

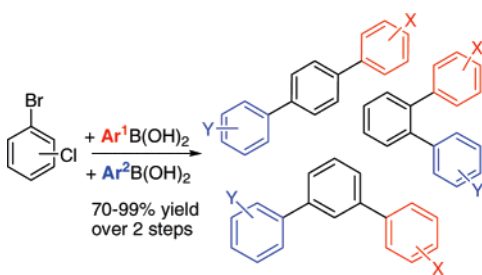
A Practical and General Synthesis of Unsymmetrical Terphenyls

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A synthetic procedure was developed that enables sequential chemoselective Suzuki–Miyaura cross-coupling of chlorobromobenzene with arylboronic acids. The first coupling is achieved at room temperature using a ligandless palladium catalyst. The chlorobiaryl product can then be subjected directly to the second coupling, facilitated by the SPhos ligand. Using this methodology, parallel synthesis of 32 unsymmetrical *o*-, *m*-, and *p*-terphenyl compounds was accomplished in good to excellent overall yields.

With aromatic rings arranged differently in the two-dimensional plane, *o*-, *m*-, and *p*-terphenyl compounds possess unique photophysical properties that are often exploited in the design of organic electroluminescent (OEL) devices¹ and liquid-crystalline materials.² Terphenyls can also be found in nature, predominantly as *p*-terphenyl derivatives,³ and synthetic terphenyls are known to possess biological activities with potential therapeutic values.⁴

To date, general methodologies described for the synthesis of unsymmetrical terphenyls include the coupling of bromobenzenesulfonates with arylboronic acids and arylmagnesium

bromides, through separate Pd- and Ni-catalyzed reactions,⁵ sequential Negishi cross-coupling reactions of diorganozinc reagents with iodoaryl nonaflates^{6a} and zinc phenoxides with aryl triflates.^{6b} Anhydrous reaction conditions are necessary in these procedures, and purification of biaryl intermediates by column chromatography is required. The reactivity of the organometallic reagents can also be incompatible with certain electrophilic functional groups (e.g., carbonyls, enones). Herein, we describe a concise, practical, and high-yielding synthesis of unsymmetrical terphenyls by employing sequential chemoselective Suzuki–Miyaura (SM) reactions.⁷ This is envisaged to have a much broader scope; aryl precursors are widely available, easy to handle, and most functional groups can be accommodated by the system.

Success of the methodology is dependent on the chemoselectivity of the first arylation. Monoarylation of symmetrical diiodo- and dibromoarenes is highly sensitive to the reaction conditions.⁸ Equally, attempted monoarylation of bromiodobenzene under harsh conditions can lead to mixtures of mono- and diarylated products.⁹ In this work, the chemoselectivity of monoarylation was achieved by using 4-, 3-, and 2-bromochlorobenzenes (**1a**, **1b**, and **1c**, respectively) as reactive substrates. Selective substitution of the bromide can be achieved at room-temperature using “ligandless” palladium catalysts:¹⁰ using Pd(OAc)₂ (1.5 mol %) and K₃PO₄ as base, the coupling was effected in a biphasic system (DMF–H₂O) at room temperature,¹¹ without phase-transfer reagents (Scheme 1). The reaction appears to be insensitive to air and the organic solvent–DMF can be substituted by toluene or THF, without noticeable

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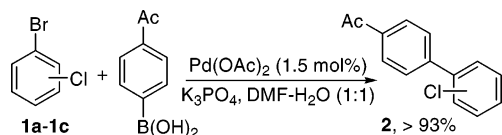
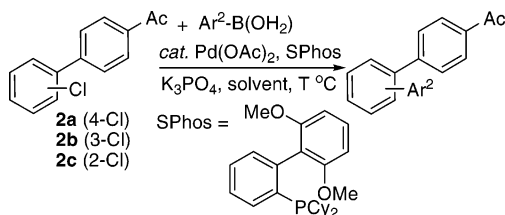
(11) The presence of water is crucial for this first SM reaction to proceed at ambient temperature; the use of anhydrous DMF did not lead to any significant product formation, unless the reaction temperature was raised to >80 °C.

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SCHEME 1. Monoarylation of Bromochlorobenzenes at Room Temperature

SCHEME 2. Suzuki–Miyaura Cross-Coupling of Chlorobiaryls by SPhos


difference. In all cases, quantitative conversions to the corresponding chlorobiphenyl compounds were obtained within 3 h.

Chemoselective cross-coupling of 2-bromochlorobenzene **1c** was previously achieved either by using $\text{Pd}(\text{PPh}_3)_4$ at reflux¹² or at ambient conditions using a ferrocenylphosphine ligand.¹³ Thus, it was gratifying to find that the reaction proceeded equally well under these conditions. These reactions were subsequently replicated on a larger scale in a round-bottom flask opened to air, without any deterioration in yield.

With the first aryl group in place, the second arylation reaction is considerably difficult as it involves cleavage of the stronger C–Cl bond. The reaction can be catalyzed by ligandless Pd/C using high temperature¹⁴ or microwave irradiation,¹⁵ but the yield remained moderate to poor, especially for deactivated aryl chlorides. Thus, we decided to effect the second coupling by using 2-(2',6'-dimethoxybiphenyl)dicyclohexylphosphine (SPhos), a good universal ligand developed by Buchwald et al. for SM reactions (Scheme 2).¹⁶

It was reported that the presence of a small amount of water is needed to effect reactions catalyzed by SPhos under ambient conditions. Adopting the literature procedure, the addition of a small quantity of water to the catalytic solution caused the solid base to form an insoluble paste, which impeded efficient mixing of the reactants, giving unrepeatable results and a poor yield of the product (Table 1, entry 1). However, by using a miscible mixture of THF–H₂O (3:1), a homogeneous mixture and a good yield of the product can be obtained (entry 2). The yield can be further improved by raising the temperature, enabling a low catalytic loading (0.5 mol %) to be used (entries 3 and 4). However, this is rather dependent on the nature of the substrate: while the reaction with **2b** required both higher temperature and catalytic loading (entries 5 and 6), coupling of **2a** with 4-fluorophenylboronic acid was complete within 3 h, using just 0.5 mol % of the catalyst (entry 7). Likewise, cross-coupling of the **2c** with other arylboronic acids did not present

TABLE 1. Second Cross-Coupling of 2a–c Catalyzed by SPhos^a

entry	precursor	Ar ²	[Pd] ^b	T (°C)	t (h)	conv (yield) ^c (%)
1 ^{d,e}	2a	Ph	0.5	rt	3	23 ^f
2	2a	Ph	0.5	rt	3	72 (69)
3	2a	Ph	1	60	2	100 (89)
4	2a	Ph	0.5	60	16	93 (87)
5	2b	Ph	1	30	24	63 (55)
6	2b	Ph	1	60	24	91 (80)
7	2a	4-F-C ₆ H ₄	0.5	60	3	100 (86)
8	2c	4-MeOC ₆ H ₄	1	60	21	100 (82)
9	2c	2-MeOC ₆ H ₄	1	60	21	100 (89)

^a General reaction conditions: **2a–c** (1 equiv), arylboronic acid (1.1 equiv), $\text{Pd}(\text{OAc})_2$ (0.5 mol % or 1 mol %), SPhos (2 equiv/Pd), K_3PO_4 (3 equiv), THF–H₂O (3:1), 24 h. ^b $\text{Pd}(\text{OAc})_2$ loading in mol %. ^c Conversions were determined by ¹H NMR spectroscopy. Isolated yield after column chromatography/crystallization. ^d $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ was used, as specified in ref 16. ^e Conducted with 1% water in THF. ^f Not isolated.

any problems, even with the sterically demanding 2-methoxyphenylboronic acid (entry 9).

During this investigation, we uncovered an important dependence of the reaction on the quality of the $\text{Pd}(\text{OAc})_2$ precursor: while the first SM reaction is insensitive to the source of the palladium precursor, a particular purified batch of $\text{Pd}_3(\text{OAc})_6$ trimer appeared to perform noticeably better in the phosphine-catalyzed coupling of the chlorobiaryl.¹⁷ Thus, we recommend that $\text{Pd}(\text{OAc})_2$ of unspecified purity should be recrystallized (e.g., from toluene) for use in these reactions.

Given that the first SM reaction proceeds with complete consumption of the dihaloarene, the inorganic salts, spent palladium catalyst, and slight excess of the arylboronic acid reagent can be removed simply by an aqueous wash, to afford compounds which can be used directly in the second coupling without further purification. Thus, the synthesis of terphenyls can be carried out in a simple synthetic sequence, which is amenable to automation.

Utilizing this methodology, a small library of 22 unsymmetrical *p*- and *m*-terphenyl compounds was synthesized from a selection of simple arylboronic acids, chosen for their steric and electronic properties (Schemes 3 and 4).

Unsymmetrical *p*-terphenyl compounds **3a–k** are highly crystalline solids, which can be purified by recrystallization. However, compounds **3d** and **3g** are only sparingly soluble in organic solvents. This affected their extraction from the reaction mixture, resulting in slightly lower yields compared to the others, which are obtained with an overall yield of ca. 85%. In comparison, *m*-terphenyl compounds **4a–k** are more soluble; hence, column chromatography can be used to afford good to excellent yields, typically >90%.

For the synthesis of the *p*- and *m*-terphenyls, neither of the cross-coupling steps was sensitive to steric and electronic characteristics of the substrates. In all cases, the chlorobiaryl intermediates **2** were obtained in quantitative yields, i.e., the overall yields of the terphenyl compounds were largely dictated by the second step, which was relatively insensitive to the nature of the arylboronic acid. For example, results obtained with 2-methoxyboronic acid are comparable with other less bulky boronic acids.

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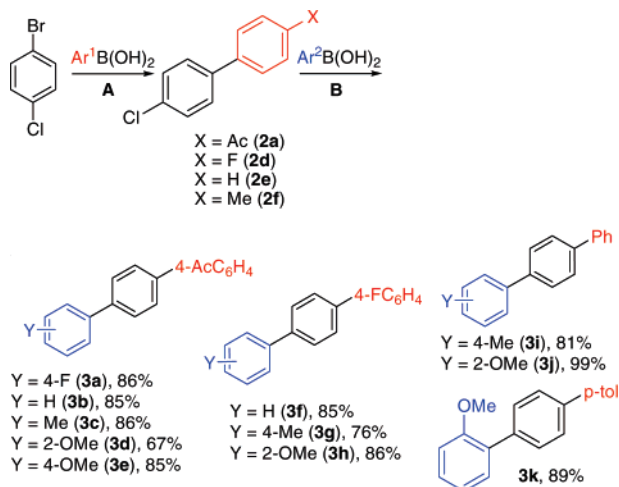
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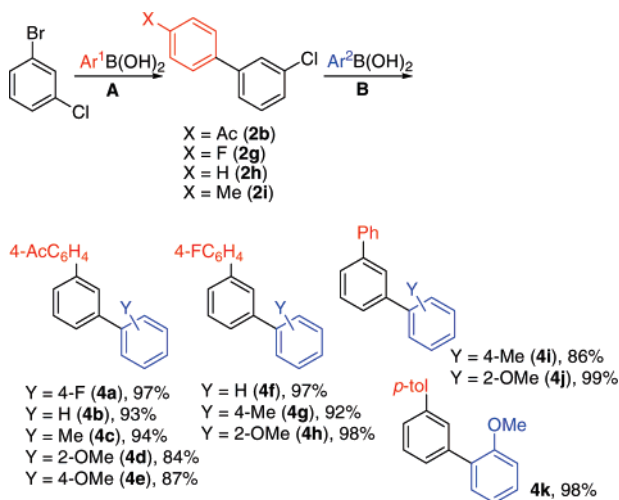
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SCHEME 3. Synthesis of 11 Unsymmetrical *p*-Terphenyls^a

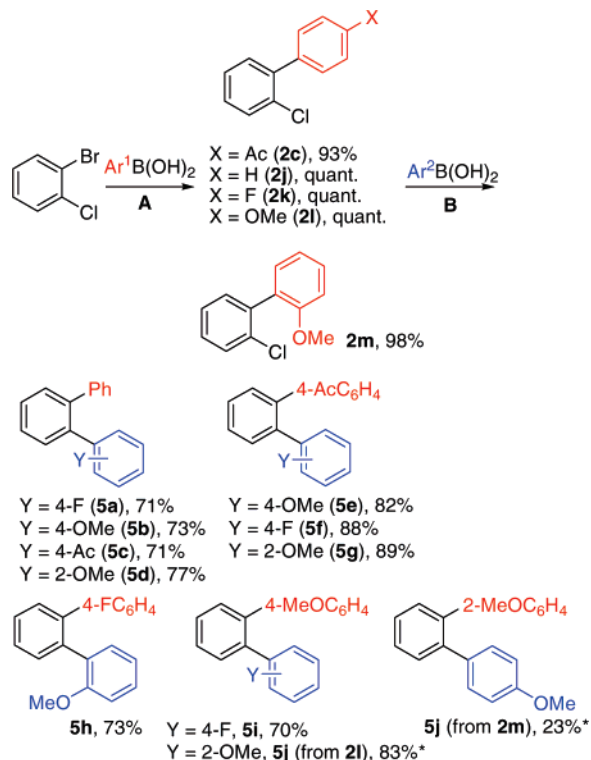
^a Aryl groups are colored red and blue, according to the order of their installation (first and second, respectively). Conditions: (A) $\text{Pd}(\text{OAc})_2$ (1.5 mol % of Pd), $\text{DMF-H}_2\text{O}$ (1:1), 4 h, rt; (B) $\text{Pd}_3(\text{OAc})_6$ (1 mol % of Pd), SPhos (2 mol %), $\text{THF-H}_2\text{O}$ (3:1), 21 h, 60 °C. Isolated yields of the terphenyls were calculated over two steps (based on bromochlorobenzene).

SCHEME 4. Synthesis of 11 Unsymmetrical *m*-Terphenyls^a

^a See footnote a, Scheme 1.

Finally, 10 unsymmetrical *o*-terphenyls were similarly constructed (Scheme 5). The synthesis of *o*-terphenyls may be envisaged to be more challenging due to the proximity of the reactive sites, which may impose unfavorable steric or cooperative effects. To examine this, five different arylboronic acids were employed in the coupling with 2-bromochlorobenzene. Again, under the “ligandless” protocol at ambient temperature, the first coupling proceeded smoothly in all cases, to furnish very good yields of the chlorobiaryls, irrespective of the electronic or steric nature of the substrates—yields of $\geq 93\%$ were obtained for all these reactions.

In contrast, the second coupling at the ortho position is much more sensitive to the constituents of the chloro intermediate: while the cross-coupling with the electronically deficient and neutral (**2c**, **2j**, and **2k**) substrates proceeded with high yields, attempts to access the dimethoxy-substituted compound **5j**, by the coupling of either **2l** or **2m** with the corresponding methoxyphenylboronic acid, did not afford any product under

SCHEME 5. Synthesis of 10 Unsymmetrical *o*-Terphenyls^a

^a See footnote a, Scheme 1. *Heated at 110 °C in toluene– H_2O for 24 h.

these conditions. While the failure of **2m** to react may be attributed to greater difficulty of palladium to access the *o*-chloride, the reason for the failure of **2l** to undergo any reaction appears to be strictly electronic, since the reactions between **2c**, **2j**, and **2k** with 2-methoxyphenylboronic acid had proceeded successfully to afford the products (**5d**, **5g**, and **5h**) in high yields. The unfavorable effect was overcome eventually by conducting these reactions at 110 °C in a mixed toluene–water system: the reaction between **2l** and 2-methoxyphenylboronic acid proceeding to give **5j** (83%). Nevertheless, the reaction between **2m** and 4-methoxyboronic acid only afforded a low yield (23%) of the same product.

These observations led to the following conclusions: (1) The ligand-assisted cross-coupling is more sensitive to steric and electronic effects on the chlorobiaryl, than the arylboronic acid substrate; therefore, (2) *o*-terphenyl compounds, such as **5j**, are assembled more efficiently by installing the sterically more demanding aryl group in the *second* SM reaction via its corresponding arylboronic acid, and (3) for substrates containing electron-donating substituents, higher reaction temperatures should be adopted for the second step.

The electro-optic properties of terphenyl molecules are dependent upon their conformations in the solid state,¹⁸ which are, in turn, dependent upon intermolecular and intra-ring torsional interactions. While the former favors a planar conformation for better crystal packing, the torsional forces favors the twisted form.¹⁹ Some of these features are displayed in the crystal structure of the *p*-terphenyl compound **3k** (Supporting

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Information). In the solid state, the molecule exhibits two different torsional angles between adjacent rings, with a smaller angle between the central arene and tolyl (34.4°) than that found between the central ring and the *o*-anisole (50.7°). Within each unit cell, the distance between the molecules and the orientation of the phenyl rings precludes any π interactions between the rings. Thus, the intra-ring torsional interaction overrides intermolecular interactions in **3k**. Preliminary studies of the UV absorption spectra of the compounds (Supporting Information) revealed discernible trends that can be correlated to the chemical structures, which may be explored further to design rigid molecules with novel optical properties.

Experimental Section

First Suzuki–Miyaura Coupling. A Radley tube was charged with a stir bar, Pd(OAc)₂ (1.5 mol %), bromochlorobenzene (95 mg, 0.5 mmol), the appropriate arylboronic acid R¹B(OH)₂ (0.55 mmol, 1.1 equiv), and K₃PO₄ (1 mmol, 2 equiv). The reaction vessel was positioned in the carousel and purged and filled with N₂, before the addition of a mixture of DMF–H₂O (1/1, 3 mL) by syringe. The reaction mixture was stirred at room temperature for 3 h, after which a solution of EtOAc–hexane (1/4, 15 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc–hexane (1/4, 15 mL × 2). The combined organic extracts were washed with H₂O (15 mL), dried (Na₂SO₄), and evaporated. The residue was used directly in the next step without further purification.

This reaction was subsequently conducted on a larger scale in air, using a round-bottom flask and reagent-grade THF (in place of DMF), with no noticeable deterioration in yield.

Second Suzuki–Miyaura Coupling. In a 5 mL volumetric flask flushed with N₂, Pd₃(OAc)₆ (5.6 mg, 0.025 mmol in Pd) and S-Phos

(20.5 mg, 0.05 mmol, 2 equiv) were mixed in degassed THF–H₂O (3/1, 5 mL). The mixture was sonicated for 6 min to generate the active catalyst. Meanwhile, a Radley reaction tube was charged with the chlorobiaryl, base (1.5 mmol, 3 equiv), and arylboronic acid Ar²B(OH)₂ (0.55 mmol), placed in the carousel, and purged and filled with N₂. A mixture of THF–H₂O (1.5 mL) was added, and the temperature of the solution was raised to 60 °C, whereupon 1 mL of the catalyst solution was injected. The reaction mixture was stirred, typically overnight. The solution was then allowed to cool to room temperature, and extracted with CH₂Cl₂ (3 × 15 mL). The combined layers were dried over Na₂SO₄, filtered, and evaporated. For products with limited solubility, these were collected and washed with an EtOAc–hexane mixture (4/1, 5 mL). Alternatively, purification was achieved by column chromatography. For reactions at high temperatures, the catalyst was generated in degassed toluene, and degassed water was added to the reaction mixture before the reaction temperature was raised to 100 °C.

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Supporting Information Available: Characterization data for all compounds, X-ray crystallographic data and CIF files for compounds **3k**, and copies of ¹H and ¹³C NMR spectra of all novel compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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