×Ph), 149.50 (dd, *J* 247, 12 Hz, Ph), 140.57 (Ph), 137.48 (dd, *J* 6, 4 Hz, Ph), 135.84 (dd, *J* 6, 5 Hz, Ph), 129.33 (Ph), 128.55 (2×Ph), 126.50 (2×Ph), 125.49 (dd, *J* 6, 4 Hz, 2×Ph), 122.14 (dd, *J* 6, 4 Hz, 2×Ph), 118.41 (d, *J* 17 Hz, 2×Ph), 117.98 (d, *J* 17 Hz, 2×Ph), 117.53 (d, *J* 17 Hz, Ph), 115.16 (d, *J* 18 Hz, Ph), ppm; MS (EI) *m/z*: calculated value: 429.0952, found value: 429.0955 (M^+); mp 194.0-194.4°C.

2,4,6-Tris(4-chlorophenyl)aniline (Table 3, entry 7). Prepared by procedure 1, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 98% yield. ^{1}H NMR: δ 7.50-7.44 (m, 10H, Ph), 7.35 (d, *J* 8.4 Hz, 2H, Ph), 7.31 (s, 2H, Ph), 3.86 (s, 2H, NH_2), ppm; ^{13}C NMR: δ 140.47 (Ph), 138.97 (Ph), 137.65 (2×Ph), 133.65 (2×Ph), 132.55 (Ph), 130.69 (4×Ph), 130.06 (Ph), 129.25 (4×Ph), 128.90 (2×Ph), 128.36 (2×Ph), 127.58 (2×Ph), 127.27 (2×Ph), ppm; MS (EI) *m/z*: calculated value: 423.0348, found value: 423.0343 (M^+); mp 152.0-153.1 °C.

2,6-Bis(4-methylphenyl)-4-nitroaniline (Table 4, entry 3). Prepared by procedure 2, and purified by column chromatography using petroleum ether/EtOAc 40/1 in 99% yield. ^{1}H NMR: δ 8.02 (s, 2H, Ph), 7.36 (d, *J* 7.6 Hz, 4H, Ph), 7.30 (d, *J* 8.0 Hz, 4H, Ph), 4.58 (s, 2H, NH_2), 2.42 (s, 6H, 2×CH_3), ppm; ^{13}C NMR: δ 147.68 (Ph), 138.65 (Ph), 138.23 (2×Ph), 134.39 (2×Ph), 130.03 (4×Ph), 128.91 (4×Ph), 126.73 (2×Ph), 125.61 (2×Ph), 21.25 (2×*C*H$_3$), ppm; MS (EI) *m/z*: calculated value: 318.1368, found value: 318.1371 (M^+); Melting Point: 180.2-182.1 °C.

2,6-Bis(4-formylphenyl)-4-nitroaniline (Table 4, entry 5). Prepared by procedure 2, and purified by column chromatography using petroleum ether/EtOAc 20/1 in 98% yield. ^{1}H NMR: δ 10.10 (s, 2H, 2×CHO), 8.11 (s, 2H, Ph), 8.05 (d, *J* 8.4 Hz, 4H, Ph), 7.70 (d, *J* 8.0 Hz, 4H, Ph), 4.57 (s, 2H, NH_2), ppm; ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 193.29 (2×*C*HO), 149.42 (Ph), 143.75 (2×Ph), 137.14 (Ph), 136.08 (2×Ph), 130.80 (4×Ph), 130.40 (4×Ph), 126.49 (2×Ph), 125.60 (2×Ph), ppm; MS (EI) *m/z*: calculated value: 346.0954, found value: 346.0959 (M^+); mp 226.9-228.3 °C.

2,6-Bis(4-fluorophenyl)-4-nitroaniline (Table 4, entry 6). Prepared by procedure 2, and purified by column chromatography using petroleum ether/EtOAc 40/1 in 99% yield. ^{1}H NMR: δ 8.03 (s, 2H, Ph), 7.47-7.44 (m, 4H, Ph), 7.21 (t, *J* 8.6 Hz, 4H, Ph), 4.47 (s, 2H, NH_2), ppm; ^{13}C NMR: δ 162.68 (d, J_{CF} = 247 Hz, 2×Ph), 147.47 (Ph), 138.72 (Ph), 133.06(d, J_{CCCCF} = 3 Hz, 2×Ph), 130.93 (d, J_{CCCF} = 9 Hz, 4×Ph), 125.93 (2×Ph), 125.87 (2×Ph), 116.47 (d, J_{CCF} = 21 Hz, 4×Ph), ppm; MS (EI) *m/z*: calculated value: 326.0867, found value: 326.0875 (M^+); mp 215.9-216.5°C.

2,6-Bis(3,4-difluorophenyl)-4-nitroaniline (Table 4, entry 7). Prepared by procedure 2, and purified by column chromatography using petroleum ether/EtOAc 40/1 in 97% yield. ^{1}H NMR: δ 8.03 (s, 2H, Ph), 7.36-7.30 (m, 4H, Ph), 7.23-7.20 (m, 2H, Ph), 4.49 (s, 2H, NH_2), ppm; ^{13}C NMR: δ 150.76 (dd, *J* 250, 13 Hz, 2×Ph), 150.45 (dd, *J* 250, 13 Hz, 2×Ph), 146.96 (Ph), 138.84 (Ph), 133.72 (dd, *J* 7, 5 Hz, 2×Ph), 126.16 (2×Ph), 125.49 (dd, *J* 8, 3 Hz, 2×Ph), 124.95 (2×Ph), 118.45 (2×Ph), 118.45 (d, *J* 34 Hz, 2×Ph), ppm; MS (EI) *m/z*: calculated value: 326.0678, found value: 362.0676 (M^+); mp 221.6-222.3 °C.

2,6-Bis(3,4,5-trifluorophenyl)-4-nitroaniline (Table 4, entry 8). Prepared by procedure 2, and purified by column chromatography using petroleum ether/EtOAc 40/1 in 75% yield. H NMR: δ 8.03 (s, 2H, Ph), 7.17-7.09 (m, 4H, Ph), 4.51 (s, 2H, NH_2), ppm; ^{13}C NMR: δ 151.83 (ddd, *J* 252, 10, 4 Hz, 4×Ph), 146.56 (Ph), 139.96 (dt, *J* 253, 15 Hz, 2×Ph), 138.88 (Ph), 132.64-132.44 (m, 2×Ph), 126.34 (2×Ph), 124.20 (2×Ph), 113.65 (dd, *J* 9, 6 Hz, 4×Ph), ppm; MS (EI) *m/z*: calculated value: 398.0490, found value: 398.0490 (M^+); mp 209.2-210.2 °C.

2,6-Bis(4-methylphenyl)aniline (Table 5, entry 2). Prepared by procedure 3, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 96% yield. ^{1}H NMR: δ7.33 (dd, *J* 48.4, 8.0 Hz, 8H, Ph), 7.10 (d, *J* 7.6 Hz, 2H, Ph), 6.86 (t, *J* 7.6 Hz, 1H, Ph), 3.85 (s, 2H, NH_2), 2.40 (s, 6H, 2×CH_3), ppm; ^{13}C NMR: δ 141.01 (Ph), 136.95 (2×Ph), 136.92 (2×Ph), 129.68 (2×Ph), 129.60 (4×Ph), 129.28 (4×Ph), 127.95 (Ph), 118.18 (2×Ph), 21.29 (2×*C*H$_3$), ppm; MS (EI) *m/z*: calculated value: 273.1517, found value: 273.1510 (M^+); mp 118.2-119.1 °C.

2,6-Bis(4-fluorophenyl)aniline (Table 5, entry 5). Prepared by procedure 3, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 96% yield.
^{1}H NMR: δ 7.48-7.45 (m, 4H, Ph), 7.17-7.12 (m, 4H, Ph), 7.09 (d, *J* 7.6 Hz, 2H, Ph), 6.87 (t, *J* 7.6 Hz, 1H, Ph), 3.75 (s, 2H, NH_2), ppm, ^{13}C NMR: δ 162.16 (d, J_{CF} = 245 Hz, 2×Ph), 140.93 (Ph), 135.50 (d, J_{CCCCF} = 3 Hz, 2×Ph), 131.01 (d, J_{CCCF} = 8 Hz, 4×Ph), 129.95 (2×Ph), 127.03 (Ph), 118.30 (2×Ph), 115.84 (d, J_{CCF} = 21 Hz, 4×Ph), ppm; MS (EI) *m/z*: calculated value: 281.1016, found value: 281.1018 (M^+); mp 146.0-147.6 °C.

2,6-Bis(3,4-difluorophenyl)aniline (Table 5, entry 6). Prepared by procedure 3, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 96% yield. ^{1}H NMR: δ 7.33-7.29 (m, 2H, Ph), 7.27-7.19 (m, 4H, Ph), 7.08 (d, *J* 7.6 Hz, 2H, Ph), 6.87 (t, *J* 7.6 Hz, 1H, Ph), 3.77 (s, 2H, NH_2), ppm, ^{13}C NMR: δ 150.46 (dd, *J* 248, 12 Hz, 2×Ph), 149.77 (dd, *J* 248, 12 Hz, 2×Ph), 140.64 (Ph), 136.28 (dd, *J* 6, 4 Hz, 2×Ph), 130.19 (Ph), 126.06 (Ph), 125.47 (dd, *J* 6, 4 Hz, 2×Ph), 118.45 (2×Ph), 118.37 (d, *J* 17 Hz, 2×Ph), 117.78 (d, *J* 17 Hz, 2×Ph) ppm; MS (EI) *m/z*: calculated value: 317.0828, found value: 317.0818 (M^+); mp 88.2-89.0 °C.

2,6-Bis(3,4,5-trifluorophenyl)aniline (Table 5, entry 7). Prepared by procedure 3, and purified by column chromatography using petroleum ether/EtOAc 200/1 in 88% yield. ^{1}H NMR: δ 7.16-7.07 (m, 6H, Ph), 6.87 (t, *J* 7.6 Hz, 1H, Ph), 3.78 (s, 2H, NH_2), ppm, ^{13}C NMR: δ 151.46 (ddd, *J* 250, 10, 4 Hz, 4×Ph), 140.37 (Ph), 139.21 (dt, *J* 251 Hz, 5 Hz, 2×Ph), 135.25-135.04 (m, 2×Ph), 130.42 (2×Ph), 125.25 (Ph), 118.67 (2×Ph), 113.52 (dd, *J* 16, 6 Hz, 4×Ph), ppm; MS (EI) *m/z*: calculated value: 353.0639, found value: 353.0637 (M^+); mp 92.5-93.1 °C.

4-(4-Fluorophenyl)aniline (Table 6, entry 6). Prepared by procedure 4, and purified by column chromatography using petroleum ether/EtOAc 20/1 in 97% yield. ^{1}H NMR: δ 7.49-7.44 (m, 2H, Ph), 7.37-7.33 (m, 2H, Ph), 7.10-7.05 (m, 2H, Ph), 6.77-6.73 (m, 2H, Ph), 3.72 (s, 2H, NH_2), ppm; ^{13}C NMR: δ 161.88 (d, J_{CF} = 244 Hz, Ph), 145.85 (Ph), 137.35 (d, J_{CCCCF} = 3 Hz, Ph), 130.64 (Ph), 127.90 (2×Ph), 127.82 (2×Ph), 115.46 (d, J_{CCF} = 21 Hz, 2×Ph), 115.42 (2×Ph), ppm; MS (EI) *m/z*: calculated value: 187.0797, found value: 187.0795 (M^+); mp 120.2-121.1 °C.

4-(3,4-Difluorophenyl)aniline (Table 6, entry 7). Prepared by procedure 4, and purified by column chromatography using petroleum ether/EtOAc 20/1 in 93% yield. ^{1}H NMR: δ 7.32-7.28 (m, 3H, Ph), 7.23-7.13 (m, 2H, Ph), 6.76-6.73 (m, 2H, Ph), 3.76 (s, 2H, NH_2), ppm; ^{13}C NMR: δ 150.48 (dd, *J* 245, 13 Hz, Ph), 149.23 (dd, *J* 245, 13 Hz, Ph), 146.37 (Ph), 138.39 (dd, *J* 6, 4 Hz, Ph), 129.36 (Ph), 127.87(2×Ph), 122.07 (dd, *J* 6, 4 Hz, Ph), 117.34 (d, *J* 17 Hz, Ph), 115.40 (2×Ph),115.07 (d, *J* 17 Hz, Ph), ppm; MS (EI) *m/z*: calculated value: 205.0703, found value: 205.0694 (M^+); mp 88.3-89.2 °C.

4-(3,4,5-Trifluorophenyl)aniline (Table 6, entry 8). Prepared by procedure 4, and purified by column chromatography using petroleum ether/EtOAc 20/1 in 92% yield. ^{1}H NMR: δ 7.32-7.29 (m, 2H, Ph), 7.13-7.07 (m, 2H, Ph), 6.75-6.72 (m, 2H, Ph), 3.80 (s, 2H, NH_2), ppm; ^{13}C NMR: δ 151.38 (ddd, *J* 247, 10, 5 Hz, 2×Ph), 146.84 (Ph), 139.85-137.06 (m, 2×Ph), 128.25 (Ph), 127.78 (2×Ph), 115.35 (2×Ph), 109.95 (dd, *J* 16, 6 Hz, 2×Ph), ppm; MS (EI) *m/z*: calculated value: 223.0609, found value: 223.0599 (M^+); mp 83.6-84.1 °C.

Acknowledgements

The authors thank the financial support from the National Natural Science Foundation of China (21076034, 20923006), the Fundamental Research Funds for the Central Universities (DUT11LK15), and the Ministry of Education (the Program for New Century Excellent Talents in University).

References

1. Langhals, H.; Ismael, R.; Yürük, O. *Tetrahedron* **2000**, *56*, 5435.
2. Li, J. J.; Wang, H.; Tino, J. A.; Robl, J. A.; Herpin, T. F.; Lawrence, R. M.; Biller, S.; Jamil, H.; Ponticiello, R.; Chen, L.; Chu, C.; Flynn, N.; Cheng, D.; Zhao, R.; Chen, B.; Schnur, D.; Obermeier, M. T.; Sasseville, V.; Padmanabha, R.; Pike, K.; Harrity, T. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 3208.
3. Miura, Y.; Nishi, T. *J. Org. Chem.* **2005**, *70*, 4177.
4. Meinhard, D.; Wegner, M.; Kipiani, G.; Hearley, A.; Reuter, P.; Fischer, S.; Mart, O.; Rieger, B. *J. Am. Chem. Soc.* **2007**, *129*, 9182.
5. Zakai, U. I.; Bloch-Mechkour, A.; Jacobsen, N. E.; Abrell, L.; Lin, G.; Nichol, G. S.; Bally, T.; Glass, R. S. *J. Org. Chem.* **2010**, *75*, 8363
6. Zuideveld, M. A.; Wehrmann, P.; Röhr, C.; Mecking, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 869.
7. Alexander, S. G.; Cole, M. L.; Morris, J. C. *New J. Chem.* **2009**, *33*, 720.
8. Eberhardt, R.; Allmendinger, M.; Luinstra, G. A.; Rieger, B. *Organometallics* **2003**, *22*, 211.
9. Bai, G.; Singh, S.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H. *J. Am. Chem. Soc.* **2005**, *127*, 3449.
10. Lee, D.; Jin, M. *Org. Lett.* **2011**, *13*, 252.
11. Fujioka, Y.; Ozasa, S.; Sato, K.; Ibuki, E. *Chem. Pharm. Bull.* **1985**, *33*, 22.
12. Ozasa, S.; Fujioka, Y.; Kikutake, J. I.; Ibuki, E. *Chem. Pharm. Bull.* **1983**, *31*, 1572.
13. Miura, Y.; Oka, H.; Momoki, M. *Synthesis* **1995**, 1419.
14. Basu, B.; Das, P.; Bhuiyan, M. M. H.; Jha, S. *Tetrahedron Lett.* **2003**, *44*, 3817.
15. Paul, S.; Clark, J. H. *Green Chem.* **2003**, *5*, 635.

16. Miura, Y.; Momoki, M.; Nakatsuji, M. *J. Org. Chem.* **1998**, *63*, 1555.
17. Bolliger, J. L.; Frech, C. M. *Adv. Synth. Catal.* **2010**, *352*, 1075.
18. Azzena, U.; Cattari, M.; Melloni, G.; Pisano, L. *Synthesis* **2003**, 2811.
19. Thiot, C.; Schmutz, M.; Wagner, A.; Mioskowski, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 2868.
20. Rao, G. K.; Kumar, A.; Ahmed, J.; Singh, A. K. *Chem. Commun.* **2010**, *46*, 5954.
21. Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122.
22. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
23. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
24. Ren, T. *Chem. Rev.* **2008**, *108*, 4185.
25. Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027.
26. Polshettiwar, V.; Decottignies, A.; Len, C.; Fihri, A. *ChemSusChem* **2010**, *3*, 502.
27. Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
28. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
29. Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419.
30. Kotha, S.; Lahiri, K. *Eur. J. Org. Chem.* **2007**, 1221.
31. Kitamura, Y.; Sako, S.; Tsutsui, A.; Monguchi, Y.; Maegawa, T.; Kitade, Y.; Sajiki, H. *Adv. Synth. Catal.* **2010**, *352*, 718.
32. Del Zotto, A.; Amoroso, F.; Baratta, W.; Rigo, P. *Eur. J. Org. Chem.* **2009**, 110.
33. Liu, L.; Zhang, Y.; Xin, B. *J. Org. Chem.* **2006**, *71*, 3994.
34. Liu, C.; Yang, W. *Chem. Commun.* **2009**, *41*, 6267.
35. Han, W.; Liu, C.; Jin, Z. *Adv. Synth. Catal.* **2008**, *350*, 501.
36. Han, W.; Liu, C.; Jin, Z. *Org. Lett.* **2007**, *9*, 4005.
37. Liu, C.; Ni, Q.; Bao, F.; Qiu, J. *Green. Chem.* **2011**, *13*, 1260.
38. Liu, C.; Han, N.; Song, X.; Qiu, J. *Eur. J. Org. Chem.* **2010**, 5548.
39. Liu, C.; Ni, Q.; Hu, P.; Qiu, J. *Org. Biomol. Chem.* **2011**, *9*, 1054.

