Mono- and Biscouplings Using Triarylbismuths for the Atom-Efficient Arylations of Functionalized Furans under Palladium Catalysis

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Received: 03.04.2012; Accepted after revision: 05.06.2012

Abstract: Palladium-catalyzed cross-coupling reactions of functionalized bromofurans with triarylbismuths have been described for the atom-economic synthesis of functionalized arylfuran systems. The coupling reactions using triarylbismuths with various 2-bromofurans and 2,5-dibromofuran underwent smoothly to afford the corresponding 2-arylfurans and 2,5-diarylfurans in high yields in a short reaction time (one hour).

Key words: palladium, triarylbismuths, 2-bromofurans, cross-coupling, arylation

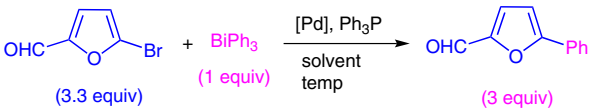
Heteroaromatic ring systems are important building blocks for various applications in organic synthesis.[1] Furan systems serve as useful synthons in various synthetic transformations to generate molecular complexity.[2] Substituted furans are also key intermediates in the synthesis of various pharmacologically important compounds for medicinal applications.[3] Furan skeletons in particular are also useful for molecular electronic applications.[4] Hence, the development of new synthetic methodologies for furan skeletons is of important concern.

Cross-coupling methodology is widely applied to enhance the molecular complexity in synthetic organic chemistry and this led to the development of various viable protocols to access challenging target structures.[5] Furthermore, arylfuran skeletons have been known for various medicinal applications. In this context, generation of arylfuran skeletons is synthetically important and can be accomplished through a cross-coupling methodology involving halofurans and organometallic reagents under metal-catalyzed conditions[6,7] in addition to other methods.[8] An alternative strategy also involves metal-catalyzed couplings of furanyl organometallics with aryl halides.[9–12] For example, the cross-couplings of 2-furanyl-boronic acids,[9] zinc,[10] or tin[11] reagents with aryl halides are reported for the synthesis of 2-arylfurans. The couplings of 2-furanyltellurides with aryltrifluroborates are also reported.[12] The corresponding biscouplings[13] with 2,5-bis(butyltellanyl)furan[13a] or 2,5-bis(tri-*n*-butylstannyl)furan[13b] with aryl halides is an extended strategy for an easy synthesis of 2,5-diarylfurans. Recently, the regioselective couplings involving furan systems have also been realized under metal-catalyzed conditions.[14]

We have demonstrated the couplings of aryl halides and triflates with triarylbismuths under palladium-catalyzed conditions.[15] The novel coupling ability of triarylbismuths with 2-bromothiophenes under palladium catalysis was also realized very recently.[16] These investigations revealed the high cross-coupling ability of triarylbismuths with three aryl groups in short reaction times with excellent product yields. This prompted us to expand the scope of triarylbismuths in couplings with halofurans under palladium-catalyzed conditions and herein we report this study as follows.

5-Bromofurfural is an important substrate for a variety of coupling reactions.[17] So, it was of interest to carry out the

Table 1 Screening Conditions[a–c]



Entry	Catalyst/ligand	Base (equiv)	Solvent	Time (h)	Yield (%)
1	$PdCl_2/2PPh_3$	Cs_2CO_3 (6)	DMA	2	62
2	$Pd(OAc)_2/4PPh_3$	K_3PO_4 (6)	DMF	1	64
3	$Pd(OAc)_2/4PPh_3$	K_3PO_4 (6)	NMP	1	71
4	$Pd(OAc)_2/4PPh_3$	Cs_2CO_3 (6)	NMP	1	87
5	$Pd(OAc)_2/4PPh_3$	Cs_2CO_3 (3)	NMP	1	89
6	$Pd(OAc)_2/4PPh_3$	Cs_2CO_3 (2)	NMP	1	62
7	$Pd(OAc)_2/4PPh_3$	Cs_2CO_3 (3)	DMF	1	62
8	$Pd(OAc)_2/4PPh_3$	Cs_2CO_3 (3)	DMA	1	65
9	$Pd(OAc)_2/4PPh_3$	Cs_2CO_3 (3)	NMP	1	05[d]
10	$Pd(OAc)_2/4PPh_3$	Cs_2CO_3 (3)	NMP	1	15[e]
11	$Pd(OAc)_2/4PPh_3$	no base	NMP	1	–
12	no catalyst	Cs_2CO_3 (3)	NMP	1	–

[a] Reaction conditions: Ph_3Bi (0.25 mmol, 1 equiv), bromide (0.825 mmol, 3.3 equiv), base, Pd catalyst (0.025 mmol, 0.1 equiv), Ph_3P (0.2 or 0.4 equiv), solvent (3 mL), 90 °C.
[b] Isolated yields were calculated considering three phenyl couplings from Ph_3Bi. Thus, 0.75 mmol of the product correspond to 100% yield.
[c] Homocoupled biphenyl formed in all the reactions in minor amounts.
[d] At 40 °C.
[e] At 60 °C.

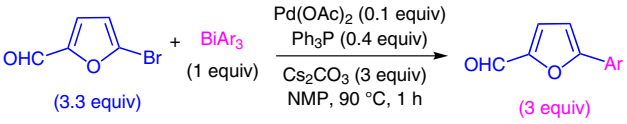
SYNLETT 2012, 23, 1907–1912
Advanced online publication: 23.07.2012
DOI: 10.1055/s-0032-1316567; Art ID: ST-2012-D0300-L

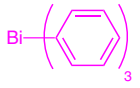
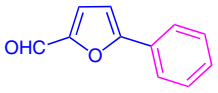
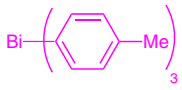
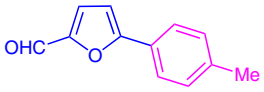
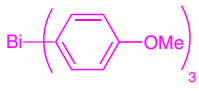
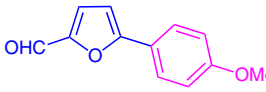
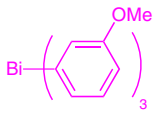
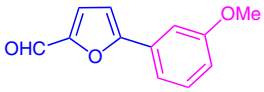
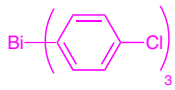
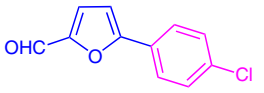
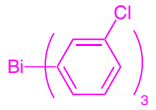
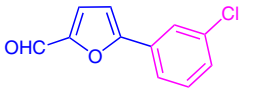
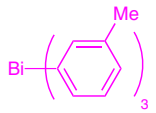
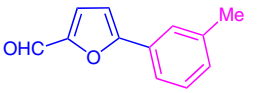
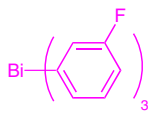
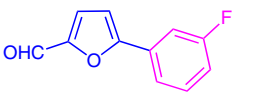
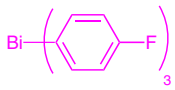
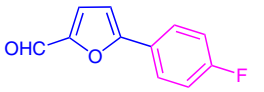
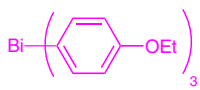
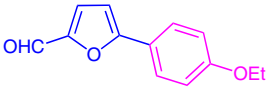
initial study with 5-bromofurfural in couplings with triarylbismuth reagents. In our earlier couplings with both aryl and thiophenes, the reactivity of routinely used palladium precursors such as $PdCl_2$ and $Pd(OAc)_2$ demonstrated excellent reactivity in the presence of Ph_3P ligand. This encouraged us to use this combination in furan couplings. The study was carried out with 3.3 equivalents of 5-bromofurfural with one equivalent of Ph_3Bi under different reaction conditions (Table 1). The study carried out with $PdCl_2$ and $Pd(OAc)_2$ provided the desired coupling between 62–64% isolated yields (Table 1, entries 1 and 2). Further study using $Pd(OAc)_2$ as a catalyst precursor and K_3PO_4 and Cs_2CO_3 bases revealed higher coupling ability in *N*-methylpyrrolidone (NMP) solvent with 71% and 87% yields, respectively (Table 1, entries 3 and 4). This led us to check the loadings of base amounts (Table 1, entries 5 and 6) and this indicated that three equivalents of Cs_2CO_3 is good enough to obtain a high cross-coupling yield up to 89%, while two equivalents of base afforded 62% yield. The coupling in *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide solvents furnished 62% and 65% yields, respectively (Table 1, entries 7 and 8). Investigations lowering the reaction temperature to 40 °C and 60 °C provided low yields (Table 1, entries 9 and 10). Expectedly, control reactions without base and catalyst–ligand combination did not furnish the coupling product (Table 1, entries 11 and 12). In these screenings, biphenyl as side product invariably formed from Ph_3Bi, which is a known process in the presence of palladium catalyst.[18] This investigation unequivocally revealed that $Pd(OAc)_2/Ph_3P$ in combination with Cs_2CO_3 (3 equiv) in NMP at 90 °C as a suitable combination to obtain high cross-coupling yield in one hour reaction time (Table 1, entry 5).

This prompted us to study the general coupling ability of different Ar_3Bi under the established conditions (Table 2).[19] The coupling reactions of 5-bromofurfural with different Ar_3Bi furnished 5-arylfurfural products in high yields. It is heartening to see that both electron-rich and electron-deficient triarylbismuths reacted very well in a facile manner delivering high product yields in short reaction time. In fact, this is not a common feature with other organometallic reagents in such couplings. In the literature, the reactivity of 5-bromofurfural under Suzuki coupling conditions was reported to require longer reaction times under different conditions even for one C–C coupling using aryl boronic acids or other reagents.[3c,7] On the other hand, the present three C–C couplings using triarylbismuths require only one hour reaction time to obtain high product yields and is noteworthy. In addition, the products 5-arylfurfurals obtained in these couplings are prominent substrates for the synthesis of Dantrolene analogues earlier studied as Ca^{2+} regulating agents.[3d] 5-Arylfurfurals have also been evaluated for the inhibition studies of severe acute respiratory syndrome (SARS).[3e] These compounds are also useful for the preparation of new gram-negative antibacterial drugs.[3f]

Further study was continued with substituted and unsubstituted furans with Ar_3Bi reagents under the established conditions (Table 3).[19] These reactions using unsubstitut-

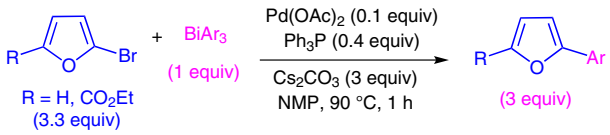
Table 2 Cross-Couplings with Different Ar_3Bi[a–d]

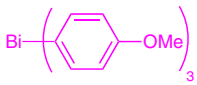
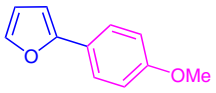
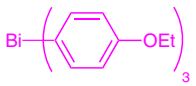
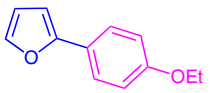
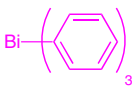
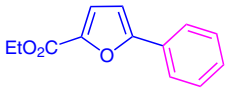
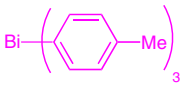
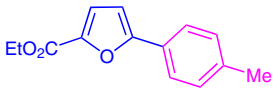
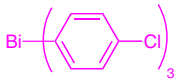
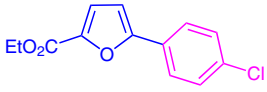
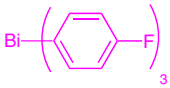
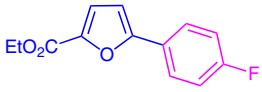
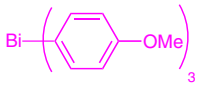
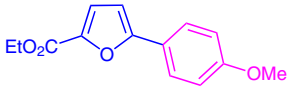
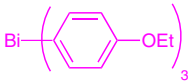
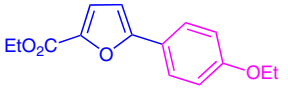


Entry	Ar_3Bi	5-Aryl-2-furfural	Yield (%)
1		 **2.1**	89
2.		 **2.2**	84
3		 **2.3**	87
4		 **2.4**	84
5		 **2.5**	88
6		 **2.6**	80
7		 **2.7**	84
8		 **2.8**	87
9		 **2.9**	85
10		 **2.10**	85

[a] Reaction conditions: Ar_3Bi (0.25 mmol, 1 equiv), bromide (0.825 mmol, 3.3 equiv), Cs_2CO_3 (0.75 mmol, 3 equiv), Pd $(OAc)_2$ (0.025 mmol, 0.1 equiv), Ph_3P (0.1 mmol, 0.4 equiv), NMP (3 mL), 90 °C, 1 h.
[b] Isolated yields were calculated considering three aryl couplings from Ar_3Bi. Thus, 0.75 mmol of the product correspond to 100% yield.
[c] Homocoupled biaryls were formed in minor amounts.
[d] All products were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy and ESI-HRMS spectrometry in comparison with literature data.

Table 3 Cross-Couplings with Different Furans[a–d]

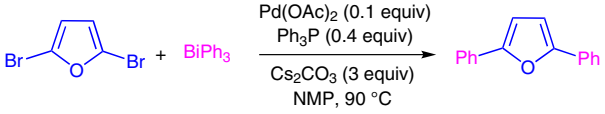


Entry	Ar_3Bi	2-Arylfuran/ethyl 5-aryl-2-furancarboxylate	Yield (%)
1		 **3.1**	92
2.		 **3.2**	91
3		 **3.3**	81
4		 **3.4**	89
5		 **3.5**	82
6		 **3.6**	80
7		 **3.7**	89
8		 **3.8**	87

[a] Reaction conditions: Ar_3Bi (0.25 mmol, 1 equiv), bromide (0.825 mmol, 3.3 equiv), Cs_2CO_3 (0.75 mmol, 3 equiv), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv), Ph_3P (0.1 mmol, 0.4 equiv), NMP (3 mL), 90 °C, 1 h.
[b] Isolated yields were calculated considering three aryl couplings from Ar_3Bi. Thus, 0.75 mmol of the product correspond to 100% yield.
[c] Homocoupled biaryls were formed in minor amounts as side products.
[d] All products were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy and ESI-HRMS spectrometry in comparison with literature data.

ed 2-bromofuran furnished 91–92% yields efficiently with Ar_3Bi reagents (Table 3, entries 1 and 2). Similarly, the couplings of ethyl 5-bromo-2-furancarboxylate also produced good to excellent yields of the corresponding cross-coupled products, ethyl 5-aryl-2-furancarboxylate with different Ar_3Bi reagents (Table 3, entries 3–8). In

Table 4 Screening with 2,5-Dibromofuran[a–c]



Entry	Ar_3Bi (equiv)	2,5-Dibromofuran (equiv)	Time (h)	Yield (%)
1	1.0	1.65	1	53
2	1.0	1.37	1	78
3	1.0	1.25	1	77
4	1.0	1.16	1	80
5	1.0	1.16	2	79

[a] Reaction conditions: Ph_3Bi (0.25mmol, 1 equiv,), 2,5-dibromofuran (1.16–1.65 equiv), Cs_2CO_3 (0.75 mmol, 3 equiv), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv), Ph_3P (0.1 mmol, 0.4 equiv), NMP (3 mL), 90 °C.
[b] Isolated yields were based on 2,5-dibromofuran. Thus, 1.16 equiv (0.29 mmol) of the product correspond to 100% yield.
[c] Isolated yields.

fact, these products are useful for the preparation of small-molecule antagonists useful for pharmacological applications.[3g]

This study with differently substituted furans overall demonstrated that a change in the electronics had no bearing on couplings with Ar_3Bi reagents.

2,5-Dibromofurans are important substrates to enhance the molecular complexity and are important synthons for the synthesis of molecular targets valuable for variety of applications.[20] Furthermore, bisarylations of 2,5-dibromofurans under metal-catalyzed conditions are also useful methodology for this purpose.[13]

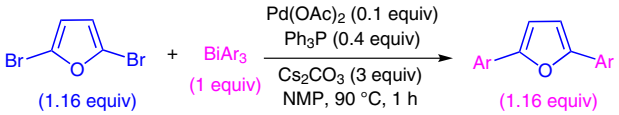
Hence, to demonstrate the scope of this study, coupling reactions were performed with 2,5-dibromofurans with Ar_3Bi reagents. Initial study under the established stoichiometric conditions provided 2,5-diphenylfuran in 53% yield (Table 4, entry 1). This was due to the formation of the homocoupling product from Ph_3Bi as a side product. In general, formation of the homocoupled product from triarylbismuths in the presence of palladium catalyst is a competitive reaction. This will be predominant or in minor amounts depending on the relative cross-coupling reactivity. So, further screening was carried out by changing the stoichiometric equivalents of coupling reagents to obtain the optimum conditions required (Table 4, entries 2–4). From this study, it was revealed that the biscoupling is effective within a range of 1.16–1.37 equivalents with only marginal change in overall yields. Notably, by increasing the reaction time to two hours, there was no further improvement in the biscoupling yield (Table 4, entry 5). Hence, it was decided to further elaborate this study using 1.16 equivalents of 2,5-dibromofuran with one equivalent of Ar_3Bi as a preferred combination.

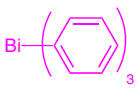
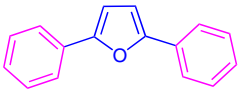
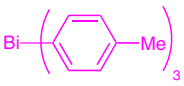
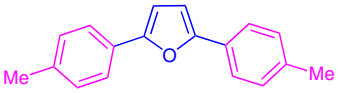
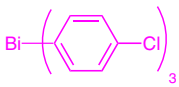
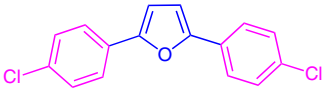
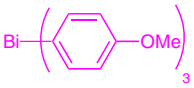
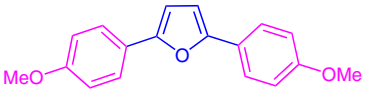
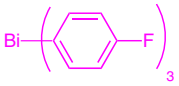
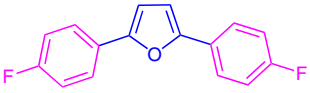
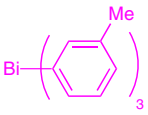
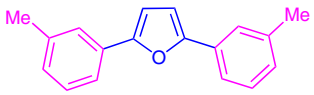
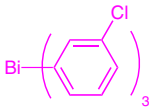
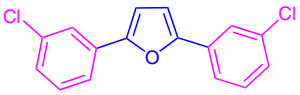
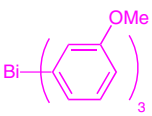
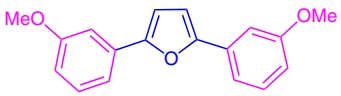
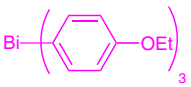
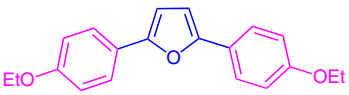
Hence, these conditions were applied to the coupling reaction of 2,5-dibromofuran with different Ar_3Bi reagents

(Table 5).[21] All the coupling reactions carried out with electronically different Ar_3Bi furnished 2,5-diarylfurans in 76–83% yields in short reaction time.

There are a few methods known for the synthesis of 2,5-diarylfurans by cross-coupling and by various other means, for example, the cross-coupling reaction of palladium-catalyzed cross-couplings of 2,5-bis(butyltellanyl)furan[13a] with aryltrifluoroborate salts or through Stille couplings involving 2,5-bis(tri-*n*-butylstannyl)furan[3b,13b] with aryl bromides. The cross-coupling reactions of 2-

Table 5 Biscouplings with Different Triarylbismuths[a–d]



Entry	Ar_3Bi	2,5-Diarylfuran	Yield (%)
1		 **5.1**	80
2.		 **5.2**	83
3		 **5.3**	79
4		 **5.4**	76
5		 **5.5**	80
6		 **5.6**	79
7		 **5.7**	77
8		 **5.8**	78
9.		 **5.9**	83

[a] Reaction conditions: 2,5-dibromofuran (0.29 mmol, 1.16 equiv), Ar_3Bi (0.25 mmol, 1 equiv), Cs_2CO_3 (0.75 mmol, 3 equiv), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv), Ph_3P (0.1 mmol. 0.4 equiv), NMP (3 mL), 90 °C, 1 h.
[b] Isolated yields were calculated considering 2,5-dibromofuran for coupling. Thus, 0.29 mmol of the product correspond to 100% yield.
[c] Homocoupled biaryls were formed in minor amounts as side products.
[d] All products were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy and ESI-HRMS spectrometry in comparison with literature data.

bromo-5-arylfurans with arylboronic acids under palladium catalysis also provide 2,5-diarylfurans.[22] Some of the other methods reported for the synthesis of 2,5-diarylfurans include (i) rhodium-catalyzed isomerization of protected 2-butyne-1,4-diols,[23] (ii) Au(I)-catalyzed hydration of 1,3-diynes,[24] (iii) Ru(II)- and Cu(II)-catalyzed sequential synthesis from alkynes,[25] (iv) Au(I)-catalyzed intramolecular cyclization of 3-alkyne-1,2-diols,[26] (v) Pt-catalyzed cyclization of propargylic oxiranes,[27] (vi) $ZnCl_2$-catalyzed cycloisomerization of alk-3-yn-1-ones,[28] (vii) Heck arylation–oxidation process catalyzed by Ru and Pd catalysts,[29] and (viii) transformation of 2-butene-1,4-diones catalyzed by Pd catalysts.[30]

Importantly, 2,5-dibromofuran couplings with organometallic reagents is a useful strategy for the synthesis of 2,5-diarylfurans, which are useful for photophysical applications,[20d] in the preparation of ligands that are useful for catalytic polymerization reactions,[20e] and also in medicinal applications.[31] Hence, despite the availability of many methods as described above, the cross-coupling reaction of 2,5-dibromofuran with organometallic reagents is still a favorite route for its simplicity and ease of preparation of starting materials and associated high coupling reactivity. It is a surprise to see that there are not many methods reported so far for this purpose. In that context, the present method involving cross-couplings of triarylbismuths with 2,5-dibromofuran under palladium-catalyzed conditions is high-yielding and involves three aryl couplings from Ar_3Bi in a one-pot operation and is hence atom-economic and requires only a short reaction time. Overall, this methodology is useful for the synthesis of substituted furans such as 2-arylfurans and 2,5-diarylfurans known to be useful for various medicinal applications.[31]

In conclusion, the efficient coupling reactions of triarylbismuths with various 2-bromofuran compounds and 2,5-dibromofuran have been demonstrated under palladium-catalyzed conditions in a short reaction time. This phenomenal reactivity of Ar_3Bi compounds as aryl coupling partners is expected to show high utility for applications in organic synthesis under metal-catalyzed conditions.

Acknowledgment

We acknowledge the financial support received from the Department of Science and Technology (DST), New Delhi under the Green Chemistry Program (SR/S5/GC-11/2008). D.K.A. and J.B.T. thank UGC, New Delhi for research fellowships.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **Representative Procedure for the Cross-Coupling Reaction of 5-Bromofurfural with Ph_3Bi**
The reaction was performed in a hot oven-dried Schlenk tube with the following reaction conditions: 5-bromofurfural (0.825 mmol, 144 mg, 3.3 equiv), Ph_3Bi (0.25 mmol, 110 mg, 1.0 equiv), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg, 0.1 equiv), Cs_2CO_3 (0.75 mmol, 244 mg, 3.0 equiv), Ph_3P (0.1 mmol, 26 mg, 0.4 equiv), dry NMP (3 mL), 90 °C, 1 h. After the reaction, it was worked up following the procedure given in ref. 16 to obtain the product **2.1**.[3d]
Analytical Data
Orange liquid (0.115 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.63 (1 H, s, CHO), 7.80–7.82 (m, 2 H, CH_{ar}), 7.30–7.44 (m, 4 H, CH_{ar}), 6.83 (d, 1 H, *J* = 3.7 Hz, CH_{ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.2, 159.4, 152.0, 129.7, 128.9, 125.3, 123.6, 107.7 ppm. IR (KBr): ν = 1671, 1435, 1210, 1040, 971, 933, 887, 784, 671 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{11}H_9O_2$ $[MH]^+$: 173.0603; found: 173.0606.
Analytical data of all the products with spectra for **2.1**–**2.10** and **3.1**–**3.8** are given in the Supporting Information.
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(21) Biscouplings of 2,5-dibromofuran were performed in a hot oven-dried Schlenk tube with the reaction conditions: 2,5-dibromofuran (0.29 mmol, 1.16 equiv), Ar_3Bi (0.25 mmol, 1 equiv), Cs_2CO_3 (0.75 mmol, 3 equiv), $Pd(OAc)_2$ (0.025 mmol, 0.1 equiv), Ph_3 P (0.1 mmol. 0.4 equiv), dry NMP (3 mL), 90 °C, 1 h. The workup procedure was followed as given in ref. 16 to obtain 2,5-diphenylfuran (**5.1**).[25]
Analytical Data
White solid (0.051 g, 80%), mp 67–69 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, 4 H, *J* = 8.3 Hz, CH_{ar}), 7.42 (t, 4 H, *J* = 7.8 Hz, CH_{ar}), 7.26–7.30 (m, 2 H, CH_{ar}), 6.75 (s, 2 H, CH_{ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.3, 130.8, 128.7, 127.3, 123.7, 107.2 ppm. IR (KBr): ν = 1597, 1473, 1020, 914, 796, 757, 686 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{16}H_{12}O$ $[M]^+$: 220.0888; found: 220.0885. Analytical data of all the products with spectra for **5.1**–**5.9** are given in the Supporting Information.
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