Traceless Liquid-Phase Synthesis of Biphenyls and Terphenyls Using Pentaerythritol as a Tetrapodal Soluble Support

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Application of a novel sulfonate-based traceless multifunctional linker system using pentaerythritol as a tetrapodal soluble support was demonstrated using liquid-phase parallel and combinatorial preparation of biphenyl and terphenyl compounds. Nickel-catalyzed reactions of pentaerythritol tetrakis(arenesulfonate)s with arylmagnesium bromides generated the desired products in sufficient yields through reductive cleavage/cross-coupling of the C–S bond. Homogeneous pentaerythritol-supported reactions could be accomplished using less nucleophile with shorter reaction periods than could the corresponding heterogeneous polymer-supported reactions. This liquid-phase approach using a small polyfunctionalized support combines advantages of solution-phase and solid-phase syntheses by allowing high reactivity, high atom economy, simple isolation, and real-time monitoring of the reaction progress.

Introduction

Since Merrifield's pioneering work in the 1960s,[1] solid-phase organic synthesis (SPOS) has been applied successfully throughout the field of parallel and combinatorial chemistry, two areas that play an important role in the search for lead molecules with a predetermined profile of properties.[2] Despite its great success, the heterogeneous nature of this strategy results in some problems, such as low reactivity and selectivity, reduced rate of reactions, and harsh reaction conditions. Furthermore, monitoring the reaction progress and identifying reaction intermediates attached to the insoluble polymer support remains difficult. Accordingly, solution-phase parallel/combinatorial synthesis without using any support has recently become of interest as an alternative approach.[3] High reaction rates and simple analysis without exerting extra effort to manipulate linkages between compounds and resins could be achieved with this method. However, this strategy would be attractive only when simple isolation and purification of the reaction intermediates and products is accomplished.

A powerful alternative technology that has recently emerged is liquid-phase combinatorial synthesis using soluble polymer supports. These supports are soluble in many organic solvents during reactions but are easily separable by precipitation after reactions.[4] Poly(ethylene glycol) and non-cross-linked polystyrene are the most common and promising soluble polymers. However, low loading capacity of polymer supports resulting in low chemical efficiency and difficult mass production of final products still remain problems. Therefore, alternative soluble supports continue to be studied. Quinoline[5] and functionalized ionic liquid[6] moieties have been recently suggested as small supports suitable for this method. The method of using polyfunctionalized core molecules[7] also seems to be useful in limited applications although it requires extra labor to prepare the complex core molecules.

Recently, we demonstrated solid-phase parallel synthesis of terphenyl compounds by traceless multifunctional cleavage of polymer-bound arenesulfonates, involving *ipso*-nucleophilic aromatic substitution of alkyloxysulfonyl moieties by aryl nucleophiles.[8] Development of traceless linker strategies that enable the release of unfunctionalized compounds from the polymer support represents an important challenge in SPOS.[9] Multifunctional linker systems, which allow introduction of certain atoms or molecular fragments at the original linking site during the cleavage step, are also of particular interest.[10] Our approach was a useful tool for the preparation of unfunctionalized oligophenyl libraries by allowing additional diversity with aryl moieties concomitantly with traceless release of the target compounds. However, typical shortcomings of solid-phase reactions, especially low reactivity and difficulty monitoring the reaction progress, might restrict this approach in general use.

In a program directed at the development of a suitable strategy for preparing conjugated hydrocarbon libraries, we looked for a system that could produce faster reactions and gram-scale synthesis without abandoning the easy isolation process of reaction intermediates. Another goal of the system was to ensure that routine analytical techniques, such as NMR, IR, and TLC, could be used to monitor the reaction progress and determine the structure of the products without cleaving them from the support.

Herein we report our efforts to develop a novel sulfonate-based traceless multifunctional linker system using pentaerythritol **1** as a tetrapodal support. This small soluble support is believed to be useful for producing conjugated hydrocarbon libraries with high atom economy.[11] Moreover,

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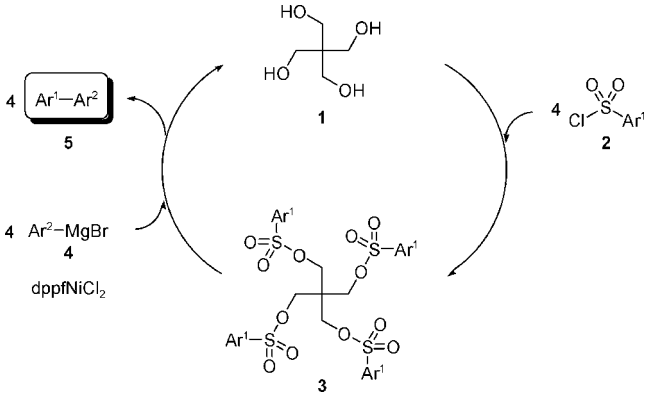
Scheme 1. Library Design for Biphenyl Compounds



substitution or elimination of arenesulfonate moieties in reactions with various nucleophiles could be naturally prevented in this system because they were attached to neopentyl carbons. Biphenyl and terphenyl compounds, known to exhibit a variety of biological,[12] optical[13] and electrical[14] properties, were preliminarily prepared and characterized by parallel and combinatorial syntheses in this study. Reaction intermediates could be obtained by simple precipitation in purities sufficient for subsequent reactions and could be further purified by simple recrystallization. The results of this study are presented and discussed below.

Result and Discussion

Biphenyl compounds were initially prepared by nickel-catalyzed reductive cleavage/cross-coupling of pentaerythritol tetrakis(arenesulfonate)s (**3**) (Scheme 1).

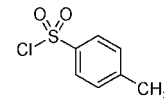
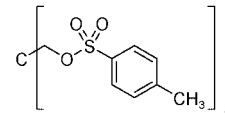
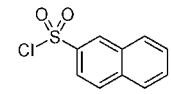
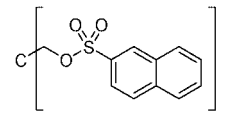
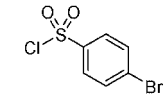
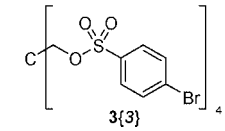
While neopentyl arenesulfonates were easily prepared by reactions of neopentyl alcohols with arenesulfonyl chlorides **2** using pyridine as a base, as in previous reports,[15] pentaerythritol **1** did not undergo the reaction efficiently in the presence of pyridine in various solvents, such as $CHCl_3$, DMF, DMSO, THF, and DME, at room or elevated temperatures. It was necessary to increase the strength of the base to make the reactions proceed. NaH gave the best result among several common bases. After a brief optimizing study, the following reactions were conducted using NaH in DME at the refluxing temperature. Results of reactions between **1** and **2** are summarized in Table 1. All three reactions generated the corresponding arenesulfonates **3**, which were easily purified by recrystallization from *i*-PrOH to give white solids in good yields within 12 h.

Benzenesulfonate moieties tethered to a flexible neopentyl core underwent the desired traceless multifunctional cleavage step, and pentaerythritol was an efficient tetrapodal soluble support for producing biphenyl compounds. Cross-coupling reactions of **3** with 5 equiv of arylmagnesium bromides **4** were performed in the presence of $dppfNiCl_2$ in refluxing THF. These conditions are the most efficient reaction conditions of benzenesulfonates.[15] Both **3**{*1*} and **3**{*2*} generated corresponding biphenyls **5** via nucleophilic aromatic substitution of the neopentyloxysulfonyl moiety by **4** in good yields (Table 2). Regeneration of **1** was identified by GC analysis.

Reactions proceeded in an atom economic manner compared to not only the original organic reactions of neopentyl arenesulfonates but also to corresponding polymer-supported reactions by generating only one equiv of small byproduct **1** while producing 4 equiv of product **5**. In addition, reactions were completed with competitive yields despite the use of only 5 equiv of **4** within 14 h. Corresponding solid-phase reactions typically require 15 equiv of **4** and 48 h to be completed.[8]

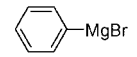
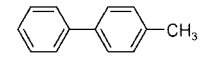
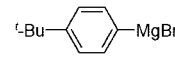
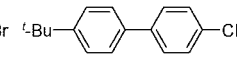
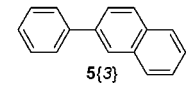
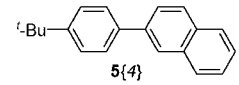
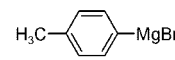
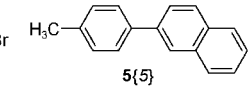
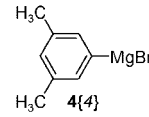
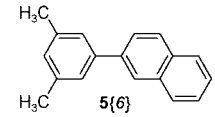
Unsymmetrical terphenyl compounds **8** were produced by Ni-catalyzed coupling reactions of pentaerythritol tetrakis-(biphenylsulfonate)s (**7**), which were prepared by palladium-catalyzed Suzuki–Miyaura reactions of tetrakis(4-bromobenzenesulfonate) **3**{*3*} with arylboronic acids **6** (Scheme 2).

Table 1. Preparation of Tetrakis(arenesulfonate)s **3**[a]

entry	sulfonyl chloride **2**	sulfonate **3**	yield (%)[b]
1	 **2**{*1*}	 **3**{*1*}	76
2	 **2**{*2*}	 **3**{*2*}	79
3	 **2**{*3*}	 **3**{*3*}	74

[a] Reactions of **1** (7.344 mmol) with **2** (35.25 mmol) were carried out at the refluxing temperature of DME (30 mL) using NaH (35.25 mmol). [b] Isolated yields based on **1**.

Table 2. Nickel-Catalyzed Coupling of **3** with **4** to Produce **5**[a]

entry	sulfonate **3**	Grignard reagent **4**	biphenyls **5**	yield (%)[b]
1	**3**{*1*}	 **4**{*1*}	 **5**{*1*}	93 [c]
2	**3**{*1*}	 **4**{*2*}	 **5**{*2*}	96 [c]
3	**3**{*2*}	**4**{*1*}	 **5**{*3*}	84
4	**3**{*2*}	**4**{*2*}	 **5**{*4*}	77
5	**3**{*2*}	 **4**{*3*}	 **5**{*5*}	81
6	**3**{*2*}	 **4**{*4*}	 **5**{*6*}	73

[a] Reactions of **3** (0.200 mmol) with **4** (2.40 + 1.60 mmol) were carried out at the refluxing temperature of THF (4.0 mL) using $dppfNiCl_2$ (0.0400 mmol). [b] Isolated yields based on **3**. [c] GC yields based on **3**{*1*}.

Scheme 2. Library Design for Terphenyl Compounds

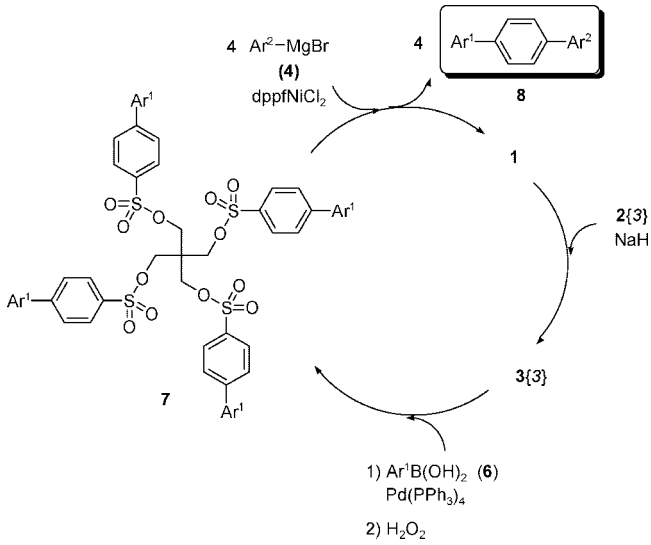
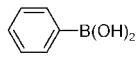
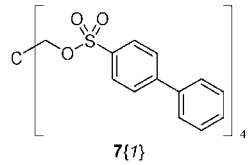
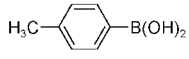
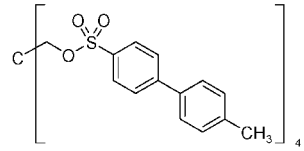
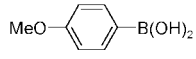
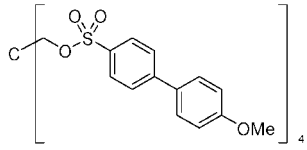
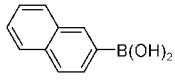
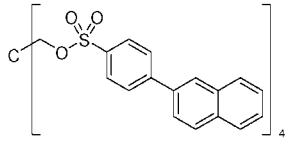


Table 3. Preparation of Tetrakis(biphenylsulfonate)s **7**[a]

entry	boronic acid **6**	product **7**	yield (%)[b]
1	 **6**{*1*}	 **7**{*1*}	77
2	 **6**{*2*}	 **7**{*2*}	80
3	 **6**{*3*}	 **7**{*3*}	75
4	 **6**{*4*}	 **7**{*4*}	65

[a] Reactions of **3**{*3*} (1.976 mmol) with **6** (8.692 mmol) were carried out at the refluxing temperature of toluene (20 mL) and EtOH (10 mL) using $Pd(PPh_3)_4$ (0.237 mmol) and 2 M *aq* Na_2CO_3 (8.0 mL). [b] Isolated yields based on **3**{*3*}.

Bromobenzenesulfonate **3**{*3*} reacted with **6** in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 to produce the corresponding biphenylsulfonates **7**{*1–4*} in good yields (Table 3). Although a detailed study to optimize reaction conditions was not undertaken, all reactions were completed within 8 h at the refluxing temperature of toluene/EtOH/water. Cleavage of C–S bonds or C–O bonds was not observed under these standard reaction conditions. Although 2-naphthylboronic acid **6**{*4*} showed relatively lower reactivity, conversion of each reactive site of **3**{*3*} was still higher than 90%. The products **7** were easily isolated by precipitation using *i*-PrOH and further purified by simple recrystallization from EtOAc or acetone.

Cross-coupling reactions of **7** with **4** were performed in the presence of $dppfNiCl_2$ in refluxing THF. Results are summarized in Table 4. Most of the reactions rapidly proceeded to produce the corresponding unsymmetrical terphenyls **8** in high yields. All reactions could be completed within 14 h with competitive yields using only 5 equiv of **4**, whereas corresponding solid-phase reactions require 15 equiv of **4** and 30 h to be completed.[8] This approach using a small tetrapodal support could be an efficient substitute for polymer-supported reactions in appropriate conditions.

Application of this strategy to the combinatorial synthesis of a terphenyl library was demonstrated. Tetrakis(bromobenzenesulfonate) **3**{*3*}, prepared by reaction of **1** with **2**{*3*} and isolated by simple precipitation using *i*-PrOH, was treated with a mixture of four boronic acids **6**{*1–4*} in the presence of $Pd(PPh_3)_4$ for 8 h. A mixture of tetrakis(biphenylsulfonate)s **7** was also obtained by precipitation using *i*-PrOH as light brown solids in good purity. Reaction intermediates **3**{*3*} and **7** did not require further purification before undergoing a subsequent coupling reaction.

Composition of biphenyl moieties in **7** was investigated by cleaving them via the reaction with excess **4**{*1*}. GC analysis of the reaction mixture indicated that all four boronic acids **6** underwent the desired coupling reactions successfully as summarized in Figure 1. The relative ratio of biphenyl moieties could be estimated by analyzing terphenyls **8**{*1–4*}, which were produced at 39.3%, 36.7%, 13.3%, and 10.6%, respectively.

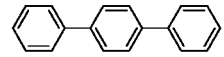
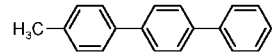
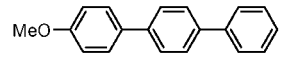
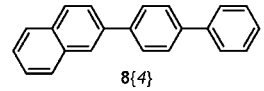
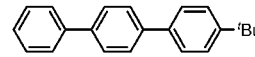
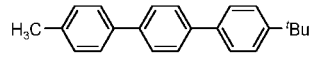
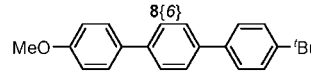
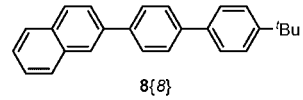
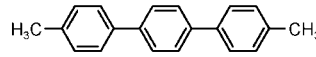
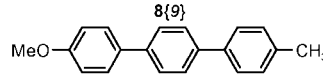
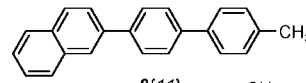
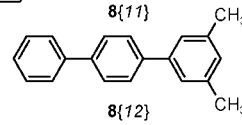
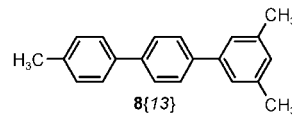
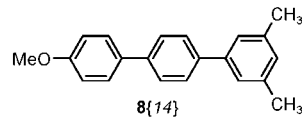
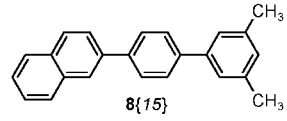
The final cross-coupling reactions of **7** with an equimolar mixture of **4**{*1–4*} were performed in the presence of $dppfNiCl_2$ in refluxing THF. This pentaerythritol-supported combinatorial synthesis allowed efficient preparation of an unsymmetrical terphenyl library in terms of reaction rate and atom economy. After 14 h of reaction and standard workup, all expected terphenyl derivatives could be identified by GC analyses (Figure 2). The relative composition of product **8** was in agreement with the result in Figure 1 (Table 5).

Conclusion

We demonstrated the application of pentaerythritol as a novel polyfunctionalized soluble support in the parallel/combinatorial synthesis of oligophenyl compounds. Four sulfonate linkers attached on a neopentyl core offer highly efficient traceless multifunctional cleavage to generate biphenyl and terphenyl derivatives leaving no "memory" of resin attachment.

This approach combines the advantages of polymer-supported syntheses with those of classical organic reactions by offering considerable advantages. First, reactions proceed in a homogeneous solution to allow faster reactions with less reagents compared to corresponding solid-phase reactions. Second, high atom economy is achieved due to the extremely high loading capacity of pentaerythritol. Third, reaction intermediates can be purified by simple recrystallization or even precipitation. Finally, progress of the reaction and structure of reaction intermediates can be determined by

Table 4. Nickel-Catalyzed Coupling of **7** with **4** to Produce **8**[a]

entry	sulfonate **7**	Grignard reagent **4**	product **8**	yield (%)[b]
1	**7**{*1*}	**4**{*1*}	 **8**{*1*}	72
2	**7**{*2*}	**4**{*1*}	 **8**{*2*}	82
3	**7**{*3*}	**4**{*1*}	 **8**{*3*}	79
4	**7**{*4*}	**4**{*1*}	 **8**{*4*}	76
5	**7**{*1*}	**4**{*2*}	 **8**{*5*}	85
6	**7**{*2*}	**4**{*2*}	 **8**{*6*}	78
7	**7**{*3*}	**4**{*2*}	 **8**{*7*}	81
8	**7**{*4*}	**4**{*2*}	 **8**{*8*}	73
9	**7**{*1*}	**4**{*3*}	**8**{*2*}	83
10	**7**{*2*}	**4**{*3*}	 **8**{*9*}	81
11	**7**{*3*}	**4**{*3*}	 **8**{*10*}	75
12	**7**{*4*}	**4**{*3*}	 **8**{*11*}	74
13	**7**{*1*}	**4**{*4*}	 **8**{*12*}	78
14	**7**{*2*}	**4**{*4*}	 **8**{*13*}	76
15	**7**{*3*}	**4**{*4*}	 **8**{*14*}	66
16	**7**{*4*}	**4**{*4*}	 **8**{*15*}	68

[a] Reaction of sulfonates **7** (0.100 mmol) with **4** (2.00 mmol) were carried out at the refluxing temperature of THF (3.0 mL) using dppfNiCl$_2$ (0.0200 mmol). [b] Isolated yields based on **7**.

routine analytical techniques, such as NMR, IR, and TLC, without extra effort to cleave compounds from the support. Also, this approach does not require expensive resins.

The method using a small tetrapodal support is believed to be an efficient substitute for polymer-supported reactions in appropriate conditions. The whole strategy combined with

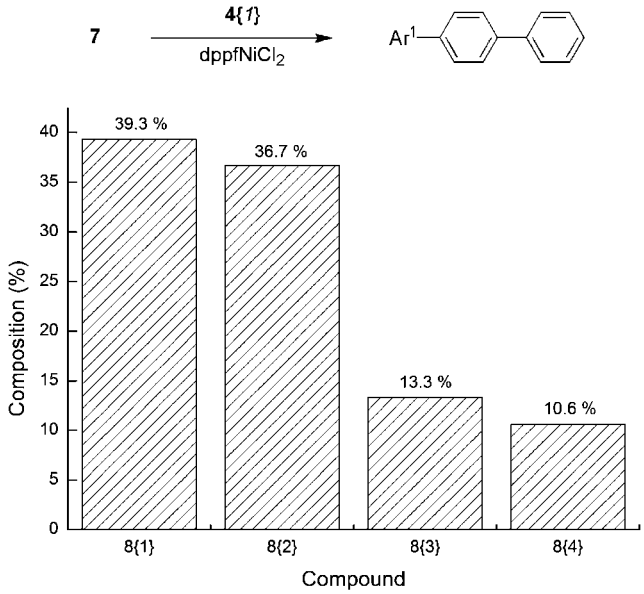


Figure 1. Composition of **8** produced by reaction of **7** with **4**{*1*}.

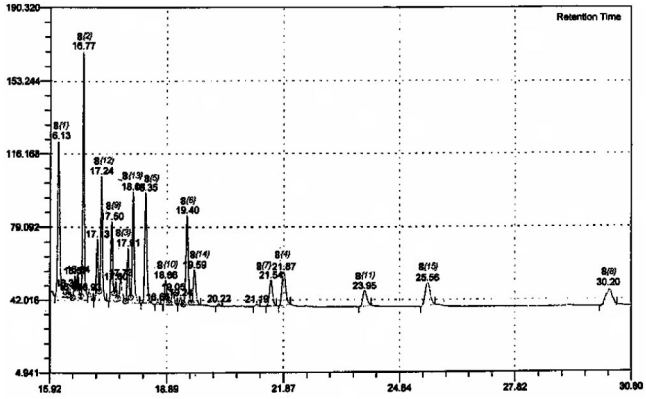


Figure 2. GC analysis of **8** produced by reaction of **7** with **4**.

traceless multifunctional cleavage of arenesulfonates shows combinatorial potential for synthesis of larger libraries of highly conjugated hydrocarbons and is ongoing in our laboratories.

Experimental Section

General Procedure for Preparation of Pentaerithritol Tetrakis(arensulfonates) 3{*1–3*}. To pentaerythritol **1** (7.344 mmol) and sodium hydride (35.25 mmol) in DME (30 mL) at 0 °C was added sulfonyl chloride **2** (35.25 mmol) in small portions via a syringe under an argon atmosphere. The reaction mixture was heated at reflux for 12 h, cooled to rt, and diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude sulfonates **3**{*1–3*} were purified by recrystallization from *i*-PrOH.

Pentaerythritol tetrakis(*p*-toluenesulfonate) 3{*1*} was prepared by the reaction of **1** (1.000 g, 7.344 mmol) with **2**{*1*} (6.721 g, 35.25 mmol). The crude compound was purified by recrystallization from *i*-PrOH to give **3**{*1*} (4.203 g, 76%) as a white solid: TLC R_f 0.18 ($CHCl_3$); mp 149–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.48 (s, 12H), 3.81 (s, 8H), 7.37 (d, J = 8.4 Hz, 8H), 7.69 (d, J = 8.4 Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8 (×4), 43.4, 65.7 (×4), 128.3 (×8), 130.5 (×8), 131.6 (×4), 146.0 (×4). Anal. Calcd for $C_{33}H_{36}O_{12}S_4$: C, 52.64; H, 4.82; S, 17.04. Found: C, 52.36; H, 4.52; S, 17.39.

Table 5. Unsymmetrical Terphenyl Library[a]

entry	Ar^1	Ar^2	terphenyls 8	composition (%)[b]
1	Ph	Ph	8 {*1*}	12.2
2	4-Me-Ph	Ph	8 {*2*}	15.6
3	4-MeO-Ph	Ph	8 {*3*}	3.8
4	2-naphthyl	Ph	8 {*4*}	5.3
5	Ph	4-*t*-Bu-Ph	8 {*5*}	9.7
6	4-Me-Ph	4-*t*-Bu-Ph	8 {*6*}	8.2
7	4-MeO-Ph	4-*t*-Bu-Ph	8 {*7*}	3.0
8	2-naphthyl	4-*t*-Bu-Ph	8 {*8*}	4.5
9	Ph	4-Me-Ph	8 {*2*}	15.6
10	4-Me-Ph	4-Me-Ph	8 {*9*}	5.8
11	4-MeO-Ph	4-Me-Ph	8 {*10*}	2.3
12	2-naphthyl	4-Me-Ph	8 {*11*}	3.1
13	Ph	3,5-di-Me-Ph	8 {*12*}	8.7
14	4-Me-Ph	3,5-di-Me-Ph	8 {*13*}	8.6
15	4-MeO-Ph	3,5-di-Me-Ph	8 {*14*}	3.8
16	2-naphthyl	3,5-di-Me-Ph	8 {*15*}	4.7

[a] Reactions of **7** (0.100 mmol) with **4** (2.00 mmol) were carried out at the refluxing temperature of THF (3.0 mL) using $dppfNiCl_2$ (0.0200 mmol). [b] Numbers in parentheses indicate relative GC ratios.

Pentaerythritol tetrakis(2-naphthalenesulfonate) 3{*2*} was prepared by the reaction of **1** (1.000 g, 7.344 mmol) with **2**{*2*} (7.991 g, 35.25 mmol). The crude compound was purified by recrystallization from *i*-PrOH to give **3**{*2*} (5.205 g, 79%) as a white solid: TLC R_f 0.17 ($CHCl_3$); mp 159–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.96 (s, 8H), 7.61 (dd, J = 8.7, 1.9 Hz, 4H), 7.65–7.74 (m, 8H), 7.90 (d, J = 8.7 Hz, 4H), 7.86–7.95 (m, 8H), 8.36 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.6, 66.0 (×4), 122.4 (×4), 128.2 (×4), 128.3 (×4), 129.8 (×4), 130.0 (×4), 130.3 (×4), 130.4 (×4), 131.5 (×4), 132.1 (×4), 135.8 (×4). Anal. Calcd for $C_{45}H_{36}O_{12}S_4$: C, 60.25; H, 4.05; S, 14.30. Found: C, 60.38; H, 3.99; S, 14.09.

Pentaerythritol tetrakis(4-bromobenzenesulfonate) 3{*3*} was prepared by the reaction of **1** (1.000 g, 7.344 mmol) with **2**{*3*} (9.008 g, 35.25 mmol). The crude compound was purified by recrystallization from *i*-PrOH to give **3**{*3*} (5.502 g, 74%) as a white solid: TLC R_f 0.28 (CH_2Cl_2); mp 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 8H), 7.67 (d, J = 8.9 Hz, 8H), 7.73 (d, J = 8.9 Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.6, 65.6 (×4), 129.7 (×8), 130.3 (×4), 133.3 (×8), 133.6 (×4); Anal. Calcd for $C_{29}H_{24}Br_4O_{12}S_4$: C, 34.41; H, 2.39; S, 12.67. Found: C, 34.23; H, 2.44; S, 12.46.

General Procedure for Cross-Coupling Reactions of 3 with 4. To a stirred solution of **3** (0.200 mmol) and $dppfNiCl_2$ (0.0400 mmol) in THF (4.0 mL) was slowly added Grignard reagents **4** (2.40 mmol) at rt under an Ar atmosphere. The reaction mixture was heated at reflux for 6 h and cooled to rt, and an additional 1.60 mmol of **4** was added to the solution. The resulting mixture was heated at reflux for 8 h, cooled to room temperature, and diluted with Et_2O. The organic layer was washed with 1% aq HCl, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude biphenyls **5**{*1–6*} were purified by either chromatography or recrystallization.

General Procedure for Preparation of Pentaerythritol Tetrakis(biphenylsulfonates) 7{*1–4*}. To a solution of **3**{*3*} (1.976 mmol) and $Pd(PPh_3)_4$ (0.237 mmol) in toluene (20 mL) was added 2.0 M aq Na_2CO_3 (8.0 mL) under an Ar atmosphere. To the resulting mixture was added **6** (8.692 mmol) dissolved in EtOH (5.0 mL). The reaction mixture was heated at reflux for 8 h with vigorous stirring. Upon cooling to rt, 30% hydrogen peroxide (0.4 mL) was added to oxidize the residual boronic acid. The mixture was stirred at rt for 1 h and diluted with $CHCl_3$. The organic layer was washed with water. dried over $MgSO_4$. and concentrated in vacuo. The crude sulfonates **7** were purified by recrystallization from acetone or EtOAc.

Pentaerythritol tetrakis(4-biphenylsulfonate) 7{*1*} was prepared by the reaction of **3**{*3*} (2.000 g, 1.976 mmol) with **6**{*1*} (1.060 g, 8.692 mmol) in the presence of $Pd(PPh_3)_4$ (0.274 g, 0.237 mmol) and 2.0 M aq Na_2CO_3 (8.0 mL) by using toluene (20 mL) as a solvent. The crude product was purified by recrystallization from acetone to give **7**{*1*} (1.523 g, 77%) as a pale yellowish solid: TLC R_f 0.19 (CH_2Cl_2); mp 188–189 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.96 (s, 8H), 7.44–7.49 (m, 12H), 7.59 (d, J = 8.3 Hz, 8H), 7.71 (d, J = 8.5 Hz, 8H), 7.85 (d, J = 8.5 Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.6, 65.7 (×), 127.7 (×8), 128.5 (×8), 128.8 (×8), 129.1 (×4), 129.4 (×8), 133.1 (×4), 139.1 (×4), 147.7 (×4); Anal. Calcd for $C_{53}H_{44}O_{12}S_4$: C, 63.58; H, 4.43; S, 12.81. Found: C, 63.23; H, 4.32; S, 12.44.

Pentaerythritol tetrakis(4′-methyl-4-biphenylsulfonate) 7{*2*} was prepared by the reaction of **3**{*3*} (2.000 g, 1.976 mmol) with **6**{*2*} (1.182 g, 8.692 mmol) in the presence of $Pd(PPh_3)_4$ (0.274 g, 0.237 mmol) and 2.0 M aq Na_2CO_3 (8.0 mL) by using toluene (20 mL) as a solvent. The crude product was purified by recrystallization from EtOAc to give **7**{*2*} (1.671 g, 80%) as a white solid: TLC R_f 0.28 ($CHCl_3$); mp 226–227 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 12H), 3.95 (s, 8H), 7.28 (d, J = 8.2 Hz, 8H), 7.49 (d, J = 8.2 Hz, 8H), 7.68 (d, J = 8.7 Hz, 8H), 7.82 (d, J = 8.7 Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (×4), 43.5, 65.7 (×4), 127.5 (×8), 128.1 (×8), 128.8 (×8), 130.1 (×8), 132.7 (×4), 136.2 (×4), 139.2 (×4), 147.6 (×4). Anal. Calcd for $C_{57}H_{52}O_{12}S_4$: C, 64.75; H, 4.96; S, 12.13. Found: C, 64.98; H, 4.92; S, 12.24.

Pentaerythritol tetrakis(4′-methoxy-4-biphenylsulfonate) 7{*3*} was prepared by the reaction of **3**{*3*} (2.000 g, 1.976 mmol) with **6**{*3*} (1.321 g, 8.692 mmol) in the presence of $Pd(PPh_3)_4$ (0.274 g, 0.237 mmol) and 2.0 M aq Na_2CO_3 (8.0 mL) by using toluene (20 mL) as a solvent. The crude product was purified by recrystallization from acetone to give **7**{*3*} (1.661 g, 75%) as a white solid: TLC R_f 0.25 ($CHCl_3$); mp 202–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 12H), 3.94 (s, 8H), 6.99 (d, J = 8.9 Hz, 8H), 7.54 (d, J = 8.9 Hz, 8H), 7.66 (d, J = 8.7 Hz, 8H), 7.81 (d, J = 8.7 Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.5, 55.5 (×4), 65.7 (×4), 114.8 (×8), 127.8 (×8), 128.8 (×8), 128.9 (×8), 131.4 (×4), 132.2 (×4), 147.3 (×4), 160.7 (×4). Anal. Calcd for $C_{57}H_{52}O_{16}S_4$: C, 61.06; H, 4.67; S, 11.44. Found: C, 60.70 H, 4.44; S, 11.13.

Pentaerythritol tetrakis(4-(2-naphtyl)benzenesulfonate) 7{*4*} was prepared by the reaction of **3**{*3*} (2.000 g, 1.976 mmol) with **6**{*4*} (1.495 g, 8.692 mmol) in the presence of $Pd(PPh_3)_4$ (0.274 g, 0.237 mmol) and 2.0 M aq Na_2CO_3 (8.0 mL) by using toluene (20 mL) as a solvent. The crude product was purified by recrystallization from EtOAc to give **7**{*4*} (1.543 g, 65%) as a white solid: TLC R_f 0.18 ($CHCl_3$); mp 208–209 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.02 (s, 8H), 7.49–7.55 (m, 8H), 7.66 (dd, J = 8.6, 1.5 Hz, 4H), 7.83 (d, J = 8.4 Hz, 8H), 7.83–7.88 (m, 12H), 7.91 (d, J = 8.4 Hz, 8H), 8.03 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 43.7, 65.9 (×4), 125.1 (×4), 127.0 (×4), 127.1 (×8), 127.9 (×4), 128.6 (×8), 128.7 (×4), 128.8 (×8), 129.2 (×4), 133.0 (×4), 133.4 (×4), 133.7 (×4), 136.3 (×4), 147.6 (×4). Anal. Calcd for $C_{57}H_{52}O_{16}S_4$: C, 68.98; H, 4.36; S, 10.68. Found: C, 69.59 H, 4.04; S, 10.55.

General Procedure for Cross-Coupling Reactions 7 with 4. To a stirred solution of **7** (0.100 mmol) and $dppfNiCl_2$ (0.0200 mmol) in THF (3.0 mL) was slowly added Grignard reagents **4** (1.20 mmol) at rt. The reaction mixture was heated for 6 h and cooled to room temperature, and an additional 0.80 mmol of **4** was added to the solution. The resulting mixture was heated at reflux for 8 h, cooled to rt, and diluted with Et_2O. The organic layer was washed with 1% aq HCl, water, and brine, dried over $MgSO_4$, and concentrated in vacuo.

2-(Biphenyl-4-yl)-naphthalene 8{*4*} was prepared by the reaction of **7**{*4*} (120 mg, 0.100 mmol) with **4**{*1*} (1.0 M in THF, 1.20 mL, 1.20 mmol + 0.80 mL, 0.80 mmol) in the presence of $dppfNiCl_2$ (13.7 mg, 0.0200 mmol). The crude product was purified by recrystallization from MeOH to give **8**{*4*} (89.7 mg, 80%) as a white solid: TLC R_f 0.63 (Et_2O/*n*-hexane = 1:1); mp 222–223 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (t, J = 7.4 Hz, 1H), 7.49 (dd, J = 7.4, 7.2 Hz, 2H), 7.46–7.53 (m, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.80 (dd, J = 8.4, 1.8 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 7.6 Hz, 1H), 7.93 (t, J = 9.9, 8.8 Hz, 2H), 8.10 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.7, 125.9, 126.2, 126.6, 127.3 (×2), 127.7, 127.9 (×2), 127.9, 128.0 (×2), 128.5, 128.8, 129.1 (×2), 133.0, 134.0, 138.3, 140.3, 140.5, 141.0. HRMS (EI, 70 eV): calcd for $C_{22}H_{16}$, 280.1254; found, 280.1181.

2-(4′-*tert*-Butylbiphenyl-4-yl)-naphthalene 8{*8*} was prepared by the reaction of **7**{*4*} (120 mg, 0.100 mmol) with **4**{*2*} (0.5 M in THF, 2.40 mL, 1.20 mmol + 1.60 mL, 0.80 mmol) in the presence of $dppfNiCl_2$ (13.7 mg, 0.0200 mmol). The crude product was purified by recrystallization from MeOH to give **8**{*8*} (110.4 mg, 82%) as a white solid: TLC R_f 0.64 (Et_2O/*n*-hexane = 1:1); mp 210–212 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (s, 9H), 7.47–7.53 (m, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.3 Hz, 3H), 7.87 (d, J = 7.8 Hz, 1H), 7.92 (t, J = 9.5, 8.8 Hz, 2H), 8.09 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.5 (×3), 34.7, 125.7, 125.9, 126.1 (×2), 126.2, 126.6, 127.0 (×2), 127.7 (×2), 127.9, 128.0 (×2), 128.5, 128.7, 132.9, 134.0, 138.0, 138.4, 140.0, 140.3, 150.7. HRMS (EI, 70 eV): calcd for $C_{26}H_{24}$, 336.1878; found, 336.1938.

4″-Methoxy-4-methyl-[1,1′,4′,1″]terphenyl 8{*10*} was prepared by the reaction of **7**{*3*} (112 mg, 0.100 mmol) with **4**{*3*} (1.0 M in THF, 1.20 mL, 1.20 mmol + 0.80 mL, 0.80

mmol) in the presence of dppfNiCl$_2$ (13.7 mg, 0.0200 mmol). The crude product was purified by recrystallization from MeOH to give **8**{*10*} (82.2 mg, 75%) as a white solid: TLC R_f 0.57 (Et$_2$O/*n*-hexane = 1:1); mp 243–244 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.36 (s, 3H), 3.81 (s, 3H), 7.04 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.70 (s, 4H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.2, 55.5, 114.5 (×2), 127.1 (×2), 127.3 (×2), 127.5 (×2), 128.3 (×2), 129.8 (×2), 133.6, 137.3, 138.2, 139.7 (×2), 159.5. HRMS (EI, 70 eV): calcd for $C_{20}H_{18}O$, 274.1358; found, 274.1340.

2-(4′-Methylbiphenyl-4-yl)-naphthalene 8{*11*} was prepared by the reaction of **7**{*4*} (120 mg, 0.100 mmol) with **4**{*3*} (1.0 M in THF, 1.20 mL, 1.20 mmol + 0.80 mL, 0.80 mmol) in the presence of dppfNiCl$_2$ (13.7 mg, 0.0200 mmol). The crude product was purified by recrystallization from MeOH to give **8**{*11*} (89.5 mg, 76%) as a white solid: TLC R_f 0.71 (Et$_2$O/*n*-hexane = 1:1); mp 227–228 °C. ^{1}H NMR (500 MHz, CDCl$_3$) δ: 2.42 (s, 3H), 7.28 (d, J = 8.0 Hz, 2H), 7.47–7.52 (dq, J = 6.9, 7.4, 1.3, 1.3, 1.9 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.92 (t, J = 9.4, 8.7 Hz, 2H), 8.09 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.2, 125.7, 125.9, 126.2, 126.6, 127.2 (×2), 127.7 (×2), 127.9, 128.0 (×2), 128.5, 128.7, 129.8 (×2), 132.9, 134.0, 137.5, 138.1, 138.4, 140.0, 140.4. HRMS (EI, 70 eV): calcd for $C_{23}H_{18}$, 294.1409; found, 294.1365.

4″-Methoxy-3,5-dimethyl-[1,1′,4′,1″]terphenyl 8{*14*} was prepared by the reaction of **7**{*3*} (112 mg, 0.100 mmol) with **4**{*4*} (0.5 M in THF, 2.40 mL, 1.20 mmol + 1.60 mL, 0.80 mmol) in the presence of dppfNiCl$_2$ (13.7 mg, 0.0200 mmol). The crude product was purified by recrystallization from MeOH to give **8**{*14*} (86.4 mg, 75%) as a white solid: TLC R_f 0.57 (Et$_2$O/*n*-hexane = 1:1); mp 143–144 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ: 2.37 (s, 6H), 3.87 (s, 3H), 7.01 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.31 (s, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.70 (s, 4H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.5 (×2), 55.5, 114.5 (×2), 125.2 (×2), 127.2 (×2), 127.7 (×2), 128.3 (×2), 129.2, 133.6, 138.6 (×2), 139.8, 140.0, 141.1, 159.5. HRMS (EI, 70 eV): calcd for $C_{21}H_{20}O$, 288.1514; found, 288.1515.

2-(3′,5′-Dimethylbiphenyl-4-yl)-naphthalene 8{*15*} was prepared by the reaction of **7**{*4*} (120 mg, 0.100 mmol) with **4**{*4*} (0.5 M in THF, 2.40 mL, 1.20 mmol + 1.60 mL, 0.80 mmol) in the presence of dppfNiCl$_2$ (13.7 mg, 0.0200 mmol). The crude product was purified by recrystallization from MeOH to give **8**{*15*} (93.8 mg, 76%) as a white solid: TLC R_f 0.60 (Et$_2$O/*n*-hexane = 1:1); mp 150–151 °C. ^{1}H NMR (500 MHz, CDCl$_3$) δ: 2.41 (s, 6H), 7.02 (s, 1H), 7.28 (s, 2H), 7.47–7.53 (dq, J = 6.9, 7.3, 1.3, 1.2, 1.9 Hz, 2H), 7.70 (d, J = 8.30, 2H), 7.79 (d, J = 8.30 Hz, 2H), 7.79–7.80 (m, 1H), 7.87 (d, J = 7.68 Hz, 1H), 7.92 (t, J = 8.7, 8.5 Hz, 2H), 8.09 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.5 (×2), 125.3 (×2), 125.7, 125.9, 126.2, 126.6, 127.9 (×4), 128.5, 128.7, 129.3, 132.9, 134.0, 138.4, 138.6 (×3), 140.1, 140.7, 141.0. HRMS (EI, 70 eV): calcd for $C_{24}H_{20}$, 308.1565; found, 308.1542.

Supporting Information Available. ^{1}H and ^{13}C NMR for compounds **3**{*1–3*}, **7**{*1–4*}, **8**{*4*}, **8**{*8*}, **8**{*10–11*}, and **8**{*14–15*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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