Synthesis of Functionalized 2-Arylthiophenes with Triarylbismuths as Atom-Efficient Multicoupling Organometallic Nucleophiles under Palladium Catalysis

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Dedicated to Professor Yashwant D. Vankar on the occasion of his 60th birthday

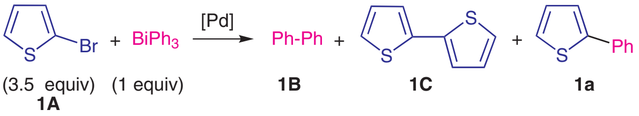
Abstract: Atom-efficient cross-coupling reactions of functionalized 2-bromo- and 2-iodothiophenes have been demonstrated using triarylbismuths as atom-efficient multicoupling organometallic nucleophiles under palladium-catalyzed conditions. These couplings with various functionalized triarylbismuths proceeded smoothly to afford the corresponding functionalized 2-arylthiophenes in high yields.

Key words: 2-halothiophenes, cross-coupling, palladium catalysis, triarylbismuths, atom-efficient, multicoupling

Utilization of organometallic reagents for C–C bond formation is in high demand for applications in synthetic organic chemistry.[1] Synthesis of various multifunctional heteroaryl[2] systems is of a special interest due to their potential applications in materials,[3] and medicinal chemistry.[4] Various functionalized aryl-substituted thiophenes have been known to have a variety of applications in pharmacology,[5] and in display and sensor technologies.[3] A popular method of synthesis of these compounds is through cross-coupling reactions as these methods provide the desired flexibility[6,7] and site selectivity.[8]

Recently, we have demonstrated the novel coupling reactivity of triarylbismuths[9] as atom-efficient multicoupling organometallic nucleophiles with different organic electrophiles.[10] In these reactions, triarylbismuths have been cross-coupled with three equivalents of organic electrophiles.[9] The nontoxic nature of bismuth compounds,[11] makes these reactions highly desirable as green reagents in organic synthesis.[12] The coupling study of triarylbismuths with heteroaryl substrates as electrophilic coupling partners has not been greatly explored hitherto. Langer et al. reported efficient coupling of tri- and tetrabromothiophenes with organometallic reagents involving site-selective couplings.[8] In this context, we wish to disclose an atom-efficient cross-coupling of triarylbismuths with functionalized 2-bromo- and 2-iodothiophenes for the novel synthesis of functionalized 2-arylthiophenes under palladium-catalyzed conditions.

Table 1 Screening Conditions[a–c]



Entry	Catalyst/ligand	1A	1B	1C	1a
1	$PdCl_2(PPh_3)_2$	7	23	20	50 (40)
2	$Pd_2(dba)_3$	80	18	–	2
3	$Pd_2(dba)_3$–PPh_3	2	28	20	48 (42)
4	$Pd(PPh_3)_4$	10	27	13	49 (40)
5	$PdCl_2(MeCN)_2$	75	22	–	2
6	$PdCl_2(PhCN)_2$	80	17	–	2
7	$Pd(OAc)_2$–PPh_3	2	12	5	78 (81)
8	$Pd(OAc)_2$–PPh_3	56	23	4	15[d]
9	$Pd(OAc)_2$–PPh_3	49	21	2	19[e]
10	$Pd(OAc)_2$–PPh_3	13	32	12	42 (40)[f]
11	$Pd(OAc)_2$–PPh_3	13	28	8	50 (48)[g]
12	$Pd(OAc)_2$–PPh_3	32	36	2	27[h]
13	$Pd(OAc)_2$	60	24	–	2
14	PPh_3	90	–	–	–

[a] Reaction conditions: $BiPh_3$ (1 equiv), 2-bromothiophene (3.5 equiv), Pd catalyst (0.1 equiv), ligand (0.4 equiv), K_3PO_4 (6 equiv), DMF (3 mL), 90 °C, 1 h.
[b] Conversions are based on GC analysis.
[c] Isolated yields are given in parenthesis.
[d] At 40 °C.
[e] At 60 °C.
[f] With K_3PO_4 (2 equiv).
[g] With K_3PO_4 (4 equiv).
[h] Without base.

To understand the coupling efficacy of halothiophenes with triarylbismuth reagents, a systematic screening was carried out (Table 1). The coupling of 2-bromothiophene, **1A** (3.5 equiv) with triphenylbismuth (1 equiv) provided varied reactivity using different palladium precursors in *N*,*N*-dimethylformamide with K_3PO_4 base (Table 1, en-

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tries 1–7). In general, three equivalents of 2-bromothiophene are sufficient to couple with three phenyl groups from one equivalent of triphenylbismuth reagent. However, we have employed 3.5 equivalents of bromide with the excess to facilitate cross-coupling over the homocoupling from triphenylbismuth in the presence of palladium catalyst.[13]

Under the conditions studied, the best cross-coupling was obtained with $Pd(OAc)_2$ catalyst. Other catalytic combinations, such as $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$–2 PPh_3 and $Pd(PPh_3)_4$ provided moderate conversions, while $Pd_2(dba)_3$, $PdCl_2(MeCN)_2$ and $PdCl_2(PhCN)_2$ gave poor cross-coupling efficiency. Additional screening was carried out by varying the temperature, when coupling reactions at 40 °C and 60 °C proved to be less efficient with lower yields (Table 1, entries 8 and 9). Further trials with two and four equivalents of base proved to be less effective (Table 1, entries 10 and 11). Other reactions carried out in the absence of base, ligand and catalyst each provided poor or no cross-coupling product (Table 1, entries 12–14). Minor amounts of both homocoupled biphenyl (**1B**)[13] from triphenylbismuth, and 2,2′-bisthiophene (**1C**)[6c] from 2-bromothiophene were seen, along with unreacted 2-bromothiophene in these screenings. In the presence of high cross-coupling, formation of side products was minimized. In summary, the efficient cross-coupling of 2-bromothiophene with triphenylbismuth was established to afford 2-phenylthiophene in high yield (Table 1, entry 7). From this, the coupling reactivity of triarylbismuth was found to be notable in comparison with the known literature methods with other organometallic reagents in similar couplings.[6]

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

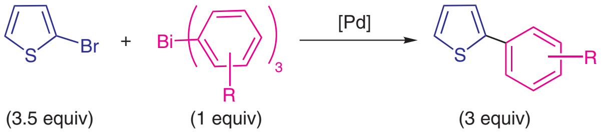
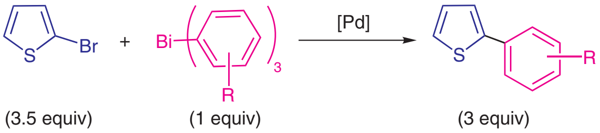
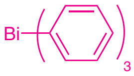
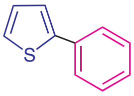
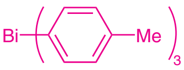
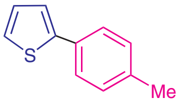
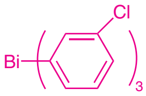
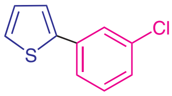
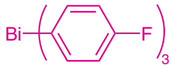
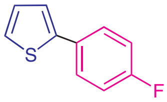
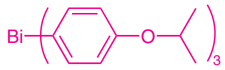
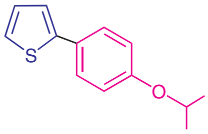
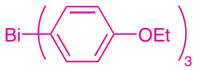
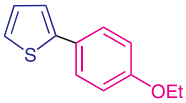
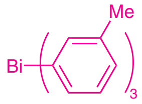
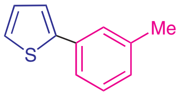
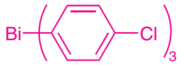
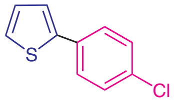
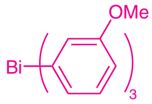
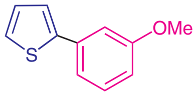
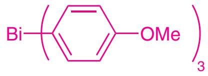
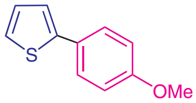


Table 2 Cross-Couplings with Different Triarylbismuths[a–d] (continued)



Entry	Triarylbismuth	2-Arylthiophene	Yield (%)
1		 **1a**	81
2		 **2a**	88
3		 **3a**	71
4		 **4a**	72
5		 **5a**	83
6		 **6a**	85
7		 **7a**	85
8		 **8a**	70
9		 **9a**	71
10		 **10a**	92

[a] Reaction conditions: $BiAr_3$ (1 equiv, 0.25 mmol), 2-bromothiophene (3.5 equiv, 0.875 mmol), $Pd(OAc)_2$ (0.1 equiv, 0.025 mmol), Ph_3P (0.4 equiv, 0.1 mmol), K_3PO_4 (6 equiv, 1.5 mmol), DMF (3 mL), 90 °C, 1 h.

[b] Isolated yields based on three aryl coupling from triarylbismuth. Thus, 3 equiv of cross-coupling product (0.75 mmol) corresponds to 100% yield.

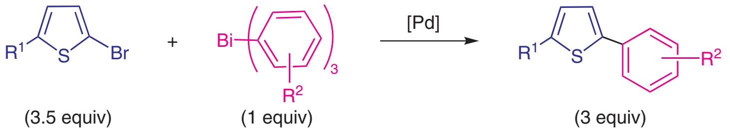
[c] All the products were characterized spectroscopically.

[d] In general, minor amounts of biaryl and 2,2′-bisthiophene were formed.

The above investigation prompted us to extend the study of 2-bromothiophene with electronically divergent triarylbismuths as summarized in Table 2.[14] The general coupling reactivity of various triarylbismuths with 2-bromothiophene was found to be facile, furnishing the corresponding functionalized 2-arylthiophenes in high yields (Table 2, entries 1–10). Participation of both electron-rich and electron-deficient triarylbismuths with comparable coupling reactivity is noteworthy in these conversions. This observed reactivity is more facile in comparison with similar couplings with arylboronic acids under Suzuki-coupling conditions. The couplings with arylboronic acids have been reported to involve longer reaction times even for one C–C bond formation.[2c,d] Thus, the present method using triarylbismuths as multicoupling nucleophiles is advantageous.

To elaborate the scope of this process further, arylation of functionalized 5-acetyl-2-bromothiophene was carried out under the optimized conditions. As summarized in Table 3,[14] arylations of 5-acetyl-2-bromothiophene with different triarylbismuths afforded functionalized 5-acetyl-2-arylthiophenes smoothly (Table 3, entries 1–11). The coupling reactivity with electronically divergent triarylbismuths has proved to be promising with good to high yields of products. It is important to note that these products are useful synthons for the preparation of trimerized polyaromatic compounds.[6a] Furthermore, 5-acetyl-2-arylthiophenes are also useful in the synthesis of nanosized molecular network systems.[6a,b] In addition, these products are also used in the synthesis of 5-aryl-5′-formyl-2,2′-bithiophenes used in photophysical applications.[15]

Table 3 Cross–Couplings of Functionalized 2-Bromothiophenes with Different Triarylbismuths[a–d]



R^1 = Ac, COPh, CHO

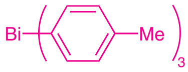
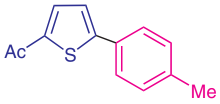
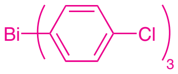
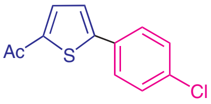
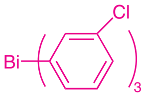
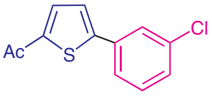
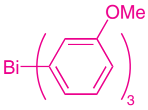
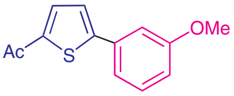
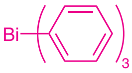
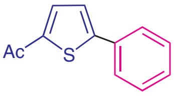
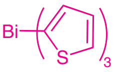
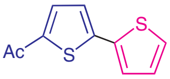
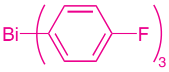
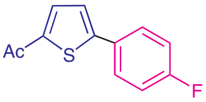
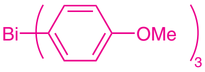
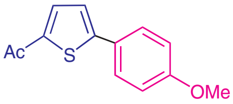
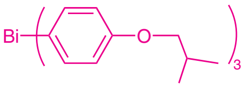
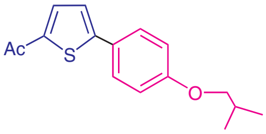
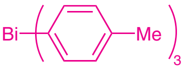
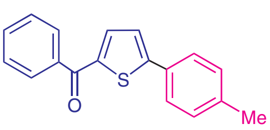
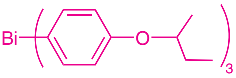
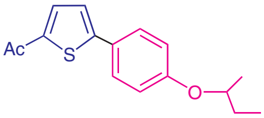
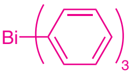
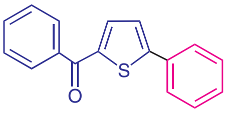
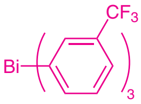
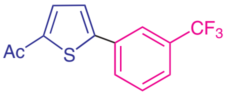
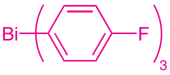
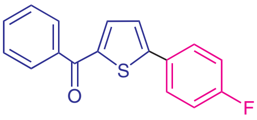
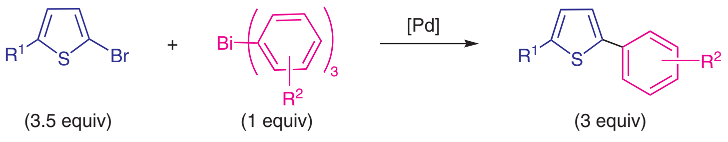
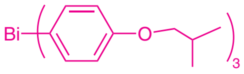
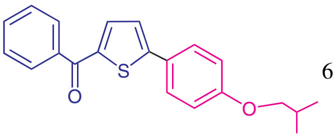
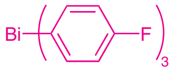
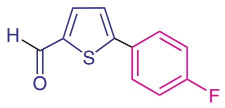
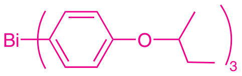
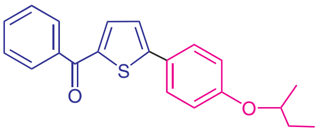
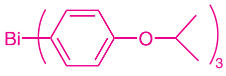
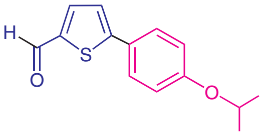
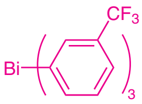
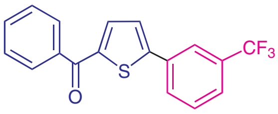
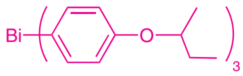
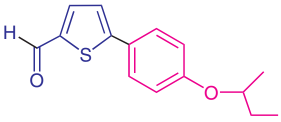
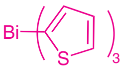
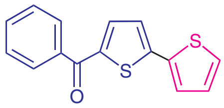
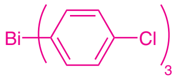
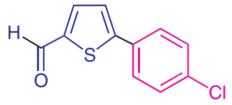
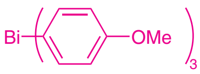
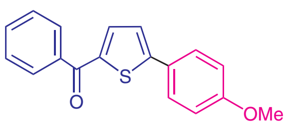
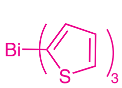
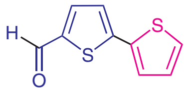
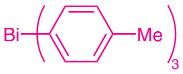
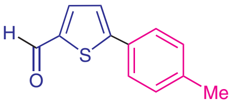
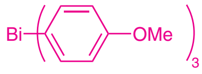
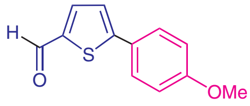
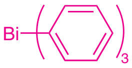
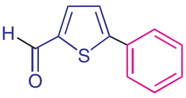
Entry	Triarylbismuth	2-Arylthiophene	Yield (%)	Entry	Triarylbismuth	2-Arylthiophene	Yield (%)
1		 **11a**	86	8		 **18a**	67
2		 **12a**	65	9		 **19a**	64
3		 **13a**	90	10		 **20a**	49
4		 **14a**	71	11		 **21a**	92
5		 **15a**	66	12		 **22a**	94
6		 **16a**	64	13		 **23a**	88
7		 **17a**	48	14		 **24a**	86

Table 3 Cross–Couplings of Functionalized 2-Bromothiophenes with Different Triarylbismuths[a–d] (continued)



R^1 = Ac, COPh, CHO

Entry	Triarylbismuth	2-Arylthiophene	Yield (%)	Entry	Triarylbismuth	2-Arylthiophene	Yield (%)
15		 **25a**	66	22		 **32a**	77
16		 **26a**	85	23		 **33a**	81
17		 **27a**	61	24		 **34a**	74
18		 **28a**	75	25		 **35a**	56
19		 **29a**	85	26		 **36a**	71
20		 **30a**	60	27		 **37a**	83
21		 **31a**	56				

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[a] Reaction conditions: $BiAr_3$ (1 equiv, 0.25 mmol), 2-bromothiophene (3.5 equiv, 0.875 mmol), $Pd(OAc)_2$ (0.1 equiv, 0.025 mmol), Ph_3P (0.4 equiv, 0.1 mmol), K_3PO_4 (6 equiv, 1.5 mmol), DMF (3 mL), 90 °C, 1 h.

[b] Isolated yields based on three aryl coupling from triarylbismuth. Thus, 3 equiv of cross-coupling product (0.75 mmol) corresponds to 100% yield.

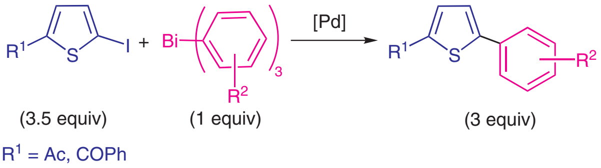
[c] All the product were characterized by spectroscopic studies.

[d] In general, minor amounts of biaryl and 2,2′-bisthiophene were formed.

Further studies were carried out with 5-benzoyl-2-bromothiophene as the organic electrophilic coupling partner with different triarylbismuth nucleophiles (Table 3, entries 12–19).[14] These reactions afforded efficient cross-coupling with high yields in short reaction time. The 2-benzoyl-5-arylthiophene products obtained in these couplings are useful in materials applications[3g] and are valuable molecular motifs for various biological and medicinal applications.[16] Further couplings of 5-bromo-2-thienylaldehyde were carried out with different triarylbismuth reagents (Table 3, entries 20–25, entry 27).[14] This study allowed the successful arylations with various triarylbismuths furnishing the chemoselective formation of 5-aryl-2-thienylaldehydes in good yields. Importantly, these products are important precursors for the preparation of compounds useful for medicinal[6e] and photophysical applications.[3f,6f] A coupling study using tris-2-thienylbismuth also furnished the corresponding 2,2′-bisthiophene, albeit in moderate yield (Table 3, entry 26).

At this stage, it was of interest to explore the corresponding couplings with 2-iodothiophene compounds.[17] This study has been carried out with different 2-iodothiophenes and the results are summarized in Table 4.[14] The coupling reactions of 5-acetyl- and 5-benzoyl-derived 2-iodothiophenes with different triarylbismuths gave the corresponding coupling products in high yields (Table 4, entries 1–10). The substituted 2-iodothiophenes demonstrated excellent reactivity with triarylbismuth nucleophiles in short reaction time under these coupling conditions.

Table 4 Cross-Couplings of 5-Acetyl- and 5-Benzoyl-2-iodothiophene with Different Triarylbismuths[a–d]



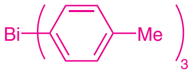
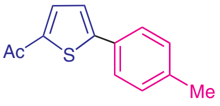
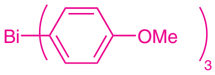
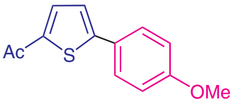
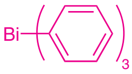
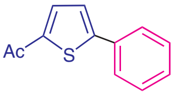
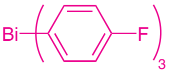
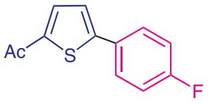
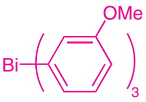
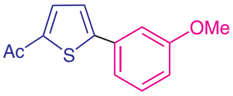
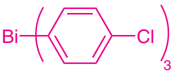
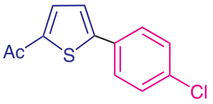
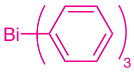
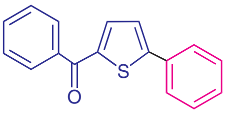
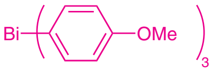
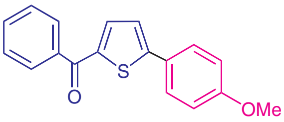
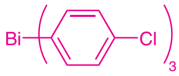
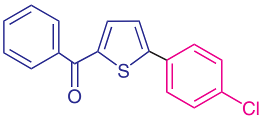
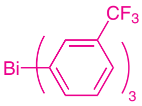
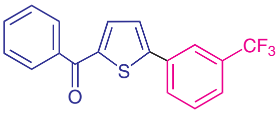
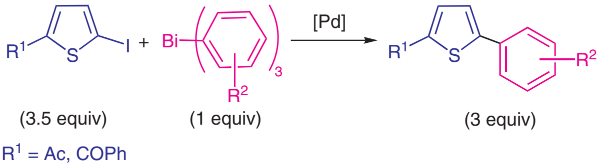
Entry	Triarylbismuth	2-Arylthiophene	Yield (%)
1		 **11a**	93
2		 **21a**	92
3		 **13a**	81
4		 **14a**	66
5		 **19a**	69
6		 **18a**	71
7		 **23a**	87
8		 **29a**	80
9		 **38a**	82
10		 **27a**	52

Table 4 Cross-Couplings of 5-Acetyl- and 5-Benzoyl-2-iodothiophene with Different Triarylbismuths[a–d] (continued)



[a] Reaction conditions: BiAr$_3$ (1 equiv, 0.25 mmol), 2-iodothiophene (3.5 equiv, 0.875 mmol), Pd(OAc)$_2$ (0.1 equiv, 0.025 mmol), Ph$_3$P (0.4 equiv, 0.1 mmol), K$_3$PO$_4$ (6 equiv, 1.5 mmol), DMF (3 mL), 90 °C, 1 h.

[b] Isolated yields based on three aryl coupling from triarylbismuth. Thus, 3 equiv of cross-coupling product (0.75 mmol) corresponds to 100% yield.

[c] All the products were characterized by spectroscopic studies.

[d] In general, minor amounts of biaryl and 2,2′-bisthiophene were formed.

Overall, the efficient coupling reactivity of triarylbismuths has been demonstrated with functionalized 2-bromothiophenes and 2-iodothiophenes under the optimized palladium-catalyzed conditions. The multicoupling and the atom-efficient reactivity of triarylbismuths has been established in couplings with three equivalents of both 2-bromo- and 2-iodothiophene derivatives. It is noteworthy that these couplings from triarylbismuths were effected within one hour reaction time affording three equivalents of coupling products This high reactivity of triarylbismuths is in sharp contrast to the corresponding reactivity known with other organometallic reagents which involves long reaction times even for a single C–C coupling under heating.[6] Thus, triarylbismuths serve as atom-efficient multicoupling organometallic nucleophiles for the arylations of various 2-bromo- and 2-iodothiophenes under palladium-catalyzed conditions.

In conclusion, an efficient cross-coupling study of triarylbismuths as multicoupling organometallic nucleophiles has been conducted with various functionalized 2-bromo- and 2-iodothiophenes under palladium-catalyzed conditions.

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

Acknowledgment

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References and Notes

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(14) **Representative Procedure**: An oven-dried Schlenk tube under a nitrogen atmosphere was charged with 2-bromothiophene (0.875 mmol, 3.5 equiv, 0.143 g) followed by BiPh$_3$ (0.25 mmol, 1 equiv, 0.110 g), K$_3$PO$_4$ (1.5 mmol, 6 equiv, 0.318 g), Ph$_3$P (0.10 mmol, 0.4 equiv, 0.026 g), Pd(OAc)$_2$ (0.025 mmol, 0.1 equiv, 0.0056 g) and anhyd

DMF (3 mL). The reaction mixture was stirred in an oil-bath at 90 °C for 1 h. The contents were cooled to r.t., quenched with H_2O (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with H_2O, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography using 100–200 silica gel and petroleum ether as eluent to obtain 2-phenylthiophene as a white, low melting solid (0.097 g, 81%; isolated yield based on three aryl coupling from triphenylbismuth).

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