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Ultrasound-assisted synthesis of unsymmetrical biaryls by Stille cross-coupling reactions

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ABSTRACT

We describe herein an efficient method for the synthesis of unsymmetrically-substituted biphenyls using a sonochemical variation of the Stille coupling, whose results have also been compared with the conventional silent reaction. Ultrasound significantly enhances this useful organometallic transformation affording products in higher yields and in shorter reaction times than non-irradiated reactions. The scope has been explored with a selection of arylstannanes as precursors and, remarkably, no by-products resulting from homo-coupling could be detected.

1. Introduction

The Stille reaction involves the coupling of an organotin compound with a sp^2-hybridized organic halide catalyzed by palladium. This transformation has become a useful synthetic tool for carbon–carbon bond formation and can also be extended to numerous organic electrophiles [1–3] (Eq. (1)).

$$R^1Sn(R^2)_3 + R^3X \xrightarrow{Pd(0)Ln} R^1{-}R^3 + (R^2)_3SnX \quad (1)$$

In general, the reaction is carried out in an inert atmosphere using anhydrous degassed solvents although there are few examples working under air atmosphere. The process was discovered in the late 1970s and it still represents a versatile reaction in contemporary organic synthesis [4–6].

The commonly accepted mechanism for this reaction is shown in Scheme 1 and follows the general principles of other cross-coupling reactions catalyzed by transition metals [7].

The catalytically active species is Pd(0), although a pre-catalyst based on Pd(II) can also be used; Pd(II) is rapidly reduced to Pd(0) by consuming the starting stannane.

The initial step of the catalytic cycle corresponds to the "oxidative addition" of the organic halide to Pd(0), leading to the coordinatively saturated intermediate [R^3Pd(II)Ln-X]. The second step is a "transmetalation" reaction, often the rate-limiting step, in which one of the groups of the stannane [$R^1Sn(R^2)_3$] is transferred. Finally, a reaction of "reductive elimination" leads to the coupled product (R^1–R^3), thus regenerating the initial complex [Pd(0)Ln]. Numerous catalysts are commercially available and they promote the coupling reaction efficiently. Among them are tetrakis (triphenylphosphine) palladium(0) [$Pd(PPh_3)_4$], tris(dibenzylideneacetonedipalladium(0) [$Pd_2(dba)_3$], bis(acetonitrile)dichloro palladium(II) [$Pd(CH_3CN)_2Cl_2$], bis(triphenylphosphine)dichloropaladium(II) [$Pd(PPh_3)_2Cl_2$], and [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) [Pd(dppf)Cl_2].

It is well known that chemical and mechanical effects supplied by ultrasound come from cavitation. Growth and implosion of microbubbles in liquids will induce high temperatures and pressures inside such cavities, while shock waves at the interface and bulk liquid are largely responsible for enhanced mass and energy transfers. Ultrasonic irradiation constitutes a convenient way to accelerate and improve numerous organic and organometallic reactions by virtue of the effects mentioned above [8–11].

The use of ultrasound in Stille reactions remains essentially ignored. However, there are a series of recent examples illustrating the advantages of microwave irradiation for this type of reactions. This subject has been reviewed by Dallinger and Kappe [12], who focus on MW-assisted reactions in aqueous media, while Cravotto et al. [13] describes Stille and other Pd-catalyzed couplings under MW in a variety of solvents and conditions.

Our purpose in this paper is the synthesis of biphenyls catalyzed by palladium using Stille reaction under ultrasound. This method provides high performance in short reaction times at moderate temperatures with a reduced amount of catalyst. This protocol is much more benign and effective than conventional syntheses and it benefits from the multiple effects of cavitation.

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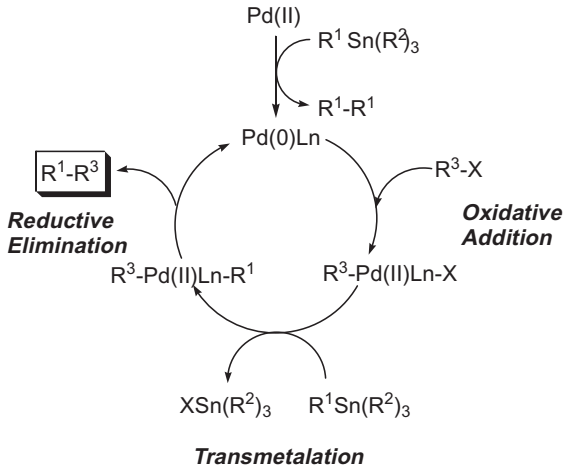


Scheme 1. Catalytic cycle.

2. Results and discussion

Our initial exploration started with the cross-coupling reaction of (*para*-methoxyphenyl) trimethylstannane with bromobenzene as a model system. The transformation was conducted in DMF, a polar solvent suitable for both reagents, and using $Pd(PPh_3)_2Cl_2$ as catalyst (Eq. (2)). The results obtained are summarized in Table 1.

Reaction times were defined according with the presence of black Pd (decomposition) in the reaction mixture. A series of parameters have been assessed searching for optimal conditions, such as the power output, temperature (oil bath), reaction time, and working under air or inert atmosphere. The latter parameter proved to be critical, since in the reactions carried out under air the catalyst rapidly decomposes (2–10 min) and, also, homo-coupling secondary product was detected. Entries 1–3 show the results obtained working in an open system under air; thus, the process was ineffective working at 420 W (70% output power) and 4 cycles where the temperature of the solution reached 50 °C (from room temperature), and no product could be observed even after prolonged irradiation. An increment of the cycles, from 4 to 7, produced an increment on the final temperature up to 90 °C and, under these conditions, cross-coupling took place giving the desired product in 41% yield, along with some homo-coupling product. In order to determine if an increment of the temperature would improve the yields of the reaction, we placed an external bath (70 °C); after 2 min of irradiation the temperature of the dissolution reached 130 °C, the catalyst decomposed and the yield of the desired product decreased to 22%.

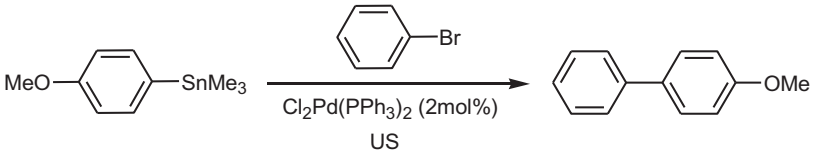
With these results in hand, we decided to work under nitrogen atmosphere (entries 4–8). With pleasure we noticed that, in all cases, the reaction gave the desired cross-coupling product and even traces of homo-coupling product were not detected (GC/EM). The temperature is an essential factor to be considered, being 90 °C (oil bath) the optimum working temperature (entry 5). Thus, working at lower (70 °C) or higher (100 °C) temperatures, under equal irradiation conditions, the desired biaryl was obtained in lower yields (entries 4 and 6). Experiment 7 shows that a lowering of the acoustic power to 300 W (50% output) produced, also, a sharp decreased in reaction yield. Moreover, when the reaction was carried out without an oil bath (entry 8), the solution temperature reached 100 °C and, under these conditions, the catalyst decomposed after 20 min, giving only 70% yield of biaryl.

As seen in Table 2, no reaction occurs without catalysis, working under the optimal reaction conditions defined. Moreover, either $Pd(0)(dba)_3$ or $Pd(II)(PhCN)_2Cl_2$ were not suitable catalysts as there was no reaction in the first case and the biaryl was obtained in only 19% yield in the second one, being $Pd(PPh_3)_2Cl_2$ the appropriate catalyst.

The scope of this sonochemical reaction was evaluated by the reaction of bromobenzene with *ortho*-, *meta*- and *para*-substituted trimethylstannyl derivatives (Table 3). In all cases, the reactions were performed at the optimal conditions of temperature, catalyst, and ultrasonic power previously found (ArSn:PhBr, 1:1.2, DMF, 2 mol% of $Cl_2Pd(PPh_3)_2$ with respect to arylstannane; power/cycle: 70/7; in an oil bath (90 °C); 30 min).

Yields ranged between 57% and 97% within 30 min, whereas the conventional thermal method required, approximately, 20 h to get comparable results [14]. As expected, the presence of an

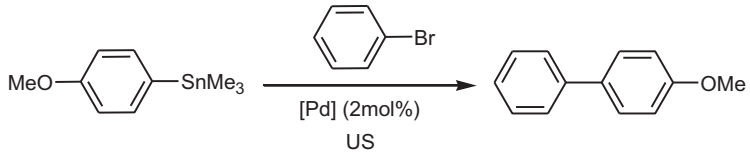
Table 1
Optimal conditions for the synthesis of *para*-methoxybiphenyl.[a]



Entry	Power ultrasound/cycles[b]	Temperature (°C)[c]	Bubbling gas	Time (min)	Yield (%GC)[d]
1	70/4	50	Air	120	0
2	70/7	90	Air	10	41[e]
3	70/7	130[f]	Air	2	22[g]
4	70/7	70[h]	N_2	30	34
5	70/7	90[h]	N_2	30	97
6	70/7	100[h]	N_2	30	83
7	50/7	90[h]	N_2	70	42
8	70/7	100	N_2	20	70

[a] Relation ArSn:PhBr = 1:1.2, DMF, 2 mol% of $Cl_2Pd(PPh_3)_2$ with respect to arylstannane.
[b] With a pulse setting of "10" the reaction is sonicated without interruption whereas with a pulse setting, for example, of "5" the reaction is sonicated for 5 s and then sonication stops for 5 s.
[c] From room temperature, unless otherwise stated.
[d] Quantified by GC, using the external standard method. Formation of the homo-coupling product was not observed under N_2 atmosphere.
[e] Together with 9% of homo-coupling product.
[f] From 70 °C (oil bath).
[g] Together with 6% of homo-coupling product.
[h] Constant temperature (oil bath).

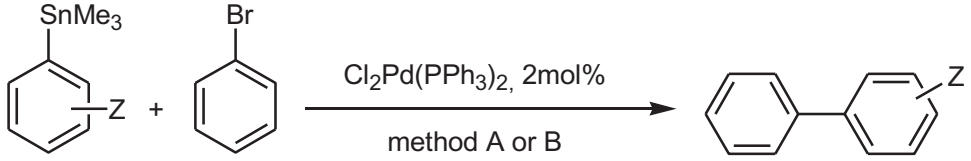
Table 2
Comparison with different catalysts.[a]

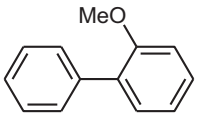
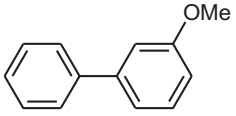
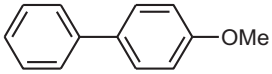
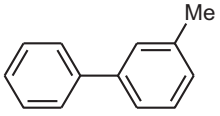
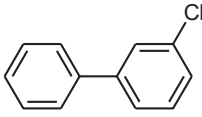


Entry	Pd catalyst	Yield[b]
1	–	0[c]
2	$Cl_2Pd(PPh_3)_2$	97
3	$Pd_2(dba)_3$	0[c]
4	$Pd(PhCN)_2Cl_2$	19

[a] Relation ArSn:PhBr = 1:1.2, DMF, 2 mol% of $Cl_2Pd(PPh_3)_2$ with respect to arylstannane; power/cycle: 70/7; 90 °C (oil bath); 30 min.
[b] Quantified by GC, using the external standard method.
[c] Arylstannane was recovered.

Table 3
Cross-coupling reactions of arylstannanes and bromobenzene.



Entry	Z	Product	Classical method A yield (%)[a] (20 h)	Ultrasonic method B yield (%)[a,b] (30 min)
1	*o*-OMe		73[c]	76
2	*m*-OMe		87[c]	87
3	*p*-OMe		75[c]	97
4	*m*-Me		52[d]	57
5	*m-Cl*		65	72

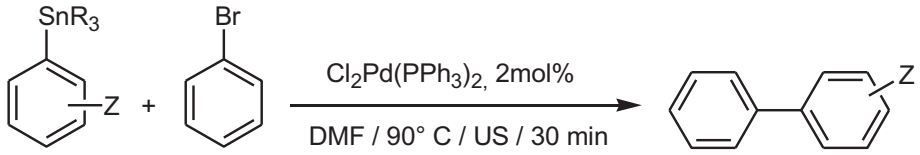
[a] Quantified by GC, using the external standard method.
[b] Formation of the homo-coupling product was not observed.
[c] See Ref. [14].
[d] See Ref. [2].

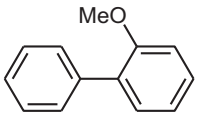
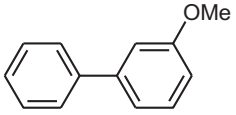
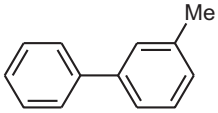
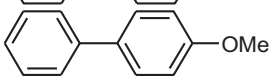
electron-donating group (–OMe) at *para*-position led to better results than other substitution patterns. Remarkably, the chromatographic analysis did not detect the presence of the Wurtz-type homo-coupling product, which represents a key advantage of the ultrasonic procedure. The latter results would be attributed to the acceleration caused by ultrasound, thus avoiding formation of side products. It is interesting to note that two equivalents of stannane are inevitably reduced per equivalent of Pd(II) and, accordingly, the Stille reaction usually generates a small percentage of homo-coupling products [15].

As it is shown in Table 4, with regard to the organotin reagent, aryl trimethylstannanes were slightly more reactive than the corresponding tributylstannyl derivatives, working at optimal conditions.

From a mechanistic viewpoint, further studies will be required to elucidate the exact role of sonication. At first glance, the observed acceleration would be ascribed to enhanced mass and energy transfers induced by the cavitational collapse. Like in other organometallic reactions, the existence of coordinative unsaturated species as intermediates could also be invoked. This would

Table 4
Comparison of the reactivity of (trimethyl)- versus tributylstannanes.[a]



Entry	R	Z	Product	Ultrasonic method B yield (%)[b,c] (30 min)
1	Me	*o*-OMe		76
2	Bu			64
3	Me	*m*-OMe		87
4	Bu			82
5	Me	*m*-Me		57
6	Bu			44
7	Me	*p*-OMe		97
8	Bu			80

[a] Relation ArSn:PhBr = 1:1.2, DMF, 2 mol% of $Cl_2Pd(PPh_3)_2$ with respect to arylstannane; power/cycle: 70/7; 90 °C (oil bath); 30 min.
[b] Quantified by GC, using the external standard method.
[c] Formation of the homo-coupling product was not observed.

be a sonication-sensitive step in agreement with type I reactions as formulated previously [16,17].

3. Conclusions

In conclusion, this work shows our preliminary results with ultrasonically-induced Stille cross-coupling reactions. This variation leads to products in moderate to good yields within 30 min at 90 °C and without Wurtz-type dimerization products. In contrast, the conventional thermal method requires 20 h at 80 °C [14] and the desired product is always accompanied by homo-coupling products between 10% and 15% yield. Further improvements and mechanistic studies are currently under way.

4. Experimental

4.1. General methods

A Cole Parmer 4710 series ultrasonic homogenizer operating at 20 kHz (600 W) provided the high intensity ultrasound. This consists of an ultrasonic generator equipped with a probe that emits the sound vibration in the solution through a titanium alloy bar (25 mm diameter) dipped into the top of the liquid in a two-necked round-bottomed Pyrex flask (volume 25 mL) equipped with a thermometer and a nitrogen inlet.

NMR spectra were recorded on a Bruker ARX 300 (300.1 MHz for ^{1}H, 75.5 MHz for ^{13}C) using $CDCl_3$ as solvent and $SiMe_4$ as internal reference. Mass spectra were obtained with a GC/MS instrument (HP5-MS capillary column, 30 m × 0.25 mm × 0.25 μm) equipped with 5972 mass selective detector operating at 70 eV (EI). Program: 50 °C for 5 min with increase 10 °C/min–250 °C.

4.2. General procedure for the synthesis of para-methoxybiphenyl

4.2.1. Classical method (A)

A two-necked, 50 mL round-bottomed flask fitted with a reflux condenser, nitrogen inlet, magnetic stirrer and rubber septum, was charged with a mixture of bromobenzene (1.20 mmol) and $PdCl_2(PPh_3)_2$ (2 mol%) suspended in dry DMF (20 mL). (*para*-Methoxy phenyl) trimethylstannane (1.00 mmol) was added dropwise via syringe and the mixture was stirred at 80 °C (oil bath) for 20 h (monitoring the disappearance of the stannane by TLC). After the resulting black precipitates were filtered through a silical gel pad, water (50 mL) was added and then the solution was extracted with ethyl ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by dry column vacuum chromatography (DCVC) [18] on silica gel (hexane:EtOAc, 9:1–6:4) to give 0.134 g (0.730 mmol, 73%) of *para*-methoxybiphenyl as a white solid. m.p.: 88–90 °C; ^{1}H NMR: δ 7.49–7.43 (m, 4H), 7.34–7.30 (m, 2H), 7.24–7.17 (m, 1H), 6.92–6.86 (m, 2H); 3.71 (s, 3H); ^{13}C NMR: δ 158.9 (C), 140.6 (C), 133.6 (C), 128.4 (CH), 127.9 (CH), 126.5 (CH), 126.4 (CH), 114.0 (CH), 55.1 (CH_3); MS (*m/z*, relative intensity): 184 (83, M^+), 169 (51, M^+-15), 141 (98), 115 (100) [14].

4.2.2. Ultrasonic irradiation (B)

To a solution of 0.02 mmol of Pd catalyst in 13 mL of DMF, 1 mmol of arylstannane and 1.2 mmol of bromobenzene were added and the reaction mixture was exposed to ultrasonic irradiation at 90 °C (oil bath) during 30 min (monitoring the disappearance of the stannane by TLC). After the resulting black precipitates were filtered through a silical gel pad, water (50 mL) was added and the solution was extracted with ethyl ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give 0.178 g (0.970 mmol, 97%) of *para*-methoxybiphenyl as a white solid.

5. Product characterization

Meta-methoxybiphenyl: Colorless oil. ^{1}H NMR: δ 7.50–7.43 (m, 2H), 7.34–7.26 (m, 2H), 7.25–7.17 (m, 2H), 7.10–6.99 (m, 2H); 6.77 (m, 1H), 3.71 (s, 3H); ^{13}C NMR: δ 159.6 (C), 142.3 (C), 140.7 (C), 129.3 (CH), 128.3 (CH), 126.9 (CH), 126.7 (CH), 119.2 (CH),

112.5 (CH), 112.2 (CH), 54.8 (CH_3); MS (*m/z*, relative intensity): 184 (70, M^+), 154 (32, M^+-30), 141 (66), 139 (36), 115 (100) [14].

Ortho-methoxybiphenyl: Colorless oil. ^{1}H NMR: δ 8.02–7.86 (m, 2H), 7.76–7.62 (m, 5H), 7.45–7.16 (m, 3H) 4.12 (s, 3H); ^{13}C NMR: δ 156.0 (C), 138.1 (C), 131.2 (C), 130.4 (CH), 129.1 (CH), 128.1 (CH), 127.5 (CH), 126.4 (CH), 121.8 (CH), 120.4 (CH), 110.9 (CH), 108.9 (CH), 55.1 (CH_3); MS (*m/z*, relative intensity): 184 (75, M^+), 141 (70); 139 (30), 115 (100) [14].

Meta-methylbiphenyl: Colorless oil. ^{1}H NMR: δ 7.48–7.45 (m, 2H), 7.30–7.27 (m, 2H), 7.24–7.19 (m, 2H), 7.07–7.02 (m, 3H), 2.35 (s, 3H); ^{13}C NMR: δ 138.4 (C), 136.8 (C), 136.6 (C), 129.4 (CH), 128.8 (CH), 128.1 (CH), 127.5 (CH), 21.5 (CH_3); MS (*m/z*, relative intensity): 168 (100, M^+); 167 (57, M^+-1); 152 (36); 139 (20); 115 (32) [19].

Meta-chlorobiphenyl: Colorless oil. ^{1}H NMR: δ 7.21–7.80 (m, 9H); ^{13}C NMR: δ 140.2 (C), 135.2 (C), 135.1 (C), 130.3 (CH), 129.3 (CH), 127.7 (CH), 127.6 (CH), 125.7 (CH); MS (*m/z*, relative intensity): 188/190 (3/1, 100, M^+); 152 (95, M^+-Cl); 151 (34, M^+-HCl); 126 (20) [20].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ultsonch.2011.08.013.

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