



Ultrasound promoted Barbier reactions and Csp^3 – Csp^2 Stille coupling for the synthesis of diarylmethanes and substituted benzophenones

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ABSTRACT

Here we present the preparation of a variety of diarylmethanes obtained via ultrasound Stille coupling under palladium catalysis between some substituted aryl compounds and benzyltributyltin compounds generated through sonicated Barbier reaction in a very short time reaction and excellent yield. The study reported below compares different methods to optimize the synthesis of usually unstable benzyltin derivatives and is another contribution to the investigation of Csp^3 – Csp^2 coupling process involving benzyl–aryl reagents. Substituted carboxylated benzophenones were easily prepared in a very good yield by oxidation of some diarylmethanes.

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1. Introduction

The extensive use of organotin compounds as reagents or intermediates in organic synthesis [1] has prompted the development of efficient preparation of these type of compounds using rapid and convenient synthetic procedures, such as, for example, the Barbier reaction [2]. As the field of Csp^3 – Csp^2 coupling reactions is always in continuous study from the last 30 years [3], the formation of this type of C–C bond via Stille coupling under palladium catalysis is of great interest in organic synthesis and, usually, tributylstannyl compounds are between the most common substrates. Compared with other coupling types, much less have been reported with these relatively more difficult couplings where the alkyl moiety is either on the substrate or on the organometallic partner [4]. The increased focus on the use of sonochemical methods in organic synthesis has been demonstrated by the many reports found in the literature [5]. The presence of ultrasound has shown to enhance the rates of reactions together with reduction of the induction period and less severe conditions. As a result of all previously mentioned, we focussed this work in the synthesis of substituted diarylmethanes taking into account that they play an important role in several biologically active compounds and drugs [6] such as Papaverin (I), a muscle relaxing agent, the synthetic antibiotic Trimethoprim (II) or the dihydrofolate reductase

inhibitor for the potential treatment of cancer, Piritrexim (III) (Scheme 1). Besides, diarylmethanes are important precursors of the corresponding benzophenones, which have demonstrated to have antibacterial activity [7] and, as is already known, the search of new antibiotics is always an important target for medicinal chemistry.

2. Results and discussion

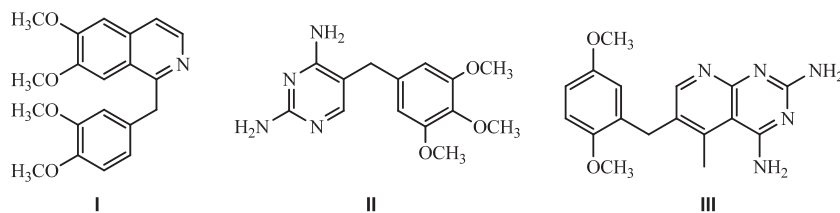
We based the synthetic strategy for the preparation of the diarylmethanes on the construction of two different aromatic “building blocks”, A and B, that will be coupled through a sonicated Stille reaction. The benzyltin group was located in the A-ring while the B-ring contains a variety of substituted aryl halides. Then, some representative products will be oxidized to the corresponding benzophenones (Fig. 1).

To achieve this, benzyl chloride and 3,5-dimethoxybenzyl chloride (**2**) were chosen as starting materials. Compound **2** was obtained (75% yield) from commercially available methyl-3,5-dimethoxybenzoate (**1**) according to Scheme 2.

The selected substrates providers of the Csp^3 moiety were benzyltri-*n*-butyltin (**3**) and 3,5-dimethoxybenzyltri-*n*-butyltin (**4**). Knowing the ease of decomposition of these type of compounds, we tested four different methods to prepare them: direct synthesis between zinc powder, tri-*n*-butyltin chloride and benzyl halide (I) [8]; Grignard reaction between tri-*n*-butyltin chloride and benzylmagnesium halide (II) [9]; reaction between lithium tri-*n*-butyltin,

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Scheme 1. Some substituted diarylmethanes with important biological activity.

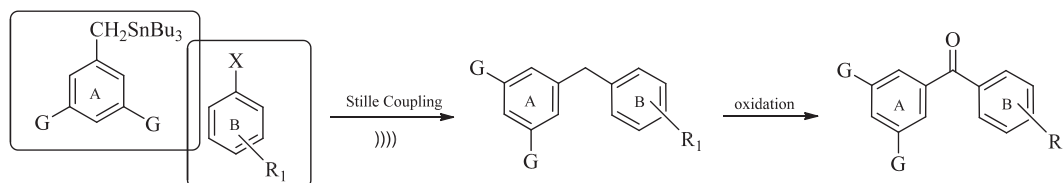
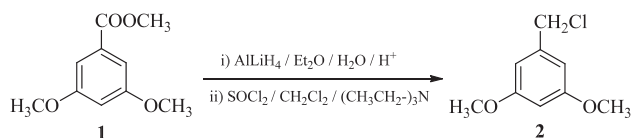


Fig. 1. Representative synthetic procedure for the preparation of the benzophenones.



Scheme 2. Synthesis reaction of 3,5-dimethoxybenzyl chloride (2).

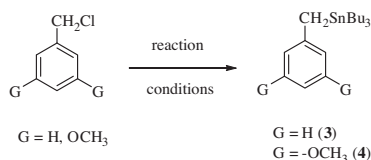
THF and benzyl halide (III) [10]; and Barbier sonicated reaction in the presence of magnesium turnings, THF, tri-*n*-butyltin chloride and benzyl halide (IV) [2c]. The results are summarized in Table 1. As can be seen in entries 4 and 8, the Barbier reaction was the best procedure for both **3** and **4** compounds, due to its simplicity, mild conditions, rate of reaction and very high yield compared with the other methods [11]. Benzyl chlorides were chosen instead of bromides to prevent the possible reduction to toluene derivatives as is pointed out in the work of Tagliavini and co-workers [8]. Besides, no side products and unreacted Bu_3SnCl were observed during the reaction. It is clear that the very short time of reaction prevents the formation of undesired byproducts. The progress of the reaction was followed by thin layer chromatography (TLC) on silica gel and checked by ^{119}Sn NMR spectra. The use of $(\text{Bu}_3\text{Sn})_2\text{O}$ as

electrophile gave very poor yields and $(\text{Bu}_3\text{Sn})_2$ as byproduct. No dimerization of R_3Sn or benzyl species was observed [12].

Once **3** and **4** were obtained, (A-ring), we tested the scope of the sonicated Stille coupling catalyzed by palladium complexes. At this point it is important to note that, usually, this coupling is carried out with benzylhalides as the Csp^3 center with a variety of arylstannanes as the Csp^2 source [13]. According to the very good results observed in the synthesis of the benzyltin compounds **3** and **4**, we proposed a reversal of this approach so these substrates will provide the Csp^3 center for the coupling reaction with several substituted aryl halides derivatives (B-ring). Thus, two reaction conditions were monitored: (i) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, THF, AsPh_3 , LiCl, r.t., ultrasound and (ii) $\text{Pd}_2(\text{dba})_3$, DMF, AsPh_3 , LiCl, r.t., ultrasound. The temperature of the sonicated bath was permanently checked and maintained at r.t. with ice or cold water. The corresponding diarylmethanes (**5**–**17**) were obtained and the results are shown in Table 2.

Except for 1-(3,5-dimethoxybenzyl)-2-methylbenzene, (**13**, entry 9), in all cases the best yields were achieved using the $\text{Pd}_2(\text{dba})_3/\text{DMF}$ system (method ii) and no traces of homocoupling byproduct was observed. On the other hand, the Stille reaction performed with the $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{THF}$ system (method i) gave the homocoupling products in almost all cases (entries 1, 2, 3, 5, 6, 8 and 10) and in a high proportion in some of them (entries 2 and 8). It is important to note that the diarylmethanes **8**, **11**, **13**, **15**, **16** and **17** (entries 4, 7, 9, 11, 12 and 13) were the only products observed, no homocoupling byproducts were obtained and the yields were regular to low for most cases. In all cases (except for entry 9) the best yields were formed under reaction conditions ii, suggesting that the catalytic species formed *in situ* using a palladium source such as $\text{Pd}_2(\text{dba})_3$ together with the $\text{AsPh}_3/\text{LiCl}/\text{DMF}$ system is better for the sonicated Stille coupling studied here than the preformed $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{AsPh}_3/\text{LiCl}/\text{THF}$ system (conditions i). This is probable because in the catalytic cycle, σ -donating ligands and DMF favored not only the oxidative addition but also the transmetalation step [14]. On the other hand the lowest yields for both conditions i and ii are observed in all cases in which the aryl halide supports the electron-donating group in para position (entries 2, 5, 8 and 11). The ortho and meta substituted halides gave better yields in almost all cases (entries 3, 4, 6, 7, 10, 12 and 13). This can be explained taking into account that this reaction is delayed in the presence of electron-donating groups in aryl halides. According to previous work [15], this effect is notorious when this type of substituents is located in para position, probably because the formation of the ArPdL_2X complex is slower in the oxidative addition

Table 1
Synthesis of benzyltin derivatives **3** and **4** under different reaction conditions.



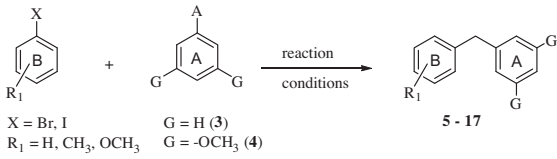
Entry	G	Reaction conditions ^b	Time (h)/yield (%) ^a
1	H	I	24/80
2	H	II	12/72
3	H	III	12/68
4	H	IV	0.5/90
5	–OCH ₃	I	– ^c
6	–OCH ₃	II	12/46
7	–OCH ₃	III	10/72
8	–OCH ₃	IV	0.5/87

^a After purification with column chromatography.

^b Zn powder, Bu_3SnCl , benzyl halide (I), Bu_3SnCl , ArCH_2MgCl (II), LiSnBu_3 , THF, ArCH_2Cl (III), Mg, THF, Bu_3SnCl , ArCH_2Cl , ultrasound (IV).

^c No reaction observed.

Table 2
Sonicated Stille reaction between benzyltributyltin compounds (**3**) and (**4**) and several substituted aryl halides.

									
Entry	G	R ₁	X	Reaction conditions ^a	Product	% Yield ^b	Time (h)	Ref.	
1	H	H	Br	i/ii	5	39 (10)/70	12/9	[16]	
2	H	<i>p</i> -CH ₃	I	i/ii	6	26 (32)/67	18/12	[17]	
3	H	<i>o</i> -CH ₃	I	i/ii	7	63 (8)/75	18/12	[18]	
4	H	<i>m</i> -CH ₃	I	i/ii	8	68/78 ^c	16/11	[19]	
5	H	<i>p</i> -OCH ₃	I	i/ii	9	45 (40)/56 ^c	18/12	[20]	
6	H	<i>o</i> -OCH ₃	I	i/ii	10	67 (20)/71	18/12	[21]	
7	H	<i>m</i> -OCH ₃	I	i/ii	11	45/60	20/14	[22]	
8	-OCH ₃	<i>p</i> -CH ₃	I	i/ii	12	28 (60)/59 ^c	26/20	–	
9	-OCH ₃	<i>o</i> -CH ₃	I	i/ii	13	42/39 ^c	28/19	–	
10	-OCH ₃	<i>m</i> -CH ₃	I	i/ii	14	51 (20)/65 ^c	27/20	–	
11	-OCH ₃	<i>p</i> -OCH ₃	I	i/ii	15	45/68	28/22	[23]	
12	-OCH ₃	<i>o</i> -OCH ₃	I	i/ii	16	55/72	30/25	[23]	
13	-OCH ₃	<i>m</i> -OCH ₃	I	i/ii	17	52/75	36/25	[23]	

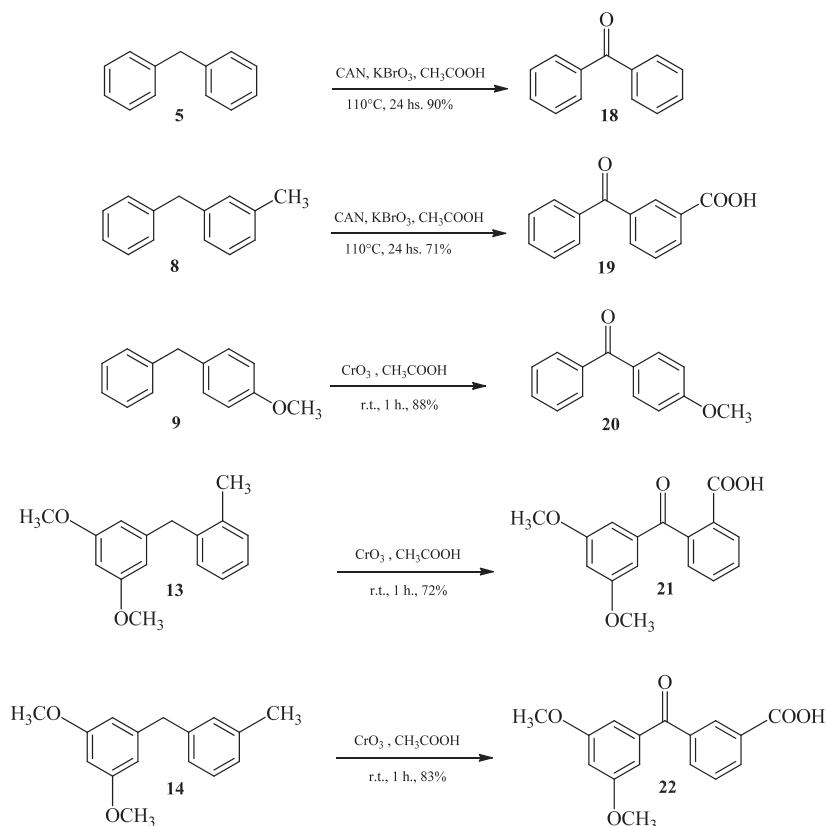
^a Reaction conditions: (i) Pd(PPh₃)₂Cl₂, THF, AsPh₃, LiCl, r.t., ultrasound; (ii) Pd₂(dba)₃, DMF, AsPh₃, LiCl, r.t., ultrasound.

^b Determined by GC/MS; calculated yields as an average of at least three independent runs and corresponds to reaction conditions i and ii respectively. In parentheses the yield of homocoupling product is shown.

^c Yields of isolated compound.

step. It is important to notice too that higher times of reaction were observed when electron-donating groups are located in ring A, so it is possible that the transfer of the benzyl moiety is delayed in the transmetallation step. The reactivity of these systems could be increased raising up the temperature but the optimization of the ultrasound conditions for Stille reactions, that was the purpose of our work, needs this parameter to be kept at r.t. After chromatographic purification with neutral alumina of compounds **5–17**, five of them (**5**, **8**, **9**, **13** and **14**) were oxidized [10] as representative cases at the benzylic center in a single reaction step (Scheme 3).

As is already known [24], the combination of cerium (IV) ammonium nitrate (CAN) in catalytic amounts and potassium bromate can be employed for benzylic oxidation. Thus, compounds **5** and **8** were oxidized, giving the already known benzophenone (**18**) and the expected 3-benzoylbenzoic acid (**19**) due to the additional oxidation of the methyl group. Because of this and taking into account that oxygen-bearing substituents like methoxy or nitro were not compatible with the latest reaction conditions [25], oxidation with chromium (VI) oxide (CrO₃) in acetic acid [26] was used in these special cases (**9**, **13** and **14**). The corresponding



Scheme 3. Oxidation of substrates **5**, **8**, **9**, **13** and **14** to the corresponding benzophenones **18–22**.

benzophenones **20–22** were synthesized in very good yields after purification. In the case of substrates **13** and **14**, 2-(3,5-dimethoxybenzoyl)benzoic acid (**21**) and 3-(3,5-dimethoxybenzoyl)benzoic acid (**22**) were obtained due to the inevitable oxidation of the methyl group.

3. Conclusions

In conclusion, we have demonstrated that the creation of a Csp³ benzyl center for the synthesis of substituted diarylmethanes structures is possible through trialkylbenzyltin intermediates generated under ultrasound Barbier reaction with excellent yields followed by the corresponding sonicated Stille coupling with substituted aryl halides. The creation of new Csp³–Csp² bond, usually very difficult to achieve, is well accomplished under mild condition reactions and suitable yields. The use of ultrasound irradiation not only improved the reaction conversion, but made the reaction run smoothly.

4. Experimental

4.1. General methods

All the reactions were performed under nitrogen or argon as indicated. The solvents used were dried and distilled in accordance with standard procedures. ¹H, ¹³C, and ¹¹⁹Sn NMR spectra were recorded in CDCl₃ on a Bruker ARX 300 Multinuclear instrument (300.1 MHz for ¹H, 75.5 MHz for ¹³C and 111.9 MHz for ¹¹⁹Sn) at 23 °C and calibrated by using signals from solvents referenced to SiMe₄ (¹H, ¹³C NMR) and with respect to Me₄Sn in the case of ¹¹⁹Sn-NMR spectra. Chemical shifts (δ) are reported in ppm and coupling constants (J) are in Hz. Compounds described in the

literature were characterized by comparing their ¹H, ¹³C and ¹¹⁹Sn NMR spectra to the previously reported data. Unknown compounds were purified and analyzed from a single run and then were repeated to determine an average yield and were characterized by ¹H and ¹³C NMR spectra, MS and elemental analysis. Mass spectra were obtained with a GC/MS instrument (HP5-MS capillary column, 30 m/0.25 mm/0.25 mm) equipped with 5972 mass selective detector operating at 70 eV (EI). High resolution mass spectra (HRMS) were recorded on a Finnigan Mat 900 (HR-EI-MS). IR spectra were recorded on a Nicolet Nexus FT spectrometer instrument. Melting points were determined with a Kofler Hot-Stage apparatus and are uncorrected. The progress of the reaction and the purity of compounds were monitored by TLC analytical silica gel plates (Merck 60 F250). The reactions under ultrasonic conditions were performed in an NDI ULTRASONIC 104X bath operating at 43–47 kHz and 30 °C (±1 °C). The reaction flask was located in the water bath of the ultrasonic cleaner, and the temperature of the water was controlled by addition or removal of water from the ultrasonic bath. Column chromatography was performed over silica gel 60 70–230 mesh ASTM. Flash chromatography was performed over alumina. All the solvents and reagents were commercially available and analytical grade.

4.2. Synthesis of 3,5-dimethoxybenzyl chloride (**2**) [27]

To a suspension of AlLiH₄ (0.6 g; 15.8 mmol) in dry ethyl ether (15 mL) under nitrogen atmosphere, a solution of commercial methyl-3,5-dimethoxybenzoate (**1**) (2 g; 10.0 mmol) in 10 mL of anhydrous ethyl ether was added dropwise with stirring. After 6 h of refluxing, the mixture was quenched with HCl 10% (20 mL). The organic layer was separated and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the crude product (1.71 g, quantitative yield, 10.2 mmol) was dissolved in

CH_2Cl_2 (48 mL) under nitrogen atmosphere and, with magnetic stirring, tionyl chloride freshly distilled (1.5 mL; 20.4 mmol) was added dropwise. The reaction mixture was heated to reflux and then a solution of triethylamine (6 mL) in CH_2Cl_2 (48 mL) was added during 2 h. The reaction mixture was quenched with saturated NaHCO_3 (100 mL) and was extracted with ether (40 mL $\times$ 3). The organic layer was separated and dried over anhydrous MgSO_4 and concentrated. The crude residue was purified by flash column chromatography with alumina and 3,5-dimethoxybenzyl chloride (**2**) eluted as a yellowish solid (1.8 g, 9.6 mmol, 94%, m.p.: 45–46 °C, lit. [7f] m.p.: 46 °C).

4.3. Synthesis of benzyltin derivatives (**3**) and (**4**). Synthesis of benzyltri-*n*-butyltin (**3**)

All the reactions were carried out following the same procedure. One experiment is described in detail in order to illustrate the methods used.

4.3.1. Method I

Tri-*n*-butyltin chloride (0.54 mL; 2 mmol) was poured to a mixture of zinc powder (0.26 g; 4 mmol) in THF (2 mL)/ NH_4Cl saturated aqueous solution (4 mL) contained in a round-bottomed two necked flask equipped with condenser and dropping funnel. With magnetic stirring, benzylbromide (0.48 mL; 4 mmol) was added dropwise at such a rate to maintain a gentle reflux due to the exothermicity of the reaction. During the addition, the disappearance of zinc powder was observed. After stirring 24 h at room temperature, the organic layer was separated and THF removed under reduced pressure. The crude product (heavy liquid) was purified by silica-gel column chromatography doped with 10% KF, eluting (**3**) with hexane as an oil [28] (0.61 g; 1.6 mmol; 80%).

4.3.2. Method II

Tri-*n*-butyltin chloride (15.3 mL; 13.2 mmol) was dissolved in a mixture of anhydrous benzene (15 mL) and anhydrous ethyl ether (8 mL) in a round bottomed two necked flask equipped with reflux condenser and dropping funnel under nitrogen atmosphere. After cooling to 0 °C (in an ice-water bath), benzylmagnesium bromide (15 mL of 1.32 M ethyl ether solution; 19.9 mmol) was added dropwise and then kept 12 h under reflux. The reaction was cooled and quenched by slow addition of 10% HCl solution. The organic layer was dried with anhydrous MgSO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography doped with 10% KF, eluting (**3**) with hexane as an oil (3.6 g; 9.5 mmol; 72%).

4.3.2.1. 3,5-Dimethoxybenzyltri-*n*-butyltin (4**).** Yellowish oil (0.17 g, 0.9 mmol, 46%). ^1H NMR (CDCl_3): δ 7.24–7.20 (s, 1H), 7.16–7.00 (m, 2H), 3.62 (s, 6H); 2.18 (s, 2H, $^2J_{\text{Sn-H}} = 55.7 \text{ CH}_2$), 1.60–1.22 (m, 6H), 0.99–0.82 (m, 15H), 0.54–0.40 (m, 6H). ^{13}C NMR (CDCl_3): δ 159.86, 144.34, 122.90, 110.27, 55.62, 25.06 ($^3J_{\text{Sn-C}} = 20.3 \text{ CH}_2$), 23.09 ($^2J_{\text{Sn-C}} = 53.9 \text{ CH}_2$), 17.29 ($^1J_{\text{Sn-C}} = 244.9 \text{ CH}_2$), 12.64, 12.29 ($^1J_{\text{Sn-C}} = 318.8 \text{ CH}_2$). HR-MS (EI): Anal. calcd. for $\text{C}_{21}\text{H}_{38}\text{O}_2\text{Sn}$ (442.1894): C, 57.16; H, 8.18%; found: C, 57.15; H, 8.14%.

4.3.3. Method III

A mixture of tri-*n*-butyltin chloride (1.35 mL; 5 mmol) and lithium chippings (0.38 g; 5 mmol) in anhydrous THF (2.5 mL) was stirred 1 h in a round-bottomed flask equipped with nitrogen atmosphere and reflux condenser. The reaction becomes exothermic and the mixture turned dark green. After 2 h stirring, the mixture was filtered through glass wool to another round bottomed flask under nitrogen atmosphere and cooled to 0 °C in an ice-water bath. Benzyl chloride (0.58 mL; 5 mmol) in anhydrous THF (1 mL) was added, followed by 12 h stirring at room temperature. The

reaction was quenched with water (5 mL) and the aqueous layer washed with ethyl ether (2 $\times$ 2 mL). The combined organic layers were dried over anhydrous MgSO_4 and after removing the solvent, the crude product was purified by 10% KF doped-silica gel column chromatography, eluting (**3**) with hexane as an oil (1.30 g; 3.4 mmol; 68%).

Following the same procedure, compound (**4**) was obtained in 72% yield (0.66 g, 3.6 mmol).

4.3.4. Method IV (Barbier reaction)

A mixture of magnesium turnings (0.32 g; 13 mmol) and tri-*n*-butyltin chloride (3.25 g; 10 mmol) in anhydrous ethyl ether (2 mL) and few drops of pure benzyl chloride was placed in a Schlenk tube under argon atmosphere and submerged into a commercial ultrasonic cleaning bath. Once the reaction starts, the remaining benzyl chloride (1.4 mL, 12 mmol) was added in ethereal solution (10 mL). When the reaction finished (30 min), the mixture was washed with a saturated solution of NaCl and extracted with diethyl ether (7 mL). The organic layer was dried over anhydrous MgSO_4 and the solvent was removed under reduced pressure. The product was purified by silica gel column chromatography doped with 10% KF, eluting (**3**) with hexane as an oil (3.42 g; 9 mmol; 90%).

Following the same procedure, compound (**4**) was obtained in 87% yield (2.07 g, 11.3 mmol).

4.4. Synthesis of diarylmethanes (**5**)–(**17**) (ultrasound Stille coupling). Synthesis of 1-benzyl-3-methylbenzene (**8**)

All the reactions were carried out following the same procedure. One experiment is described in detail in order to illustrate the methods used.

4.4.1. Method i [29]

A solution of benzyltri-*n*-butyltin (**3**) (0.38 g, 1 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2 mol%), AsPh_3 (30 mg, 0.012 mmol), LiCl (0.13 g, 3 mmol), 3-iodotoluene (0.22 g, 1 mmol) and THF (4 mL) under argon atmosphere was maintained in an ultrasonic bath. After 16 h of reaction no progress in the reaction was seen by TLC analysis. The crude product was filtered through Celite to separate the inorganic insoluble salts together with the catalyst. The solvent was distilled off under reduced pressure and product **8** was isolated by column chromatography with alumina doped with 10% of KF to retain tributyltin halides formed during the reaction. **8** eluted with 95:5 (hexane/diethyl ether) as a yellowish oil. (0.12 g, 0.68 mmol, 68%, b.p.: 276.9 °C/760 mm Hg, lit: [15] b.p.: 279.2/760 mm Hg).

4.4.2. Method ii [30]

A solution of benzyltri-*n*-butyltin (**3**) (0.19 g, 0.5 mmol), $\text{Pd}(\text{dba})_3$ (7.5 mg, 0.013 mmol), AsPh_3 (7.5 mg, 0.03 mmol), LiCl (31.3 mg, 0.75 mmol), 4-iodotoluene (0.11 g, 0.5 mmol) and DMF (10 mL) under argon atmosphere was maintained in an ultrasonic bath. After 11 h the reaction was complete and no starting product was observed by TLC (SiO_2). The crude product was filtered through Celite to separate the inorganic insoluble salts together with the catalyst. The solvent was distilled off under reduced pressure and product **9** was isolated by column chromatography with alumina doped with 10% of KF to retain tributyltin halides formed during the reaction. **9** (0.06 g, 0.28 mmol, 56%) eluted with 95:5 (hexane/diethyl ether).

4.4.2.1. 1-(3,5-Dimethoxybenzyl)-4-methylbenzene (12**).** Yellowish oil, ^1H NMR (CDCl_3): δ 7.19 (d, 2H); 7.05 (d, 2H); 6.55–6.48 (m, 3H); 3.96 (s, 2H); 3.62 (s, 6H); 2.09 (s, 3H). ^{13}C NMR (CDCl_3): δ 162.23; 142.05; 139.23; 135.15; 129.02; 128.42; 107.62; 100.90;

57.21; 40.93; 21.14. HR-MS (EI): Anal. calcd. for $C_{16}H_{18}O_2$ (242.1307): C, 79.31; H, 7.49%; found: C, 79.29; H, 7.53%.

4.4.2.2. 1-(3,5-Dimethoxybenzyl)-2-methylbenzene (**13**). Yellowish oil, 1H NMR ($CDCl_3$): δ 7.39–7.30 (m, 2H), 7.21–7.16 (m, 2H), 6.46–6.40 (m, 3H), 3.95 (s, 2H), 3.65 (s, 6H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 161.87, 143.96, 141.89, 135.51, 129.23, 128.60, 127.52, 126.00, 106.94, 99.32, 58.63, 40.12, 20.67. HR-MS (EI): Anal. calcd. for $C_{16}H_{18}O_2$ (242.1307): C, 79.31; H, 7.49%; found: C, 79.34; H, 7.45%.

4.4.2.3. 1-(3,5-Dimethoxybenzyl)-3-methylbenzene (**14**). Yellowish oil, 1H NMR ($CDCl_3$): δ 7.26–7.00 (m, 4H), 6.34–6.30 (m, 3H), 3.86 (s, 2H), 3.75 (s, 6H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 160.11, 143.61, 140.70, 138.13, 130.40, 130.12, 129.67, 126.05, 107.70, 98.10, 55.70, 42.06, 22.12. HR-MS (EI): Anal. calcd. for $C_{16}H_{18}O_2$ (242.1307): C, 79.31; H, 7.49%; found: C, 79.35; H, 7.50%.

4.5. Synthesis of benzophenones (**18**)–(**22**)

All the reactions were carried out following the same procedure. One experiment is described in detail in order to illustrate the methods used.

4.5.1. 3-Benzoylbenzoic acid (**19**)

A solution of 1-benzyl-3-methylbenzene (**8**) (0.182 g, 1 mmol), potassium bromate (0.083 g, 0.5 mmol) and cerium (IV) ammonium nitrate (CAN) (0.055 g, 0.1 mmol) was added to acetic acid (1.5 mL). The solution was stirred and heated 24 h at 110 °C or until no starting product was observed by TLC (SiO_2). The reaction mixture was poured into a cold mixture of water (2 mL) and CH_2Cl_2 (2 mL). The organic layer was separated, washed with water (2×3 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by recrystallization as a white solid from $CHCl_3$ /hexane (0.14 g, 0.71 mmol, 71%, m.p.: 153–154 °C, lit. [31] m.p.: 157–158 °C).

4.5.2. 4-Methoxybenzophenone (**20**)

To a solution of 1-benzyl-4-methoxybenzene (**9**) (0.16 g, 0.8 mmol) in acetic acid (15 mL), chromium trioxide (0.12 g, 1.2 mmol) was added. The mixture was left at room temperature during 1 h or until no starting product was observed by TLC (SiO_2). The solution was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with water (5×15 mL) and brine (10 mL). After drying over anhydrous Na_2SO_4 , the solvent was removed off under reduced pressure. The crude product was purified by silica gel column chromatography and **20** eluted as a white solid with hexane/diethyl ether (70/30), (0.15 g, 0.7 mmol, 88%, m.p.: 60–61 °C, lit.: [32] m.p.: 60–63 °C).

4.5.3. 2-(3,5-Dimethoxybenzoyl)benzoic acid (**21**)

Yellowish oil, IR (ν_{max} cm^{-1}): 3448 (O–H), 1683 and 1662 (C=O), 1253 (C–O). 1H NMR ($CDCl_3$): δ 11.80 (s, 1H), 8.17–7.50 (m, 4H), 7.06–6.44 (m, 3H), 3.62 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 193.46, 165.83, 161.55, 137.68, 137.20, 134.75, 131.76, 131.14, 128.30, 127.80, 107.20, 107.81, 58.90. HR-MS (EI): Anal. calcd. for $C_{16}H_{14}O_5$ (242.1307): C, 67.13; H, 4.93%; found: C, 67.10; H, 4.89%.

4.5.4. 3-(3,5-Dimethoxybenzoyl)benzoic acid (**22**)

Yellowish oil, IR (ν_{max} cm^{-1}): 3440 (O–H); 1687 and 1641 (C=O); 1250 (C–O). 1H NMR ($CDCl_3$): δ 10.78 (s, 1H), 8.35–7.46 (m, 4H), 7.23–6.60 (m, 3H), 3.68 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 192.09, 166.22, 162.40, 142.01, 136.98, 135.44, 132.54, 130.21, 130.06, 129.60, 107.20, 106.71, 59.04. HR-MS (EI): Anal. calcd. for $C_{16}H_{14}O_5$ (242.1307): C, 67.13; H, 4.93%; found: C, 67.18; H, 4.90%.

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