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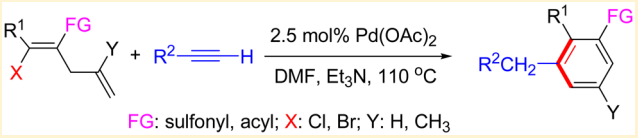
Construction of Substituted Benzenes via Pd-Catalyzed Cross-Coupling/Cyclization Reaction of Vinyl Halides and Terminal Alkynes

Meihua Xie,* Shengke Wang, Jun Wang, Kuang Fang, Changqing Liu, Chao Zha, and Jing Jia

Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, China

Supporting Information

ABSTRACT: A tandem Sonogashira coupling/cyclization/aromatization sequence of β-halo vinyl sulfones/ketones with terminal alkynes has been developed for the construction of benzene rings. Polysubstituted functionalized benzenes containing a sulfonyl or an acyl group could be obtained in up to 95% yield.



INTRODUCTION

Substituted benzenes are the core structural units of many functional materials and natural products and/or synthetic compounds displaying significant biological and pharmaceutical activities.[1] They are also valuable synthetic building blocks in organic chemistry.[2] For example, sulfonyl-substituted benzenes exhibit inhibitory activities against various enzymes such as sodium proton exchanger 1, cyclooxygenase-2 (COX-2), and HIV-1 reverse transcriptase and are valuable synthetic targets due to their versatile reactivity and coordinating properties (Figure 1).[3]

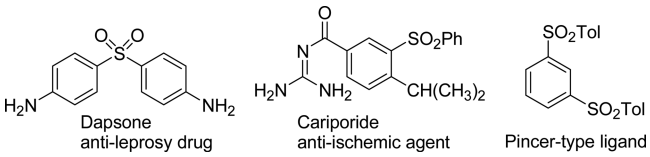


Figure 1. Examples of substituted benzenes.

Traditionally, polysubstituted benzenes are prepared by stepwise introduction of functional groups into simple benzenoid systems through various functionalization reactions.[4] Transition-metal-catalyzed tandem cyclization reactions are particularly attractive in that they enable facile access to substituted benzenes from simple acyclic precursors and thus have received extensive research efforts.[5] Despite the great progress achieved in this field, most reported methods, more or less, suffer from several drawbacks such as poor regioselectivity, multistep manipulations, and unsatisfactory yields, which may limit their practical applications. Therefore, the development of new, simple, and efficient methods for constructing multisubstituted benzenes in a regioselective way is still highly desirable and remains a quite challenging task.[6]

Vinyl halides are versatile building blocks in organic synthesis with numerous applications in transition-metal-catalyzed cross-coupling reactions, such as palladium-catalyzed Sonogashira, Stille, and Suzuki coupling reactions.[7] However, to the best of our knowledge, the construction of substituted benzene rings via intermolecular reaction of haloalkenes and alkynes is rare.[8] On the other hand, tandem reactions, in which multistep transformations are combined into one synthetic operation, have received much attention for their efficiency and environmental benignity in the construction of complex molecular skeletons.[9] Recently, we reported a method for the synthesis of β-halo vinyl sulfones/ketones by haloallylation of alkynes.[10] In order to investigate the potential of the resulting products in organic synthesis, we studied the Pd-catalyzed reaction of β-halo vinyl sulfones/ketones and terminal alkynes. Interestingly, we observed the formation of polysubstituted benzenes via a tandem Sonogashira coupling/cyclization/aromatization sequence instead of the expected simple Sonogashira coupling products. Herein, we report the details of this finding.

RESULTS AND DISCUSSION

The reaction of (*E*)-1-chloro-1-phenyl-2-(*p*-tolylsulfonyl)penta-1,4-diene (**1a**) with phenylacetylene (**2a**) was chosen as the model reaction for initial studies. The results are summarized in Table 1. First, the reaction was performed under standard Sonogashira reaction conditions, that is, treating **1a** with 1.6 equiv of phenylacetylene in the presence of 2.5 mol % of $Pd(PPh_3)_2Cl_2$, 2.5 mol % of CuI, and 1 mL of Et_3N in 2 mL of THF, with the expectation to obtain a Sonogashira coupling product. Unexpectedly, 2-benzyl-6-(*p*-tolylsulfonyl)biphenyl (**3a**) was isolated instead in 30% yield with the recovery of **1a** in 63% yield when the reaction mixture was stirred at 65 °C for 18 h (Table 1, entry 1). This interesting result prompted us to do further investigation on the formation of **3a**. As shown in Table 1, among the tested solvents such as THF, toluene, DMSO, and DMF, DMF was the best choice (Table 1, entries 1−4), with which the reaction proceeded to completion within 1 h to give product **3a** in 84% yield (Table 1, entry 4). The use

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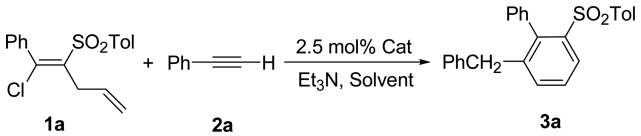
Table 1. Optimization of the Reaction Conditions for the Palladium-Catalyzed Reaction of β-Chloro Vinyl Sulfones (1a) with Phenylacetylene (2a)[a]



entry	solvent	catalyst	T (°C)	time (h)	yield (%)[b]
1	THF	$Pd(PPh_3)_2Cl_2$/CuI	65	18	30
2	toluene	$Pd(PPh_3)_2Cl_2$/CuI	110	18	35
3	DMSO	$Pd(PPh_3)_2Cl_2$/CuI	110	1	81
4	DMF	$Pd(PPh_3)_2Cl_2$/CuI	110	1	84
5	DMF	$Pd(OAc)_2$/CuI	110	1	91
6	DMF	$Pd(OAc)_2$	110	0.3	90
7	DMF	$Pd(PhCN)_2Cl_2$	110	3	76
8	DMF	$PdCl_2$	110	3	78
9	DMF	$Ni(PPh_3)_2Cl_2$	110	12	0
10	DMF	$Pd(OAc)_2$	90	2	50
11[c]	DMF	$Pd(OAc)_2$	110	1	0
12[d]	DMF	$Pd(OAc)_2$	110	0.3	91
13[e]	DMF	$Pd(OAc)_2$	110	1	85

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.8 mmol) catalyzed by 2.5 mol % of catalyst in 3 mL of a mixture of Et_3N/solvent (v/v 1/2) under argon atmosphere. [b]Isolated yield. [c]No Et_3N was added. [d]With 5 mol % of catalyst. [e]With 1 mol % of catalyst.

of $Pd(OAc)_2$ as catalyst improved the yield further to 90% even in the absence of the cocatalyst CuI (Table 1, entries 5 and 6). While the use of $Pd(PhCN)_2Cl_2$ and $PdCl_2$ as catalyst resulted in decreased yields (Table 1, entries 7 and 8), $Ni(PPh_3)_2Cl_2$ showed no catalytic activity for the reaction (Table 1, entry 9). When the reaction temperature was decreased to 90 °C, the yield of **3a** dramatically decreased to 50% (Table 1, entry 10). It was observed that Et_3N was necessary for this reaction to work (Table 1, entry 11). Increasing the catalyst loading amount to 5 mol % failed to improve the yield, while reducing it to 1 mol % led to a lower yield (Table 1, entries 12 and 13). Thus, $Pd(OAc)_2$ (2.5 mol %) and 1 mL of Et_3N in 2 mL of DMF at 110 °C were defined as the optimal reaction conditions for the scope study.

Under the optimized reaction conditions, the reaction of differently substituted β-halo vinyl sulfones and terminal alkynes was investigated for the construction of substituted benzene rings. The reactions worked well with differently substituted β-chloro vinyl sulfones **1**, and R^1 can be phenyl, *p*-tolyl, or *p*-fluorophenyl groups. Terminal alkynes **2** can be aromatic or alkyl alkynes, and R^2 can be phenyl, *p*-tolyl, *p*-fluorophenyl, *n*-pentyl, cyclopropyl, or *tert*-butyl. Products **3** were obtained in yields of 78−95%. It should be pointed out that in the case of R^1 being an alkyl group, such as *n*-pentyl or cyclopropyl, the use of β-bromo vinyl sulfone is necessary to give moderate yields (Table 2, entries 14 and 15). Notably, substituted benzenes containing a long-chain alkyl group (such as *n*-hexyl or *n*-pentyl) at different positions (Table 2, entries 4 and 14) and a tetrasubstituted benzene (Table 2, entry 7) could all be obtained in good yields by this method. The structure of compound **3a** was confirmed by X-ray crystallographic analysis (see Supporting Information).

However, when the reaction was extended to β-chloro vinyl ketones, no reaction occurred and β-chloro vinyl ketones were recovered completely. The result was assumed to be due to the lower reactivity of β-chloro vinyl ketones for the Sonogashira coupling step. Gratifyingly, acyl-substituted polysubstituted benzenes were obtained in moderate to good yields when the more reactive β-bromo vinyl ketones **4** were subjected to the reaction with terminal alkynes under the otherwise similar reaction conditions. The results are summarized in Table 3. The reaction showed a good scope for different vinyl ketones **4** with exclusive regioselectivity, in which the R^1 substituent can be a phenyl or *p*-tolyl group, and the R^2 can be a *p*-tolyl, *n*-propyl, *p*-chlorophenyl, or *p*-nitrophenyl group. Terminal alkynes were well-tolerated in the reaction, and the R^3 group can be a phenyl, *p*-tolyl, *p*-fluorophenyl, or cyclopropyl group. However, when R^1 is an *n*-pentyl group, an unidentifiable complex mixture was obtained.

To investigate the reaction mechanism, some control experiments were conducted (Scheme 1). When the reaction of **1a** with phenylacetylene **2a** under the optimized conditions was quenched after 2 min, the Sonogashira coupling product **6a** was obtained in 56% yield along with the formation of **3a** in 28% yield (Scheme 1, eq 1). Subsequent treatment of **6a** in Et_3N/DMF in the presence of 2.5 mol % of $Pd(OAc)_2$ at 110 °C afforded the cyclization product **3a** in 95% yield (Scheme 1, eq 2), supporting the role of **6a** as an intermediate in the tandem reaction. Notably, the cyclization of the isolated **6a** also took place in the absence of the Pd catalyst, but the reaction proceeded much slower to provide 63% yield of **3a** after 24 h (Scheme 1, eq 2), suggesting that the presence of the Pd catalyst facilitated the cyclization step.

On the basis of these experimental results, a mechanism for the cyclization step was proposed as shown in Scheme 2. First, [1,5]-H migration of the Sonogashira coupling product **6** afforded the intermediate ***Int*-1**, which was followed by 6π-electrocyclization to generate the intermediate ***Int*-2**. It is assumed that $Pd(OAc)_2$ might act as a Lewis acid to promote this electrocyclization process.[11] Finally, aromatization of the intermediate ***Int*-2** via [1,7]-H migration afforded product **3**.

CONCLUSION

In summary, we have developed a one-pot tandem reaction for the construction of polysubstituted benzenes from an intermolecular reaction of vinyl chlorides/bromides and terminal alkynes, involving a sequential Sonogashira coupling, cyclization, and aromatization reaction. The resulting polysubstituted benzenes containing versatile sulfonyl or carbonyl functionality would be highly useful intermediates for organic synthesis.

EXPERIMENTAL SECTION

Synthesis of Polysubstituted Benzenes by Palladium-Catalyzed Tandem Reaction of Vinyl Halides with Terminal Alkynes: A Representative Procedure. A Schlenk flask equipped with a condenser was charged with 0.5 mmol (166 mg) of (*E*)-1-chloro-1-phenyl-2-(*p*-tolylsulfonyl)penta-1,4-diene (**1a**), 0.8 mmol (0.09 mL) of phenylacetylene (**2a**), 0.013 mmol (2.9 mg) of $Pd(OAc)_2$, and 3 mL of Et_3N/DMF (v/v 1/2) under argon atmosphere. The reaction mixture was stirred at 110 °C for 0.3 h (monitored by TLC until the full consumption of **1a**). The reaction was then quenched with saturated NaCl and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether = 1/20) to give product **3a**.

*2-Benzyl-6-(4-tolylsulfonyl)biphenyl (**3a**):* White solid; mp 133−134 °C; yield 91% (181 mg); ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.35

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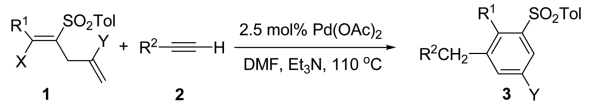
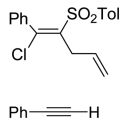
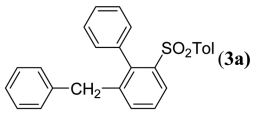
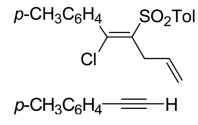
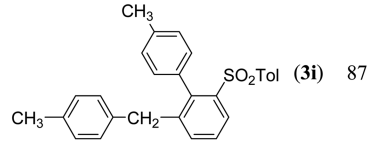
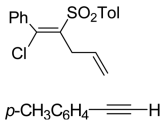
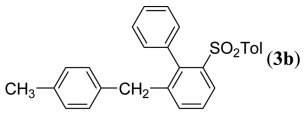
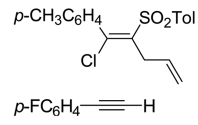
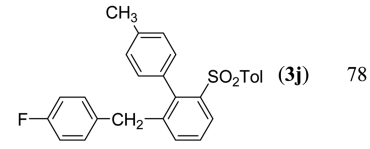
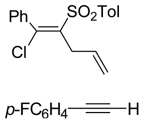
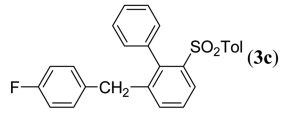
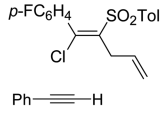
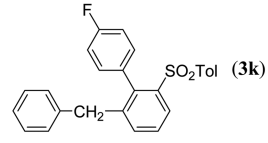
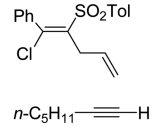
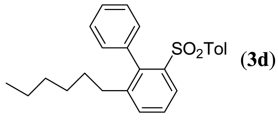
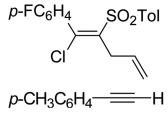
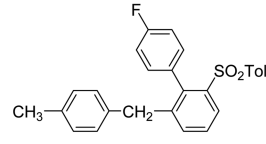
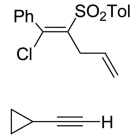
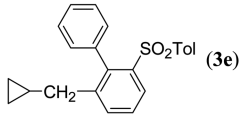
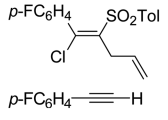
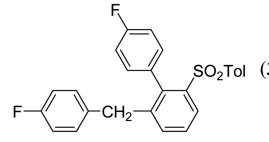
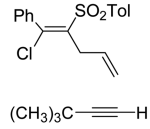
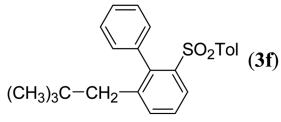
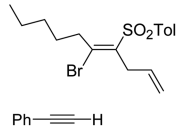
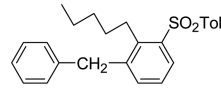
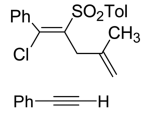
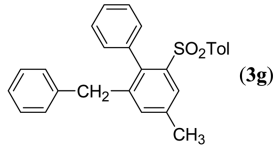
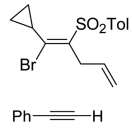
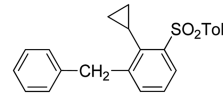
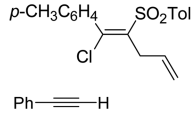
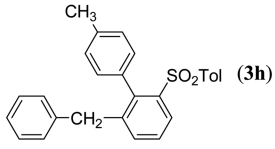
Table 2. Synthesis of Sulfonyl-Substituted Benzenes 3 from β-Halo Vinyl Sulfones 1 and Terminal Alkynes 2[a]



Entry	Vinyl sulfone **1** terminal alkyne **2**	Product **3**	Yield (%)[b]	Entry	Vinyl sulfone **1** terminal alkyne **2**	Product **3**	Yield (%)[b]
1		 **(3a)**	91	9		 **(3i)**	87
2		 **(3b)**	95	10		 **(3j)**	78
3		 **(3c)**	82	11		 **(3k)**	81
4		 **(3d)**	71	12		 **(3l)**	85
5		 **(3e)**	76	13		 **(3m)**	90
6		 **(3f)**	72	14		 **(3n)**	70
7		 **(3g)**	68	15		 **(3o)**	67
8		 **(3h)**	79				

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.8 mmol), 2.5 mol % of $Pd(OAc)_2$ in 3 mL of a mixture of Et_3N/DMF (v/v 1/2) at 110 °C under argon atmosphere. [b]Isolated yield.

(d, J = 7.5 Hz, 1H), 7.52−7.41 (m, 2H), 7.25−7.08 (m, 8H), 7.02−6.99 (m, 2H), 6.81 (d, J = 6.1 Hz, 2H), 6.71 (d, J = 7.3 Hz, 2H), 3.56 (s, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.2, 141.2, 140.0, 139.5, 139.0, 137.4, 134.4, 133.9, 129.5, 128.0, 127.8, 127.3, 126.7, 126.6, 126.4, 126.3, 125.8, 125.1, 38.1, 20.5; IR (KBr, ν, cm^{-1}) 1597, 1492, 1454, 1315, 1161, 1128, 1082; HRMS m/z (ESI) calcd for $C_{26}H_{23}O_2S$ $(M + H)^+$ 399.1419, found 399.1413.

2-(4-Methylbenzyl)-6-(4-tolylsulfonyl)biphenyl (**3b**)*:* White solid; mp 121−122 °C; yield 95% (196 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.33 (d, J = 7.7 Hz, 1H), 7.50−7.39 (m, 2H), 7.27−7.21 (m, 2H), 7.14−7.08 (m, 4H), 6.99 (t, J = 8.4 Hz, 3H), 6.72 (d, J = 5.7 Hz, 4H), 3.51 (s, 2H), 2.35 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.2, 141.5, 139.9, 139.4, 137.4, 135.9, 134.6, 134.5, 133.8, 129.5, 128.0, 127.7, 127.4, 126.7, 126.5, 126.4, 126.3, 125.7, 37.5, 20.5, 20.0; IR (KBr, ν, cm^{-1}) 1676, 1597, 1512, 1450, 1303, 1159, 1130; HRMS m/z (ESI) calcd for $C_{27}H_{25}O_2S$ $(M + H)^+$ 413.1575, found 413.1570.

2-(4-Fluorobenzyl)-6-(4-tolylsulfonyl)biphenyl (**3c**)*:* White solid; mp 137−138 °C; yield 82% (171 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.36 (d, J = 7.6 Hz, 1H), 7.53−7.41 (m, 2H), 7.27−7.23 (m, 1H), 7.13−7.07 (m, 4H), 7.02−6.99 (m, 2H), 6.84 (t, J = 8.6 Hz, 2H), 6.75−6.65 (m, 4H), 3.54 (s, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 160.3 (d, J = 242.9 Hz), 142.3, 141.0, 140.0, 139.6, 137.2, 134.6 (d, J = 2.4 Hz), 134.2, 133.9, 129.4, 129.1 (d, J = 7.8 Hz), 128.0, 126.7, 126.6, 126.4, 126.3, 125.9, 114.0 (d, J = 21.1 Hz), 37.3, 20.5; IR (KBr, ν, cm^{-1}) 1597, 1508, 1435, 1292, 1215, 1153, 1128; HRMS m/z (ESI) calcd for $C_{26}H_{22}FO_2S$ $(M + H)^+$ 417.1325, found 417.1319.

2-Hexyl-6-(4-tolylsulfonyl)biphenyl (**3d**)*:* Yellow oil; yield 71% (139 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.31−8.28 (m, 1H),

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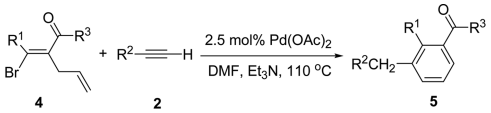
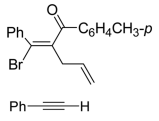
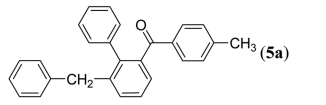
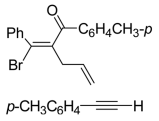
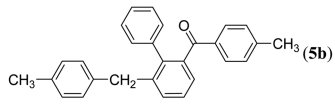
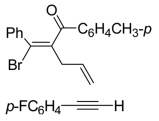
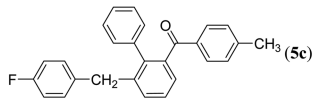
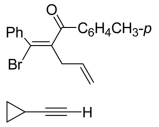
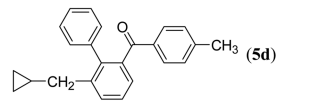
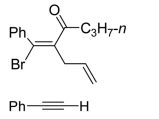
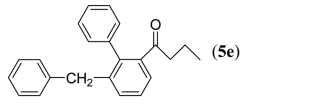
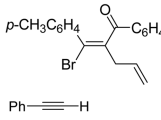
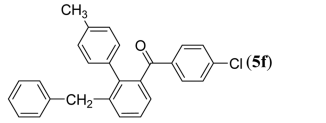
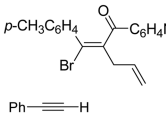
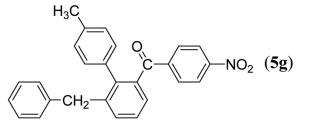
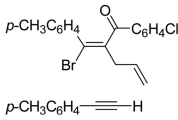
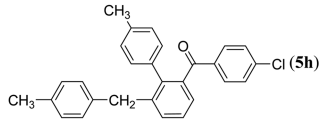
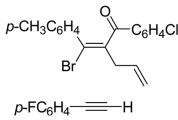
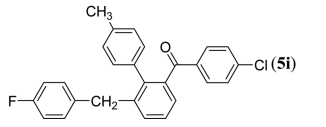
Table 3. Synthesis of Acyl-Substituted Benzenes 5 from β-Bromo Vinyl Ketones 4 and Terminal Alkynes 2[a]



4 2 5

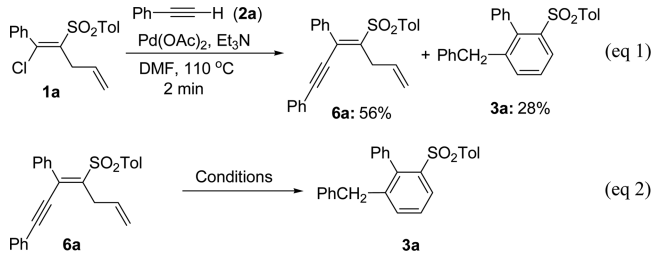
Entry	Vinyl ketone **4** terminal alkyne **2**	Product **5**	Yield (%)[b]
1		 (**5a**)	74
2		 (**5b**)	75
3		 (**5c**)	85
4		 (**5d**)	73
5		 (**5e**)	64
6		 (**5f**)	79
7		 (**5g**)	77
8		 (**5h**)	73
9		 (**5i**)	75

[a]Reaction conditions: **4** (0.5 mmol), **2** (0.8 mmol), 2.5 mol % of $Pd(OAc)_2$ in 3 mL of a mixture of Et_3N/DMF (v/v 1/2) at 110 °C under argon atmosphere. [b]Isolated yield.

7.51−7.47 (m, 2H), 7.28−7.23 (m, 1H), 7.16−7.07 (m, 4H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 2.16 (t, *J* = 7.8 Hz, 2H), 1.34−1.23 (m, 3H), 1.16−1.09 (m, 2H), 1.05−1.04 (m, 3H), 0.77 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 144.5, 143.5, 140.9, 140.6, 138.8, 136.0, 134.5, 130.9, 129.4, 128.0, 127.8, 127.6, 127.5, 126.6, 33.4, 31.7, 31.4, 29.3, 22.7, 21.9, 14.3; IR (KBr, ν, cm^{-1}) 1683, 1653, 1558, 1316, 1158, 1134; HRMS *m*/*z* (ESI) calcd for $C_{25}H_{29}O_2S$ (M + H)$^+$ 393.1888, found 393.1887.

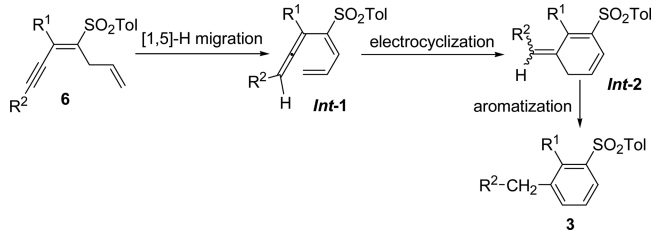
2-(Cyclopropylmethyl)-6-(4-tolylsulfonyl)biphenyl (***3e***)*:* Yellow solid; mp 82−83 °C; yield 76% (138 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.33 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.53 (t,

Scheme 1. Mechanistic Studies[a]



[a]Conditions A: $Pd(OAc)_2$ (2 mol %), Et_3N, DMF, 110 °C, 15 min; yield 95%. Conditions B: $Pd(OAc)_2$ (2 mol %), DMF, 110 °C, 20 min; yield 93%. Conditions C: DMF, 110 °C, 24 h; yield 63%.

Scheme 2. Plausible Reaction Mechanism for the Cyclization Step



J = 7.8 Hz, 1H), 7.29−7.24 (m, 1H), 7.16−7.07 (m, 4H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 7.4 Hz, 2H), 2.34 (s, 3H), 2.07 (d, *J* = 6.9 Hz, 2H), 0.73−0.64 (m, 1H), 0.39 (q, *J* = 5.4 Hz, 2H), −0.05 (q, *J* = 4.9 Hz, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ = 143.4, 143.2, 140.5, 140.1, 138.4, 135.7, 133.8, 130.5, 129.0, 127.6, 127.5, 127.3, 126.4, 37.5, 21.6, 11.1, 4.9; IR (KBr, ν, cm^{-1}) 1681, 1650, 1594, 1311, 1159, 1081; HRMS *m*/*z* (ESI) calcd for $C_{23}H_{23}O_2S$ (M + H)$^+$ 363.1419, found 363.1413.

2-Neopentyl-6-(4-tolylsulfonyl)biphenyl (***3f***)*:* Yellow liquid; yield 72% (136 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 7.6 Hz, 1H), 7.55−7.45 (m, 2H), 7.25−7.21 (m, 1H), 7.12−6.95 (m, 6H), 6.77 (d, *J* = 7.3 Hz, 2H), 2.32(s, 3H), 2.27 (s, 2H), 0.68 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.0, 141.6, 141.0, 140.6, 138.3, 136.2, 135.6, 132.0, 128.9, 127.4, 127.2, 126.8, 126.7, 126.5, 44.8, 32.5, 29.9, 21.5; IR (KBr, ν, cm^{-1}) 1564, 1442, 1311, 1145, 1123; HRMS *m*/*z* (ESI) calcd for $C_{24}H_{27}O_2S$ (M + H)$^+$ 379.1732, found 379.1726.

2-Benzyl-4-methyl-6-(4-tolylsulfonyl)biphenyl (***3g***)*:* Yellow solid; mp 123−124 °C; yield 68% (140 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.17 (s, 1H), 7.23−7.07 (m, 9H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 6.2 Hz, 2H), 6.68 (d, *J* = 7.3 Hz, 2H), 3.52 (s, 2H), 2.44 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.1, 142.0, 140.2, 140.1, 138.4, 138.2, 137.7, 135.6, 135.5, 130.8, 129.0, 128.8, 128.3, 127.6, 127.3, 127.2, 126.0, 39.0, 21.6, 21.3; IR (KBr,ν,cm^{-1}) 1455, 1302, 1155, 1121, 1085; HRMS *m*/*z* (ESI) calcd for $C_{27}H_{25}O_2S$ (M + H)$^+$ 413.1570, found 413.1572.

2-Benzyl-4′-methyl-6-(4-tolylsulfonyl)biphenyl (***3h***)*:* White solid; mp 153−154 °C; yield 79% (163 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.30−8.33 (m, 1H), 7.49−7.37 (m, 2H), 7.26 (s, 1H), 7.17−7.11 (m, 4H), 7.03−7.00 (m, 2H), 6.94−6.91 (m, 2H), 6.85−6.83 (m, 2H), 6.61 (d, *J* = 8.1 Hz, 2H), 3.57 (s, 2H), 2.37 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.2, 141.4, 140.1, 139.7, 139.2, 139.1, 137.4, 136.1, 133.8, 131.4, 129.3, 127.9, 127.3, 127.0, 126.7, 126.4, 125.7, 125.0, 37.9, 20.5, 20.3; IR (KBr, ν, cm^{-1}) 1672, 1593, 1494, 1450, 1311, 1159, 1125; HRMS *m*/*z* (ESI) calcd for $C_{27}H_{25}O_2S$ (M + H)$^+$ 413.1575, found 413.1570.

4′-Methyl-2-(4-methylbenzyl)-6-(4-tolylsulfonyl)biphenyl (***3i***)*:* White solid; mp 151−152 °C; yield 87% (185 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.32−8.29 (m, 1H), 7.47−7.36 (m, 2H), 7.14−7.10 (m, 2H), 7.03−6.97 (m, 4H), 6.95−6.92 (m, 2H), 6.74 (d, *J* = 7.9 Hz, 2H), 6.64−6.60 (m, 2H), 3.51 (s, 2H), 2.37 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 142.2, 141.7,

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140.0, 139.6, 137.4, 136.1, 136.0, 134.6, 133.7, 131.5, 129.4, 128.0, 127.9, 127.8, 127.0, 126.7, 126.4, 125.6, 37.5, 20.6, 20.3, 20.0; IR (KBr, ν, cm^{-1}) 1595, 1512, 1450, 1433, 1292, 1159, 1130; HRMS m/z (ESI) calcd for $C_{28}H_{27}O_2S$ $(M + H)^+$ 427.1732, found 427.1726.

2-(4-Fluorobenzyl)-4′-methyl-6-(4-tolylsulfonyl)biphenyl (**3j**): White solid; mp 120−121 °C; yield 78% (168 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.34−8.31 (m, 1H), 7.48 (t, J = 8.1 Hz, 1H), 7.40−7.37 (m, 1H), 7.12−7.09 (m, 2H), 7.03−7.00 (m, 2H), 6.93−6.91 (m, 2H), 6.88−6.81 (m, 2H), 6.78−6.73 (m, 2H), 6.58−6.55 (m, 2H), 3.54 (s, 2H), 2.37 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 160.3 (d, J = 242.7 Hz), 142.3, 141.2, 140.1, 139.6, 137.3, 136.1, 134.7 (d, J = 3.1 Hz), 133.7, 131.3, 129.3, 129.2 (d, J = 7.9 Hz), 127.9, 127.0, 126.7, 126.5, 125.8, 114.0 (d, J = 21.1 Hz), 37.2, 20.5, 20.3; IR (KBr, ν, cm^{-1}) 1595, 1506, 1435, 1301, 1157, 1126; HRMS m/z (ESI) calcd for $C_{27}H_{24}FO_2S$ $(M + H)^+$ 431.1481, found 431.1476.

2-Benzyl-4′-fluoro-6-(4-tolylsulfonyl)biphenyl (**3k**): White solid; mp 121−122 °C; yield 81% (169 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.36−8.33 (m, 1H), 7.54−7.44 (m, 2H), 7.16−7.08 (m, 7H), 6.81−6.74 (m, 4H), 6.66−6.61 (m, 2H), 3.57 (s, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 161.2 (d, J = 245.6 Hz), 142.5, 141.4, 139.8, 139.0, 138.7, 137.3, 134.2, 131.3 (d, J = 8.1 Hz), 130.2 (d, J = 3.3 Hz), 128.1, 127.7, 127.3 126.9, 126.5, 125.9, 125.2, 113.3 (d, J = 21.3 Hz), 38.2, 20.6; IR (KBr, ν, cm^{-1}) 1595, 1510, 1452, 1402, 1317, 1161, 1128; HRMS m/z (ESI) calcd for $C_{26}H_{22}FO_2S$ $(M + H)^+$ 417.1325, found 417.1319.

4′-Fluoro-2-(4-methylbenzyl)-6-(4-tolylsulfonyl)biphenyl (**3l**): White solid; mp 150−151 °C; yield 85% (183 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.34 (d, J = 7.7 Hz, 1H), 7.53−7.43 (m, 2H), 7.14−7.04 (m, 4H), 6.98 (d, J = 7.6 Hz, 2H), 6.80 (t, J = 8.6 Hz, 2H) 6.70−6.63 (m, 4H), 3.51 (s, 2H), 2.36 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 161.2 (d, J = 245.4 Hz), 142.5, 141.6, 139.7, 138.9, 137.3, 135.6, 134.7, 134.0, 131.3 (d, J = 8.1 Hz), 130.3 (d, J = 3.5 Hz), 128.1, 128.0, 127.6, 126.8, 126.5, 125.8, 113.3 (d, J = 21.3 Hz), 37.7, 20.6, 20.0; IR (KBr, ν, cm^{-1}) 1595, 1512, 1435, 1311, 1298, 1157, 1130; HRMS m/z (ESI) calcd for $C_{27}H_{24}FO_2S$ $(M + H)^+$ 431.1481, found 431.1476.

4′-Fluoro-2-(4-fluorobenzyl)-6-(4-tolylsulfonyl)biphenyl (**3m**): White solid; mp 159−160 °C; yield 90% (195 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.36 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.46−7.43 (m, 1H), 7.14−7.04 (m, 4H) 6.87−6.76 (m, 4H), 6.73−6.68 (m, 2H), 6.63−6.58 (m, 2H), 3.54 (s, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 161.2 (d, J = 245.7 Hz), 160.3 (d, J = 243.0 Hz), 142.6, 141.2, 139.9, 139.0, 137.2, 134.4 (d, J = 3.2 Hz), 134.1, 131.3 (d, J = 8.1 Hz), 130.1 (d, J = 3.3 Hz), 129.1 (d, J = 7.8 Hz), 128.1, 127.0, 126.5, 126.1, 114.1 (d, J = 21.1 Hz), 113.3 (d, J = 21.3 Hz), 37.5, 20.5; IR (KBr, ν, cm^{-1}) 1595, 1508, 1436, 1303, 1155, 1128; HRMS m/z (ESI) calcd for $C_{26}H_{21}F_2O_2S$ $(M + H)^+$ 435.1230, found 435.1225.

1-Benzyl-2-pentyl-3-(4-tolylsulfonyl)benzene (**3n**): Brown liquid; yield 70% (137 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13−8.10 (m, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.30−7.16 (m, 7H), 7.04 (d, J = 7.2 Hz, 2H), 4.00 (s, 2H), 2.83 (t, J = 7.9 Hz, 2H), 2.41 (s, 3H), 1.25−1.14 (m, 6H), 0.83 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.9, 141.9, 141.3, 139.9, 139.8, 139.4, 136.0, 129.8, 128.9, 128.7, 128.3, 127.6, 126.5, 126.1, 38.1, 32.7, 30.2, 29.9, 22.5, 21.7, 14.1; IR (KBr, ν, cm^{-1}) 1453, 1314, 1300, 1156, 1131, 1092; HRMS m/z (ESI) calcd for $C_{25}H_{29}O_2S$ $(M + H)^+$ 393.1888, found 393.1883.

1-Benzyl-2-cyclopropyl-3-(4-tolylsulfonyl)benzene (**3o**): Brown solid; mp 100−101 °C; yield 67% (121 mg) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.95−7.92 (m, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.29−7.15 (m, 7H), 7.01 (d, J = 7.1 Hz, 2H), 4.26 (s, 2H), 2.42 (s, 3H), 1.59−1.52 (m, 1H), 0.92 (q, J = 6.2 Hz, 2H), 0.61 (q, J = 5.9 Hz, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ = 144.2, 143.7, 142.8, 140.7, 140.5, 139.1, 135.5, 129.4, 128.8, 128.5, 128.2, 127.5, 126.4, 126.1, 39.4, 21.6, 12.7, 10.1; IR (KBr, ν, cm^{-1}) 1497, 1445, 1298, 1151, 1148, 1123, 912; HRMS m/z (ESI) calcd for $C_{23}H_{23}O_2S$ $(M + H)^+$ 363.1419, found 363.1413.

2-Benzyl-6-(4-methylbenzoyl)biphenyl (**5a**): White solid; mp 97−98 °C; yield 74% (134 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.52−7.49 (m, 2H), 7.37−7.35 (m, 2H), 7.30−7.28 (m, 1H), 7.23−7.16 (m, 2H), 7.14−7.12 (m, 4H), 7.10−7.08 (m, 2H), 7.05−7.01 (m, 2H), 6.97−6.93 (m, 2H), 3.87 (s, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.3, 142.6, 139.8, 139.7, 139.0, 138.7, 137.2, 134.2, 130.5, 129.0, 128.9, 127.9, 127.7, 127.2, 126.7, 126.1, 126.0, 124.9, 124.5, 38.0, 20.6; IR (KBr, ν, cm^{-1}) 1666, 1602, 1494, 1440, 1311; HRMS m/z (ESI) calcd for $C_{27}H_{23}O$ $(M + H)^+$ 363.1749, found 363.1743.

2-(4-Methylbenzyl)-6-(4-methylbenzoyl)biphenyl (**5b**): White solid; mp 127−128 °C; yield 75% (141 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.51 (d, J = 8.1 Hz, 2H), 7.38−7.32 (m, 2H), 7.28−7.27 (m,, 1H), 7.13−7.10 (m, 4H), 7.07−7.01 (m, 5H), 6.85 (d, J = 7.8 Hz, 2H), 3.82 (s, 2H), 2.34 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.2, 142.4, 139.5, 138.8, 137.1, 136.7, 134.3, 134.2, 130.3, 128.9, 127.9, 127.7, 127.6, 126.6, 126.0, 125.9, 124.3, 37.4, 20.5, 19.9; IR (KBr, ν, cm^{-1}) 1666, 1600, 1512, 1440, 1311; HRMS m/z (ESI) calcd for $C_{28}H_{25}O$ $(M + H)^+$ 377.1905, found 377.1900.

2-(4-Fluorobenzyl)-6-(4-methylbenzoyl)biphenyl (**5c**): White solid; mp 126−127 °C; yield 85% (162 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.52−7.49 (m, 2H), 7.36−7.30 (m, 4H), 7.13−7.08 (m, 5H), 7.01−6.98 (m, 2H), 6.88−6.86 (m, 3H), 3.84 (s, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.2, 160.4 (d, J = 242.5 Hz), 142.7, 139.8, 139.0, 138.5, 137.1, 135.4 (d, J = 2.2 Hz), 134.2, 130.4, 129.2 (d, J = 7.7 Hz), 129.0, 128.9, 127.8, 126.7, 126.2, 124.7, 114.0 (d, J = 21.1 Hz), 37.3, 20.6; IR (KBr, ν, cm^{-1}) 1660, 1604, 1504, 1440, 1286; HRMS m/z (ESI) calcd for $C_{27}H_{22}FO$ $(M + H)^+$ 381.1655, found 381.1649.

2-(Cyclopropylmethyl)-6-(4-methylbenzoyl)biphenyl (**5d**): Yellow liquid; yield 73% (119 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.62 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 6.7 Hz, 1H), 7.17−7.07 (m, 7H), 2.41 (d, J = 6.8 Hz, 2H), 2.34 (s, 3H), 0.85−0.78 (m, 1H), 0.47−0.41 (m, 2H), 0.04−0.01 (m, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ = 198.5, 143.5, 140.9, 140.4, 139.5, 138.5, 135.3, 130.3, 130.0, 129.9, 128.7, 127.7, 127.0, 126.9, 125.1, 37.5, 21.7, 11.4, 4.9; IR (KBr, ν, cm^{-1}) 1666, 1608, 1444, 1314, 1287, 1177; HRMS m/z (ESI) calcd for $C_{24}H_{23}O$ $(M + H)^+$ 327.1749, found 327.1746.

6-Butyryl-2-benzylbiphenyl (**5e**): Yellow oil; yield 64% (101 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.37−7.34 (m, 6H), 7.23−7.15 (m, 5H), 6.93 (d, J = 6.6 Hz, 2H), 3.89 (s, 2H), 2.17 (t, J = 7.2 Hz, 2H), 1.42−1.35 (m, 2H), 0.68 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 208.3, 143.2, 141.2, 139.9, 139.3, 139.2, 132.5, 130.3, 129.2, 128.7, 128.6, 128.0, 126.3, 125.4, 45.4, 39.5, 18.0, 13.9; IR (KBr, ν, cm^{-1}) 1739, 1683, 1658, 1550, 1270; HRMS m/z (ESI) calcd for $C_{23}H_{23}O$ $(M + H)^+$ 315.1749, found 315.1746.

2-Benzyl-4′-methyl-6-(4-chlorobenzoyl)biphenyl (**5f**): White solid; mp 104−105 °C; yield 79% (157 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.52 (d, J = 8.2 Hz, 2H), 7.40−7.33 (m, 2H), 7.30−7.16 (m, 6H), 6.98−6.89 (m, 6H), 3.88 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.7, 140.9, 140.2, 140.1, 140.0, 139.1, 137.0, 136.3, 135.0, 132.0, 131.2, 129.9, 129.0, 128.6, 128.4, 128.3, 127.2, 126.0, 125.6, 38.9, 21.2; IR (KBr, ν, cm^{-1}) 1670, 1583, 1444, 1398, 1282; HRMS m/z (ESI) calcd for $C_{27}H_{22}ClO$ $(M + H)^+$ 397.1359 (^{35}Cl), found 397.1354.

2-Benzyl-4′-methyl-6-(4-nitrobenzoyl)biphenyl (**5g**): Brown solid; mp 80−81 °C; yield 77% (157 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.06 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.43−7.37 (m, 3H), 7.29−7.13 (m, 3H), 6.97−6.84 (m, 6H), 3.90 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.8, 149.6, 143.0, 140.6, 140.2, 140.1, 139.6, 137.3, 134.8, 132.8, 130.1, 130.0, 128.9, 128.7, 128.4, 127.5, 126.1, 126.0, 123.1, 38.8, 21.1; IR (KBr, ν, cm^{-1}) 1677, 1600, 1516, 1491, 1343, 1280; HRMS m/z (ESI) calcd for $C_{27}H_{22}NO_3$ $(M + H)^+$ 408.1600, found 408.1598.

2-(4-Methylbenzyl)-4′-methyl-6-(4-chlorobenzoyl)biphenyl (**5h**): White solid; mp 105−106 °C; yield 73% (150 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.52 (d, J = 8.2 Hz, 2H), 7.35−7.23 (m, 5H), 7.03 (d, J = 7.6 Hz, 2H), 6.99−6.85 (m, 6H), 3.83 (s, 2H), 2.30 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.7, 140.2, 140.1, 140.0, 139.0, 137.8, 136.9, 136.2, 135.5, 135.0, 131.9, 131.1, 129.9, 129.0, 128.8, 128.6, 128.3, 127.1, 125.5, 38.4, 21.2, 21.0; IR (KBr, ν, cm^{-1}) 1668, 1583, 1514, 1284, 1168; HRMS m/z (ESI) calcd for $C_{28}H_{24}ClO$ $(M + H)^+$ 411.1516 (^{35}Cl), found 411.1510.

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*2-(4-Fluorobenzyl)-4′-methyl-6-(4-chlorobenzoyl)biphenyl (**5i**):* White solid; mp 98−99 °C; yield 75% (155 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.51 (d, J = 8.1 Hz, 2H), 7.40−7.34 (m, 2H), 7.30−7.24 (m, 4H), 6.9−6.85 (m, 7H), 3.84 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.6, 161.3 (d, J = 242.5 Hz), 140.2, 140.0, 139.8, 139.1, 137.0, 136.4 (d, J = 3.2 Hz), 136.1, 134.8, 131.8, 131.1, 130.2 (d, J = 7.8 Hz), 129.7, 128.6, 128.3, 127.2, 125.7, 115.0 (d, J = 21.0 Hz), 38.2, 21.2; IR (KBr, ν, cm^{-1}) 1664, 1583, 1508, 1435, 1398, 1284, 1220; HRMS m/z (ESI) calcd for $C_{27}H_{21}ClFO$ $(M + H)^+$ 415.1265, found 415.1259.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00308.

Copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)
X-ray data of **3a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xiemh@mail.ahnu.edu.cn.

Notes

The authors declare no competing financial interest.

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