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Base-Controlled One-Pot Chemoselective Suzuki–Miyaura Reactions for the Synthesis of Unsymmetrical Terphenyls

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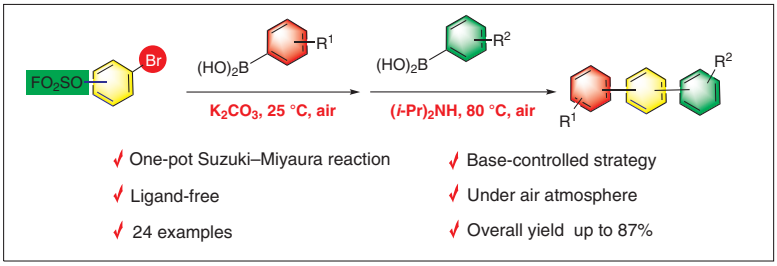

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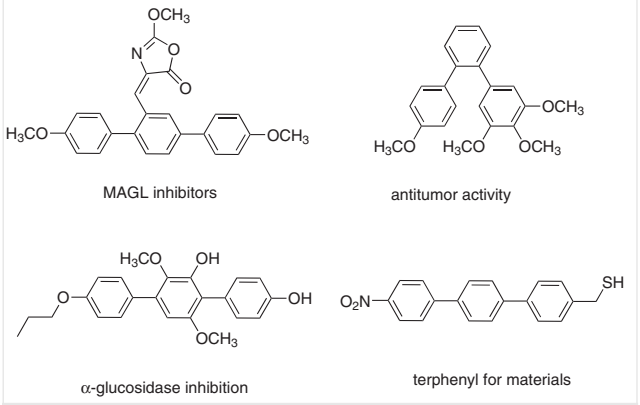
Abstract We report a chemoselective Suzuki–Miyaura reaction protocol of using bromophenyl fluorosulfonate as building block for the preparation of unsymmetrical terphenyls. The chemoselective cross-coupling of bromophenyl fluorosulfonate and arylboronic acids can be achieved by controlling base species without using any ligands. Under this methodology, various of *m*- and *p*-unsymmetrical terphenyls were obtained in moderate to good yields.

Key words chemoselective, Suzuki–Miyaura reactions, unsymmetrical terphenyls, one-pot, ligand-free

Terphenyl compounds can be widely found in the natural products, which exhibit significant biological activities including potent immunosuppressant, neuroprotective, and antimicrobial activities.[1] They are also important structural motifs in various liquid crystals and fluorescent compounds[2] (Scheme 1). Because of their functional and biological activities, the synthesis of terphenyls has attracted significant interest from organic chemists. Methods for the formation of these compounds include transition-metal-catalyzed cross-coupling reactions[3] and cyclization reactions[4]. Over the past decade, the palladium-catalyzed Suzuki–Miyaura (SM) cross-coupling reaction that offers advantages of mild reaction conditions, good functional group tolerance, and widespread applications has been widely used for preparing unsymmetrical terphenyls.[5] The classical process requires multistep synthesis, including the first SM reaction step, then halogenation of the biphenyl intermediates, and finally the cross-coupling reaction to yield the terphenyl products.[6] The tedious steps and harsh reaction conditions restrict their applications. Recently, great advances have been achieved for obtaining these compounds by one-pot chemoselective SM cross-coupling reaction.[7] Felpin's group[8] reported arene diazonium tetrafluoroborate salts chemoselectively coupled with different arylboronic acids to provide unsymmetrical tri(hetero)aryl derivatives through stepwise added base. Watson's group[7c] reported a one-pot selective coupling reaction of bromo-chlorobenzene with arylboronic acid and arylboronic acid pinacol esters. Recently, Hearn's group[9] described that 1,4-dibromo-2-nitrobenzene could couple with different arylboronic acids in a one-pot SM reaction to provide unsymmetrically substituted *p*-terphenyl in good yields. However, most of these methods suffer from harsh reaction conditions, expensive ligands, and/or low yields. It is thus highly desirable to develop a mild and efficient method for the synthesis of unsymmetrical terphenyls.



Scheme 1 Representative biologically active molecules and materials containing terphenyl compounds

Recently, we report a temperature-controlled sequential SM coupling strategy for the synthesis of unsymmetrical terphenyls using potassium bromophenyltrifluoroborates as building blocks.[10] Herein, we report that controlling of base species, bromoaryl fluorosulfonate can proceed che-

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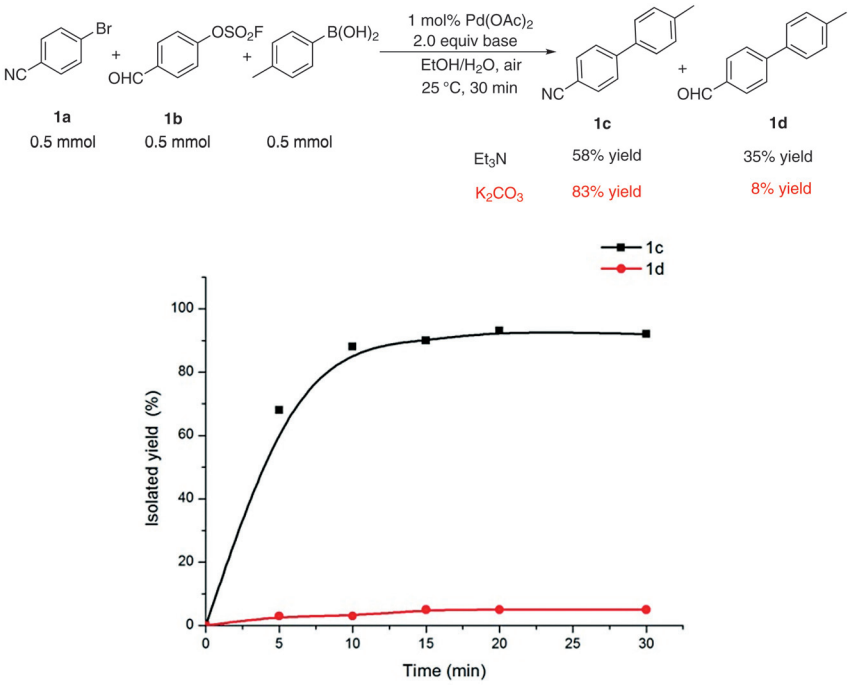
moselective cross-coupling reaction with different arylboron compounds in the absence of phosphine ligand. This mild and convenient protocol can be used for the synthesis of biaryl fluorosulfonates and unsymmetrical terphenyls in moderate to high yield.

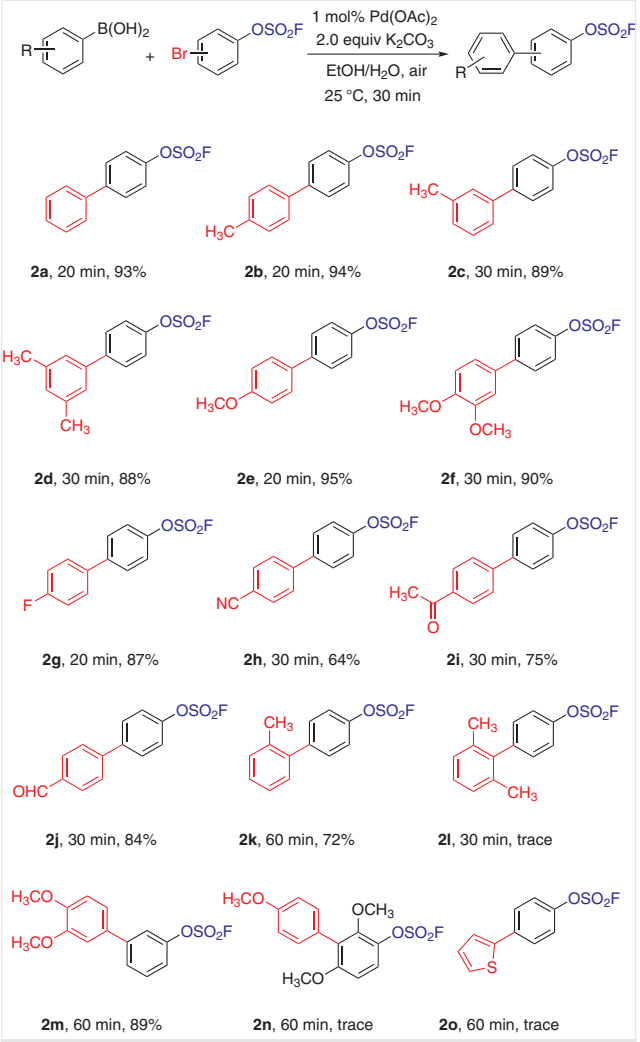
Aryl fluorosulfonates as a new 'click' reagent has been investigated by Dong and Sharpleess group.[11] The potential of these compounds in drug discovery has received great attention.[12] This reagent also offers an inexpensive alternative to aryl halides for the SM reaction.[13] According our preliminary studies, both aryl bromide and aryl fluorosulfate were effective electrophilic coupling partners for the SM reactions. However, it has been noted that both base and temperature have a great effect for the reaction activity with different electrophiles (Table S1 in the Supporting Information). The cross-coupling reactions of aryl bromides were more favorable using inorganic bases at room temperature. Instead, the desired cross-coupling products were obtained in high yield using aryl fluorosulfate under organic bases at room temperature. Therefore, we questioned whether chemoselective cross-coupling of aryl bromide over aryl fluorosulfate might be possible via control of the base species. Thus, we carried out the cross-coupling reaction using 4-bromobenzonitrile and 4-formylphenyl fluorosulfonate as electrophilic reagents under a competitive catalytic system. As shown in Scheme 2, low selectivity was observed in the presence of Et_3N. To our delight, 4-bromobenzonitrile outcompeted 4-formylphenyl fluorosulfonate with ca. 8:1 selectivity significantly while using K_2CO_3 as base, and **1a** was transformed into the corresponding cross-coupled product **1c** with an 83% yield, while **1b** only provided an 8% yield of product **1d**.

To further test the chemoselectivity, the cross-couping reaction of bromophenyl fluorosulfonates with arylboronic acids were carried out.[14] In the presence of 1 mol% $Pd(OAc)_2$ as catalyst and 2.0 equiv of K_2CO_3 as base, 4-bromophenyl fluorosulfonate coupled with various arylboronic acids bearing electron-donating or electron-withdrawing groups to provide biaryl fluorosulfonates in good to excellent yield. For the cross-coupling reactions, arylboronic acids bearing electron-donating groups showed better activity than that of bearing electron-withdrawing groups (Scheme 3, **2b–f** vs **2g–j**). In the case of *ortho*-substituted arylboronic acids, 2-methylphenylboronic acid coupled with 4-bromophenyl fluorosulfonate to afford a 72% product yield (Scheme 3, **2k**), however, 2,6-dimethylphenylboronic acid only gave trace product due to the steric hindrance (Scheme 3, **2l**). *meta*-Substituted bromo phenyl fluorosulfonate coupled with 3,4-dimethoxyphenylboronic acid to afford an 89% yield in 60 min (Scheme 3, **2m**). However, trace product was observed while using sterically hindered 3-bromo-2,4-dimethoxyphenyl sulfofluoridate (Scheme 3, **2n**). Thiophen-2-ylboronic acid was also examined, but no product was obtained in 60 minutes (Scheme 3, **2o**).

Based on the above results, we next performed the one-pot double SM reactions using 4-bromophenyl fluorosulfonate as building block for preparing unsymmetrical terphenyls. As shown in Scheme 4, the first step of selective



Scheme 2 Competitive cross-coupling of 4-bromobenzonitrile vs 4-formylphenyl fluorosulfonate with phenylboronic acid using K_2CO_3 as base

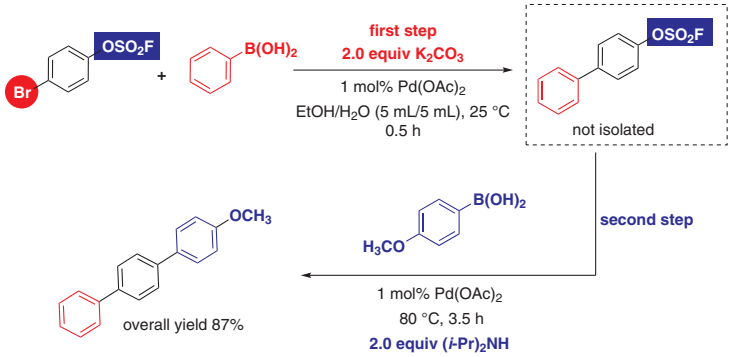


Scheme 3 Chemoselective Suzuki–Miyaura reactions for the synthesis of biaryl fluorosulfonates.
Reagents and conditions: bromophenyl fluorosulfonate (0.5 mmol), arylboronic acid (0.55 mmol), K_2CO_3 (1 mmol), $Pd(OAc)_2$ (1 mol%), EtOH/H_2O (2 mL/2 mL), 25 °C, air; isolated yield is given.

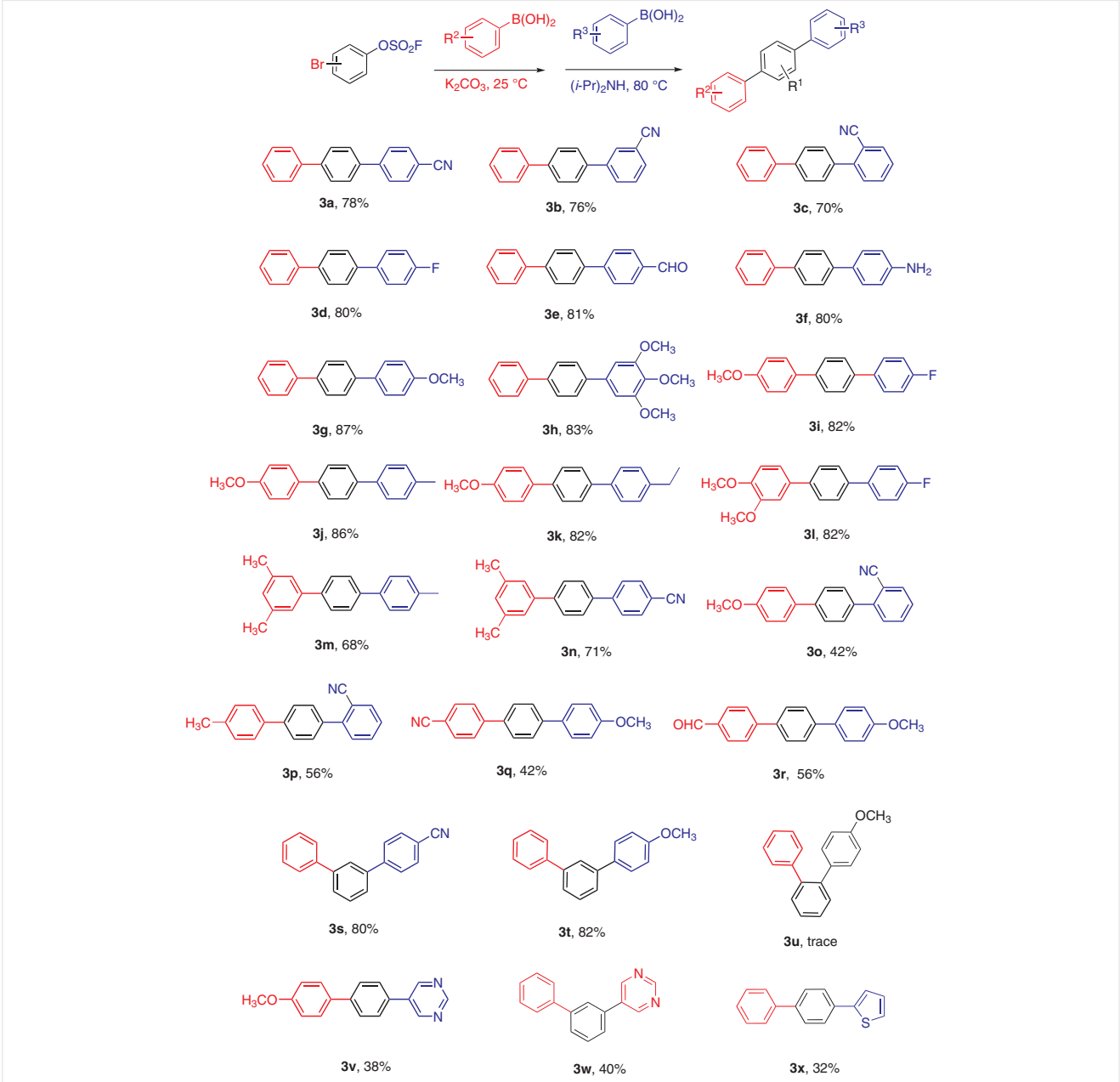
cross-coupling reaction was performed at room temperature with 1 mol% $Pd(OAc)_2$ and 2.0 equiv of K_2CO_3. After 0.5 h, 1 mol% $Pd(OAc)_2$ and 2.0 equiv of $(i\text{-Pr})_2NH_2$ were added, and the reaction temperature was raised to 80 °C. Then, 1.0 equiv of 4-methoxyphenylboronic acid was added for the second-step reaction, and an 87% overall yield was obtained by this method. In this protocol, the first chemoselective SM reaction of the bromine group with boronic acid is achieved by using K_2CO_3 as base, and the stepwise addition of arylboronic acids could avoid the selectivity issues of nucleophile. The scope and limitations for this one-pot protocol were next examined.[15]

As shown in Scheme 5, 24 unsymmetrical *p*-, *m*- and *o*-terphenyl compounds were examined, and the highest overall yield was up to 87% (Scheme 5, **3g**). These results suggested that electronic characteristics of the substrates have an effect to the product yield. For the first cross-coupling step, arylboronic acids bearing electron-withdrawing groups, only moderate yields were observed (Scheme 5, **3q** and **3r**). However, arylboronic acids bearing electron-donating or electron-withdrawing groups were both effective for the second step, and good overall yields could be achieved (Scheme 5, **3a–n**). Only 42% and 56% yield were obtained while using 2-bromobenzonitrile as the substrate for the second cross-coupling step (Scheme 5, **3o** and **3p**). *m*-Terphenyls were also examined in this protocol with 80% and 82% yield (Scheme 5, **3s** and **3t**). However, almost no product was observed by using steric 2-bromophenyl fluorosulfonate as substrate (Scheme 5, **3u**). We finally investigated the more difficult case of using heteroaryl bromides as substrates, and bromopyridine and bromopyrimidine as the second-step coupling partners could provide moderate terphenyl yields (Scheme 5, **3v–x**).

In summary, we have reported a one-pot chemoselective SM reaction of bromophenyl fluorosulfonate with arylboronic acids without using any ligands. The chemoselective cross-coupling reactions were achieved by controlling base species. Various biaryl sulfonylfluorides and unsymmetrical terphenyls bearing functional groups were successfully obtained by this process in good yields. This meth-



Scheme 4 One-pot double SM reaction for the preparation of unsymmetrical terphenyls



Scheme 5 One-pot double SM reaction for the preparation of unsymmetrical terphenyls
Reagents and conditions: first step: bromophenyl fluorosulfonate, arylboronic acid (0.55 mmol), K_2CO_3 (1 mmol), $Pd(OAc)_2$ (1 mol%), EtOH/H_2O (5 mL/5 mL), 25 °C, air,30 min; second step: arylboronic acid (0.5 mmol), $Pd(OAc)_2$ (1 mol%), (*i*-Pr)$_2$NH (1 mmol), 80 °C, 3.5 h, under air; isolated yield is given.

od provides a potentially mild and efficient pathway to synthesize pharmaceuticals and functional material containing biaryl and terphenyls units.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690227.

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(14) **General Procedure for the Preparation of Biaryl Fluorosulfonates**

A mixture of bromophenyl fluorosulfonates (0.5 mmol), arylboronic acid (0.55 mmol), K_2CO_3 (1 mmol), $Pd(OAc)_2$ (1 mol%), and EtOH/H_2O (2 mL/2 mL) was stirred at 25 °C under air for the indicated time. After the reaction, the mixture was added to brine (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were concentrated in vacuo, and the product was isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C).

3′,4′-Dimethoxybiphenyl-4-yl fluorosulfate (2f) Colorless liquid (140.8 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 6.4 Hz, 2 H), 7.38 (d, *J* = 6.7 Hz, 2 H), 7.08 (d, *J* = 19.1 Hz, 2 H), 6.96 (s, 1 H), 3.93 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.3, 149.2, 149.0, 141.8, 132.1, 128.6, 121.1, 119.6, 111.5, 110.3, 55.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 37.4 (s, 1 F).

3′,4′-Dimethoxybiphenyl-3-yl fluorosulfate (2m) Colorless liquid (140.1 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.8 Hz, 1 H), 7.40 (s, 2 H), 7.18 (d, *J* = 7.3 Hz, 1 H), 7.03 (d, *J* = 8.2 Hz, 1 H), 6.97 (s, 1 H), 6.86 (d, *J* = 8.3 Hz, 1 H), 3.84 (d, *J* = 11.5 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.4, 149.4, 149.3, 143.8, 131.6, 130.5, 126.8, 119.60, 118.9, 118.6, 111.5, 110.1, 55.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 37.1 (s, 1 F).

(15) **General Procedure for the Preparation of Unsymmetrical Terphenyls**

A mixture of bromophenyl fluorosulfonate (0.5 mmol), arylboronic acid (0.5 mmol), K_2CO_3 (1 mmol), $Pd(OAc)_2$ (1 mol%), and EtOH/H_2O (5 mL/5 mL) was stirred at 25 °C under air for 0.5 h. Then, arylboronic acid (0.5 mmol), $(i\text{-Pr})_2$NH (1 mmol), and $Pd(OAc)_2$ (1 mol%) were added to the reaction mixture and stirred for 3.5 h at 80 °C. Afterwards, the mixture was cooled to room temperature and concentrated in vacuo. The terphenyl product was isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether and ethyl acetate.

4″-Fluoro-3,4-dimethoxy-1,1′:4′,1″-terphenyl (3l) White solid (126.7 mg, 82%); mp 149–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.51 (m, 6 H), 7.19 (dd, *J* = 8.3, 2.1 Hz, 1 H), 7.17–7.10 (m, 3 H), 6.97 (d, *J* = 8.3 Hz, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.2, 148.7, 139.9, 138.7, 133.6, 128.5, 128.5, 127.3, 127.2, 119.3, 115.8, 115.5, 111.5, 110.3, 56.0, 55.9.

5-[3′,4′-Dimethoxy-(1,1′-biphenyl)-4-yl]pyrimidine (3v) White solid (50.2 mg, 38%); mp 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (d, *J* = 21.5 Hz, 1 H), 8.96 (d, *J* = 32.8 Hz, 2 H), 7.68 (dd, *J* = 27.4, 8.2 Hz, 3 H), 7.56 (dd, *J* = 24.1, 8.4 Hz, 2 H), 7.03 (dd, *J* = 12.6, 8.8 Hz, 2 H), 3.87 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.4, 159.5, 157.3, 156.8, 154.6, 154.4, 141.5, 133.9, 132.4, 132.3, 128.1, 127.6, 127.2, 114.9, 114.3, 55.3.

