ChemInform Abstract: Palladium-Catalyzed Microwave-Assisted Direct Arylation of Imidazo[2,1-b]thiazoles with Aryl Bromides: Synthesis and Mechanistic Study.

ARTICLE *in* ORGANIC & BIOMOLECULAR CHEMISTRY · JUNE 2014

Impact Factor: 3.56 · DOI: 10.1039/c4ob00600c · Source: PubMed

5 AUTHORS, INCLUDING:

Ran Fang
Lanzhou University
39 PUBLICATIONS **405** CITATIONS
SEE PROFILE

Huanwang Jing
Lanzhou University
52 PUBLICATIONS **898** CITATIONS
SEE PROFILE

Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 5773

Palladium-catalyzed microwave-assisted direct arylation of imidazo[2,1-*b*]thiazoles with aryl bromides: synthesis and mechanistic study†

Yi-Shuo Zhu, Benyi Shi, Ran Fang, Xiaoxuan Wang and Huanwang Jing*

Received 20th March 2014,
Accepted 30th May 2014

DOI: 10.1039/c4ob00600c

www.rsc.org/obc

A palladium-catalyzed direct C–H arylation of various imidazo[2,1-*b*]thiazoles with a range of aryl bromides under microwave irradiation is described. 6-Phenyl substituted imidazo[2,1-*b*]thiazoles could be regioselectively C-5 arylated using the developed protocol. The utility of this method enables the representative coupling product to be achieved by a sequential one-pot reaction. Density functional theory (DFT) calculations show that this arylation proceeds *via* a concerted metalation–deprotonation (CMD) pathway, which is in agreement with our experimental results. This work provides a convenient access to a variety of biologically active imidazo[2,1-*b*]thiazole derivatives. Also, it enriches the mechanism study of site-selective C–H arylation in fused heterocycles, and offers a valuable guide to design highly efficient catalytic systems for the preparation of similar compounds.

Introduction

Imidazo[2,1-*b*]thiazoles represent an important class of heteroaromatic compounds that are key structural motifs of numerous bioactive molecules and functional materials,[1] such as tetramisole (**i**),[2] pifithrin-β (**ii**),[3] 4-imidazo[2,1-*b*]thiazole-1,4-dihydropyridines (**iii**),[4] 5,6-di(hetero)arylimidazo[2,1-*b*]thiazoles (**iv**),[5] 3-methyl-5,6-diarylimidazo[2,1-*b*]thiazoles (**v**),[6] and 2,3-diarylbenzo[*d*]imidazo[2,1-*b*]thiazoles (**vi**)[1b] (Fig. 1). Although a variety of methods have been reported for the synthesis of di(hetero)arylimidazo[2,1-*b*]thiazoles,[5,7] they have the restrictions of particular substitution patterns,[7b] low overall yields and long experimental periods,[7c] as well as stoichiometric organoboron reagents and extra synthetic manipulations in Pd-mediated Suzuki-type cross-coupling.[7d]

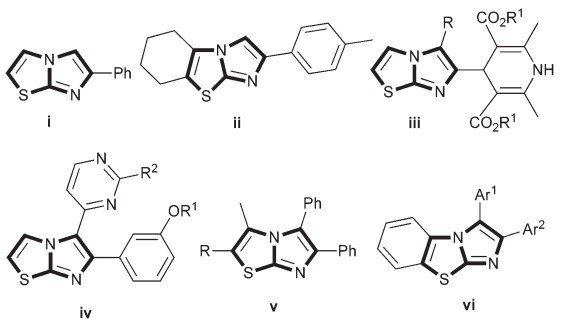


Fig. 1 Structure of bioactive imidazo[2,1-*b*]thiazoles.

In recent years, transition metal catalyzed direct C–H arylation[8] has emerged as a promising strategy for the formation of biaryl compounds without prior functionalization to metalated or halogenated substrates. This new approach avoids availability problems, metal waste, and additional synthetic steps for arylmetals. In this context, a broad range of useful heterocyclic compounds have been developed to construct heteroarenes by metal-catalyzed direct arylations.[9] However, regioselective C–H arylation towards the specific location of heterocycles bearing multiple C–H bonds is still problematic. It is widely believed that, on one hand, for electron-rich heterocyclic molecules such as imidazole, thiazole, oxazole, pyrrole, and indole, C–H arylation is prone to suffer from the electrophilic aromatic substitution (S_EAr) pathway[10] owing to their high nucleophilicity, though Heck-like,[11] oxidative C–H insertion[12] and stepwise 1,2-migratory insertion[13] process can also occur in rare circumstances. On the other hand, as for electron-poor heterocycles such as pyridine, diazine, and azine N-oxides, C–H arylation often takes place through a concerted metalation–deprotonation (CMD) mechanism.[14] Besides, several direct arylations of electron-rich heterocyclic compounds also have been demonstrated *via* a CMD process.[15] Nevertheless, the mechanism study on condensed heterocyclic ring systems containing two or more π-excessive heterocycles is less explored. In view of the illustrated importance of 5,5-fused

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China. E-mail: hw-jing@163.com

†Electronic supplementary information (ESI) available. CCDC 942540. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00600c

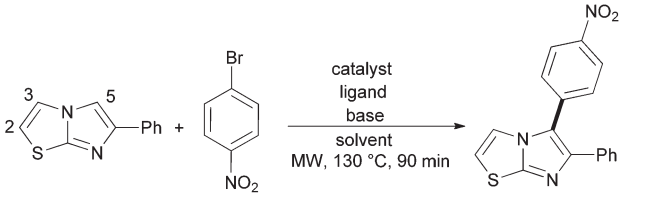
imidazo[2,1-*b*]thiazoles, we set out to retrieve the reported direct C–H arylations of these compounds. Surprisingly, few examples have been disclosed to arylate at the C-4 position of the imidazole moiety of the fused ring under palladium catalysis,[5,7a] and in these reports the scope defined for the imidazo-[2,1-*b*]thiazole scaffold was very narrow, although direct C-5 arylation of the 4-methyl substituted thiazole ring of the parent heterocycle has been achieved by copper catalysts.[16] So far, a general synthetic route to accomplish regioselective C-4 arylation of the imidazole ring of 6-arylimidazo[2,1-*b*]thiazoles (or called: C5-arylation of 6-arylimidazo[2,1-*b*]thiazoles) has not been established. Hence, we attempt to develop a practical and efficient protocol to access these molecules from readily available aryl bromides, and further investigate the relevant reaction mechanism.

Results and discussion

Prior to investigation of the arylation, various imidazo[2,1-*b*]-thiazoles were evaluated by ^{1}H NMR for the selection of the model substrate (Fig. 2, **1a–d**). It is revealed that each C–H bond of different imidazo[2,1-*b*]thiazoles exhibits unequal acidity, even in the identical substrate such as **1a** or **1d**, multiple C–H bonds are rather divergent, thereby furnishing possibilities of site-selective arylation.

Since more attention in medicinal chemistry and synthetic chemistry was focused on 6-arylimidazo[2,1-*b*]thiazole, **1a** was chosen as a model substrate to couple with 1-bromo-4-nitrobenzene (**2a**)[10b] in our initial exploration of this Pd-catalyzed arylation. It is pleasing that **1a** and **2a** led to the coupling product **3aa** in 15% yield and a trace of byproduct from which no C-2 arylated product could be isolated utilizing $PdCl_2$/PPh_3. Unambiguously, the structure of the C-5-arylated product **3aa** was in concordance with all the spectral data and further independently confirmed by an X-ray crystal structure (CCDC 942540).[17] Then, **1a** and **2a** were selected as model substrates to optimize the reaction conditions (Table 1). A number of palladium catalysts in conjunction with different ligands, bases and solvents were screened. Some palladium catalysts, such as $PdCl_2$, $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$, resulted in moderate yields of 35–59% (Table 1, entries 1–3). To our delight, the desired product **3aa** was obtained in 72% yield, when the reaction was performed in the presence of K_2CO_3 using $Pd(OAc)_2$/PPh_3 as the catalytic system in DMF (Table 1, entry 4). No improvement was observed by increasing the reaction time or temperature. In contrast, conventional heating led to lower yield (45%) within 13 h. This demonstrates that the green microwave heating could greatly accelerate the arylation, not only in reduced reaction time, but also with enhanced yield. In the absence of the palladium catalyst, no arylated product was found. In an attempt to increase the yield of reaction, various ligands such as PBu_3, PCy_3, Phen (1,10-phenanthroline) and Phen·H_2O (1,10-phenanthroline monohydrate) were tested, and none showed better activities than PPh_3 (Table 1, entries 5–8). Increasing the amount of PPh_3 from 10 mol% to 25 mol% seemed to be detrimental to reactivity (Table 1, entry 9), while a decrease was observed in the absence of a ligand (Table 1, entry 10). Next the effects of different bases were also investigated. Compared with Cs_2CO_3, K_3PO_4, KOAc, *t*-BuOK, AgOAc, Cs_2CO_3 were found to be as effective as K_2CO_3 and a

Table 1 Optimization of direct arylation of **1a**[a]



1a **2a** **3aa**

Entry	Catalyst	Ligand	Base	Solvent	Yield (%)
1	$PdCl_2$	PPh_3	K_2CO_3	DMF	35
2	$Pd(PPh_3)_4$	—	K_2CO_3	DMF	57
3	$Pd(PPh_3)_2Cl_2$	—	K_2CO_3	DMF	59
4	**$Pd(OAc)_2$**	**PPh_3**	**K_2CO_3**	**DMF**	**72 (45)**[b]
5	$Pd(OAc)_2$	PBu_3	K_2CO_3	DMF	39
6	$Pd(OAc)_2$	PCy_3	K_2CO_3	DMF	36
7[c]	$Pd(OAc)_2$	Phen	K_2CO_3	DMF	5
8	$Pd(OAc)_2$	Phen·H_2O	K_2CO_3	DMF	19
9[d]	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	46
10	$Pd(OAc)_2$	—	K_2CO_3	DMF	48
11	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	72
12	$Pd(OAc)_2$	PPh_3	K_3PO_4	DMF	59
13	$Pd(OAc)_2$	PPh_3	KOAc	DMF	62
14	$Pd(OAc)_2$	PPh_3	*t*-BuOK	DMF	9
15[e]	$Pd(OAc)_2$	PPh_3	AgOAc	DMF	n.r.
16	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMSO	64
17	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMA	66
18	$Pd(OAc)_2$	PPh_3	K_2CO_3	NMP	59
19	$Pd(OAc)_2$	PPh_3	K_2CO_3	Toluene	14
20	$Pd(OAc)_2$	PPh_3	K_2CO_3	Dioxane	11
21	$Pd(OAc)_2$	PPh_3	K_2CO_3	CH_3CN	37
22[f]	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	49
23[g]	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	59

[a] General conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), Pd-catalyst (5 mol%), ligand (10 mol%), base (3.0 equiv.) in solvent (1 ml), MW, 130 °C, 90 min. Isolated yields were given. [b] Under an air atmosphere, oil bath, 130 °C, 13 h. [c] Phen = 1,10-phenanthroline. [d] PPh_3 (25 mol%). [e] n.r. = no reaction. [f] PivOH (30 mol%) was used as an additive. [g] **2a** was 1-iodo-4-nitrobenzene.

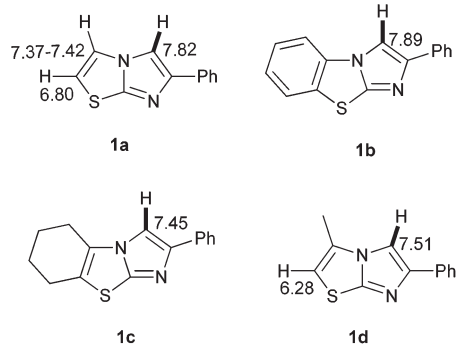
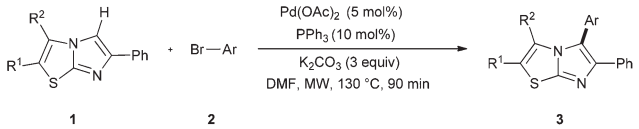


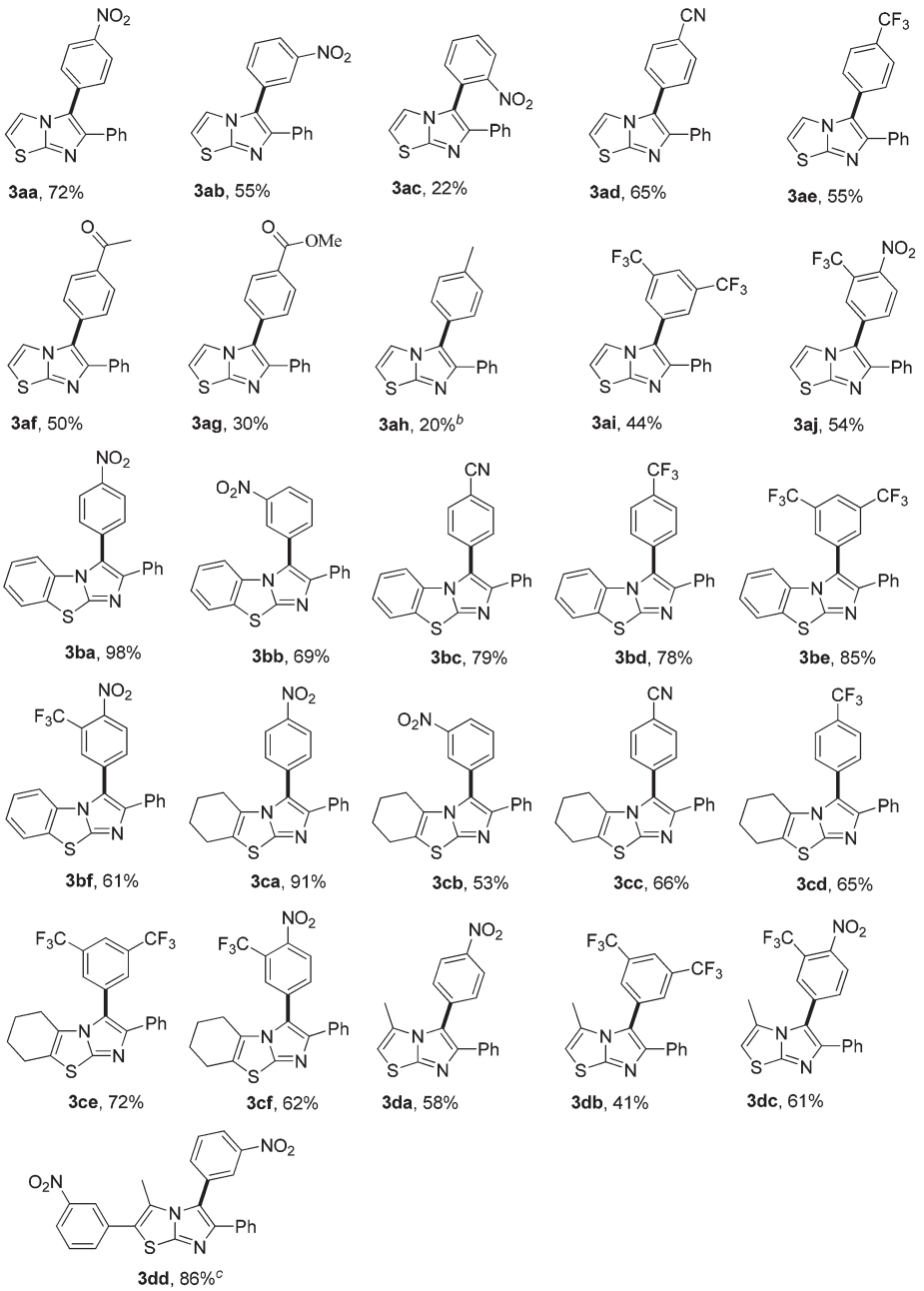
Fig. 2 δ_{C-H} of ^{1}H NMR (300 MHz, $CDCl_3$) in various imidazo[2,1-*b*]thiazoles cores.

maximum yield of 72% was achieved (Table 1, entries 11–15). Subsequently, variations in solvent were examined. Polar solvents generally gave a better reaction performance but less effective than DMF, while apolar solvents led to significantly low yields of **3aa** (Table 1, entries 16–21). Additional use of PivOH (pivalic acid) as a proton shuttle precursor proved to be deleterious to the reaction (Table 1, entry 22). Furthermore, aryl iodide was found to be inferior to aryl bromide possibly

Table 2 Substrate scope of the Pd-catalyzed direct arylation of imidazo[2,1-*b*]thiazoles with aryl bromides[a]



1 2 3



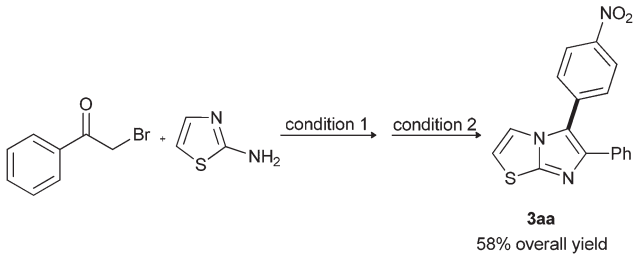
[a] General conditions: **1** (0.25 mmol), **2** (0.30 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (3.0 equiv.) in DMF (1 ml), MW, 130 °C, 90 min. All reported reaction yields were isolated yields. [b] Pivalic acid (30 mol%) was added. [c] The present yield was given on the basis of relatively insufficient amount of aryl bromide.

due to poisoning of the catalyst by accumulated iodide in DMF (Table 1, entry 23).[15c,18] Therefore, the optimum reaction conditions were described as follows: using K_2CO_3 (3 equiv.) as a base in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) in DMF at 130 °C for 90 min under microwave irradiation. It is worth mentioning that the poisoning effect of sulfur[19] was not found in the arylation of this S-containing heterocycle.

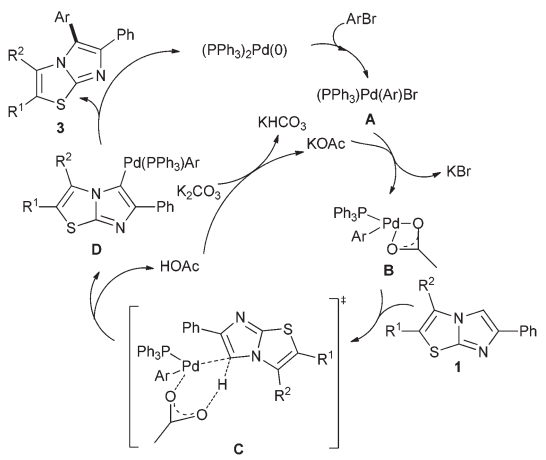
With the optimized conditions in hand, we next evaluated the substrate scope of the reaction employing various aryl bromides and imidazo[2,1-*b*]thiazoles. These results are summarized in Table 2. It was found that a variety of aryl bromides containing important functional groups such as *p*-NO_2, *m*-NO_2, *o*-NO_2, *p*-CN, *p*-CF_3, *p*-COMe and *p*-COOMe were compatible under this transformation (**3aa–g**). In all cases, C5 arylated products were successfully formed in moderate to good yields without any modification of the reaction conditions. Moreover, modestly electron-rich aryl bromide was also tolerated in the presence of small amounts of pivalic acid while comparatively low yield was detected (**3ah**). It is demonstrated that both electron-deficient and moderately electron-rich aryl bromides could couple with **1a**, and electron-deficient aryl bromides generally resulted in higher yields which might be attributed to lower oxidative addition barriers for electron-deficient aryl bromides.[20] This can be understood since the black $Pd^{(0)}$ was precipitated from the solution regardless of the addition of pivalic acid when **1a** was used to arylate with 4-bromotoluene, while the phenomenon was not observed utilizing electron-depleted aryl bromides. Besides, some poly-substituted aryl bromides were then proved to be applicable, providing the expected products **3ai** and **3aj** in 44% and 54% yields, respectively. Furthermore, other different substituted imidazo[2,1-*b*]thiazoles, such as 2-phenylbenzo[*d*]imidazo[2,1-*b*]-thiazole (**1b**), 2-phenyl-5,6,7,8-tetrahydrobenzo[*d*]imidazo-[2,1-*b*]-thiazole (**1c**) and 3-methyl-6-phenylimidazo[2,1-*b*]thiazole (**1d**) were probed. When **1b** possessing a well conjugated system was applied to the arylation, a maximum yield of 98% (**3ba**) was observed using **2a** as the coupling partner. With an array of aryl bromides, **1b** proceeded smoothly in 61%–85% yields (**3bb–f**). Subsequently, the use of pifithrin-β derivatives **1c** and **2a** resulted in 91% yield of **3ca**. Actually, **1c** was tolerant of different aryl bromides and gave the coupling products in moderate to good yields (**3cb–f**). Then, electron-rich imidazo-[2,1-*b*]thiazoles **1d** was also found to be amenable to the reaction conditions and arylated with aryl bromides in moderate to satisfactory yields (**3da–d**). Among them, it was interesting that 2,5-diarylated products of **1d** were achieved in 86% yield (**3dd**).

To further minimize the synthetic steps and wastes, this method was extended to a one-pot reaction for the construction of diarylimidazo[2,1-*b*]thiazoles starting from 2-aminothiazol and 2-bromoacetophenone. Delightfully, a typical product of **3aa** was attained by a sequential reaction sequence in overall 58% yield within 95 min under microwave irradiation (Scheme 1).

Although the participation of AgOAc was demonstrated to efficiently catalyze C–H arylation under a electrophilic palladation process,[21] it has been proved to be unreactive in this reaction (Table 1, entry 15), indicating that the authentic arylation mechanism is likely to conflict with the S_EAr pathway. In addition, since exclusively regioselective arylation of **1a** at the C-4 position of the less π-electron rich imidazole ring rather than the C-5/4 position of the more π-electron rich thiazole ring was observed, it suggests that the preferential regiochemistry for the reactive sites, to some extent, depends on C–H acidity of **1a**, not on heterocyclic nucleophilicity. For these reasons, the S_EAr process could be excluded. In contrast, the CMD mechanism seems to be hopeful. Moreover, **1b** with a much more acidic sp^2 C–H bond (Fig. 2) was used to couple with **2a** in higher yield compared to other substrates such as **1a**, **1c**, and **1d** (Table 2, **3aa** *vs.* **3ba** *vs.* **3ca** *vs.* **3da**). In this regard, the C–H acidity also exerts an effect on the reactivity of the arylation. All of these above imply that the C–H bond functionalization may undergo a CMD pathway (Scheme 2). The process consists of oxidative addition of aryl bromide to $Pd^{(0)}$ to generate ArPdBr (**A**), a nucleophilic attack of KOAc on **A** to form the ArPd(OAc) complex (**B**), substrate **1** in reaction with **B** to produce **C** as a transition-state, as well as reductive elimination of **D** to give the coupling product **3** and regenerate $Pd^{(0)}$. As delineated by us, the generation of ArPdBr (**A**) is



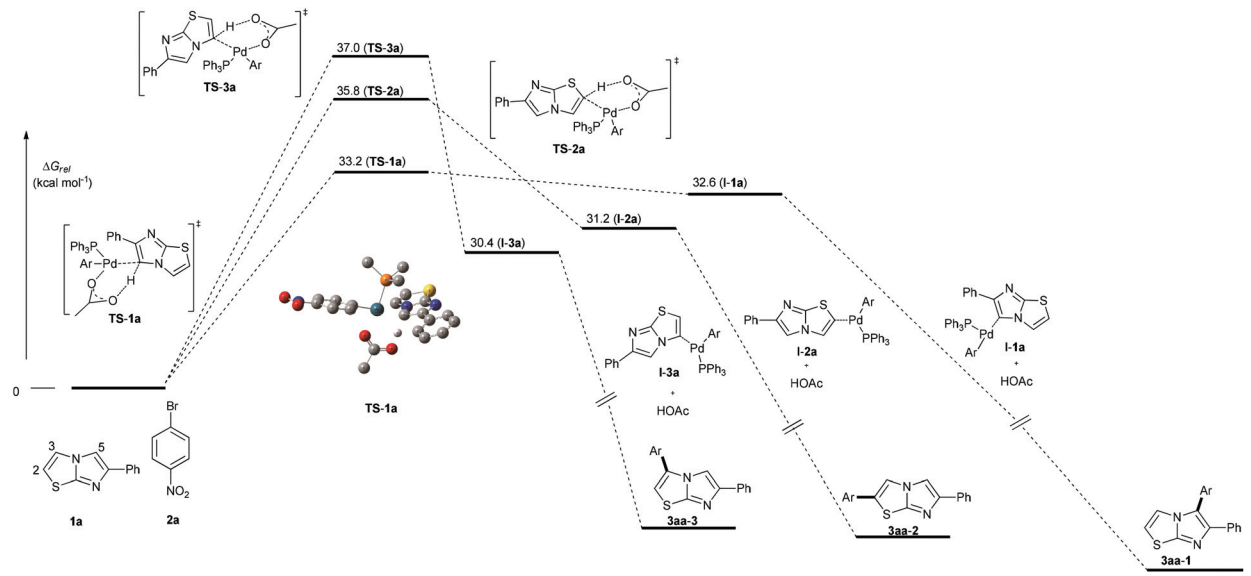
Scheme 1 Sequential one-pot synthesis of **3aa**. Condition 1: 2-aminothiazol (0.50 mmol), 2-bromoacetophenone (0.50 mmol), Na_2CO_3 (0.30 mmol, 0.60 equiv.) in DMF (1 ml), MW, 120 °C, 5 min; condition 2: **2a** (0.60 mmol, 1.2 equiv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (3.0 equiv.), MW, 130 °C, 90 min. Reported reaction yields were isolated yields.



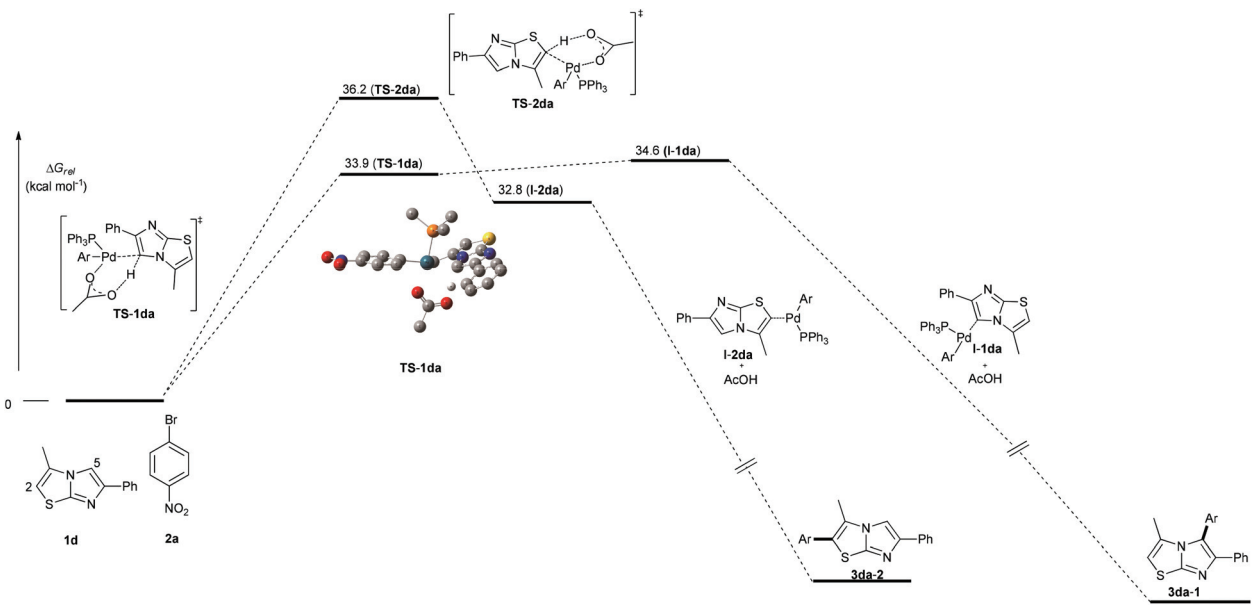
Scheme 2 Possible mechanism.

susceptible to the nature of aryl bromides due to an oxidative addition barrier. As a result, the performances of pivalic acid in the arylation (**3ah** of Table 2 *vs.* entry 22 of Table 1) were distinct. For modest electron-rich aryl bromide 4-bromotoluene which is difficult to accomplish oxidative addition, the effect of pivalic acid was found to be positive (Table 2, **3ah**), since KOPiv produced by the added PivOH and K_2CO_3 is more alkaline than KOAc generated from HOAc and K_2CO_3 and thus considered to be helpful for the crucial dehydrogenation process; as for electron-deficient aryl bromide **2a**, the effect of pivalic acid was found to be negative (Table 1, entry 22). Since oxidative addition is effortless for **2a**, KOPiv might be alkaline excessively and result in partial homocoupling of **2a**,[14e,22] thus hampering the catalytic activity. For the same reason, the slight decrease in yield resulted from the addition of KOAc could be understood (Table 1, entry 13).

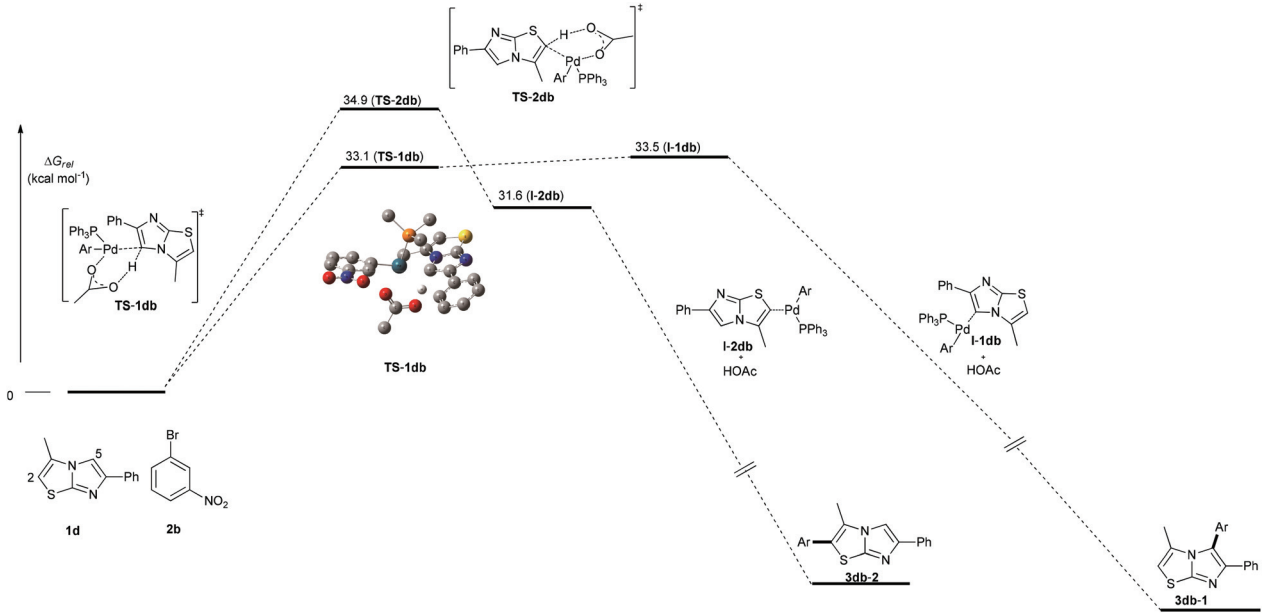
To gain some insight into the mechanism, density functional theory (DFT) analysis with the B3LYP exchange correlation functional[23] was performed to examine this pathway (for details, see ESI†). Computational studies reveal that the predominance of regioselective arylation at the C-5 position in our experimental observations resulted from the lowest C–H activation energy of CMD transition state (TS) in comparison with other sites (C2, C3). As is shown in Scheme 3, when **1a**



Scheme 3 Free energy diagram ($\Delta G^{\ddagger}_{rel}$) for CMD TS of **1a**.



Scheme 4 Free energy diagram ($\Delta G^{\ddagger}_{rel}$) for CMD TS of **1d** (with **2a**).



Scheme 5 Free energy diagram ($\Delta G^{\ddagger}_{rel}$) for CMD TS of **1d** (with **2b**).

and **2a** were used to calculate the barriers of the CMD TS, C5-TS was found to require the lowest energy barrier (**TS-1a**, 33.2 kcal mol^{-1}), followed by C2-TS (**TS-2a**, 35.8 kcal mol^{-1}), and the highest reaction barrier (**TS-3a**, 37.0 kcal mol^{-1}) was required for C3-TS. These calculated results are well in agreement with the available experimental results. Similar computational results were found when **1d** and *para*/*meta* substituted aryl bromide **2a**/**2b** (Scheme 4/5) were employed to calculate the barriers of the CMD TS, the lowest energy barriers still were C5 transition states (33.9 kcal mol^{-1} of **TS-1da** and 33.1 kcal mol^{-1} of **TS-1db**). It is worth noting that energy barrier gaps between C5-TS and C2-TS of **1d** (2.3 kcal mol^{-1} for **2a** and 1.8 kcal mol^{-1} for **2b**) decreased relative to **1a** (2.6 kcal mol^{-1} for **2a**). This indicates that the formation of double-arylated products **3dd** (Table 2) was probably due to the smaller energy barrier differences (1.8 kcal mol^{-1}).

Conclusion

In summary, we have developed a new strategy to access diarylimidazo[2,1-*b*]thiazole derivatives *via* Pd-catalyzed direct arylation as a key step. With MW irradiation, the coupling reaction for the synthesis of title compounds can proceed smoothly under non-inert conditions. This method is atom-economic, convenient, regioselective and tolerant to a series of functional groups on the aryl bromide. Electron-deficient aryl bromides commonly exhibit a better performance in yield than the moderately electron-rich one due to easier oxidative addition. DFT studies towards the mechanism demonstrate that this regioselective C-5 arylation of imidazo[2,1-*b*]thiazoles undergoes a CMD pathway that is consistent with our experimental results. Briefly, this work not only offers a straightforward route to a number of novel imidazo[2,1-*b*]thiazoles which enrich the heterocyclic library, but also provides a better mechanism for understanding site-selectivity of C–H arylation in fused heterocycles which would be a valuable guide for the synthesis of similar molecules. We believe that this work should be profitable in synthetic and pharmaceutical chemistry.

Experimental section

General information

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury plus 300 MHz spectrometer (75 MHz for carbon). Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (δ = 0.0 ppm) with the solvent resonance as an internal reference ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm, DMSO-d_6: δ_H = 2.50 ppm), and coupling constants (J) are given in hertz (Hz). Multiplicity is indicated by one or more of the following abbreviations: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Melting points (mp) were determined on a XT-4 melting point apparatus and are uncorrected. Infrared spectra (IR) were obtained from a NEXUS670 FT-IR spectrometer and reported in cm^{-1} (%T). Mass spectra (EI) were recorded on a Thermo TRACE DSQ spectrometer. ESI-MS were measured with Bruker ESQ6000 instruments. High resolution mass spectra (HRMS) were carried out on an LTQ Orbitrap Elite (Thermo) mass spectrometer with ESI mode unless otherwise stated. Microwave irradiation experiments were performed in a dedicated CEM-Discover monomode microwave reactor, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The reaction temperature was measured with an IR sensor on the outer surface of the process vessel and monitored using the associated ChemDriver

Discover Application program. Reaction times refer to the hold time at the desired set temperature. Control experiment employing conventional oil bath heating was run under an air atmosphere in an oven-dried round-bottom flask equipped with a magnetic stir bar.

General procedure for the arylation of substituted imidazo[2,1-*b*]thiazoles (Table 2, 3aa–dd)

To a 10 ml oven dried microwave vessel capped with a Teflon septum was sequentially added **1** (0.25 mmol), **2** (0.30 mmol, 1.2 equiv.), $Pd(OAc)_2$ (2.8 mg, 5 mol%), PPh_3 (6.6 mg, 10 mol %), K_2CO_3 (104 mg, 0.75 mmol, 3.0 equiv.) and DMF (1 ml). Then the reaction tube was placed in the microwave cavity. The reaction mixture in the vessel was continuously stirred and irradiated with microwaves at 130 °C for 90 min. After cooling to ambient temperature, the mixture was poured into water (15 ml) and extracted with ethyl acetate (3 × 15 ml). The combined organic layer was washed with brine, dried over Na_2SO_4, gravity filtered, and concentrated on a rotatory evaporator under vacuum. The crude residue was purified by column chromatography over silica gel using 25% EtOAc in petroleum ether as the eluent to afford **3**.

Typical procedure for sequential one-pot synthesis of 3aa (Scheme 1)

An oven-dried microwave vial (10 ml) was charged with 2-bromoacetophenone (100 mg, 0.50 mmol), 2-aminothiazol (50 mg, 0.50 mmol), Na_2CO_3 (32 mg, 0.30 mmol, 0.60 equiv.) and DMF (1 ml). The reaction tube was sealed with a Teflon septum and placed in the microwave cavity. The reaction mixture in the vial was continuously stirred and irradiated with microwaves at 120 °C for 5 min. After cooled to ambient temperature, 1-bromo-4-nitrobenzene (**2a**, 121 mg, 0.60 mmol, 1.2 equiv.), $Pd(OAc)_2$ (5.6 mg, 5 mol%), PPh_3 (13.2 mg, 10 mol%), K_2CO_3 (208 mg, 1.50 mmol, 3.0 equiv.) were added to the reaction mixture and subjected to microwave irradiation at 130 °C for 90 min. After cooling to room temperature, the mixture was poured into water (15 ml) and extracted with ethyl acetate (3 × 15 ml). The combined organic layer was washed with brine, dried over Na_2SO_4, gravity filtered, and concentrated on a rotatory evaporator under vacuum. The crude residue was purified by column chromatography over silica gel using 25% EtOAc in petroleum ether as the eluent to afford **3aa**.

Acknowledgements

We thank the National Natural Science Foundation of China (NSFC 21173106, 21203080) for financial support.

Notes and references

1 (*a*) A. Andreani, M. Granaiola, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, N. Calonghi, C. Cappadone, G. Farruggia and C. Stefanelli, *J. Med. Chem.*, 2012, **55**, 2078; (*b*) L. Gharat, L. Narayana, P. Yadav, N. Khairatkar-Joshi and M. Bajpai, WO2011132048, 2011; (*c*) A. Scribner, S. Meitz, M. Fisher, M. Wyvratt, P. Leavitt, P. Liberator, A. Gurnett, C. Brown, J. Mathew, D. Thompson, D. Schmatz and T. Biftu, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5263; (*d*) S. D. Barchéchath, R. I. Tawatao, M. Corr, D. A. Carson and H. B. Cottam, *J. Med. Chem.*, 2005, **48**, 6409; (*e*) T. Metaye, C. Millet, J. L. Kraimps, B. Saunier, J. Barbier and F. Begon, *Biochem. Pharmacol.*, 1992, **43**, 1507.

2 A. H. M. Raeymaekers, F. T. N. Allewijn, J. Vandenberk, P. J. A. Demoen, T. T. T. Van Offenwert and P. A. J. Janssen, *J. Med. Chem.*, 1966, **9**, 545.

3 M. I. Walton, S. C. Wilson, I. R. Hardcastle, A. R. Mirza and P. Workman, *Mol. Cancer. Ther.*, 2005, **4**, 1369.

4 R. Budriesi, P. Ioan, A. Leoni, N. Pedemonte, A. Locatelli, M. Micucci, A. Chiarini and L. J. V. Galietta, *J. Med. Chem.*, 2011, **54**, 3885.

5 (*a*) J.-H. Park, M. I. El-Gamal, Y. S. Lee and C.-H. Oh, *Eur. J. Med. Chem.*, 2011, **46**, 5769; (*b*) J.-H. Park and C.-H. Oh, *Bull. Korean Chem. Soc.*, 2010, **31**, 2854.

6 Z. A. Hozien, A. El-Wareth, A. Sarhan, H. A. El-Sherief and A. M. Mahmoud, *J. Heterocycl. Chem.*, 2000, **37**, 943.

7 (*a*) A. Kamal, F. Sultana, M. J. Ramaiah, Y. Srikanth, A. Viswanath, C. Kishor, P. Sharma, S. Pushpavalli, A. Addlagatta and M. Pal-Bhadra, *ChemMedChem*, 2012, **7**, 292; (*b*) M. Palkar, M. Noolvi, R. Sankangoud, V. Maddi, A. Gadad and L. V. G. Nargund, *Arch. Pharm.*, 2010, **343**, 353; (*c*) R. Budriesi, P. Ioan, A. Locatelli, S. Cosconati, A. Leoni, M. P. Ugenti, A. Andreani, R. Di Toro, A. Bedini and S. Spampinato, *J. Med. Chem.*, 2008, **51**, 1592; (*d*) S.-J. Lee, Y.-K. Kim, S.-H. Hwang, S.-G. Yang, H.-Y. Kim, Y.-R. Do and J.-H. Song, US20050074362, 2005.

8 (*a*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*b*) J. J. Mousseau and A. B. Charette, *Acc. Chem. Res.*, 2012, **46**, 412; (*c*) L. T. Ball, G. C. Lloyd-Jones and C. A. Russell, *Science*, 2012, **337**, 1644; (*d*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*e*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*f*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2010, **111**, 1293; (*g*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*h*) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; (*i*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*j*) O. Daugulis, *Top. Curr. Chem.*, 2010, **292**, 57; (*k*) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447.

9 For selected reviews, see: (*a*) A. Sharma, D. Vacchani and E. Van der Eycken, *Chem. – Eur. J.*, 2013, **19**, 1158; (*b*) T.-S. Mei, L. Kou, S. Ma, K. M. Engle and J.-Q. Yu, *Synthesis*, 2012, 1778; (*c*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (*d*) D. Zhao, J. You and C. Hu, *Chem. – Eur. J.*, 2011, **17**, 5466; (*e*) J. Roger, A. L. Gottumukkala and H. Doucet, *ChemCatChem*, 2010, **2**, 20; (*f*) E. Beck and M. Gaunt, *Top. Curr. Chem.*, 2010, **292**, 85; (*g*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792;

(*h*) L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673; (*i*) C. L. Jared, G. B. Robert and A. E. Jonathan, *Acc. Chem. Res.*, 2008, **41**, 1013; (*j*) I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036.

10 (*a*) B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050; (*b*) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek and V. Gevorgyan, *Org. Lett.*, 2004, **6**, 1159; (*c*) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 467.

11 (*a*) J.-X. Wang, J. A. McCubbin, M. Jin, R. S. Laufer, Y. Mao, A. P. Crew, M. J. Mulvihill and V. Snieckus, *Org. Lett.*, 2008, **10**, 2923; (*b*) W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, G. J. Javadi, D. Cai and R. D. Larsen, *Org. Lett.*, 2003, **5**, 4835.

12 T. Okazawa, T. Satoh, M. Miura and M. Nomura, *J. Am. Chem. Soc.*, 2002, **124**, 5286.

13 S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer and K. Itami, *Angew. Chem., Int. Ed.*, 2011, **50**, 2387.

14 (*a*) H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 8180; (*b*) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2007, **129**, 6880; (*c*) D. García-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066; (*d*) M. Lafrance, C. N. Rowley, T. K. Woo and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 8754; (*e*) M. Lafrance and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 16496; (*f*) D. L. Davies, S. M. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754.

15 (*a*) S. I. Gorelsky, *Coord. Chem. Rev.*, 2013, **257**, 153; (*b*) S. I. Gorelsky, D. Lapointe and K. Fagnou, *J. Org. Chem.*, 2012, **77**, 658; (*c*) B. Liégault, D. Lapointe, L. Caron, A. Vlassova and K. Fagnou, *J. Org. Chem.*, 2009, **74**, 1826; (*d*) S. I. Gorelsky, D. Lapointe and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 10848.

16 G. Huang, H. Sun, X. Qiu, C. Jin, C. Lin, Y. Shen, J. Jiang and L. Wang, *Org. Lett.*, 2011, **13**, 5224.

17 Crystallographic data of compound **3aa** are detailed in the ESI.†

18 L. C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581.

19 (*a*) S. Bryan, J. A. Braunger and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **121**, 7198; (*b*) M. A. Fernández-Rodríguez, Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 2180.

20 K. C. Lam, T. B. Marder and Z. Lin, *Organometallics*, 2007, **26**, 758.

21 N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926.

22 The byproduct generated from homocoupling of 1-bromo-4-nitrobenzene **2a** was detected with the addition of PivOH in this arylation.

23 (*a*) V. A. Rassolov, M. A. Ratner, J. A. Pople, P. C. Redfern and L. A. Curtiss, *J. Comput. Chem.*, 2001, **22**, 976; (*b*) V. A. Rassolov, J. A. Pople, M. A. Ratner and T. L. Windus, *J. Chem. Phys.*, 1998, **109**, 1223; (*c*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter*, 1988, **37**, 785.