JOC Note

Expedient Synthesis of Substituted (Diphenylphosphinoylmethyl)benzenes

Sean P. Bew,* Rebecca A. Brimage, David L. Hughes,
Laurent Legentil, Sunil V. Sharma, and Martin A. Wilson

School of Chemical Sciences & Pharmacy, University of East Anglia, Norwich, NR4 7TJ, U.K.

s.bew@uea.ac.uk

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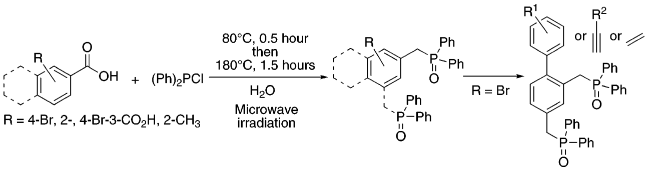
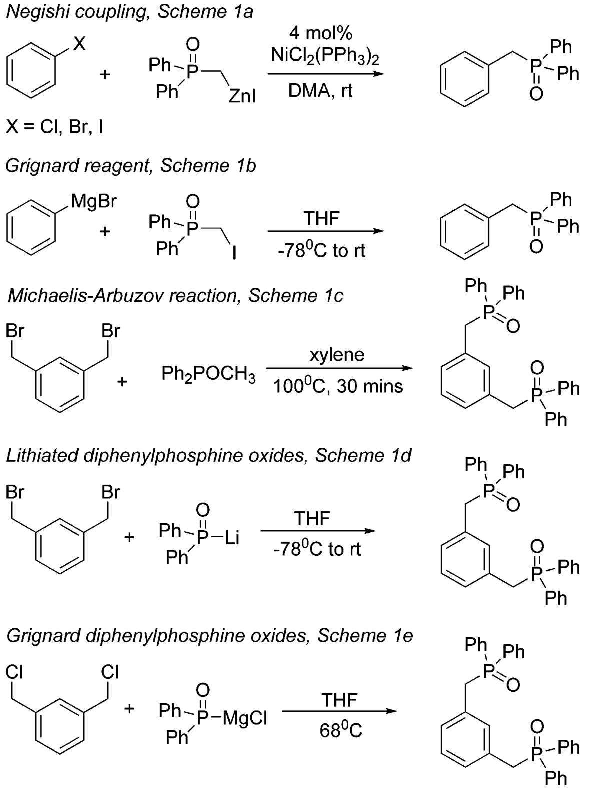


An efficient protocol for the synthesis of structurally diverse (diphenylphosphinoylmethyl)benzenes is described. The reaction employs readily available carboxylic acids, chlorodiphenylphosphine, and water as the reagents. A 97% reduction in the reaction times and substantially higher yields of products result, up to a 60% increase, if the reactions are performed under microwave irradiation. The first examples of transition-metal-catalyzed reactions applied to 4-bromo-1,3-bis(diphenylphosphinoylmethyl)benzene are also reported.

At first sight, (diphenylphosphinoylmethyl)benzenes appear as unreactive and or unexciting chemical entities, but in fact, they have been used in a wide spectra of interesting and diverse reactions. They have, for example, been employed as key reagents and or catalysts in novel podands for the complexation of ammonium cations,[1] ligands for the hydroformylation of alkenes,[2] hydrogen-bonding hosts,[3] ligands for metal−ion extraction,[4] analogues of methadone,[5] precursor ligands to caged platinacycles,[6] precursors of PCP pincer ligands,[7] and synthesis of coordination complexes[8] and as key reagents within the Ramburg−Bäcklund reaction.[9] Surveying the literature, we were surprised that the application of microwave irradiation for the efficient and expedient synthesis of (diphenylphosphinoylmethyl)benzene adducts had not been reported.[10] We report in this Note a convenient, straightforward microwave-mediated method that affords, after a simple workup and purification procedure, structurally diverse (diphenylphosphinoylmethyl)-benzene adducts in good to high yields and, compared to conventional heating protocols, significantly reduced reaction times.

SCHEME 1. Protocols for the Synthesis of (Diphenylphosphinoylmethyl)benzene Adducts



Our interest in (diphenylphosphinoylmethyl)benzene as well as 1,2- and 1,3-bis(diphenylphosphinoylmethyl)benzene adducts stems from a series of ongoing research projects. Critical to their use for us was their synthesis in reasonable quantities (∼0.5−2 g) from cheap and commercially available starting materials. A few examples will serve to illustrate current protocols for the synthesis of (diphenylphosphinoylmethyl)-benzene, 1,2-, or 1,3-bis(diphenylphosphinoylmethyl)benzenes: (i) Negishi couplings employing substoichiometric amounts of nickel or palladium catalysts between aryl halides and organozinc reagents derived from iodomethyldiphenylphosphine oxide (Scheme 1a); (ii) nucleophilic displacement reactions between aryl Grignard reagents and iodomethyldiphenylphosphine oxides (Scheme 1b); (iii) Michaelis−Arbuzov reaction processes between α,α′-dibromo-*meta*-xylene and methyl diphenylphosphinite (Scheme 1c); (iv) S$_N$2 displacements using

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* To whom correspondence should be addressed. Phone: + 44 (0)1603 593142. Fax: + 44 (0)1603 592003.

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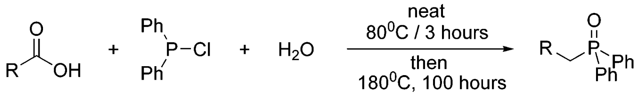
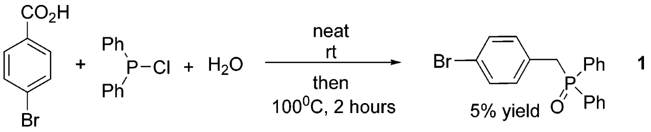
10.1021/jo062114k CCC: $37.00

SCHEME 2. Generic Reaction Protocol Reported by Sartori and Mosler



SCHEME 3. Low-Yielding Synthesis of 1 Using Modified Sartori and Mosler Reaction Conditions

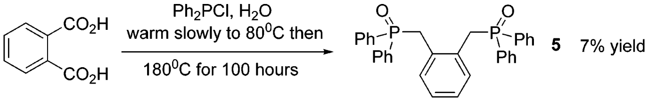


lithiated diphenylphosphine oxides and alkyl halides (Scheme 1d) and similarly S_N2 displacements using Grignard-derived diphenylphosphine oxides on alkyl halides (Scheme 1e). In 1980, Sartori and Mosler reported the synthesis of a series of (diphenylphosphinoylmethyl)benzenes via a high-temperature (180 °C) and time-consuming 100 h reaction process that employed carboxylic acids, chlorodiphenylphosphine, and water (Scheme 2).[11] More recently, Ishibashi et al. reported the synthesis of 2,2,2-trifluoroethyldiphenylphosphine oxide via an almost identical process, employing trifluoroacetic acid, chlorodiphenylphosphine, and water via a procedure that also required a high reaction temperature (180 °C) but a slightly shorter reaction time (80 h).[12]

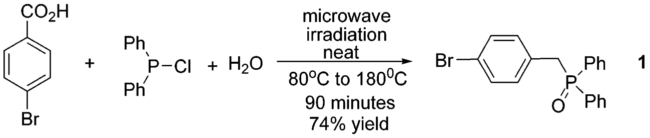
It is interesting to note that although the Sartori and Mosler methodology was reported over 25 years ago its utilization, as judged by citations, by the synthetic chemistry community has been largely nonexistent,[13] a fact that may be attributed to the very long, highly inconvenient reaction times and the relatively poor yields of the resulting (diphenylphosphinoylmethyl)-benzenes.

We considered the Sartori and Mosler process to have a number of merits: viz., in the majority of cases, the starting materials are cheap and readily available; the protocol is straightforward and uncomplicated, with no requirement for the use of anhydrous solvents, an inert atmosphere, or expensive catalysts; and the reaction process appears to be versatile with the capacity to afford multigram quantities of products. For our use, it was important that the aryl ring *not directly* connected to the phosphorus be equipped with a halogen “handle”. With this in mind, we attempted the synthesis of **1** (Scheme 3) using a procedure similar to that reported by Sartori and Mosler. Stirring a mixture of 4-bromobenzoic acid, water (3 equiv of each), and chlorodiphenylphosphine (4 equiv) at ambient temperature (30 min) and subsequently at 100 °C for 2 h afforded a very low 5% yield of **1**, the majority of the mass balance comprising unreacted 4-bromobenzoic acid. Concerned that the electron-withdrawing properties of the bromine atom may be having an adverse effect on the progress of the reaction, we undertook two “test” reactions (employing the same reaction conditions used for 4-bromobenzoic acid, i.e., ambient temperature for 30 min then 100 °C for 2 h) using: (a) benzoic acid, water (3 equiv of each), and chlorodiphenylphosphine (4 equiv) and (b) phthalic acid, water (6 equiv of each), and chlorodiphenylphosphine (8 equiv). Both test reactions afforded less than 5% of the desired products, returning instead the unreacted carboxylic acids.

SCHEME 4. Low-Yielding Synthesis of 5



SCHEME 5. Efficient Synthesis of 1 Using Microwave Irradiation



Employing the higher temperature (180 °C) and longer reaction time conditions (100 h) reported,[13] we repeated the reaction outlined in Scheme 3. Chlorodiphenylphosphine (4 equiv) was added dropwise to a mixture of 4-bromobenzoic acid and water (3 equiv of each) at ambient temperature. The resulting mixture was warmed slowly to 80 °C then to 180 °C over 3 h and held at this temperature for 100 h. Quenching the reaction afforded, after purification, a 44% yield of **1**. With this positive result in hand, we repeated one of our test reactions. Utilizing the higher temperature and longer reaction time protocol recounted and phthalic acid as the starting material, we attempted the synthesis of **5** (Scheme 4). After workup, a very poor 7% yield of the desired 1,2-bis(diphenylphosphinoylmethyl)benzene (**5**) was afforded.

Microwave irradiation is often employed to heat and drive chemical reactions; one of the advantages of using microwaves in chemical synthesis is the often dramatic reduction in reaction times that are observed.[14] The possibility that focused microwave irradiation may result in a significant shortening of the very long reaction times reported by Sartori and Mosler intrigued us. Microwave irradiating a mixture of 4-bromobenzoic acid (1 equiv), chlorodiphenylphosphine (3 equiv of each), and water (2 equiv) at 150 °C for 4 h afforded **1** in a mediocre 34% yield. However, when the reaction was repeated at 180 °C, **1** was isolated in a significantly improved 74% yield after only 3 h. Repeating the reaction at 180 °C but further reducing the reaction time to 90 min (cf. 100 h), we again isolated a 74% yield of **1**. A 60% yield increase, compared to the conventional Sartori and Mosler procedure (cf. 44% yield), was achieved via a *97% reduction* in the reaction time (Scheme 5). Further reduction of the irradiation reaction time to 30 min returned a 43% yield of **1**, which is essentially identical to that of Sartori and Mosler but was achieved via a 99.5% reduction in the reaction time. An X-ray crystal structure of **1** confirmed that the potentially labile bromine was still intact (see Figure 1 in the Supporting Information).

With a reliable and robust procedure in place, we probed the versatility of the procedure applying it to a range of aryl monocarboxylic acids (Table 1). This study confirmed that unsubstituted arylcarboxylic acids (entry 2), 2-substituted carboxylic acids (entry 3), as well as 2-napthoic acid, a bicyclic arylcarboxylic acid (entry 4, Table 1), afforded the desired products **2**−**4** in 79%, 71%, and 68% yields, respectively.

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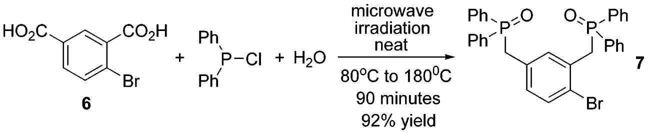
TABLE 1. Substrates Utilized in the Synthesis of (Diphenylphosphinoylmethyl)benzenes

entry	carboxylic acid	yield or result
1	4-bromobenzoic acid	74%
2	benzoic acid	79%
3	2-toluic acid	71%
4	2-napthoic acid	68%
5	phthalic acid	62%
6	4-bromoisophthalic acid	54%
7	5-hydroxyisophthalic acid	many products
8	2-methoxybenzoic acid	decomposition
9	2-iodobenzoic acid	decomposition
10	monomethyl phthalate	no product
11	trimellitic anhydride	no product
12	salicylaldehyde	decomposition
13	2,4-dinitrobenzoic acid	no product
14	phthalamic acid	no product
15	anthranilic acid	no product
16	4-cyanobenzoic acid	no product

SCHEME 6. Synthesis of 4-Bromo-1,3-bis(diphenylphosphinoylmethyl)benzene 7

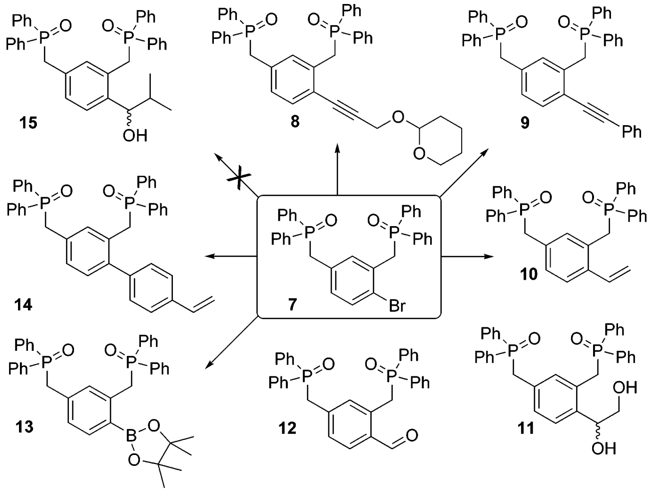


Exemplifying this methodology and for the purposes of our research, we specifically required 1,2- and 1,3-bis(diphenylphosphinoylmethyl)benzene adducts. Utilizing phthalic acid as our starting material, the synthesis of 1,2-bis(diphenylphosphinoylmethyl)benzene **5** was attempted. After microwave irradiation (180 °C, 90 min), workup, and purification, the previously unattainable 1,2-bis(diphenylphosphinoylmethyl)benzene **5** was afforded in an unoptimized 62% yield (entry 5, Table 1; see Figure 2 in the Supporting Information for the X-ray crystal structure of **5**). Particularly noteworthy, repeating this reaction at 180 °C (i.e., no warming to 80 °C first) employing a *conventional* oil bath failed to afford any of **5**, even after the reaction time was considerably extended (36 h).

Our requirement for a 1,3-bis(diphenylphosphinoyl)benzene adduct that contained a bromine atom compelled us to investigate the potential of **6** (4-iodoisophthalic acid is not commercially available) as a possible starting material for the synthesis of **7** (Scheme 6). Subjecting 4-bromoisophthalic acid (**6**) to the same reaction conditions and quantities of chlorodiphenylphosphine and water (3 equiv of each) utilized previously for the synthesis of **3**, we isolated a 54% yield of the desired 4-bromo-1,3-bis(diphenylphosphinoyl)benzene adduct **7** as a white solid (entry 6, Table 1). Undertaking a larger-scale synthesis of **8**, we efficiently transformed multigram quantities (2 g) of **6** into **7** in an excellent 92% yield.

Attempting to employ either a starting material containing a “free” phenol−OH group (entry 7, Table 1) or its *O*-TBDMS variant afforded a complex, unidentifiable mixture of compounds. Employing the aryl methyl ether containing 2-methoxybenzoic acid as the starting material (entry 8) failed to return any of the desired diphenylphosphinoylmethyl adduct. Instead, a complex polar mixture of compounds was returned, none of which, as judged by ^{1}H NMR, appeared to contain the methyl group located on the ether. Likewise, the utilization of 2-iodobenzoic acid (entry 9) resulted in the thermally labile C−I bond decomposing under the reaction conditions. Probing the possibility of using starting materials that contained a methyl ester (entry 10), anhydride (entry 11), aldehyde (entry 12), nitro (entry 13), amide (entry 14), amine (entry 15), or nitrile (entry 16) afforded none of the desired adducts, and in many cases, decomposition of the starting materials was observed.

SCHEME 7. Sonogashira, Stille, and Suzuki Transformations Applied to 7



With gram quantities of **7** in hand, its transformation via transition-metal-mediated processes into a subset of chemically diverse 1,3-bis(diphenylphosphinoylmethyl)benzene analogues was investigated. Utilizing standard reaction conditions, **7** underwent Sonogashira couplings with *O*-THP-protected propargyl alcohol or phenylacetylene, affording the desired alkynes **8** and **9** in 90% and 88% yields, respectively. Curiously, all attempts at coupling trimethylsilylacetylene to **7** using typical Sonogashira conditions failed to afford any of the expected trimethylsilylalkyne-derived product. During the course of our studies, we observed the tenacious capacity of 1,3-bis(diphenylphosphinoylmethyl)benzenes to hydrogen bond to water and/or amines (in our case, diisopropylamine), a property that has been previously observed by Philp et al.[3] and is clearly evident in the ^{1}H NMR of, for example, **8** and **9**. Subjecting **7** and vinyltri-*n*-butylstannane to typical Stille coupling reaction conditions afforded the vinyl derivative **10** in a 51% yield, and subsequent dihydroxylation of the alkene afforded **11** which after sodium periodate cleavage returned aldehyde **12** (Scheme 7) in a 76% yield. Utilizing a palladium(0)-mediated reaction process, the pinacolboronate **13** was readily synthesized, but not isolated, from **7** and bis(pinacolato)diboron. Subsequent attempts at utilizing **13** via Suzuki coupling procedures were plagued by incomplete reactions and or the formation of byproducts resulting from the decomposition of the organopalladium(II) intermediate derived from oxidative addition of **13** to the catalyst. Negating this, we switched to coupling **7** with arylboronic acids. The Suzuki coupling between **7** and *para*-vinylphenylboronic acid was investigated. Using standard reaction conditions, we synthesized styrene adduct **14** in an unoptimized but satisfactory 56% yield. Transmetalating the bromine atom on **7** with 2 equiv of *n*-BuLi at −78 °C followed by quenching of the presumably formed lithiated species with isobutanal afforded a complex mixture comprising **7**, 1,3-bis(diphenylphosphinoylmethyl)benzene, and polar compounds that were in our hands inseparable and unidentifiable.

We have developed the first efficient microwave-mediated, short reaction time protocol for the synthesis of structurally diverse (diphenylphosphinoylmethyl)benzenes. Using our improved procedure, the synthesis of the previously unreported 4-bromo-1,3-bis(diphenylphosphinoyl)benzene (**7**) has been accomplished. The transformation and elaboration of **7** via transition-metal-mediated procedures affording functionalized (diphenylphosphinoylmethyl)benzenes has been accomplished. The products of these reactions would not be available using the original Sartori and Mosler reaction conditions. Furthermore, we have elucidated the structures of **1** and **5** using X-ray crystal analysis. The ease with which it is now possible to synthesize multigram quantities of these entities should ensure their applications within the synthetic, pharmaceutical, agrochemical, and material chemistry arenas.

Experimental

Compound 1. Chlorodiphenylphosphine (1 mL, 5.46 mmol) was added dropwise to a process vial charged with 4-bromobenzoic acid (360 mg, 1.82 mmol) and water (65 μL, 3.64 mmol, CARE hydrogen chloride evolved). The vial was capped, and the mixture was heated at 80 °C for 30 min, then at 180 °C for 1.5 h (microwave irradiation, Biotage Emrys Creator, reactions conducted at a constant 180 °C with a maximum of 300 W energy input). The vial was allowed to cool to ambient temperature, and the residue was suspended in DCM (15 mL), washed with 10% aqueous sodium carbonate (3 × 15 mL) and water (15 mL), dried over magnesium sulfate, filtered, and concentrated to dryness in vacuo. The product was purified by column chromatography on silica gel (3% methanol in DCM) to afford **1**[15] as a white solid in a 74% yield (503 mg). Uncorrected melting point: mp > 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (d, 2H), 6.98−7.01 (m, 2H), 7.44−7.49 (m, 4H), 7.52−7.56 (m, 2H), 7.67−7.72 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.7, 131.9 (d $J_{PC} = 9.1$), 131.7 (d $J_{PC} = 5.7$), 131.1, 130.3, 128.6, 120.9, 37.4. IR (KBr) ν 2941, 1590, 1492, 1485, 1440, 1436, 1418, 1407, 1312 cm^{-1}. m/z (CI/NH_3) 374.1 (^{79}Br, 52%), 373.1 (^{81}Br, 50%), 293.2 (92), 126.2 (32), 114.2 (39), 112.1 (63), 106.0 (88), 98.1 (100), 96.1 (69), 94.1 (64), 84.1 (48), 78.1 (42), 72.1 (39). HRMS calcd for $C_{19}H_{16}{}^{79}BrOP$ 371.0195, found 371.0195.

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Supporting Information Available: Details and results (including the CIF files) of the crystallographic analysis of compounds **1** and **5**, the synthesis of **2**−**5**, **7**−**12**, and **14**, and NMR spectral data for **1**−**5**, **7**−**12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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