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# Highly efficient copper/palladium-catalyzed tandem Ullman reaction/arylation of azoles via C–H activation: synthesis of benzofuranyl and indolyl azoles from 2-(*gem*-dibromovinyl)phenols(anilines) with azoles

Wei Chen [a], Min Wang [a], Pinhua Li [a], Lei Wang [a,b,*]

[a] Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, PR China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China

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ABSTRACT

In this paper, a novel and highly efficient copper/palladium-catalyzed tandem intramolecular Ullman-type C–O(N) coupling reaction of 2-(*gem*-dibromovinyl)phenols(anilines) followed by an intermolecular arylation of azoles through C–H activation has been developed. In the presence of CuBr with $Pd(PPh_3)_2Cl_2$ used as co-catalyst, and Li$O^tBu$ as a base, the one-pot reactions of 2-(*gem*-dibromovinyl)phenols and 2-(*gem*-dibromovinyl)anilines with a variety of azoles, including oxazoles, imidazoles, thiazoles, and oxadiazoles underwent smoothly in toluene at 100 °C to generate the corresponding biheteroaryl products in high yields. A tentative mechanism of copper/palladium-catalyzed tandem reaction was described.



## 1. Introduction

The heteroaryl azole skeletons are key structural units in numerous biologically active natural products and unnatural synthetic materials.[1] Over the last few years, considerable attention has been directed toward the synthesis and functionalization of organic compounds containing the biheteroaryl structural units.[2] Transition-metal-catalyzed reactions, especially the palladium-catalyzed organic transformations in construction of carbon–carbon and carbon–heteroatom bonds have increasingly attracted attention in the pharmaceutical and fine chemical industries.[3] In general, these carbon–carbon biheteroaryl linkages are achieved via transition-metal-catalyzed cross-coupling reactions of heteroaryl halides or pseudohalides with heteroaryl organometallic reagents,[4] which rank as the most powerful biheteroaryl formation reactions in organic synthesis. However, reactivation of heteroaromatic carbon fragments with metal-containing functionalities and halides may involve several tedious synthetic steps. Direct transition-metal-catalyzed functionalization of C–H bonds in heterocycles has received extraordinary attention in modern organic chemistry owing to its environmentally benign features and atom economy,[5] and transition metals, such as Pd-, Cu-, Co-, Ni-, and Mn-catalyzed C–H functionalization of heterocycles, especially azoles has received much attention in the most recent years.[6]

Compared with the traditional multiple step synthesis, tandem/domino reactions could enhance the efficiency of preparing the target products from simple starting materials, avoid the separation of intermediates, save the number of steps, and reduce the amount of pollutant waste emission. Moreover, the versatility of the catalyst system can also be exploited through different types of reactions occurring in one-pot. So, most of the recently reported methodologies were based on the use of this type reactions.[7] The versatility of *gem*-dihaloolefins, owing to higher reactivity and easy accessibility from inexpensive aldehydes, has been exploited,[8] notably, as a key unit for the synthesis of various heterocycles, such as indoles,[9] benzothiophenes,[10] benzofurans,[11,9i,10b] isocoumarins,[12] and other heterocycles[13] through metal-catalyzed tandem Ullman-type or Suzuki–Miyaura coupling/amination, Suzuki, Sonogashira, Heck, or intramolecular C–H activation. It is desirable to develop the tandem reactions of *gem*-dihaloolefins with azoles through an intermolecular C–H activation to generate biheteroaryl compounds.[14]

Herein, we wish to report a mild and highly efficient copper/palladium-catalyzed tandem reaction of intramolecular Ullman-type C–O(N) coupling reaction of 2-(*gem*-dibromovinyl)phenols and 2-(*gem*-dibromovinyl)anilines followed by a intermolecular arylation of azoles through C–H activation. The reactions of 2-(*gem*-dibromovinyl)phenols and 2-(*gem*-dibromovinyl)anilines

* Corresponding author. Tel.: +86 561 3802 069; fax: +86 561 3090 518; e-mail address: leiwang@chnu.edu.cn (L. Wang).

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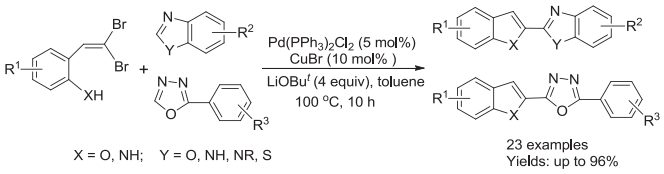
with a variety of azoles including oxazoles, imidazoles, thiazoles, and oxadiazoles underwent smoothly in the presence of $Pd(PPh_3)_2Cl_2$/CuBr/LiO$^t$Bu in toluene, and generated the corresponding benzofuranyl and indolyl azoles in high yields. This one-pot sequential process provides a wide range of substrate applicability, which is commercially available and easily prepared from aromatic aldehydes, and in most cases, nearly quantitative yields were obtained (Scheme 1).



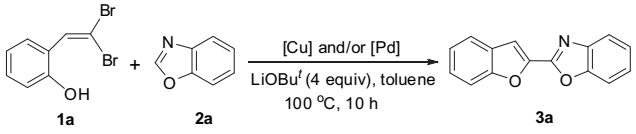

**Scheme 1.**

## 2. Results and discussion

Initially, 2-(*gem*-dibromovinyl)phenol (**1a**) and benzoxazole (**2a**) were chosen as the model substrates for surveying parameters of the reaction condition, and the results were listed in Table 1. When the model substrates were carried out in the presence of CuI (10 mol %), $Pd(OAc)_2$ (5 mol %), and $PPh_3$ (10 mol %) with LiO$^t$Bu used as a base in toluene at significantly milder reaction temperature of 100 °C for 10 h, to our delight, 2-(benzofuran-2-yl)benzoxazole (**3a**) was obtained in 41% yield (Table 1, entry 1). By screening the other palladium sources, such as $PdCl_2$, Pd/C, and $Pd(PPh_3)Cl_2$, it was revealed that $Pd(PPh_3)_2Cl_2$ was the most effective one, affording the desired biheteroaryl product **3a** in 73% yield (Table 1, entries 2–4). When the copper source was switched to CuBr, the desired product **3a** was isolated in nearly quantitative yield (98%, Table 1, entry 5). Other sources of the copper salt [e.g., CuCl, $Cu_2O$, $Cu(OAc)_2$, CuO, and Cu powder] were greatly inferior to CuBr (Table 1, entries 6–10). Subsequently, several phosphine ligands, such as P($^t$Bu)$_3$, P(Cy)$_3$, $PPh_3$, dppf, and dppe were examined, and the reaction with dppf, dppe, or $PPh_3$ used a ligand produced **3a** in comparable yield over 97%. Meanwhile, P($^t$Bu)$_3$, and P(Cy)$_3$ delivered inferior yields to those of dppf, dppe, and $PPh_3$ (Table 1, entries 5, and 11–14). Of particular note is the use of phosphine-free conditions, which greatly simplifies the reaction work-up procedure and avoids phosphine ligand emission, and gratifyingly, 96% of the desired tandem reaction product **3a** was isolated (Table 1, entry 15). However, it should be noted that when $Pd(PPh_3)_2Cl_2$ was used as catalyst without CuBr, or CuBr/$PPh_3$ was used as catalyst without $Pd(PPh_3)_2Cl_2$, the reaction generated biheteroaryl product **3a** only in 24% or 38% yield (Table 1, entries 16 and 17). Unfortunately, no desired product **3a** was obtained when the reaction was catalyzed by CuBr in the absence of $Pd(PPh_3)_2Cl_2$ and $PPh_3$ (Table 1, entry 18).

The choice of base was also important and several bases for the model reaction. LiO$^t$Bu was found to be the most effective one, and the desired product **3a** was generated in 96% isolated yield (Table 2, entry 1). Other bases, such as KF, ($^i$Pr)$_2$NH, $K_3PO_4$, $Cs_2CO_3$, DABCO, $Et_3N$, and KO$^t$Bu were substantially less effective (Table 2, entries 2–8).

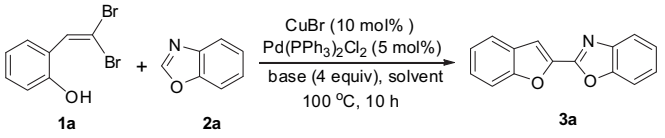
**Table 1**
Effect of Pd, Cu sources and ligand on the model reaction[a]




| Entry | Pd Source | Cu Source | Ligand | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | CuI | $PPh_3$ | 41 |
| 2 | $PdCl_2$ | CuI | $PPh_3$ | 35 |
| 3 | Pd/C | CuI | $PPh_3$ | 21 |
| 4 | $Pd(PPh_3)Cl_2$ | CuI | $PPh_3$ | 73 |
| 5 | $Pd(PPh_3)Cl_2$ | CuBr | $PPh_3$ | 98 |
| 6 | $Pd(PPh_3)Cl_2$ | CuCl | $PPh_3$ | 47 |
| 7 | $Pd(PPh_3)Cl_2$ | $Cu_2O$ | $PPh_3$ | 35 |
| 8 | $Pd(PPh_3)Cl_2$ | $Cu(OAc)_2$ | $PPh_3$ | 44 |
| 9 | $Pd(PPh_3)Cl_2$ | CuO | $PPh_3$ | 22 |
| 10 | $Pd(PPh_3)Cl_2$ | Cu powder | $PPh_3$ | 28 |
| 11 | $Pd(PPh_3)Cl_2$ | CuBr | P($^t$Bu)$_3$ | 62 |
| 12 | $Pd(PPh_3)Cl_2$ | CuBr | P(Cy)$_3$ | 88 |
| 13 | $Pd(PPh_3)Cl_2$ | CuBr | dppf | 98 |
| 14 | $Pd(PPh_3)Cl_2$ | CuBr | dppe | 97 |
| 15 | $Pd(PPh_3)Cl_2$ | CuBr | — | 96 |
| 16 | $Pd(PPh_3)Cl_2$ | — | — | 24 |
| 17 | — | CuBr | $PPh_3$ | 38 |
| 18 | — | CuBr | — | NR |

[a] Reaction conditions: 2-(*gem*-dibromovinyl)phenol **1a** (0.50 mmol), benzoxazole **2a** (0.50 mmol), [Cu] (0.05 mmol), [Pd] (0.025 mmol), ligand (0.05 mmol), LiO$^t$Bu (2.0 mmol) in toluene (2.0 mL) at 100 °C for 10 h.
[b] Isolated yields.

**Table 2**
Effect of base and solvent on the model reaction[a]



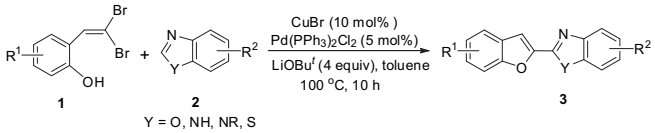

| Entry | Base | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | LiO$^t$Bu | Toluene | 96 |
| 2 | KF | Toluene | 74 |
| 3 | ($^i$Pr)$_2$NH | Toluene | 47 |
| 4 | $K_3PO_4$ | Toluene | 42 |
| 5 | $Cs_2CO_3$ | Toluene | 37 |
| 6 | DABCO | Toluene | 33 |
| 7 | $Et_3N$ | Toluene | 25 |
| 8 | KO$^t$Bu | Toluene | 15 |
| 9 | LiO$^t$Bu | DMF | 34 |
| 10 | LiO$^t$Bu | DCE | 42 |
| 11 | LiO$^t$Bu | THF | 52 |
| 12 | LiO$^t$Bu | 1,4-Dioxane | 77 |

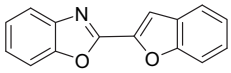
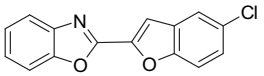
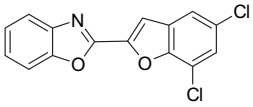
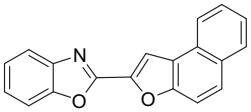
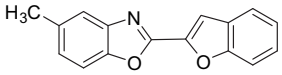
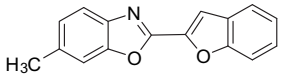
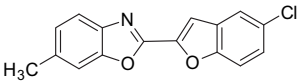
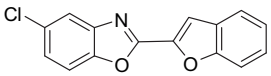
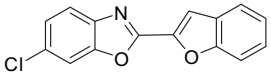
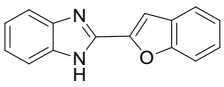
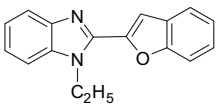
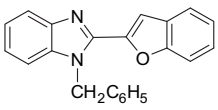
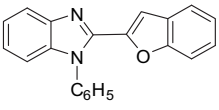
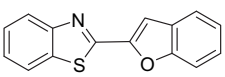
[a] Reaction conditions: 2-(*gem*-dibromovinyl)phenol **1a** (0.50 mmol), benzoxazole **2a** (0.50 mmol), CuBr (0.05 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 mmol), LiO$^t$Bu (2.0 mmol) in toluene (2.0 mL) at 100 °C for 10 h.
[b] Isolated yields.

The solvent also plays an important role in the model tandem reaction. Several solvents, such as DMF, DCE, THF, 1,4-dioxane, and toluene were examined, and toluene was proved to be the most efficient medium for the reaction (Table 2, entries 9–12 and 1). Thus, the optimized reaction conditions for this tandem reaction are CuBr (10 mol %) and $Pd(PPh_3)_2Cl_2$ (5 mol %) with LiO$^t$Bu (4 equiv) used as a base in toluene at 100 °C for 10 h.

Under the above optimized reaction conditions, various substituted 2-(*gem*-dibromovinyl)phenols and azoles, including oxazoles, imidazoles, and thiazoles were used as substrates to examine the generality of the reaction (Table 3). In the most of cases, the expected biheteroaryl products were isolated in good to excellent yields (Table 3, entries 1–9 and 11–13). 2-(*gem*-Dibromovinyl)phenol, substituted 2-(*gem*-dibromovinyl)phenols, such as 4-chloro-2-(*gem*-dibromovinyl)phenol, 4,6-dichloro-2-(*gem*-dibromovinyl)phenol, and 1-(2,2-dibromovinyl)-2-naphthalenol reacted with benzoxazole smoothly under the present reaction conditions to afford the corresponding products **3a**–**d** in 88–96% yields (Table 3, entries 1–4). Benzoxazoles with both electron-donating (5-Me, 6-Me) and electron-withdrawing (5-Cl, 6-Cl) groups on the benzene rings, reacted with 2-(*gem*-dibromovinyl)

**Table 3**
Scope of benzoxazoles, benzimidazoles, and benzothiazoles[a]



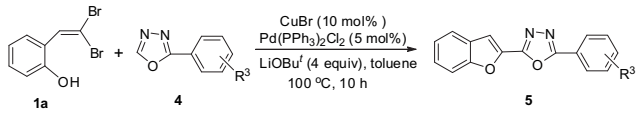

| Entry | Product (**3**) | | Yield (%)[b] |
|---|---|---|---|
| 1 |  | **3a** | 96 |
| 2 |  | **3b** | 94 |
| 3 |  | **3c** | 90 |
| 4 |  | **3d** | 88 |
| 5 |  | **3e** | 89 |
| 6 |  | **3f** | 91 |
| 7 |  | **3g** | 87 |
| 8 |  | **3h** | 93 |
| 9 |  | **3i** | 95 |
| 10 |  | **3j** | 70 |
| 11 |  | **3k** | 83 |
| 12 |  | **3l** | 91 |
| 13 |  | **3m** | 87 |
| 14 |  | **3n** | 66 |

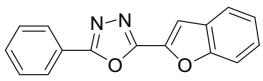
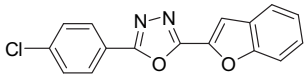
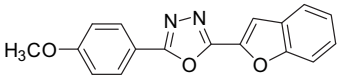
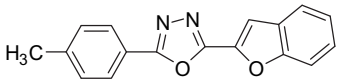
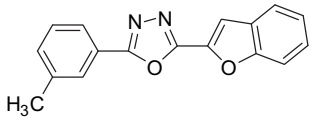
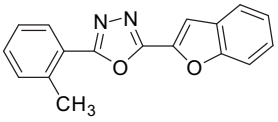
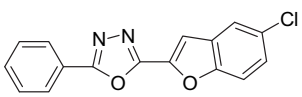
[a] Reaction conditions: 2(*gem*-dibromovinyl)phenol (0.50 mmol), azole (0.50 mmol), CuBr (0.05 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 mmol), $LiO^tBu$ (2.0 mmol) in toluene (2.0 mL) at 100 °C for 10 h.
[b] Isolated yields.

phenol or 4-chloro-2-(*gem*-dibromovinyl)phenol completely and 87–95% yields of the desired products **3e**–**i** were isolated (Table 3, entries 5–9). It was worth noting that the present reaction conditions were also suitable for the tandem reaction of benzimidazole, *N*-alkyl benzimidazoles, and *N*-aryl benzimidazoles with 2-(*gem*-dibromovinyl)phenol. The results indicated that the corresponding benzofuranyl benzimidazole derivatives **3j**–**m** were obtained in 70–91% yields (Table 3, entries 10–13). It is obvious that *N*-alkyl(aryl) benzimidazoles displayed higher reactivity than that of benzimidazole (Table 3, entries 11–13 vs 10). Notably, benzothiazole reacted with 2-(*gem*-dibromovinyl)phenol and the expected product **3n** was formed in 66% yield (Table 3, entry 14).

To further extend the scope of azoles, the tandem Ullman reaction of 2-(*gem*-dibromovinyl)phenol/arylation of azoles via C–H activation of 1,3,4-oxadiazole derivatives were investigated, as shown in Table 4. Various 2-aryl-1,3,4-oxadiazoles with either electron-donating or electron-withdrawing groups on their benzene rings displayed high reactivity to 2-(*gem*-dibromovinyl)phenol and 4-chloro-2-(*gem*-dibromovinyl)phenol under the optimized reaction conditions. The corresponding biheteroaryl products **5a**–**g** were obtained in excellent yields (Table 4, entries 1–7). The results also showed that the electronic and steric effect of substituted groups on benzene rings had little impact on the yields of the products.

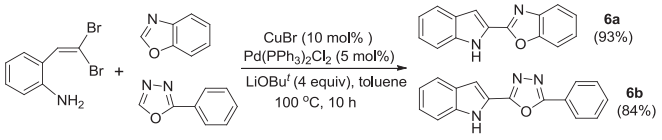
**Table 4**
The scope of 2-aryl-1,3,4-oxadiazoles[a]




| Entry | Product (**5**) | | Yield (%)[b] |
|---|---|---|---|
| 1 |  | **5a** | 95 |
| 2 |  | **5b** | 92 |
| 3 |  | **5c** | 86 |
| 4 |  | **5d** | 94 |
| 5 |  | **5e** | 90 |
| 6 |  | **5f** | 91 |
| 7 |  | **5g** | 87 |

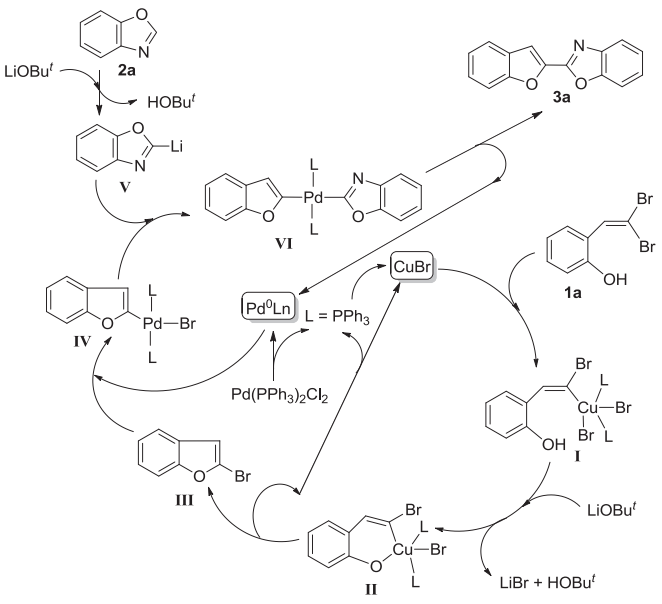
[a] Reaction conditions: 2-(*gem*-dibromovinyl)phenol (0.50 mmol), 1,3,4-oxadiazole (0.50 mmol), CuBr (0.05 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 mmol), $LiO^tBu$ (2.0 mmol) in toluene (2.0 mL) at 100 °C for 10 h.
[b] Isolated yields.

Having developed a highly efficient procedure for the synthesis of benzofuranyl azoles from 2-(*gem*-dibromovinyl)phenols and azoles, we next expanded the scope of this methodology to 2-(*gem*-dibromovinyl)anilines with azoles. Fortunately, the tandem Ullman reaction 2-(*gem*-dibromovinyl)aniline, followed by arylation of benzoxazole and 2-phenyl-1,3,4-oxadiazole proceeded well under the present reaction conditions, affording the corresponding indolyl azoles **6a** and **6b** in 93% and 84% yields, respectively (Scheme 2).



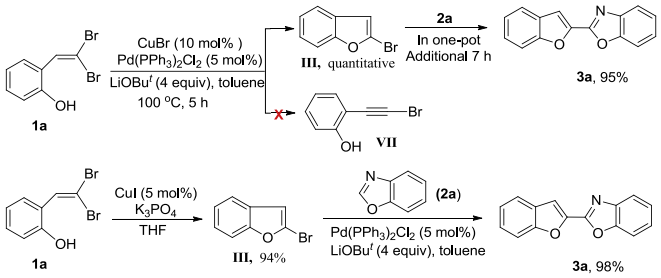

**Scheme 2.** The reactions of 2-(*gem*-dibromovinyl)aniline with azoles.

A proposed mechanism of copper/palladium-catalyzed tandem reaction through C–H activation was shown in Scheme 3. The reaction occurs probably involving (1) an intramolecular Ullman-type reaction of 2-(*gem*-dibromovinyl)phenol (**1a**), affording 2-bromobenzofuran (**III**), and (2) an intermolecular arylation of benzoxazole (**2a**) with obtained **III** through C–H activation, affording biheteroaryl product 2-(benzofuran-2-yl)benzoxazole (**3a**). Firstly, in the intramolecular classic Ullman reaction of **1a** catalyzed by $Cu^{I}Br$,[15] **1a** reacted with $Cu^{I}Br$ to form an intermediate **I** through oxidative addition with the assistance of $PPh_3$ as ligand from the dissociation of $Pd(PPh_3)_2Cl_2$. Then the obtained **I** underwent an intramolecular transmetallation to generate **II**, which followed by a reductive elimination to afford 2-bromobenzofuran (**III**) and regenerate the $Cu^{I}Br$ for next run. Subsequently, in the intermolecular arylation of **2a** with **III** catalyzed by $Pd^0$ from its precursor $Pd(PPh_3)_2Cl_2$, **1a** reacted with $Pd^0$ to form intermediate **IV** via oxidative addition. Then, **IV** reacted with **V**, which was generated from the deprotonation of **2a** by $LiO^tBu$, and followed by a transmetalation to generate intermediate **VI**. Finally, **3a** was produced via reductive elimination and $Pd^0$ was regenerated to complete this catalytic cycle.




**Scheme 3.** Possible mechanism of Cu/Pd-catalyzed tandem reaction.

When the tandem reaction was performed in the absence of CuBr under the optimized conditions, only 24% yield of the product was obtained. On the other hand, when the reaction was performed in the absence of $Pd(PPh_3)_2Cl_2$ without additional ligand, no desired product was obtained. In addition, **1a** could transform to 2-bromobenzofuran (**III**) in nearly quantitative yield in the absence of **2a** under the present reaction conditions, but, no any 2-(bromoethynyl)phenol (**VII**) was detected. Presumably, the formation of **III** was through an intramolecular Ullman reaction process. When **2a** was added the above reaction system for additional 7 h under same reaction conditions in one-pot, as expected, **3a** was obtained in 95% yield (Scheme 4). A prepared 2-bromobenzofuran (**III**) from **1a**,[10b] could stoichiometrically transform to **3a** under the present conditions in the absence of CuBr (Scheme 4), which offered a further proof for this proposed mechanism. On the basis of this evidence, we believe that the Cu-catalyzed C–O coupling process occurs prior to the Pd-catalyzed arylation of azole via C–H activation in this sequence.




**Scheme 4.**

## 3. Conclusions

In conclusion, we have developed a general, highly efficient one-pot protocol for the synthesis of benzofuranyl and indolyl azoles through a copper/palladium-catalyzed tandem reaction of intramolecular Ullman-type C–O(N) coupling reaction of 2-(*gem*-dibromovinyl)phenols and 2-(*gem*-dibromovinyl)anilines followed by an intermolecular arylation of azoles through their C–H activation. The reactions of 2-(*gem*-dibromovinyl)phenols and 2-(*gem*-dibromovinyl)anilines with a variety of azoles including oxazoles, imidazoles, thiazoles, and oxadiazoles underwent smoothly in the presence of CuBr with $Pd(PPh_3)_2Cl_2$ used as co-catalyst, and $LiO^tBu$ as a base in toluene at 100 °C for 10 h, and the corresponding products were generated in high yields. This reaction utilizes easily accessible *gem*-dibromovinyl substrates and azoles, and provides a straightforward route to diverse biheteroaryl compounds. Further investigation on the application of this kind of catalyst system in organic synthesis is underway in our laboratory.

## 4. Experimental

### 4.1. General methods

All reactions were carried out under nitrogen atmosphere. All reagents were purchased from commercial suppliers and used after further purification. $^1H$ NMR, $^{13}C$ NMR spectra were measured on a Bruker Avance NMR spectrometer (400 MHz or 100 MHz, respectively) with $CDCl_3$ or DMSO-$d_6$ as solvent and recorded in ppm relative to internal tetramethylsilane standard. High resolution mass spectroscopy data of the product were collected on a Waters Micromass GCT instrument.

### 4.2. General procedure for the synthesis of benzofuranyl and indolyl azoles from 2-(*gem*-dibromovinyl)phenols and 2-(*gem*-dibromovinyl)anilines with azoles

Under the nitrogen atmosphere, an over-dried Schlenk tube with a magnetic stirring bar was charged with 2-(*gem*-dibromovinyl)phenol or 2-(*gem*-dibromovinyl)aniline (0.50 mmol), azole (0.50 mmol), CuBr (0.05 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 mmol), Li$O^tBu$ (2.0 mmol), and toluene (2.0 mL). The reaction vessel was placed in an oil bath at 100 °C and the mixture was stirred for 10 h, then it was cooled to room temperature. The solvent was filtered and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (eluant: hexane/ethyl acetate) to give the corresponding benzofuranyl or indolyl azole product.

### 4.3. Characterization data of benzofuranyl and indolyl azoles

*4.3.1. Compound* ***3a***. Pale yellow solid; mp 171–173 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.83–7.80 (m, 1H), 7.69 (d, $J$=7.6 Hz, 1H), 7.64 (d, $J$=8.4 Hz, 1H), 7.61–7.59 (m, 2H), 7.45–7.37 (m, 3H), 7.31 (t, $J$=8.0 Hz, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=155.8, 155.3, 150.3, 143.5, 141.5, 127.5, 126.9, 125.8, 125.0, 123.9, 122.2, 120.4, 112.0, 110.7, 110.3; IR (KBr, cm$^{-1}$): 3112, 3028, 1637, 1597, 1439, 1343, 1242, 1066; HRMS (ESI) ([M]$^+$) calcd for $C_{15}H_9NO_2$: 235.0633, found: 235.0635.

*4.3.2. Compound* ***3b***. White solid; mp 193–195 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.81–7.79 (m, 1H), 7.65 (d, $J$=2.0 Hz, 1H), 7.60–7.58 (m, 1H), 7.55–7.51 (m, 2H), 7.40–7.35 (m, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=154.7, 154.1, 150.4, 144.9, 141.4, 129.6, 128.8, 127.1, 126.1, 125.2, 121.6, 120.6, 113.0, 110.7, 109.4; IR (KBr, cm$^{-1}$): 3096, 2921, 1630, 1584, 1439, 1158, 1061; HRMS (ESI) ([M]$^+$) calcd for $C_{15}H_8NO_2Cl$: 269.0244, found: 269.0246.

*4.3.3. Compound* ***3c***. White solid; mp 190–192 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.85 (dd, $J$=6.4, 2.4 Hz, 1H), 7.65–7.63 (m, 1H), 7.60–7.58 (m, 2H), 7.46–7.42 (m, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=154.2, 150.5, 150.3, 145.8, 141.5, 129.8, 129.8, 126.9, 126.3, 125.3, 120.7, 120.2, 118.2, 110.9, 109.8; IR (KBr, cm$^{-1}$): 3069, 2922, 1574, 1441, 1292, 1160, 1072; HRMS (ESI) ([M]$^+$) calcd for $C_{15}H_7NO_2Cl_2$: 302.9854, found: 302.9852.

*4.3.4. Compound* ***3d***. Pale yellow solid; mp 166–167 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.21 (d, $J$=8.0 Hz, 1H), 8.10 (s, 1H), 7.98 (d, $J$=8.0 Hz, 1H), 7.88–7.82 (m, 2H), 7.78 (d, $J$=9.2 Hz, 1H), 7.69–7.63 (m, 2H), 7.56 (t, $J$=7.2 Hz, 1H), 7.43–7.40 (m, 2H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=155.4, 154.0, 150.4, 143.0, 141.7, 130.6, 129.0, 128.3, 127.6, 127.1, 125.7, 125.4, 125.0, 123.4, 123.3, 120.3, 112.5, 110.7, 109.3; IR (KBr, cm$^{-1}$): 3054, 2922, 1634, 1586, 1448, 1243, 1159; HRMS (ESI) ([M]$^+$) calcd for $C_{19}H_{11}NO_2$: 285.0790, found: 285.0787.

*4.3.5. Compound* ***3e***. White solid; mp 142–144 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.71 (d, $J$=7.6 Hz, 1H), 7.65 (d, $J$=8.4 Hz, 1H), 7.61–7.58 (m, 2H), 7.49–7.42 (m, 2H), 7.33 (t, $J$=7.6 Hz, 1H), 7.25–7.19 (m, 1H), 2.50 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=155.7, 155.4, 148.6, 143.8, 141.8, 135.0, 127.5, 127.0, 126.8, 123.8, 122.2, 120.3, 112.0, 110.0, 109.9, 21.5; IR (KBr, cm$^{-1}$): 3061, 2922, 1641, 1595, 1437, 1167, 1072; HRMS (ESI) ([M]$^+$) calcd for $C_{16}H_{11}NO_2$: 249.0790, found: 249.0794.

*4.3.6. Compound* ***3f***. White solid; mp 150–152 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.70–7.63 (m, 3H), 7.56 (s, 1H), 7.44–7.39 (m, 2H), 7.33–7.29 (m, 1H), 7.20–7.18 (dd, $J$=8.0, 0.4 Hz, 1H), 2.50 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=155.7, 154.8, 150.7, 143.7, 139.4, 136.4, 127.5, 126.7, 126.3, 123.8, 122.1, 119.7, 112.0, 110.8, 109.7, 21.8; IR (KBr, cm$^{-1}$): 3022, 2921, 1637, 1248, 1160, 1065; HRMS (ESI) ([M]$^+$) calcd for $C_{16}H_{11}NO_2$: 249.0790, found: 249.0795.

*4.3.7. Compound* ***3g***. White solid; mp 184–186 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.68–7.65 (m, 2H), 7.55 (d, $J$=8.8 Hz, 1H), 7.48 (s, 1H), 7.39–7.35 (m, 2H), 7.21 (d, $J$=8.4 Hz, 1H), 2.52 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=154.3, 154.0, 150.7, 145.1, 139.3, 136.8, 129.5, 128.9, 127.0, 126.5, 121.6, 120.0, 113.0, 110.8, 108.9, 21.9; IR (KBr, cm$^{-1}$): 3095, 2917, 1635, 1435, 1325, 1123, 1066; HRMS (ESI) ([M]$^+$) calcd for $C_{16}H_{10}NO_2Cl$: 283.0400, found: 283.0402.

*4.3.8. Compound* ***3h***. White solid; mp 179–181 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.76 (s, 1H), 7.70 (d, $J$=7.6 Hz, 1H), 7.64 (d, $J$=8.4 Hz, 1H), 7.61 (s, 1H), 7.51 (d, $J$=8.4 Hz, 1H), 7.45 (t, $J$=7.6 Hz, 1H), 7.36–7.31 (m, 2H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=156.5, 155.9, 148.9, 143.0, 142.7, 130.5, 127.3, 127.2, 126.0, 124.0, 122.3, 120.3, 112.1, 111.4, 110.9; IR (KBr, cm$^{-1}$): 3078, 2923, 1637, 1582, 1442, 1203, 1066; HRMS (ESI) ([M]$^+$) calcd for $C_{15}H_8NO_2Cl$: 269.0244, found: 269.0239.

*4.3.9. Compound* ***3i***. White solid; mp 168–170 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.72–7.70 (m, 2H), 7.66–7.61 (m, 3H), 7.46 (t, $J$=7.2 Hz, 1H), 7.37 (dd, $J$=8.4, 1.6 Hz, 1H), 7.34 (t, $J$=7.6 Hz, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=155.9, 155.9, 150.6, 143.1, 140.4, 131.4, 127.4, 127.2, 125.8, 124.0, 122.3, 120.9, 112.1, 111.3, 110.7; IR (KBr, cm$^{-1}$): 3105, 2923, 1637, 1501, 1453, 1259, 1065; HRMS (ESI) ([M]$^+$) calcd for $C_{15}H_8NO_2Cl$: 269.0244, found: 269.0245.

*4.3.10. Compound* ***3j***. Pale yellow solid; mp 112–114 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.42 (s, 1H), 7.91 (d, $J$=7.6 Hz, 1H), 7.81 (d, $J$=8.0 Hz, 1H), 7.66 (d, $J$=7.2 Hz, 1H), 7.58 (d, $J$=7.6 Hz, 1H), 7.44 (t, $J$=8.0 Hz, 2H), 7.36 (t, $J$=7.6 Hz, 2H), 6.76 (s, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=151.7, 145.8, 143.7, 140.7, 132.1, 128.0, 124.6, 124.6, 123.9, 123.7, 121.0, 120.9, 111.4, 111.1, 92.9; IR (KBr, cm$^{-1}$): 3134, 2923, 1627, 1494, 1224, 1012; HRMS (ESI) ([M]$^+$) calcd for $C_{15}H_{10}N_2O$: 234.0793, found: 234.0790.

*4.3.11. Compound* ***3k***. White solid; mp 137–139 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.87 (d, $J$=7.2 Hz, 1H), 7.72 (d, $J$=8.0 Hz, 1H), 7.63 (d, $J$=8.0 Hz, 1H), 7.54 (s, 1H), 7.46–7.39 (m, 2H), 7.36–7.32 (m, 3H), 4.67 (q, $J$=7.2 Hz, 2H), 1.59 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=155.1, 147.0, 143.4, 143.2, 135.4, 127.9, 125.7, 123.6, 123.4, 122.9, 121.8, 120.1, 111.6, 109.5, 108.4, 40.1, 15.5; IR (KBr, cm$^{-1}$): 2926, 2359, 1642, 1457, 1390, 1262; HRMS (ESI) ([M]$^+$) calcd for $C_{17}H_{14}N_2O$: 262.1106, found: 262.1107.

*4.3.12. Compound* ***3l***. White solid; mp 156–158 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.92 (d, $J$=8.4 Hz, 1H), 7.65 (d, $J$=7.6 Hz, 1H), 7.57 (d, $J$=8.0 Hz, 1H), 7.40 (s, 1H), 7.37–7.27 (m, 8H), 7.21–7.20 (m, 2H), 5.81 (s, 2H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=155.1, 146.5, 144.1, 143.2, 136.2, 136.1, 128.9, 127.8, 127.8, 126.3, 125.8, 123.7, 123.6, 123.1, 121.8, 120.2, 111.6, 110.1, 108.6, 48.5; IR (KBr, cm$^{-1}$): 3061, 2922, 1641, 1595, 1437, 1257, 1167, 1072; HRMS (ESI) ([M]$^+$) calcd for $C_{22}H_{16}N_2O$: 324.1263, found: 324.1264.

*4.3.13. Compound* ***3m***. White solid; mp 143–145 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.96 (d, $J$=8.0 Hz, 1H), 7.68–7.65 (m, 3H), 7.57 (d, $J$=8.0 Hz, 1H), 7.48–7.46 (m, 3H), 7.39–7.27 (m, 3H), 7.22 (t, $J$=7.2 Hz, 1H), 7.14 (d, $J$=8.0 Hz, 1H), 6.36 (s, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=154.9, 145.8, 143.9, 142.9, 137.5, 136.2, 130.1, 129.7, 128.0, 127.7, 125.9, 124.1, 123.3, 123.3, 121.6, 120.3, 111.8, 110.3, 108.1; IR (KBr, cm$^{-1}$): 3060, 2924, 1643, 1497, 1422, 1265; HRMS (ESI) ([M]$^+$) calcd for $C_{21}H_{14}N_2O$: 310.1106, found: 310.1105.

*4.3.14. Compound* ***3n***. Yellow solid; mp 216–218 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.14 (d, $J$=7.6 Hz, 1H), 7.95 (d, $J$=8.0 Hz, 1H), 7.70

(d, $J$=7.6 Hz, 1H), 7.64 (d, $J$=7.6 Hz, 1H), 7.55–7.53 (m, 2H), 7.46–7.41 (m, 2H), 7.32 (t, $J$=7.6 Hz, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=157.6, 155.5, 153.8, 149.7, 128.1, 126.7, 126.6, 126.5, 125.7, 123.8, 123.5, 122.1, 121.7, 111.9, 107.6; IR (KBr, $cm^{-1}$): 3115, 3051, 1586, 1439, 1243, 1152, 1004; HRMS (ESI) ($[M]^+$) calcd for $C_{15}H_9NOS$: 251.0405, found: 251.0407.

*4.3.15. Compound* ***5a***. White solid; mp 146–148 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.16 (d, $J$=6.8 Hz, 2H), 7.71 (d, $J$=7.6 Hz, 1H), 7.64 (d, $J$=8.4 Hz, 1H), 7.58–7.53 (m, 4H), 7.45 (t, $J$=7.6 Hz, 1H), 7.33 (t, $J$=7.6 Hz, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=164.5, 157.7, 155.7, 140.6, 132.0, 129.1, 127.2, 127.1, 127.1, 124.0, 123.3, 122.3, 112.0, 110.1; IR (KBr, $cm^{-1}$): 3068, 1632, 1548, 1484, 1442, 1176, 1075; HRMS (ESI) ($[M]^+$) calcd for $C_{16}H_{10}N_2O_2$: 262.0742, found: 262.0746.

*4.3.16. Compound* ***5b***. White solid; mp 175–177 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.13 (d, $J$=8.4 Hz, 2H), 7.74 (d, $J$=7.6 Hz, 1H), 7.66 (d, $J$=8.0 Hz, 1H), 7.61 (s, 1H), 7.55 (d, $J$=8.4 Hz, 2H), 7.48 (t, $J$=7.6 Hz, 1H), 7.37 (t, $J$=7.6 Hz, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=163.7, 157.8, 155.7, 140.3, 138.3, 129.5, 128.3, 127.2, 127.1, 124.1, 122.3, 121.7, 112.0, 110.4; IR (KBr, $cm^{-1}$): 3088, 1633, 1481, 1439, 1181, 1095, 1011; HRMS (ESI) ($[M]^+$) calcd for $C_{16}H_9N_2O_2Cl$: 296.0353, found: 296.0354.

*4.3.17. Compound* ***5c***. White solid; mp 164–166 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.12 (d, $J$=8.8 Hz, 2H), 7.72 (d, $J$=8.0 Hz, 1H), 7.65 (d, $J$=8.4 Hz, 1H), 7.56 (s, 1H), 7.46 (t, $J$=7.6 Hz, 1H), 7.35 (t, $J$=7.6 Hz, 1H), 7.05 (d, $J$=8.8 Hz, 2H), 3.91 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=164.5, 162.5, 157.3, 155.6, 140.7, 128.9, 127.2, 126.9, 124.0, 122.2, 115.7, 114.5, 112.0, 109.7, 55.4; IR (KBr, $cm^{-1}$): 3123, 1642, 1500, 1437, 1262, 1177, 1016; HRMS (ESI) ($[M]^+$) calcd for $C_{17}H_{12}N_2O_3$: 292.0848, found: 292.0852.

*4.3.18. Compound* ***5d***. White solid; mp 151–153 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.05 (d, $J$=8.0 Hz, 2H), 7.71 (d, $J$=7.6 Hz, 1H), 7.64 (d, $J$=8.4 Hz, 1H), 7.56 (s, 1H), 7.45 (t, $J$=7.2 Hz, 1H), 7.35–7.32 (m, 3H), 2.44 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=164.7, 157.5, 155.6, 142.7, 140.6, 129.8, 127.2, 127.0, 127.0, 124.0, 122.2, 120.5, 112.0, 109.9, 21.6; IR (KBr, $cm^{-1}$): 3116, 1623, 1490, 1437, 1250, 1172, 1082; HRMS (ESI) ($[M]^+$) calcd for $C_{17}H_{12}N_2O_2$: 276.0899, found: 276.0901.

*4.3.19. Compound* ***5e***. White solid; mp 115–117 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=7.96–7.93 (m 2H), 7.69 (d, $J$=7.6 Hz, 1H), 7.63 (d, $J$=7.6 Hz, 1H), 7.55 (s, 1H), 7.45–7.39 (m, 2H), 7.36–7.30 (m, 2H), 2.44 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=164.6, 157.6, 155.6, 140.5, 138.9, 132.8, 128.9, 127.5, 127.1, 127.0, 124.1, 123.9, 123.0, 122.2, 112.0, 110.0, 21.2; IR (KBr, $cm^{-1}$): 3143, 1627, 1545, 1470, 1437, 1172, 1075; HRMS (ESI) ($[M]^+$) calcd for $C_{17}H_{12}N_2O_2$: 276.0899, found: 276.0902.

*4.3.20. Compound* ***5f***. White solid; mp 111–113 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.05 (d, $J$=7.6 Hz, 1H), 7.69 (d, $J$=7.6 Hz, 1H), 7.63 (d, $J$=7.6 Hz, 1H), 7.55 (s, 1H), 7.43 (t, $J$=7.6 Hz, 2H), 7.37–7.30 (m, 3H), 2.77 (s, 3H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=164.6, 157.1, 155.5, 140.5, 138.6, 131.7, 131.4, 128.9, 127.1, 126.9, 126.1, 123.9, 122.2, 122.1, 111.9, 110.0, 22.1; IR (KBr, $cm^{-1}$): 3063, 1623, 1538, 1440, 1172, 1046; HRMS (ESI) ($[M]^+$) calcd for $C_{17}H_{12}N_2O_2$: 276.0899, found: 276.0898.

*4.3.21. Compound* ***5g***. White solid; mp 193–195 °C; $^1$H NMR (400 Hz, $CDCl_3$): $\delta$=8.16 (d, $J$=6.8 Hz, 2H), 7.69 (s, 1H), 7.60–7.54 (m, 4H), 7.53 (s, 1H), 7.42–7.39 (m, 1H); $^{13}$C NMR (100 Hz, $CDCl_3$): $\delta$=164.7, 157.3, 154.0, 141.9, 132.2, 129.7, 129.2, 128.5, 127.4, 127.1, 123.1, 121.7, 113.1, 109.4; IR (KBr, $cm^{-1}$): 3097, 1623, 1542, 1432, 1313, 1168, 1069; HRMS (ESI) ($[M]^+$) calcd for $C_{16}H_9N_2O_2Cl$: 296.0353, found: 296.0355.

*4.3.22. Compound* ***6a***. White solid; mp 167–169 °C; $^1$H NMR (400 Hz, DMSO-$d_6$): $\delta$=12.34 (s, 1H), 7.80–7.76 (m, 2H), 7.68 (d, $J$=8.0 Hz, 1H), 7.50 (d, $J$=8.4 Hz, 1H), 7.42–7.40 (m, 2H), 7.34 (s, 1H), 7.27–7.24 (m, 1H), 7.11–7.07 (m, 1H); $^{13}$C NMR (100 Hz, DMSO-$d_6$): $\delta$=157.9, 150.4, 141.9, 138.4, 127.9, 125.8, 125.4, 124.8, 124.7, 122.0, 120.8, 119.9, 112.8, 111.2, 105.9; IR (KBr, $cm^{-1}$): 3035, 1626, 1577, 1444, 1335, 1235, 1169; HRMS (ESI) ($[M]^+$) calcd for $C_{15}H_{10}N_2O$: 234.0793, found: 234.0789.

*4.3.23. Compound* ***6b***. White solid; mp 154–157 °C; $^1$H NMR (400 Hz, DMSO-$d_6$): $\delta$=12.34 (s, 1H), 8.14–8.12 (m, 2H), 7.70–7.64 (m, 4H), 7.50 (d, $J$=8.0 Hz, 1H), 7.33 (s, 1H), 7.29–7.25 (m, 1H), 7.13–7.09 (m, 1H); $^{13}$C NMR (100 Hz, DMSO-$d_6$): $\delta$=163.8, 159.8, 138.3, 132.5, 129.9, 127.8, 127.1, 124.8, 123.7, 122.0, 121.5, 120.9, 112.7, 105.6; IR (KBr, $cm^{-1}$): 3191, 2923, 1609, 1477, 1342, 1187; HRMS (ESI) ($[M]^+$) calcd for $C_{16}H_{11}N_3O$: 261.0902, found: 261.0900.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.044. These data include MOL files and InChIKeys of the most important compounds described in this article.

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