

Article

Solventless Synthesis of Quaterphenyls and Terphenyls from Chalcones and Allylsulfones under Phase Transfer Catalysis Conditions

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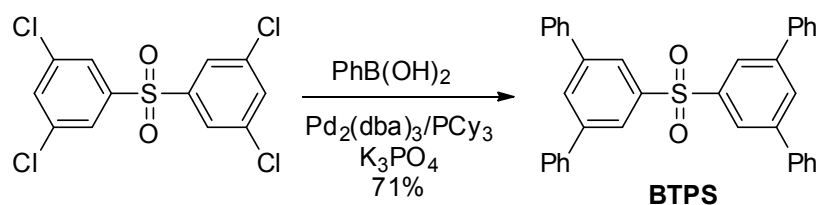
Abstract: Easily available chalcones and allyl sulfones along with cheap solid NaOH and polyethyleneglycol (PEG) 1000 have been used to directly generate the *meta*-terphenyl or quaterphenyl motifs under Phase Transfer Catalysis solventless conditions. The new approach provides an economic and environmentally friendly solution to removal of hazardous bases as well as organic solvents.

Keywords: terphenyls; quaterphenyls; Phase Transfer Catalysis; PEG; green chemistry; solventless

1. Introduction

The synthesis of polysubstituted aromatic compounds relies on various strategies involving multistep approaches using organometallic species [1–5] or cycloadditions [6,7], or under acid or basic reaction conditions [8].

The synthesis of terphenyls has recently aroused a great deal of interest since this skeleton has been found in many natural products, for example fungi, exhibiting diverse bioactivity [9]. Moreover, *meta*-terphenyls have been used as ligands [10], as intermediates for the synthesis of covalent nanostructures [11] and as electron transporting material [12]. For example, 5',5''''-sulfonyl-di-[1,1':3',1''']-terphenyl (BTSP, Scheme 1), bearing two *meta*-terphenyl subunits, has been recently prepared from *bis*(3,5-dichlorophenyl)sulfone [13] by Suzuki-Miyaura coupling in order to develop new highly efficient organic light emitting diodes (OLED) [14].

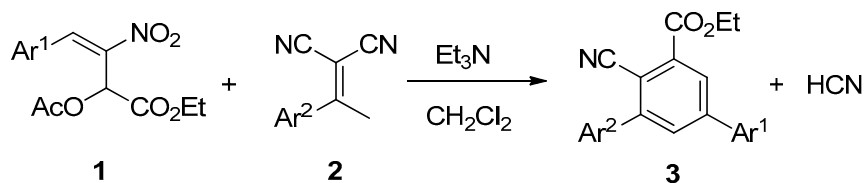


Scheme 1. Synthesis of 5',5''''-sulfonyl-di-[1,1':3',1''']-terphenyl (BTSP).

Although several procedures allow the synthesis of the terphenyl skeleton, the development of alternative methods is still an issue since the regioselective construction of carbon–carbon bonds is a goal not always easy to be achieved.

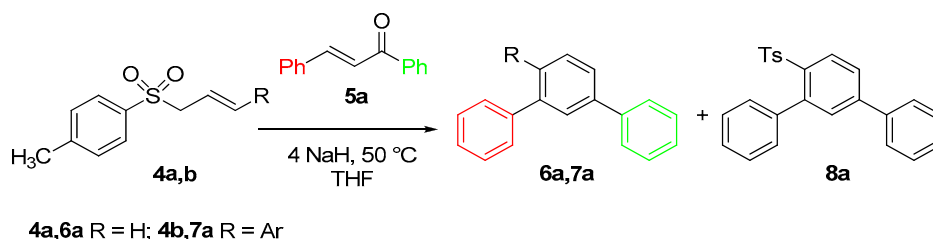
A more practical approach to terphenyls has been realized by direct procedures capable of generating the central benzene ring with a single reaction involving easily available reagents.

For example, the Morita-Baylis-Hillman reaction of nitroalkenes **1** and alkylidene malono nitriles **2** gave good yields of the desired substituted terphenyls **3** under mild conditions (Scheme 2). However, this approach suffers from the need for additional steps to prepare reactants and the formation of toxic HCN during annulation [15].



Scheme 2. Morita-Baylis-Hillman route to *meta*-terphenyls.

On the other hand, a mixture of *meta*-terphenyl **6a** along with sulfonyl-*meta*-terphenyl **8a** has been obtained by reacting allylsulfone **4a** with chalcone **5a** in the presence of excess of NaH in THF at 50 °C (Scheme 3) [16]. By the same approach, 1,2,4-quaterphenyls **7a** can also be obtained by using an aryl substituted allyl sulfone **4b** [17].



Scheme 3. Base promoted route to *meta*-terphenyls. The red and green benzenic rings are used to highlight the position of aryl groups of the starting chalcone in the produced *meta*-terphenyl.

The aryl groups in the 1,3-position of *meta*-terphenyls **6** derive from the starting chalcones **5**; therefore, a variety of substituted terphenyls can be prepared by using substituted chalcones, easily accessed by the Claisen-Schmidt condensation of methylketones with aldehydes. Sulfones are versatile intermediates used in many different applications [18–21]. Sulfones **4a** and **4c** have been prepared by alkylation of the proper sulfinic acid with allyl bromide or cinnamyl chloride under Phase Transfer Catalysis (PTC) conditions.

However, this approach requires the use of excess NaH (4 equiv) in order to deprotonate the allylsulfone, thus triggering the reaction cascade leading to terphenyls [16]. Moreover, the hydrogen evolution and the need to remove THF before aqueous work-up of the crude reaction mixture constitute additional drawbacks. Under such reaction conditions huge amounts of sulfonyl-*meta*-terphenyls (30%–53% yield) are generated along with the desired products (40%–53% yield).

In order to develop a more practical approach and increase the selectivity, we planned to carry out this reaction under PTC conditions [22–27]. In fact, PTC represents a powerful tool to replace hazardous and relatively expensive reactants such as NaH with cheap and practical bases such as alkaline carbonates and hydroxides [28]. In addition, mild reaction conditions, safety, operational simplicity, and high selectivity are widely accepted typical features of PTC processes that allow an easy scale-up of reactions.

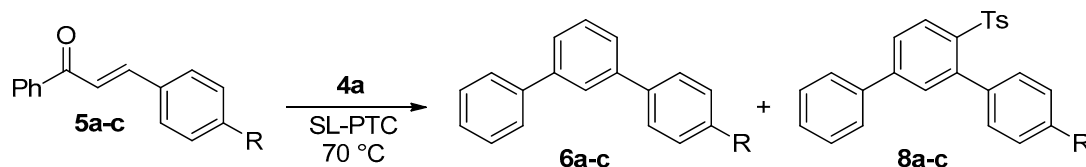
2. Results and Discussion

Here we report that the synthesis of a variety of *meta*-terphenyls and quaterphenyls can be carried out in a chemoselective fashion by using NaOH as base under solid-liquid (SL) PTC conditions.

A preliminary set of reactions using allylsulfone **4a** and chalcone **5a** showed that solid NaOH was capable to promote the reaction, whereas solid K₂CO₃ or K₃PO₄ were less effective. On the other

hand, no conversion was observed by using 1,5-diazabicyclo[5.4.0]undec-5-ene (1.5 equiv) as base under homogeneous conditions in THF as solvent. Although similar selectivity was observed by using stoichiometric or excess NaOH, it was preferred to use excess NaOH since higher yields of terphenyls could be obtained (Table 1, entries 1 and 2).

Table 1. Synthesis of *meta*-terphenyls **6** under Phase Transfer Catalysis (PTC) conditions ^a.



a, R = H; **b**, R = Br; **c**, R = OMe

Entry	Base (equiv)	Catalyst (equiv)	Chalcone	Solvent	t (h)	6 (%)	8 (%)
1	NaOH (1)	TEBA (0.1)	5a	Toluene	3	13	23
2	NaOH (4)	TEBA (0.1)	5a	Toluene	3	20	28
3	NaOH (4)	TEBA (0.1)	5a	CH ₃ CN	3	14	17
4 ^b	NaOH (4)	TEBA (0.1)	5a	CH ₃ CN	3	5	29
5 ^c	NaOH (4)	TEBA (0.1)	5a	CH ₃ CN	3	38	36
6	NaOH (4)	TEBA (0.1)	5a	DMSO	1	31	8
7	NaOH (4)	TEBA (0.1)	5b	DMSO	3	23	6
8	NaOH (4)	TEBA (0.1)	5c	DMSO	3	39	2
9	(C ₃ H ₇) ₄ NOH 1M (1)		5a	Toluene	3	31	8
10	50% NaOH (4.1)	Bu ₄ N ⁺ HSO ₄ ⁻ (0.1)	5a	Toluene	21	11	26
11	NaOH (4)	PEG 1000 (0.4)	5a	–	1	22	–

^a Reaction conditions: **4a** (0.4 mmol), **5a** (0.4 mmol), TEBA (0.04 mmol), 70 °C; ^b **4a** (0.8 mmol); ^c **5a** (0.8 mmol).

The reaction did not proceed significantly in the presence of 10% of base only, and various quaternary ammonium salts such as triethylbenzylammonium chloride (TEBA), Aliquat and tetrabutylammonium hydrogensulfate (TBAHSO₄) gave similar results both as regards the yield and chemoselectivity.

In toluene the main product was sulfonyl-*meta*-terphenyl **8a** whereas nearly equimolar amounts of *meta*-terphenyl **6a** and **8a** were obtained in CH₃CN (Table 1, entries 1–3).

When the reaction has been carried out in the presence of a molar excess of allylsulfone **1a**, the sulfonyl-*meta*-terphenyl **8a** was isolated as the major compound (Table 1, entry 4). It was also found that an excess of chalcone **5a** provided higher yields of products **6a** and **8a**, although with the same selectivity (Table 1, entry 5). A good selectivity favoring the desired *meta*-terphenyl was obtained in DMSO (Table 2, entry 6). Similar results have been obtained by using substituted chalcones **5b** and **5c** (Table 1, entries 7 and 8).

Since the results suggested a possible positive influence of solvent polarity on the selectivity to **6a**, more practical alternatives to DMSO were sought.

When a stoichiometric amount of (C₃H₇)₄NOH was used as base and catalyst in toluene, a good selectivity towards the desired *meta*-terphenyl was observed (Table 1, entry 9). On the other hand, a reversed selectivity was obtained by working under liquid-liquid PTC conditions using 50% aq. NaOH/toluene biphasic system (Table 1, entry 10).

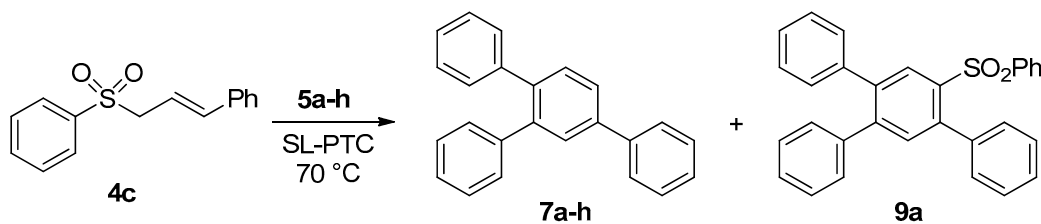
The well-known metal cation coordination ability of polyethyleneglycols (PEG) [29], and the appropriate physical and solvent properties of low molecular weight liquid/low melting solid PEG, suggested us to use PEG 1000 as a Phase Transfer Catalyst. In fact, it is a low melting solid (mp 37–40 °C) easier to manipulate than viscous PEG 400. We were indeed delighted to find that the best result as regards to the selectivity was achieved when the reaction was carried out in the presence of PEG 1000 as catalyst, without any other solvent (Table 1, entry 11). Indeed the desired terphenyl **6a** was isolated as a single compound, although in modest yield.

Higher yields of the desired terphenyl **6a** can be obtained by working under unselective conditions in CH₃CN as solvent (Table 1, entry 5) affording good yields of the combined terphenyls mixture

(**6a** + **8a**), followed by desulfonylation in order to convert **8a** to the desired **6a**. Thus, the mixture of **6a** and **8a** was dissolved in THF, cooled to $-80\text{ }^{\circ}\text{C}$, and dropwise added to a stirred THF solution of freshly prepared sodium naphthalenide solution at $-80\text{ }^{\circ}\text{C}$. The *meta*-terphenyl **6a** was isolated in a 72% overall yield by quenching with water after 40 min, followed by usual work-up and chromatographic purification.

In order to determine the influence of the sulfone on the outcome of the reaction, the (cinnamylsulfonyl)benzene (**4c**) was reacted with chalcone **5a** under the previously optimized reaction conditions (Table 2).

Table 2. Synthesis of quaterphenyls **7** under PTC conditions ^a.



Entry	Base (equiv)	Catalyst (equiv)	Chalcone	Solvent	<i>t</i> (h)	7a (%)	9a (%)
1	NaOH (4)	Aliquat (0.1)	5a	DMSO	1	65	–
2 ^b	NaOH (4)	Aliquat (0.1)	5a	DMSO	1	60	5
3	NaOH (1.1)	Aliquat (0.1)	5a	DMSO	3	48	9
4	NaOH (4)	–	5a	DMSO	1	42	24
5	NaOH (4)	PEG 1000 (0.4)	5a	–	1	66	–
6	NaOH (4)	PEG 1000 (1.2)	5a	–	1	58	–
7	NaOH (4)	PEG 1000 (0.1)	5a	–	1	41	–

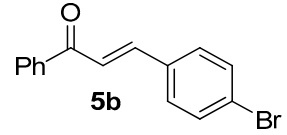
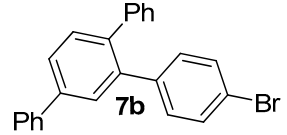
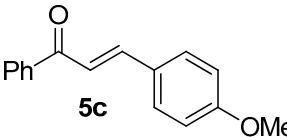
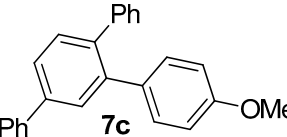
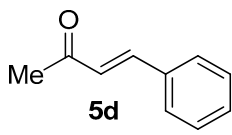
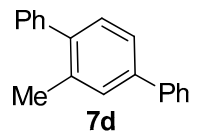
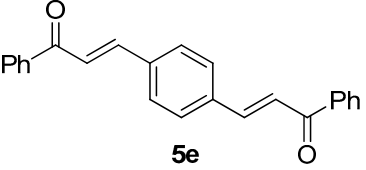
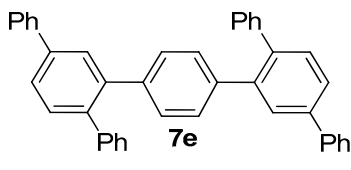
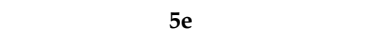
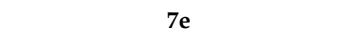
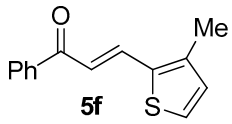
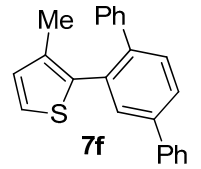
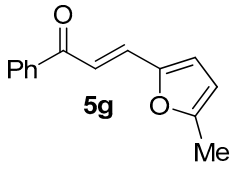
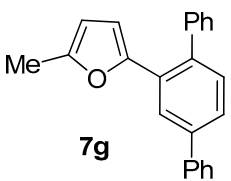
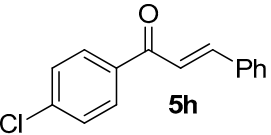
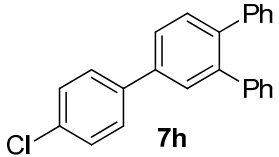
^a Reaction conditions: **4c** (0.4 mmol), **5** (0.4 mmol), $70\text{ }^{\circ}\text{C}$; ^b at $100\text{ }^{\circ}\text{C}$.

When the reaction was carried out in the presence of Aliquat as catalyst in DMSO, only the desired 1,2,4-triphenylbenzene **7a** was recovered in 65% yield (Table 2, entry 1). When the temperature was increased to $100\text{ }^{\circ}\text{C}$ a slight drop of the yield of **7a** was observed along with the formation of 5% of the sulfonyl derivative **9a** (Table 2, entry 2). Lower yield of **7a** was obtained by using 1.1 equiv of NaOH, whereas a sharp decrease in selectivity was observed without Aliquat (Table 2, entries 3 and 4). A completely chemoselective reaction was obtained in the presence of PEG 1000 (0.4 equiv) without organic solvent (Table 2, entry 5). Lower yields were obtained when lower or higher amounts of PEG were used (Table 2, entries 6 and 7).

Although the two chemoselective methods gave similar results (Table 2, entries 1 and 5) the reaction scope was investigated using the method employing PEG 1000 since it is more practical and economic. In fact, PEG 1000 is a cheap, easy to handle solid that successfully replace both Aliquat, a viscous liquid, and DMSO, a dipolar aprotic solvent that is difficult to remove completely from the reaction mixture. Moreover, 160 mg of PEG 1000 only are used to promote the reaction instead of 16 mg of Aliquat along with 1.1 g of DMSO.

A variety of substituted chalcones **5b–h** afforded the corresponding 1,2,4-triphenylbenzenes **7b–h** in 51%–71% yield (Table 3).

Table 3. Synthesis of quaterphenyls under solventless PTC conditions ^a.

Entry	Chalcone 5	Quaterphenyl 7	Yield (%)
1			71
2			69
3			70
4 ^b			19
5 ^c			15
6			63
7			51
8			63

^a Reaction conditions: **4c** (0.4 mmol), **5** (0.4 mmol), PEG 1000 (0.16 mmol), 1 h, 70 °C; ^b **4c** (0.4 mmol), **5e** (0.2 mmol); ^c **4c** (0.4 mmol), **5e** (0.4 mmol).

Good yields were obtained with electronwithdrawing or electrondonating groups on the benzene ring of chalcones **5b**, **5c** and **5h** (Table 3, entries 1, 2 and 8). Heteroaromatic chalcones **5f** and **5g** were also shown to be good substrates for the reaction (Table 3, entries 6 and 7), whereas (*E*)-4-phenylbut-3-en-2-one (**5d**), bearing a methyl group instead of a benzene ring also provided good yield of the terphenyl **7d** (Table 3, entry 3).

The polycyclic aromatic hydrocarbon **7e**, bearing seven benzenic rings could be isolated, although in low yield, when the bifunctional enone **5e** was used as starting material. Similar results have been obtained by using a stoichiometric or 0.5 equiv of the sulfone **4c** (Table 3, entries 4 and 5).

In summary, in this paper we have described a new, practical and chemoselective environmentally friendly method for the assembly of *meta*-terphenyl and 1,2,4-tetraphenyl skeleton under PTC conditions. The method uses allyl sulfones **4** and chalcones **5** as easily available starting materials along with cheap, solid NaOH and PEG 1000. Moreover, no organometallic species or inert atmosphere

are required. In particular, the use of PEG 1000 as a PTC catalyst enables to avoid the use of any organic solvent thus adding value to the procedure. The choice of PEG 1000 was found to be crucial in order to develop a completely chemoselective method generating the desired compounds **6** and **7** without formation of the corresponding sulfonylated byproducts **8** and **9**.

Further work is in progress in order to increase the yield of *meta*-terphenyls **6** involving the use of allylsulfone **4a** and ascertain the role of PTC in the chemoselective reaction.

3. Experimental Section

3.1. Materials and Methods

Reagents and solvents were purchased from commercial suppliers and used as received, without further purification. Melting points were determined with a BÜCHI 535 melting point apparatus (BÜCHI, Flawil, Switzerland) and are corrected. NMR spectra were recorded with a Bruker Fourier 300 spectrometer (Bruker Billerica, Massachusetts, MA, USA). Chemical shifts are reported by using CHCl₃ as an external standard ($\delta = 7.24$ ppm for ¹H NMR and 77.0 for ¹³C NMR). APT experiments were used in the assignment of carbon spectra. Mass spectra (electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI)) were measured with a LCQ Advantage Thermo-Finnigan LLC spectrometer (Thermo-Finnigan LLC San Jose, California, CA, USA). Column chromatography on silica gel (230–400 mesh) was performed by the flash technique. Petroleum ether (PE) refers to the fraction boiling in the range of 40–60 °C.

3.2. Synthesis of Sulfonyl Compounds **4** and Chalcones **5**

Allyl sulfonyl compounds **4a** and **4c** were prepared by alkylation of the proper commercially available sodium arylsulfinate under PTC conditions. The following detailed procedure for **4a** is typical.

1-(Allylsulfonyl)-4-methylbenzene (**4a**): in a two-neck flask provided with a reflux condenser and calcium chloride drying tube sodium 4-methylbenzenesulfinate (8.91 g, 50 mmol) and TEBA (1.14 g, 5 mmol) were dissolved in CH₃CN (50 mL). Allyl bromide (4.23 g, 35 mmol) was added and the mixture was heated and magnetically stirred at 70 °C for 21 h. Some solid material formed during reaction was dissolved by adding H₂O (5 mL) and the reaction mixture was then extracted with AcOEt (3 × 20 mL). The organic layer was dried (MgSO₄) and evaporated at reduced pressure. The crude product was purified through a small silica plug (AcOEt/PE = 1:1) to give 5.36 g of the title compound (78% yield). The analytical data match those reported in the literature [30].

3-Benzenesulfonylpropenylbenzene (**4c**). The title compound was generated in a 75% yield (6.78 g, white solid, mp 110.6–112.0 °C) with the same protocol described above for **4a** and using cinnamyl chloride (4.08 g, 35 mmol) instead of allyl bromide. The analytical data of **4c** are consistent with those reported in the literature [31].

Chalcones **5a** and **5c** are commercially available. Other chalcones have been prepared by the Claisen-Schmidt condensation of methylketones with aldehydes [32] and their spectroscopic and physical properties matched those reported in literature:

(*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (**5b**) [33], (*E*)-4-phenylbut-3-en-2-one (**5d**) [34], (*2E,2'E*)-3,3'-(1,4-phenylene)bis(1-phenylprop-2-en-1-one) (**5e**) [35], (*E*)-3-(3-methylthio phen-2-yl)-1-phenylprop-2-en-1-one (**5f**) [36], (*E*)-3-(5-methylfuran-2-yl)-1-phenylprop-2-en-1-one (**5g**) [37], (*E*)-1-(4-Chlorophenyl)-3-phenylprop-2-en-1-one (**5h**) [38].

3.3. General Procedure for the Synthesis of *meta*-Terphenyls **6a–c** under PTC Conditions

In a screw cap vial allylsulfone **4a** (79 mg, 0.40 mmol) and chalcone **5** (0.40 mmol) were dissolved in DMSO (1 mL). Solid NaOH (1.6 mmol, 64 mg) and TEBA (0.04 mmol, 9 mg) were added and the resulting mixture was stirred at 70 °C until completion. The reaction mixture was quenched with sat NH₄Cl solution and extracted with AcOEt (3 × 5 mL). The combined organic solution was dried and evaporated to dryness. The pure compounds were obtained by column chromatography (AcOEt/hexane from 1:20 to 1:3).

1,1':3',1''-terphenyl (**6a**): yield 22%; mp 86.5–87 °C, lit. [16] mp 86–88 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.82 (m, 1H), 7.67–7.26 (m, 13 H). ¹³C NMR (300 MHz, CDCl₃): δ 141.7 (C), 141.1 (C), 129.0 (CH), 128.6 (CH), 127.2 (CH), 127.1 (CH), 126.0 (CH).

4'-sulfonyl-1,1':2',1''-terphenyl (**8a**): ¹H NMR (300 MHz, CDCl₃): δ 8.46 (m, 1H), 7.78–6.99 (m, 16H), 2.34 (s, 3H).

4-bromo-1,1':3',1''-terphenyl (**6b**): yield 23%; mp 91–92 °C, lit. [39] mp 91.5–92 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.78 (s, 1H), 7.61 (m, 5H), 7.51 (m, 6H), 7.39 (m, 1H). ¹³C NMR (300 MHz, CDCl₃): δ 142.0 (C), 141.0 (C), 140.6 (C), 140.1 (C), 131.9 (CH), 129.3 (CH), 128.8 (CH), 127.5 (CH), 127.2 (CH), 126.5 (CH), 125.9 (CH), 125.9 (CH), 121.7 (C). 4-methoxy-1,1':3',1''-terphenyl (**6c**): yield 39%, mp 122–123 °C, lit. [40] mp 123–124 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.76 (m, 1H), 7.66–7.374 (m, 10H), 7.00 (d, 2H, *J* = 9 Hz), 3.86 (s, 3H). ¹³C NMR (300 MHz, CDCl₃): δ 159.2 (C), 141.6 (C), 141.3 (C), 141.2 (C), 133.6 (C), 129.0 (CH), 128.6 (CH), 18.1 (CH), 127.2 (CH), 127.1 (CH), 125.6 (CH), 125.4 (CH), 114.2 (CH), 55.2 (CH₃).

3.4. General Procedure for the Solventless Synthesis of Quaterphenyls **8** under PTC Conditions

A screw cap vial was charged with allylsulfone **4c** (0.40 mmol, 103 mg), chalcone **5** (0.40 mmol), solid NaOH (1.6 mmol, 64 mg) and PEG 1000 (0.16 mmol, 162 mg). After stirring at 70 °C until completion, the reaction mixture was quenched with sat NH₄Cl solution and extracted with AcOEt (3 × 5 mL). The combined organic solution was dried and evaporated to dryness. The pure compounds were obtained by column chromatography (AcOEt/hexane from 1:20 to 1:3).

4'-phenyl-1,1':2',1''-terphenyl (**7a**): yield 66%, mp 120.5–121 °C, lit. [41] mp 121–122 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.75–7.69 (m, 4H), 7.59–7.48 (m, 3H), 7.44–7.40 (m, 1H), 7.28–7.24 (m, 10H).

4-bromo-5'-phenyl-1,1':2',1''-terphenyl (**7b**): yield 71%, mp 210.5–211.2 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.63–7.50 (m, 7H), 7.26–7.16 (m, 10H). ¹³C NMR (300 MHz, CDCl₃): δ 141.3 (C), 141.2 (C), 141.0 (C), 140.0 (C), 139.5 (C), 139.1 (C), 131.9 (CH), 131.2 (CH), 129.8 (CH), 129.2 (CH), 128.7 (CH), 127.9 (CH), 126.7 (CH), 126.6 (CH), 125.9 (CH), 121.7 (C).

4-methoxy-5'-phenyl-1,1':2',1''-terphenyl (**7c**): yield 69%, mp 165.4–166.0 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.66 (m, 4H), 7.53 (m, 1H), 7.25 (m, 10H), 7.04 (m, 2H), 3.90 (s, 3H). ¹³C NMR (300 MHz, CDCl₃): δ 159.4 (C), 141.6 (C), 141.2 (C), 141.0 (C), 140.0 (C), 139.0 (C), 133.1 (C), 131.1 (CH), 129.9 (CH), 129.9 (CH), 129.0 (CH), 128.2 (CH), 127.9 (CH), 127.9 (CH), 126.6 (CH), 126.5 (CH), 125.7 (CH), 114.3 (CH), 55.4 (CH₃).

2'-methyl-1,1':4',1''-terphenyl (**7d**): yield 70%, mp 84.5–86.8 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.64 (m, 2H), 7.51–7.26 (m, 11H), 2.36 (s, 3H). ¹³C NMR (300 MHz, CDCl₃): δ 141.6 (C), 141.0 (2C), 140.2 (C), 135.8 (C), 130.3 (CH), 129.2 (CH), 129.1 (CH), 128.8 (C), 128.1 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 124.6 (CH), 20.7 (CH₃).

4',5'''-diphenyl-1,1':2',1''':4'',1''':2''',1''''-quinquephenyl (**7e**): yield 15%, mp 255.6–258.1 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.79–7.06 (m, 30H). ¹³C NMR (300 MHz, CDCl₃): δ 141.5, 141.1, 139.7, 131.2, 131.1, 130.4, 129.9, 129.3, 128.8, 127.9, 127.5, 127.2, 126.6, 126.2, 126.0, 125.9. APCI-MS: *m/z* = 535.3 [M + H]⁺.

2-(2'-1,1':4',1''-terphenyl)-3-methyl-thiophene (**7f**): yield 63%, mp 111.8–114.3 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.46–7.37 (m, 4H), 7.17–7.07 (m, 10H), 6.64 (d, 1H), 2.33 (s, 3H). ¹³C NMR (300 MHz, CDCl₃): δ 141.2 (C), 141.1 (C), 140.7 (C), 139.4 (C), 137.3 (C), 134.0 (C), 133.4 (C), 131.1 (CH), 130.8 (CH), 129.90 (CH), 129.8 (CH), 127.9 (CH), 126.6 (CH), 126.6 (CH), 123.6 (CH), 15.1 (CH₃).

2-(2'-1,1':4',1''-terphenyl)-3-methyl-furan (**7g**): yield 51%, oil. ¹H NMR (300 MHz, CDCl₃): δ 7.7–7.2 (m, 13H), 6.61 (d, 1H, *J* = 3.2), 6.08 (d, 1H, *J* = 3.2), 2.39 (s, 3H). ¹³C NMR (300 MHz, CDCl₃): δ 152.2 (C), 151.9 (C), 141.5 (C), 141.2 (C), 140.9 (C), 138.9 (C), 137.9 (C), 131–125 (13CH), 107.8 (CH₂), 106.2 (CH₂), 13.7 (CH₃).

4-chloro-3'-phenyl-1,1':4',1''-terphenyl (**7h**): yield 63%, mp 206.4–208.6 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.60–7.63 (m, 4H), 7.50–7.53 (m, 1H), 7.42–7.45 (m, 2H), 7.15–7.26 (m, 10H). ¹³C NMR (300 MHz,

CDCl₃): δ 141.3 (C), 141.2 (C), 140.9 (C), 139.9 (C), 139.1 (C), 139.0 (C), 133.6 (C), 131.2 (CH), 129.8 (CH), 129.2 (CH), 129.0 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 126.7 (CH), 126.6 (CH), 125.9 (CH).

3.5. Desulfonation of the meta-Terphenyl (6a) and Sulphonyl-meta-terphenyl (8a) Mixture

The mixture of compounds **6a** (0.152 mmol, 35 mg) and **8a** (0.144 mmol, 55.4 mg), as recovered after usual work-up of reaction carried out under condition reported in Table 1 (entry 5), was dissolved in anhydrous THF (1 mL), cooled to −80 °C and subsequently added to a stirred THF solution of freshly prepared sodium naphthalenide (0.86 mmol) at −80 °C. After 40 min at the same temperature the reaction was quenched by water addition. The reaction mixture was allowed to come to room temperature and was extracted with CH₂Cl₂ (3 × 5 mL). The organic phase was dried over Na₂SO₄, evaporated under reduced pressure and purified by column chromatography (AcOEt/PE) to give 66 mg of meta-terphenyl (**3a**), overall yield 72%.

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References and Note

1. Cho, C.H.; Kim, I.S.; Park, K. Preparation of unsymmetrical terphenyls via the nickel-catalyzed cross-coupling of alkyl biphenylsulfonates with aryl Grignard reagents. *Tetrahedron* **2004**, *60*, 4589–4599. [[CrossRef](#)]
2. Miguez, J.M.A.; Adrio, L.A.; Sousa-Pedrares, A.; Vila, J.M.; Hii, K.K. A practical and general synthesis of unsymmetrical terphenyls. *J. Org. Chem.* **2007**, *72*, 7771–7774. [[CrossRef](#)] [[PubMed](#)]
3. Todd, M.H.; Balasubramanian, S.; Abell, C. Studies on the synthesis, characterisation and reactivity of aromatic diboronic acids. *Tetrahedron Lett.* **1997**, *38*, 6781–6784. [[CrossRef](#)]
4. Shimizu, H.; Manabe, K. Negishi coupling strategy of a repetitive two-step method for oligoarene synthesis. *Tetrahedron Lett.* **2006**, *47*, 5927–5931. [[CrossRef](#)]
5. Taylor, R.H.; Felpin, F.X. Suzuki–Miyaura reactions of arenediazonium salts catalyzed by Pd(0)/C. One-pot chemoselective double cross-coupling reactions. *Org. Lett.* **2007**, *9*, 2911–2914. [[CrossRef](#)] [[PubMed](#)]
6. Saito, S.; Yamamoto, Y. Recent advances in the transition-metal-catalyzed regioselective approaches to polysubstituted benzene derivatives. *Chem. Rev.* **2000**, *100*, 2901–2916. [[CrossRef](#)] [[PubMed](#)]
7. Zhang, L.; Liang, F.; Cheng, X.; Liu, Q. A new route to multifunctionalized *p*-terphenyls and heteroaryl analogues via [5C + 1C(N)] annulation strategy. *J. Org. Chem.* **2009**, *74*, 899–902. [[CrossRef](#)] [[PubMed](#)]
8. Ballini, R.; Palmieri, A.; Bartoni, L. Nitroalkanes as new, ideal precursors for the synthesis of benzene derivatives. *Chem. Commun.* **2008**. [[CrossRef](#)] [[PubMed](#)]
9. Liu, J.K. Natural terphenyls: Developments since 1877. *Chem. Rev.* **2006**, *106*, 2209–2223. [[CrossRef](#)] [[PubMed](#)]
10. Kays, D.L. Recent developments in transition metal diaryl chemistry. *Dalton Trans.* **2011**, *40*, 769–778. [[CrossRef](#)] [[PubMed](#)]
11. Fan, Q.; Wang, C.; Han, Y.; Zhu, J.; Kuttner, J.; Hilt, G.; Gottfried, J.M. Surface-assisted formation, assembly, and dynamics of planar organometallic macrocycles and zigzag shaped polymer chains with C–Cu–C bonds. *ACS Nano* **2014**, *8*, 709–718. [[CrossRef](#)] [[PubMed](#)]
12. Wu, C.A.; Chou, H.H.; Shih, C.H.; Wu, F.I.; Cheng, C.H.; Huang, H.L.; Chao, T.C.; Tseng, M.R. Synthesis and physical properties of meta-terphenyloxadiazole derivatives and their application as electron transporting materials for blue phosphorescent and fluorescent devices. *J. Mater. Chem.* **2012**, *22*, 17792–17799. [[CrossRef](#)]
13. Taylor, P.C.; Wall, M.D.; Woodward, P.R. Synthesis of dendritic oligo(aryl sulfone)s as supports for synthesis. *Tetrahedron* **2005**, *61*, 12314–12322. [[CrossRef](#)]
14. Sasabe, H.; Seino, Y.; Kimura, M.; Kido, J. A *m*-terphenyl-modified sulfone derivative as a host material for high-efficiency blue and green phosphorescent OLEDs. *Chem. Mater.* **2012**, *24*, 1404–1406. [[CrossRef](#)]
15. Gopi, E.; Namboothiri, I.N. One-pot regioselective synthesis of meta-terphenyls via [3 + 3] annulation of nitroallylic acetates with alkylidenemalononitriles. *J. Org. Chem.* **2014**, *79*, 7468–7476. [[CrossRef](#)] [[PubMed](#)]
16. Chang, M.Y.; Chan, C.K.; Lin, S.Y.; Wu, M.H. One-pot synthesis of multifunctionalized *m*-terphenyls. *Tetrahedron* **2013**, *69*, 9616–9624. [[CrossRef](#)]

17. Chang, M.Y.; Chan, C.K.; Lin, S.Y.; Wu, M.H. One-pot synthesis of multisubstituted quaterphenyls and cyclopropanes. *Tetrahedron* **2013**, *69*, 10036–10044. [[CrossRef](#)]
18. El-Awa, A.; Noshi, M.N.; Mollat du Jourdin, X.; Fuchs, P.L. Evolving organic synthesis fostered by the pluripotent phenylsulfone moiety. *Chem. Rev.* **2009**, *109*, 2315–2349. [[CrossRef](#)] [[PubMed](#)]
19. Trost, B.M. Chemical chameleons. organosulfones as synthetic building blocks. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107–124. [[CrossRef](#)]
20. Simpkins, N.S. *Sulphones in Organic Synthesis*; Pergamon: Oxford, UK, 1993.
21. *Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.Z.; Stirling, C. (Eds.) Wiley: Chichester, UK, 1988.
22. Dehmlow, E.V.; Dehmlow, S.S. *Phase Transfer Catalysis*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 1993.
23. Starks, C.M.; Liotta, C.L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman & Hall: New York, NY, USA, 1994.
24. *Handbook of Phase-Transfer Catalysis*; Sasson, Y.; Neumann, R. (Eds.) Blackie Academic & Professional: London, UK, 1997.
25. *Phase-Transfer Catalysis*; Halpern, M.E. (Ed.) ACS Symposium Series 659; American Chemical Society: Washington, DC, USA, 1997.
26. Albanese, D. Phase-Transfer Catalysis. In *Kirk-Othmer Encyclopedia of Chemical Technology*; John Wiley & Sons: New York, NY, USA, 2008; pp. 1–22. [[CrossRef](#)]
27. Albanese, D.; Foschi, F.; Penso, M. Sustainable oxidations under phase-transfer catalysis conditions. *Org. Proc. Res. Dev.* **2016**, *20*, 129–139. [[CrossRef](#)]
28. Albanese, D.; Landini, D.; Penso, M. Synthesis of 2-amino acids via selective mono-N-alkylation of trichloroacetamide by 2-bromo carboxylic esters under solid-liquid phase-transfer catalysis conditions. *J. Org. Chem.* **1992**, *57*, 1603–1605. [[CrossRef](#)]
29. Dramatically reduced cost of PEG related to crown ether discouraged us to test crown ethers as alternative phase transfer catalysts.
30. Fukuda, N.; Ikemoto, T. Imide-catalyzed oxidation system: Sulfides to sulfoxides and sulfones. *J. Org. Chem.* **2010**, *75*, 4629–4631. [[CrossRef](#)] [[PubMed](#)]
31. Caldwell, J.J.; Craig, D.; East, S.P. Application of 5-endo-trig cyclisation in the total synthesis of (+)-preussin. *Arkivoc* **2007**, *xii*, 67–90.
32. Kohler, E.P.; Chadwell, H.M. Benzalacetophenone. *Org. Synth.* **1922**, *2*, 1.
33. Stroba, A.; Schaeffer, F.; Hindie, V.; Lopez-Garcia, L.; Adrian, I.; Fröhner, W.; Hartmann, R.W.; Biondi, R.M.; Engel, M. 3,5-Diphenylpent-2-enoic acids as allosteric activators of the protein kinase PDK1: structure-activity relationship and thermodynamic characterization of binding as paradigms for PIF-binding pocket-targeting compounds PDB code of 2Z with PDK1:3HRF. *J. Med. Chem.* **2009**, *52*, 4683–4693. [[CrossRef](#)] [[PubMed](#)]
34. Gottumukkala, A.L.; Teichert, J.F.; Heijnen, D.; Eisink, N.; van Dijk, S.; Ferrer, C.; van den Hoogenband, A.; Minnaard, A.J. Pd-Diimine: A highly selective catalyst system for the base-free oxidative Heck reaction. *J. Org. Chem.* **2011**, *76*, 3498–3501. [[CrossRef](#)] [[PubMed](#)]
35. Bhat, A.R.; Athar, F.; Azam, A. Bis-pyrazolines: Synthesis, characterization and antiamebic activity as inhibitors of growth of *Entamoeba histolytica*. *Eur. J. Med. Chem.* **2009**, *44*, 426–431. [[CrossRef](#)] [[PubMed](#)]
36. Li, W.; Wu, X.F. Ruthenium-catalyzed conjugate hydrogenation of α,β -enones by in situ generated dihydrogen from paraformaldehyde and water. *Eur. J. Org. Chem.* **2015**, 331–335. [[CrossRef](#)]
37. Jin, H.; Geng, Y.; Yu, Z.; Tao, K.; Hou, T. Lead optimization and anti-plant pathogenic fungi activities of daphneolone analogues from *Stellera chamaejasme* L. *Pestic. Biochem. Physiol.* **2009**, *93*, 133–137. [[CrossRef](#)]
38. Schmink, J.R.; Holcomb, J.L.; Leadbeater, N.E. Testing the validity of microwave-interfaced, in situ Raman spectroscopy as a tool for kinetic studies. *Org. Lett.* **2009**, *11*, 365–368. [[CrossRef](#)] [[PubMed](#)]
39. Bradsher, C.K.; Swerlick, I. Reactions in the *m*-terphenyl series. *J. Am. Chem. Soc.* **1950**, *72*, 4189–4192. [[CrossRef](#)]
40. Beaumard, F.; Dauban, P.; Dodd, R.H. One-pot double Suzuki–Miyaura couplings: Rapid access to nonsymmetrical tri(hetero)aryl derivatives. *Org. Lett.* **2009**, *11*, 1801–1804. [[CrossRef](#)] [[PubMed](#)]
41. Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. RhCl_3 /amine-catalyzed [2 + 2 + 2] cyclization of alkynes. *Tetrahedron* **2008**, *64*, 5800–5807. [[CrossRef](#)]

