An efficient and convenient $Cu(OAc)_2$/air mediated oxidative coupling of azoles *via* C–H activation†

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An efficient and convenient approach to construct C–C bonds at the 2-position of azoles *via* $Cu(OAc)_2$/air mediated oxidative homo- and cross-coupling reaction was reported. The corresponding products were obtained in good to excellent yield.

The formation of carbon–carbon bonds is one of the most useful and fundamental reactions since it represents a key step in the synthesis of complex molecules.[1] In particular, construction of C–C bonds at the 2-position of azoles is important for the synthesis of many pharmaceutically relevant compounds.[2] The most developed methods for C–C bond formation at the 2-position of azoles involve transition-metal-catalyzed cross-coupling reactions between prefunctionalized azoles (usually including organozinc reagents, organotin reagents) and R–X (R = Ar, alkyl; X = I, Br, Cl, OTf)[3,4] or 2-halo azoles and R–M (R = Ar, alkyl; M = SnR_3, $B(OR)_2$).[5–7] Quite often, these functionalized starting materials are either expensive or have to be prepared in several steps.[8] In recent years, research activities have focused on generating these C–C bonds by transition-metal catalyzed direct C–H activation because of its conciseness and "atom economy"[9] and a number of excellent results have been obtained.[8,10] However, for most of these methods, expensive metal catalysts are inevitable. As a more challenging subject, oxidative intermolecular C–C bond formation using two C–H bonds of azoles has been rarely reported.

More recently, replacing these expensive metal catalysts with more abundant and less expensive ones to execute similar C–H activation reactions has attracted great interest.[11] Daugulis[12] and You[13] both found that CuI could catalyze the arylation of heterocycle C–H bonds. Miura recently discovered an arylation of azoles with aryl bromides catalyzed by nickel.[14] A similar nickel catalyzed coupling of heteroarenes with aryl halides/triflates has been uncovered by Itami and co-workers.[15] Cu(II) catalysts have also found increasing applications in the oxidative coupling of two C–H bonds.[16,17] With the emergence of the concept of "green chemistry",[18] air as an environmentally benign, mild and facile terminal oxidant is attracting more and more attention. A Cu(II)-catalyzed air oxidative functionalization of aryl C–H bonds has been achieved by Yu.[19] Li used palladium and air to synthesize (*E*)-3-(isobenzofuran-3(1*H*)-ylidene)-indolin-2-ones.[20] Herein, we report an efficient and convenient $Cu(OAc)_2$ mediated oxidative homo- and cross-coupling reaction of azoles *via* C–H activation using air as the terminal oxidant.

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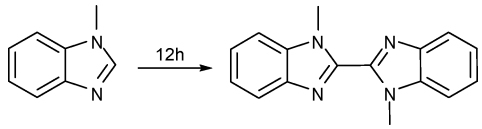
In experiments searching for the best reaction conditions, we initially examined the oxidative homo-coupling of *N*-methylbenzimidazole with 1.2 equiv. $Cu(OAc)_2$ and 2 mL xylene under N_2 atmosphere at 140 °C. 12 h later, the desired product was obtained in 85% yield (Table 1, entry 7). The reaction proceeded successfully with mild oxidant. The result of the reaction decreased obviously when DDQ, 1,4-benzoquinone, $PhI(OAc)_2$ were used as the oxidant (Table 1, entries 6, 8 and 9). When the reaction was carried out under air using 20 mol% $Cu(OAc)_2$ as the catalyst, a better result was obtained (Table 1, entry 1). Using pure oxygen instead of air, the yield was almost the same (Table 1, entry 14). Other metal catalysts were also screened. However, the yield declined to 42% when CuCl was used (Table 1, entry 11) and no product was formed when $CuSO_4$ and $FeCl_3$ catalyzed the reaction (Table 1, entries 10 and 12). Among the solvents investigated, xylene was clearly the best choice (Table 1, entries 1–5). As for the influence of $Cu(OAc)_2$ dosage, it was found that decreasing the amount of $Cu(OAc)_2$ resulted in reduced yield (Table 1, entry 15). No product was obtained in the absence of $Cu(OAc)_2$ (Table 1, entry 16). $Cu(OAc)_2$ could be recovered and recycled. However, the yield slightly declined as the number of times the catalyst was recycled increased (Table 1, entry 17 and 18). The yield fell to 70% when the reaction temperature was set to 125 °C (Table 1, entry 13). Therefore, the optimized conditions were *N*-methylbenzimidazole (0.5 mmol)/$Cu(OAc)_2$ (20 mol%)/xylene (2 mL) at 140 °C.

With the optimized conditions in hand, various substrates were subjected to this coupling reaction. The method could be successfully applied to the oxidative homo-coupling reactions of various azoles (imidazoles, benzimidazoles, thiazoles, oxadiazoles and benoxazoles) (Table 2). Benzimidazoles bearing different substituents including alkyl and aryl groups at the 1-position could all give the product in good to excellent yield (Table 2, entries 1–3). As for imidazoles, the yields were slightly reduced (Table 2, entries 4–6). No distinct electronic effect was observed. Other azoles such as thiazoles, benzoxazoles and oxadiazoles could all react smoothly and give the corresponding products in good yield (Table 2, entries 7–11). No methyl oxidation was found in our catalytic systems. And our protocol was regioselective: all the dimerizations of these azole derivatives occurred at 2-position.

Encouraged by the above results, we further investigated the cross-coupling reaction between two different azoles (Table 3). To our delight, the corresponding cross-coupling products were formed in moderate yield. The coupling of *N*-methylbenzimidazole with *N*-benzylbenzimidazole gave 56% cross-coupling products (Table 3, entry 1). For the coupling of *N*-benzylbenzimidazole with *N*-phenylbenzimidazole, cross-coupling products were obtained in more than 50% yield no matter whether the ratio of **1** to **2** was 2 : 1 or 1 : 2 (Table 3,

Table 1 Screening of reaction conditions[a]

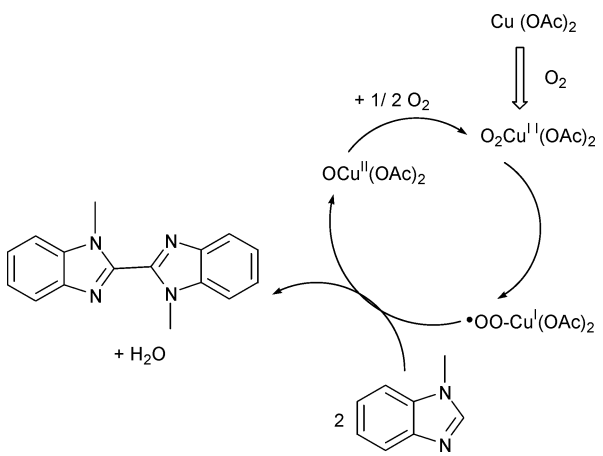


Entry	Solvent	Oxidant	Cat.	T/°C	Yield (%)[b]
1	xylene	air	$Cu(OAc)_2$	140	90
2	toluene	air	$Cu(OAc)_2$	110	53
3	$PhNO_2$	air	$Cu(OAc)_2$	140	0
4	NMP	air	$Cu(OAc)_2$	140	<5
5	DMF	air	$Cu(OAc)_2$	140	64
6	xylene	DDQ	$Cu(OAc)_2$	140	<5[c]
7	xylene	$Cu(OAc)_2$	—	140	85[d]
8	xylene	1,4-benzoquinone	$Cu(OAc)_2$	140	15[c]
9	xylene	$PhI(OAc)_2$	$Cu(OAc)_2$	140	23[c]
10	xylene	air	$CuSO_4$	140	0
11	xylene	air	CuCl	140	42
12	xylene	air	$FeCl_3$	140	trace
13	xylene	air	$Cu(OAc)_2$	125	70
14	xylene	O_2	$Cu(OAc)_2$	140	90
15	xylene	air	$Cu(OAc)_2$	140	86[e]
16	xylene	air	—	140	0
17	xylene	air	$Cu(OAc)_2$[f]	140	87
18	xylene	air	$Cu(OAc)_2$[g]	140	83

[a] 0.5 mmol of *N*-methylbenzimidazole, 20 mol% of catalyst, 2 mL solvent, 12 h. [b] Isolated yield. [c] 1.2 equiv. oxidant and under N_2 atmosphere. [d] 1.2 equiv. $Cu(OAc)_2$ and under N_2 atmosphere. [e] 15 mol% of $Cu(OAc)_2$. [f] $Cu(OAc)_2$ was recycled once. [g] $Cu(OAc)_2$ was recycled twice.

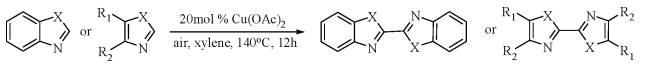
entries 2 and 3). When benzoxazole reacted with *N*-methylimidazole, the cross-coupling product was formed in 45% yield. While *N*-benzylimidazole with 4,5-dimethylthiazole, the yield was 49%. Though the cross-coupling yields were moderate, the method provided a concise and convenient procedure to construct these cross bisazoles.

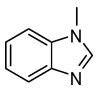
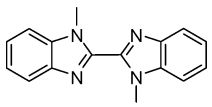
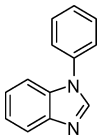
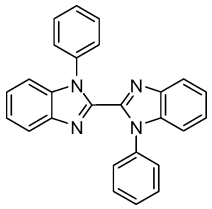
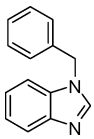
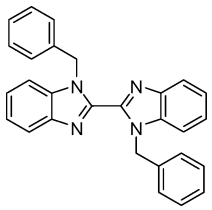
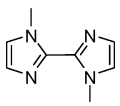
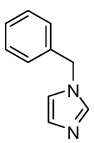
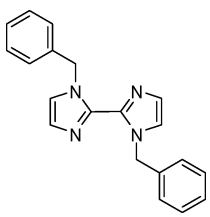
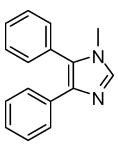
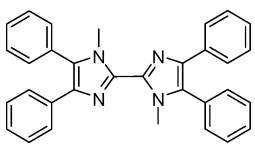
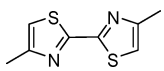
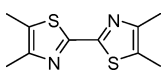
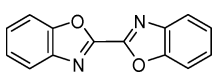
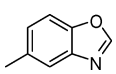
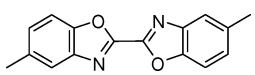
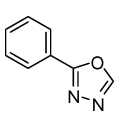
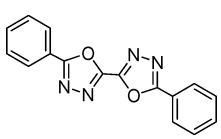
The exact mechanism of the $Cu(OAc)_2$ catalyzed air oxidative coupling of azoles is not clear at the moment. According to the literature[21] and the observation in our reactions, a possible mechanism was proposed (Scheme 1). The reaction started from $O_2Cu^{II}(OAc)_2$, which was formed by the combination of $Cu(OAc)_2$ and molecule oxygen. An electron transfer from O to Cu to give $^{\bullet}OOCu^{I}(OAc)_2$.Then $^{\bullet}OOCu^{I}(OAc)_2$ abstracted the hydrogen



Scheme 1 Possible mechanism.

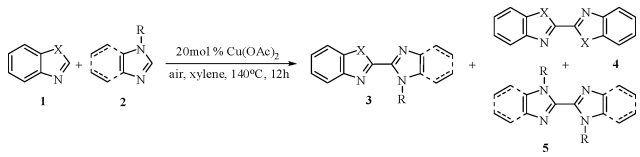
Table 2 Formation of bisazole[a]

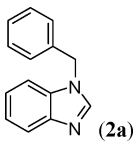
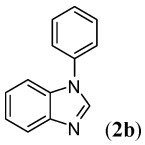
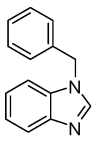
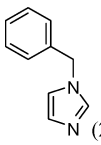
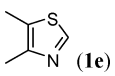
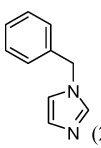


Entry	Substrate	Product	Yield (%)[b]
1			90
2			91
3			88
4			80
5			83
6			81
7			79
8			79
9			86
10			84
11			75

[a] 0.5 mmol of substrate, 20 mol% of $Cu(OAc)_2$, 2 mL xylene, 140 °C, 12 h. [b] Isolated yield.

Table 3 Cross-coupling of two different benzimidazoles[a]



Entry	X	Substrate **2**	Yield (%) 3[b]	4[c]	5[b]
1	N–CH_3 (**1a**)	 (**2a**)	56(**3a**)	31(**4a**)	19(**5a**)
2	N–CH_2Ph (**1b**)	 (**2b**)	54(**3b**)	22(**4b**)	32(**5b**)
3	N–Ph (**1c**)	 (**2a**)	52(**3b**)	28(**4c**)	23(**5a**)
4	N–CH_3 (**1a**)	 (**2c**)	66(**3c**)	44(**4a**)	31(**5c**)
5	O (**1d**)	 (**2d**)	45(**3d**)	25(**4d**)	25(**5d**)
6	 (**1e**)	 (**2c**)	49(**3e**)	24(**4e**)	35(**5c**)

[a] 0.5 mmol of **1**, 0.25 mmol of **2**, 20 mol% of $Cu(OAc)_2$, 2 mL xylene, 140 °C, 12 h. [b] Isolated yield and based on **2**. [c] Isolated yield and based on **1**

atom at the 2-position of azole and bisazole and H_2O were produced.

In conclusion, we have developed an efficient and convenient air oxidative coupling reaction of azoles. It provides a new and regioselective approach to construct C–C bonds at the 2-position of azoles.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AMX-400 MHz instrument with TMS as internal standard. Coupling constants are reported in Hertz (Hz). MS was obtained using EI ionization. Melting points were uncorrected.

General procedures

General procedure for the formation of homo-coupling product. A dry Schlenk tube was charged with the *N*-methylbenzimidazole (0.5 mmol, 0.066 g) and $Cu(OAc)_2$ (20 mol%, 0.0182 g) in 2 mL xylene. Then the Schlenk tube was sealed and the reaction mixture was heated to 140 °C for 12 h. Purification was done by column chromatography on silica gel (200–300 mesh) with dichloromethane and ethyl acetate (5 : 1) as the eluent to give the pure product (0.058 g, 90%).

Formation of cross-coupling product. A dry Schlenk tube was charged with *N*-methylbenzimidazole (0.5 mmol, 0.066 g), *N*-benzylbenzimidazole (0.25 mmol, 0.052 g) and $Cu(OAc)_2$ (20 mol%, 0.0182 g) in 2 mL xylene. Then the Schlenk tube was sealed and the reaction mixture was heated to 140 °C for 12 h. Purification was done by column chromatography on silica gel (200–300 mesh) with dichloromethane and ethyl acetate (10 : 1) as the eluent to give the pure product **3a** (0.048 g, 56%).

1,1′-Dimethyl-1*H*,1′*H*-2,2′-bibenzo[*d*]imidazole[22]. M.p.: 208–209 °C, ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 4.33 (s, 6H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.41 (t, $J = 7.4$ Hz, 2H), 7.49 (d, $J = 7.6$ Hz, 2H), 7.88 (d, $J = 7.6$ Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 32.4, 110.0, 120.3, 122.8, 123.9, 136.2, 142.5, 143.2.

1,1′-Diphenyl-1*H*,1′*H*-2,2′-bibenzo[*d*]imidazole[23]. M.p.: 189–199 °C, ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 6.85 (d, $J = 7.6$ Hz, 4H), 7.19–7.31 (m, 10H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.92 (d, $J = 8.4$ Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 110.5, 120.9, 123.2, 124.3, 125.4, 127.7, 129.3, 135.1, 135.2, 142.9, 143.0.

1,1′-Dibenzyl-1*H*,1′*H*-2,2′-bibenzo[*d*]imidazole[24]. M.p.: 215–216 °C, ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 6.22 (s, 4H), 7.00–7.01 (m, 4H), 7.11–7.14 (m, 6H), 7.27–7.32 (m, 4H), 7.36–7.38 (m, 2H), 7.83–7.85 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 48.5, 110.8, 120.4, 122.9, 124.1, 126.8, 127.4, 128.6, 135.5, 136.8, 142.6, 142.8.

1,1′-Dimethyl-1*H*,1′*H*-2,2′-biimidazole[25]. M.p.: 105–106 °C, ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 4.03 (s, 6H), 6.95 (d, $J = 0.4$ Hz, 2H), 7.10 (d, $J = 0.4$ Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 35.2, 122.5, 127.7, 138.5.

1,1′-Dibenzyl-1*H*,1′*H*-2,2′-biimidazole[26]. M.p.: 148–149 °C, ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 5.69 (s, 4H), 6.92 (d, $J = 1.2$ Hz, 2H), 7.01–7.04 (m, 4H), 7.12 (d, $J = 1.2$ Hz, 2H), 7.22–7.24 (m, 6H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 50.7, 121.4, 127.4, 127.5, 128.3, 128.6, 137.2, 138.2.

1,1′-Dimethyl-4,4′,5,5′-tetraphenyl-1*H*,1′*H*-2,2′-biimidazole. M.p.: 258–259 °C ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 3.94 (s, 6H), 7.13–7.16 (m, 2H), 7.19–7.23 (m, 4H), 7.41–7.43 (m, 4H), 7.47–7.55 (m, 10H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 33.6, 126.3, 126.6, 128.1, 128.7, 129.0, 130.7, 130.9, 134.4, 137.2, 138.2. Anal. Calc. for $C_{32}H_{26}N_4$: C, 82.38; H, 5.62; N, 12.01. Found: C, 82.41; H, 5.65; N, 11.96%

4,4′-Dimethyl-2,2′-bithiazole[27]. M.p.: 136–137 °C, ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 2.50 (s, 6H), 6.95 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 17.1, 115.3, 154.0, 160.7.

4,4′,5,5′-Tetramethyl-2,2′-bithiazole[28]. M.p.: 174–175 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 2.36 (s, 6H), 2.38 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 11.5, 14.7, 128.1, 149.5, 157.0.

2,2′-Bibenzo[*d*]oxazole[29]. M.p.: 258–259 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.45–7.54 (m, 4H), 7.71 (d, $J = 8.8$ Hz, 2H), 7.92 (d, $J = 8.0$ Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 111.4, 121.4, 125.7, 127.4, 141.1, 150.9, 151.8.

5,5′-Dimethyl-2,2′-bibenzo[*d*]oxazole[30]. M.p.: 217–218 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 2.51 (s, 6H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.67 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 21.4, 110.7, 121.0, 128.6, 135.7, 141.3, 149.1, 151.9.

5,5′-Diphenyl-2,2′-bi(1,3,4-oxadiazole)[31]. M.p.: 269–270 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.57–7.66 (m, 6H), 8.24 (d, $J = 7.6$ Hz, 4H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 122.5, 127.7, 129.3, 132.9, 153.0, 166.3.

1-Benzyl-1′-methyl-1*H*,1′*H*-2,2′-bibenzo[*d*]imidazole. M.p.: 176-177 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 4.30 (s, 3H), 6.23 (s, 2H), 7.15–7.21 (m, 5H), 7.29–7.34 (m, 3H), 7.36–7.40 (m, 2H), 7.46 (d, $J = 8.0$ Hz, 1H). 7.82 (d, $J = 8.4$ Hz, 1H), 7.87–7.89 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 32.4, 48.7, 110.0, 110.9, 120.3, 120.4, 122.8, 122.9, 123.9, 124.1, 127.0, 127.4, 128.6, 135.6, 136.1, 137.0, 142.4, 142.7, 143.0, 143.1. Anal. Calc. for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56. Found: C, 78.03; H, 5.38; N, 16.64%

1-Benzyl-1′-phenyl-1*H*,1′*H*-2,2′-bibenzo[*d*]imidazole. M.p.: 186–187 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 6.02 (s, 2H), 7.04–7.06 (m, 2H), 7.16–7.20 (m, 5H), 7.21–7.26 (m, 2H), 7.28–7.36 (m, 3H), 7.38–7.41 (m, 4H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.92 (d, $J = 7.6$ Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 48.2, 110.5, 111.0, 120.4, 120.8, 122.6, 123.3, 123.9, 124.4, 126.9, 127.2, 127.6, 128.3, 128.6, 129.2, 135.3, 136.4, 136.5, 136.8, 142.5, 142.6, 142.7, 143.0. Anal. Calc. for $C_{27}H_{20}N_4$: C, 80.98; H, 5.03; N, 13.99. Found: C, 80.90; H, 5.15; N, 14.02%

2-(1-Benzyl-1*H*-imidazol-2-yl)-1-methyl-1*H*-benzo[*d*]imidazole. M.p.: 89–90 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): 4.17 (s, 3H), 5.93 (s, 2H), 7.04 (s, 1H), 7.19–7.35 (m, 8H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 7.2$ Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 32.1, 51.3, 109.7, 119.9, 122.4, 122.5, 123.2, 127.7, 127.8, 128.7, 128.9, 135.9, 137.2, 137.9, 142.4, 143.6. EI-MS: $m/z = 288$.

2-(1-Methyl-1*H*-imidazol-2-yl)benzo[*d*]oxazole. M.p.: 140–141 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): 4.23 (s, 3H), 7.12 (s, 1H), 7.26 (s, 1H), 7.35–7.40 (m, 2H), 7.61–7.63 (m, 1H), 7.75–7.77 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 35.6, 111.0, 120.0, 124.7, 125.2, 125.6, 130.1, 135.6, 141.5, 149.8, 154.8. EI-MS: $m/z = 199$.

2-(1-Benzyl-1*H*-imidazol-2-yl)-4,5-dimethylthiazole. M.p.: 91–92 °C, ^{1}H NMR (400 MHz, $CDCl_3$/TMS): 2.32 (s, 3H), 2.36 (s, 3H), 5.83 (s, 2H), 6.92 (s, 1H), 7.08 (s, 1H), 7.23 (d, $J = 7.6$ Hz, 2H), 7.26–7.32 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 11.1, 14.8, 50.7, 122.3, 127.1, 127.72, 127.73, 128.6, 129.2, 137.1, 140.7, 148.8, 154.8. EI-MS: $m/z = 269$.

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