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Cu(II)-mediated oxidative dimerization of 2-phenylpyridine derivatives

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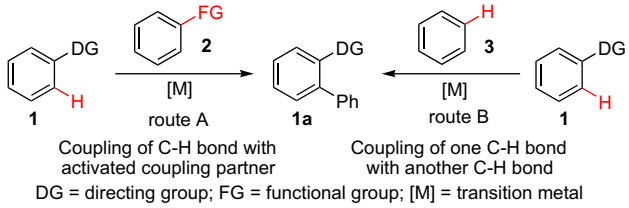
ABSTRACT

A Cu(II)/I_2-mediated C–H bond activation is described. A variety of 2-phenylpyridine derivatives are oxidatively dimerized at the *ortho*-position of the phenyl ring in which a net loss of two hydrogen atoms results in the formation of a biaryl compound via a double C–H activation/C–C bond-forming process. Moderate functional group tolerance was observed on both the aryl and the pyridyl rings. A single electron transfer (SET) or electrophilic metalation process for iodination followed by Ullmann coupling of the intermediate iodinated product is proposed as the operating mechanism for the dimerization process.

1. Introduction

Biaryl compounds have attracted remarkable attention because of their prevalence in natural products and pharmaceuticals,[1] and pervasive utility as chiral ligands in organic synthesis.[2] In recent years, great emphasis has been placed on the development of transition-metal catalyzed C–H bond activation/C–C bond formation as a novel approach to construct biaryl scaffolds,[3] and several metal catalysts, such as Ru, Rh, and Pd, have already been utilized with varying degrees of success.[4] This process utilizes the substrate **1** with unactivated C–H bonds, and activated molecules, such as arylboronic acid/ester or aryl halide **2**, as coupling partners (Scheme 1, route A).[5] However, from economic and environmental perspectives, a more attractive approach would be the direct coupling of two C–H bonds. In particular, oxidatively coupling the two unactivated C–H bonds of the substrate **1** and the coupling partner **3**, respectively, on a metal center to form a C–C coupling product **1a** would be the most atom-efficient approach and would involve the least number of steps for the synthesis of complex target molecules (Scheme 1, route B).[6] As such, the synthesis of biaryl molecules using this alternative process has received significant attention.[7]



Scheme 1. Biaryl synthesis via oxidative coupling of C–H bonds.

Pd(II) catalysts have frequently been used in the oxidative coupling of two arenes via the activation of C–H bonds.[8,9] In most cases, a homodimer is obtained as the final product.[10] Itahara has shown that an oxidative coupling of quinones and heterocycles with excess arene could be performed inter- and intramolecularly using $Pd(OAc)_2$ as the catalyst.[11,12] Fagnou and co-workers have recently discovered an additive effect of acetate ions and $Cu(OAc)_2$ on the regioselective arylation of indoles with excess arenes under Pd(II)-catalysis.[13] A similar regioselective arylation of indoles and benzofurans with excess arene has also been achieved by DeBoef and co-workers.[14] Sanford and Hull reported a moderate level of regioselectivity by the combined effect of a directing group and steric hindrance in the oxidative coupling of benzoquinoline with arenes.[15] A similar level of regioselectivity was also observed in the coupling of acetanilides with arenes under Pd(II)-catalysis.[16] Excellent diastereoselectivity was obtained in the oxidative coupling of chiral ferrocenyl oxazolines with excess benzene, providing a facile method to synthesize planar chiral aryl-substituted ferrocenyl oxazolines.[17] Formation of unsymmetrical biaryls from simple

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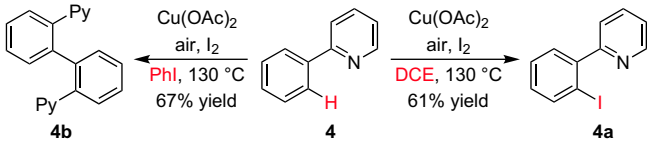
arenes has been achieved by Lu and co-workers under Pd-catalysis by tuning the concentrations of arenes and trifluoroacetic acid.[18] Buchwald and co-workers have arylated *ortho*-C–H bonds in anilides with benzene derivatives (4–11 equiv) to form biphenyls via a Pd-catalyzed twofold C–H functionalization/C–C bond-forming process.[19]

More recently, research activities have focused on replacing these expensive metal catalysts with more abundant and less expensive Cu salts to execute similar C–H activation reactions.[20] We have reported a Cu(II)-catalyzed functionalization, including amination with $TsNH_2$, of unactivated C–H bonds of 2-phenylpyridines using O_2 as the oxidant.[21] Chatani and co-workers later showed that 2-phenylpyridine could also be aminated with anilines in moderate yields using stoichiometric amounts of $Cu(OAc)_2$.[22] Daugulis and Do have demonstrated the arylation of C–H bonds in heterocycles and polyfluoroarenes with aryl halides using CuI as the catalyst.[23] Buchwald and Brasche have synthesized benzimidazoles from amidines through a Cu-catalyzed C–H activation/C–N bond-forming process using O_2 as the oxidant.[24] 2-Arylbenzoxazoles have been prepared from benzanilides by a Cu-catalyzed C–H activation/intramolecular C–O bond-forming reaction.[25]

Cu catalysts have also found increasing applications in the oxidative coupling of two C–H bonds.[3b,26,27] Various Cu salts have been extensively used to synthesize racemic and chiral binaphthols via the oxidative coupling of two aryl C–H bonds of naphthol molecules.[28,29] Herein, we report a Cu(II)-mediated oxidative dimerization of 2-phenylpyridine derivatives in which a net loss of two hydrogen atoms results in the formation of biaryl compounds via a C–H activation/C–C bond-forming process.

2. Results and discussion

During our recent work on a Cu(II)-catalyzed functionalization of C–H bonds with a variety of nucleophiles, we observed the dimer **4b** of 2-phenylpyridine **4** when I_2 was used as a nucleophile source under a slightly modified reaction condition (Scheme 2).[21] Iodine is crucial for the dimerization reaction as no product was obtained in its absence. Sanford and co-workers also showed an interesting case of dimerization of 2-phenylpyridines via Pd(II)/Pd(IV) catalysis.[10c]

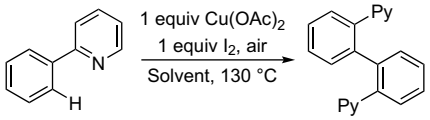


Scheme 2. Cu(II)-catalyzed C–H functionalization.

The reaction was further optimized using various reaction parameters (Table 1). Substrate **4** was quantitatively dimerized to **4b** when the reaction was carried out in 2.0 mL of MeCN with stoichiometric amounts of $Cu(OAc)_2$ and I_2 at 130 °C under air for 24 h (Table 1, entry 1). The reaction could also be run in iodobenzene with similar yield (Table 1, entry 2). While the reaction carried out in DMF provided reasonable yield, only small quantities of the dimerized product **4b** were observed in toluene or DMSO (Table 1, entries 3–5). Decreasing the amount of either the solvent, $Cu(OAc)_2$, or I_2 resulted in the reduction of the product yield (Table 1, entries 6–9).

A variety of 2-phenylpyridine derivatives bearing substituents on either rings were oxidatively dimerized in reasonable to excellent yields under the optimized reaction conditions. 2-Phenylpyridine derivatives **5**–**8** containing both electron-donating and electron-withdrawing substituents on the phenyl ring were dimerized in reasonable yields (Table 2, entries 1–4). Substrate **8**

Table 1
Optimization of reaction conditions[a]



4 4b

Entry	Solvent	$Cu(OAc)_2$ (equiv)	I_2 (equiv)	Yield[b] (%)
1	MeCN	1.0	1.0	85[c]
2	PhI	1.0	1.0	76[c]
3	DMF	1.0	1.0	69
4	Toluene	1.0	1.0	33
5	DMSO	1.0	1.0	14
6	MeCN	1.0	1.0	65[d]
7	MeCN	1.0	0.5	43
8	MeCN	0.5	1.0	53
9	MeCN	0.5	0.5	62

[a] Reaction was run under air on a 0.4 mmol scale in 2.0 mL solvent at 130 °C for 24 h in a sealed tube.
[b] ^1H NMR yields based on dibromomethane as an internal standard.
[c] Isolated yields from a 1.0 mmol scale reaction in 5 mL solvent.
[d] Solvent (1.0 mL) was used.

with a *meta*-fluoro substituent on the phenyl ring also underwent dimerization regioselectively at the less hindered C–H bond (Table 2, entry 4). Substrate **9** with a free hydroxy functional group was also tolerated and the corresponding dimerized product **9a** was obtained in reasonable yield (Table 2, entry 5). Substrate **10** bearing an electron-donating group on the pyridyl ring dimerized with excellent product yield (Table 2, entry 6). 2-(Naphthalen-2-yl)pyridine **11** gave a 2:1 mixture of symmetrically and unsymmetrically homodimerized products **11a** and **11b**, respectively, in acceptable yields (Table 2, entry 7).

The reaction requires 1 equiv of $Cu(OAc)_2$ and I_2 to obtain quantitative dimerization of the substrate **4** (Table 1, entries 1 and 7–9). Based on this stoichiometry, the following reaction equation can be drawn for the dimerization of **4** (Scheme 3).

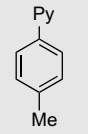
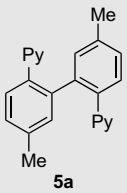
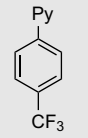
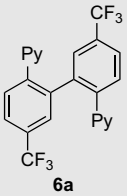
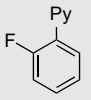
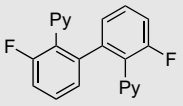
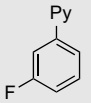
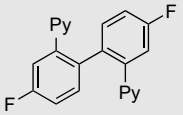
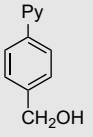
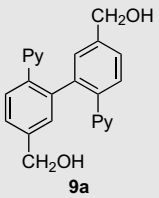
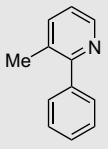
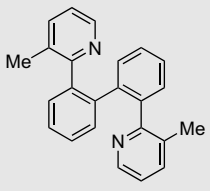
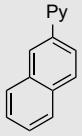
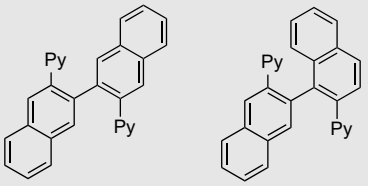
Although we do not have concrete experimental evidence, the following mechanistic pathway can be invoked to explain the current Cu(II)-mediated oxidative dimerization process based on the literature precedent and the stoichiometry of the reaction (Scheme 4).

Iodination of aryl C–H bond using $I_2/Cu(OAc)_2$ reagent is known.[21,30] The reaction could possibly involve Cu(OAc)I species **12** generated in situ from the reaction of I_2 with $Cu(OAc)_2$ analogous to the reaction of I_2 with $Hg(OAc)_2$ (Scheme 3, route A).[31] 2-Phenylpyridine **4** could presumably give the intermediate iodinated product **4a** in the presence of $Cu(OAc)_2/I_2$ reagent via a single electron transfer (SET) (Scheme 4, route A).[21] The intermediate iodinated product **4a** could also be formed via the metalacycle **4f** by electrophilic metalation/iodination process (Scheme 4, route B).[24] Finally, the intermediate iodinated product **4a** could undergo Ullmann coupling to give the homodimerized product **4b**. Although the formation of the product **4b** through the iodinated intermediate **4a** appears feasible, an alternative mechanism in which 2-phenylpyridine **4** is directly homodimerized via double C–H activation cannot also be ruled out.

3. Conclusions

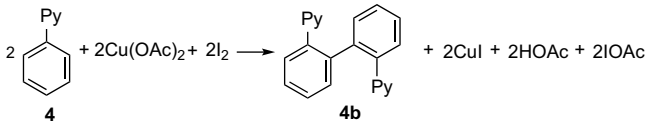
2-Phenylpyridine derivatives are oxidatively dimerized at the *ortho*-position of the phenyl ring in which the loss of two hydrogen atoms results in the formation of a biaryl compound via a $Cu(OAc)_2$-promoted C–H activation/C–C bond formation. A small range of functional groups are tolerated on both the aryl and the pyridyl

Table 2
Cu(II)-mediated oxidative dimerization of 2-phenylpyridines[a]

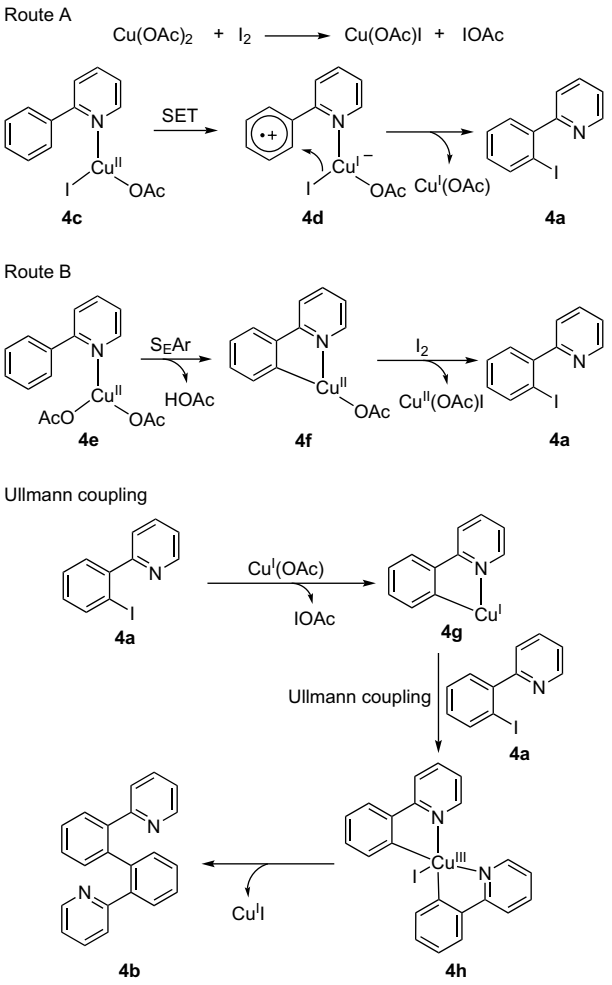
Entry	Substrate	Product	Yield (%)[b]
1	 **5**	 **5a**	68
2	 **6**	 **6a**	58
3	 **7**	 **7a**	24
4	 **8**	 **8a**	44
5	 **9**	 **9a**	40
6	 **10**	 **10a**	88
7	 **11**	 **11a** (2:1) **11b**	42

[a] Reactions were run under air on a 0.4 mmol scale in 2.0 mL MeCN at 130 °C for 24 h in a sealed tube.
[b] Isolated yields.

rings. A single electron transfer (SET) or electrophilic metalation process for iodination followed by Ullmann coupling of the intermediate iodinated product is proposed as the operating mechanism for the dimerization process.



Scheme 3. Balanced reaction equation for the dimerization of **4**.



Scheme 4. Possible mechanisms of Cu(II)-mediated oxidative dimerization of 2-phenylpyridine.

4. Experimental

4.1. General experimental

Solvents were obtained from Acros and used directly without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to the $SiMe_4$ signal. Exact mass spectra for new compounds were recorded on a VG 7070 high resolution mass spectrometer. Substrates **4**, **5**, and **7** were purchased from Aldrich.

4.2. Preparation of 2-phenylpyridine substrates

Other substrates (**6** and **8**–**11**) were prepared via Suzuki coupling of the corresponding boronic acid and 2-bromopyridine using a literature procedure.[32]

4.3. General procedure for Cu(II)-mediated dimerization of 2-phenylpyridines

In a 20 mL reaction tube, the substrate (0.4 mmol), $Cu(OAc)_2$ (72.8 mg, 0.4 mmol), and I_2 (101.6 mg, 0.4 mmol) were dissolved in 2 mL of MeCN under atmospheric air. The reaction tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 130 °C for 24 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and then treated with saturated aqueous solutions of $Na_2S_2O_3$ (5 mL) and Na_2S (5 mL) sequentially. The mixture was

filtered through a pad of Celite and the filtrate was washed twice with brine. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with hexane/ether (1:1 to 0:1 ratio) to give the dimerized products.

*4.3.1. 2,2′-Bis(pyridin-2-yl)biphenyl (**4b**)*

Substrate **4** was dimerized following the general procedure. After purification by column chromatography, **4b** was obtained as a yellow solid (47.7 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J=4.8 Hz, 2H), 7.54 (d J=7.6 Hz, 1H), 7.41–7.36 (m, 6H), 7.30 (t, J=8.0 Hz, 2H), 6.99 (dd, J=7.6, 4.8 Hz, 1H), 6.76 (d, J=7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 149.2, 140.1, 140.1, 135.4, 131.5, 130.2, 128.8, 128.0, 124.6, 121.4; HRMS (EI) calcd for $C_{22}H_{16}N_2$ (M^+) 308.1314, found 308.1310.

*4.3.2. 2,2′-(5,5′-Dimethylbiphenyl-2,2′-diyl)dipyridine (**5a**)*

Substrate **5** was dimerized following the general procedure. After purification by column chromatography, **5a** was obtained as a yellow solid (45.4 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J=4.8 Hz, 2H), 7.48–7.19 (m, 8H), 6.99–6.90 (m, 2H), 6.68 (d, J=7.9 Hz, 2H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 149.0, 139.9, 138.7, 137.4, 135.3, 132.1, 130.1, 128.7, 124.5, 121.1, 21.5; HRMS (EI) calcd for $C_{24}H_{20}N_2$ (M^+) 336.1627, found 336.1623.

*4.3.3. 2,2′-(5,5′-Bis(trifluoromethyl)biphenyl-2,2′-diyl)-dipyridine (**6a**)*

Substrate **6** (0.2 mmol) was reacted with $Cu(OAc)_2$ (36.4 mg, 0.2 mmol) and I_2 (50.8 mg, 0.2 mmol). The general procedure was followed to give product **6a** as a brown solid (26.0 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J=4.6 Hz, 2H), 7.66 (s, 4H), 7.59 (s, 2H), 7.42 (t, J=7.7 Hz, 2H), 7.10 (dd, J=7.5, 4.9 Hz, 2H), 6.86 (d, J=7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 149.6, 143.4, 139.5, 135.9, 130.9, 128.2, 125.4, 125.1, 124.5, 122.7, 122.3; HRMS (EI) calcd for $C_{24}H_{14}F_6N_2$ (M^+) 444.1061, found 444.1060.

*4.3.4. 2,2′-(3,3′-Difluorobiphenyl-2,2′-diyl)dipyridine (**7a**)*

Substrate **7** was dimerized following the general procedure. After purification by column chromatography, **7a** was obtained as a brown oil (17.1 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J=4.9 Hz, 2H), 7.51 (dt, J=7.8, 1.5 Hz, 2H), 7.34–6.80 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (d, J_{C-F}=246.0 Hz), 153.6, 149.2, 141.9, 135.8, 129.1 (d, J_{C-F}=9.0 Hz), 127.2 (d, J_{C-F}=4.0 Hz), 126.3, 122.1, 114.9, 115.1; HRMS (EI) calcd for $C_{22}H_{14}F_2N_2$ (M^+) 344.1125, found 344.1127.

*4.3.5. 2,2′-(4,4′-Difluorobiphenyl-2,2′-diyl)dipyridine (**8a**)*

Substrate **8** (0.25 mmol) was reacted with $Cu(OAc)_2$ (72.8 mg, 0.4 mmol) and I_2 (101.6 mg, 0.4 mmol). The general procedure was followed to give product **8a** as a brown solid (19.4 mg, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (t, J=4.8 Hz, 2H), 7.46–7.31 (m, 4H), 7.29–7.24 (m, 2H), 7.14–7.05 (m, 4H), 6.95 (dd, J=7.9, 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (d, J_{C-F}=245.0 Hz), 159.4, 157.0, 149.2, 142.9, 135.7, 130.1 (d, J_{C-F}=9.0 Hz), 125.7, 123.9, 122.0, 115.4; HRMS (EI) calcd for $C_{22}H_{14}F_2N_2$ (M^+) 344.1125, found 344.1121.

*4.3.6. (6,6′-Di(pyridin-2-yl)biphenyl-3,3′-diyl)dimethanol (**9a**)*

Substrate **9** was dimerized following the general procedure. After purification by column chromatography, **9a** was obtained as a brown oil (33.3 mg, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J=4.5 Hz, 2H), 7.85 (d, J=8.0 Hz, 2H), 7.51–7.41 (m, 2H), 7.39–7.30 (m, 2H), 7.20–7.08 (m, 4H), 7.00 (t, J=7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.9, 141.9, 138.9, 137.1, 128.4, 127.5, 127.3, 122.6, 122.4, 120.8, 65.1; HRMS (EI) calcd for $C_{24}H_{20}N_2O_2$ (M^+) 368.1525, found 368.1528.

*4.3.7. 2,2′-Bis(3-methylpyridin-2-yl)biphenyl (**10a**)*

Substrate **10** was dimerized following the general procedure. After purification by column chromatography, **10a** was obtained as a brown oil (60.2 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J=4.5 Hz, 2H), 7.85 (d, J=8.0 Hz, 2H), 7.59–6.86 (m, 12H), 1.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 147.2, 145.6, 139.2, 138.2, 131.6, 129.4, 128.5, 128.1, 123.3, 122.3, 19.4; HRMS (EI) calcd for $C_{24}H_{20}N_2$ (M^+) 336.1627, found 336.1624.

*4.3.8. 3,3′-Di(pyridin-2-yl)-2,2′-binaphthyl (**11a**) and 2,2′-(1,2′-binaphthyl-2,3′-diyl)dipyridine (**11b**)*

Substrate **11** was dimerized following the general procedure. After purification by column chromatography, **11a** was obtained as a yellow solid (21.2 mg, 26% yield) and **11b** was obtained as a white solid (13.3 mg, 16% yield).

Compound **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J=4.2 Hz, 2H), 8.14 (s, 2H), 8.03 (s, 2H), 7.96 (d, J=7.8 Hz, 2H), 7.91 (d, J=7.8 Hz, 2H), 7.50–7.55 (m, 4H), 7.27–7.19 (m, 2H), 7.08–6.93 (m, 2H), 6.71 (d, J=7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 149.2, 138.5, 135.5, 133.6, 133.1, 130.8, 129.7, 128.6, 127.9, 126.9, 126.6, 124.6, 121.5; HRMS (EI) calcd for $C_{30}H_{20}N_2$ (M^+) 408.1627, found 408.1627.

Compound **11b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J=4.8 Hz, 1H), 8.33 (d, J=4.9 Hz, 1H), 8.22 (s, 1H), 7.94 (m, 5H), 7.81–7.87 (m, 2H), 7.73 (d, J=8.5 Hz, 1H), 7.56–7.49 (m, 3H), 7.41–7.38 (m, 1H), 7.19 (m, 2H), 7.00–6.92 (m, 2H), 6.85 (d, J=7.9 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.7, 149.1, 149.1, 139.6, 137.7, 136.8, 135.4, 135.4, 135.0, 133.7, 133.2, 133.1, 133.0, 132.3, 129.9, 128.7, 128.3, 127.9, 127.2, 126.9, 126.8, 126.7, 126.6, 126.3, 125.2, 124.0, 121.6, 121.4; HRMS (EI) calcd for $C_{30}H_{20}N_2$ (M^+) 408.1627, found 408.1626.

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