First Microwave-Accelerated Hiyama Coupling of Aryl- and Vinylsiloxane Derivatives: Clean Cross-Coupling of Aryl Chlorides within Minutes

Matthew L Clarke

School of Chemistry, University of St Andrews, St Andrews, Fife, Scotland, UK
Fax: (+44)-1334-463-808, e-mail: mc28@st-andrews.ac.uk

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Abstract: The first microwave-accelerated Hiyama cross-coupling reactions are reported. The reactions of aryl bromides and activated aryl chlorides with $PhSi(OMe)_3$ [or $C_2H_3Si(OMe)_3$] are complete within minutes using a modified catalyst system that can be prepared from commercially available reagents *in situ*. The microwave-accelerated reactions proceed under relatively mild conditions (110–115 °C)

Keywords: cross-coupling; homogeneous catalysis; microwave heating; palladium; phosphane ligands

Introduction

Palladium-catalysed C–C bond forming reactions are an extremely useful tool in modern organic synthesis. The synthesis of biaryls which are constituent parts of aromatic polymers, liquid crystals, natural products and medicines can be accomplished using either palladium-catalysed Suzuki (organoboron reagents),[1] Negishi (organozinc reagents),[2] Kumada (organomagnesium reagents),[3] Hiyama (organosilicon)[4] or Stille (organotin reagents)[5] cross-coupling reactions. The latter two reactions are especially useful in the preparation of alkylarenes, arylalkenes, and dienes. The Stille reaction is disadvantaged by the high toxicity and high expense of the organotin reagent. However, it remains in use to this day, perhaps because it is very useful in the stereoselective coupling of vinyl- and alkenylstannanes.

Potentially the most attractive of all these methodologies is the cross-coupling of organosilicon compounds (Hiyama reaction). These reagents are available at low cost or very easily prepared, non-toxic, and are very stable to other functionalities and reaction conditions. However, this reaction has not yet superseded the Stille and Suzuki reactions because the organosilanes are rather unreactive nucleophiles. There are frequent reports where certain aryl electrophiles fail to react, and the scope of the reaction has not been fully evaluated. Thus, in contrast to Suzuki, Kumada and Stille couplings, there is at present no general method for cross-coupling of the considerably cheaper, more widely available aryl chlorides with organosilicon compounds.

Hiyama and co-workers made significant progress back in 1996 by showing that aryl(ethyl)dichlorosilanes could be coupled with activated aryl chlorides to give good yields after 24–48 hours at 120 °C in DMF.[4b] Deshong and Mowery developed a useful protocol for the coupling of aryl bromides and iodides with siloxane derivatives, which have been touted as the most convenient organosilane for Hiyama cross-coupling.[4c] They encountered considerable difficulty with aryl chloride substrates. Thus many ligands [PPh_3, $(t\text{-Bu})_3P$, $t\text{-Bu}_2P$-biphenyl] were completely ineffective. Even the most effective catalyst, (Cy_2P-biphenyl/Pd_2dba_3), originally developed by Buchwald and co-workers and efficient for a range of aryl chloride cross-coupling processes,[1c] only produced a 47% yield in the cross-coupling of $PhSi(OMe)_3$ with 4-chloroacetophenone (10 mol % Pd_2dba_3; TON < 3). Nolan and co-workers reported that an imadazolium chloride/$Pd(OAc)_2$ catalyst (3 mol %) was a more useful catalyst for three activated aryl chlorides, but the unactivated substrates gave unsatisfactory yields.[4f] Before the organosilicon methodology sees widespread use there are clearly some challenges to be overcome. Indeed, in a very recent review article, Denmark and co-workers concluded that one of the key challenges in this area was developing new methods of activating the organosilicon cross-coupling process.[6]

Results and Discussion

In 2001, the $Pd_2dba_3 \cdot CHCl_3$/ligand **1** catalyst system was reported to give good yields in Suzuki coupling of a range of aryl chlorides.[7] In this update, the use of a new catalyst system derived from this ligand in the Hiyama cross-coupling is reported. The use of this catalyst with microwave heating seems to go some way to overcoming the problems with this methodology.

One advantage to the system developed in St Andrews was that ligand **1** could be rapidly prepared in quantitative yield with no purification steps. Consequently, the development of an *in situ* ligand synthesis

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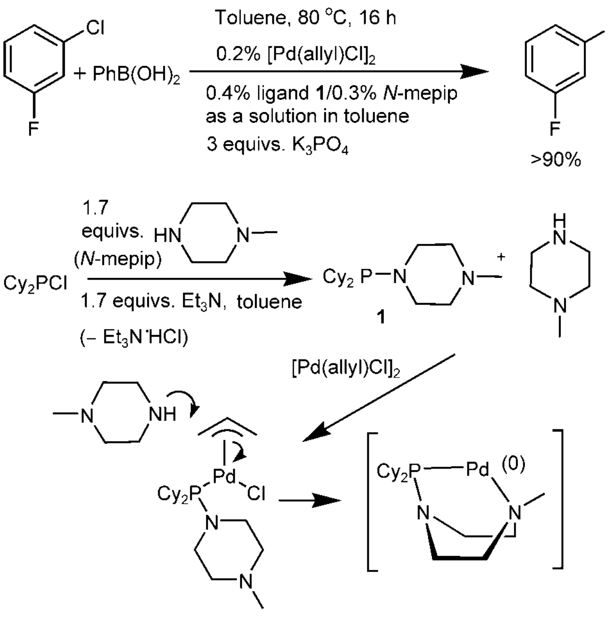
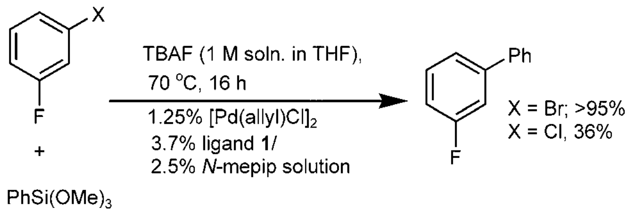
and pre-catalyst activation procedure was attempted. Adding an excess of *N*-methylpiperazine/triethylamine to a toluene solution of commercially available chlorodicyclohexylphosphine gave after 10 hours a solution of ligand and amines ($+Et_3N\cdot HCl$ precipitate). This ligand solution can then be conveniently stored in a Young's flask, and used when required. In this work, ligand solutions that were several months old performed equally well as freshly prepared material. The ligand solution was then added to commercially available $[Pd(allyl)Cl]_2$ and the aryl halide being studied directly before the cross-coupling reactions. This catalyst system seems to work at least as well as the original system in Suzuki cross-coupling reactions (Scheme 1). It is proposed that the desired reactive palladium-monophosphine catalyst is formed by the reaction sequence shown in Scheme 1 (co-ordination of phosphine, followed by allylic amination).

A preliminary experiment suggested that this catalyst could be useful for the cross-coupling of arylsiloxane derivatives with aryl bromides under mild conditions. A commercially available THF solution of TBAF was used as activator and solvent for these reactions for convenience. However, the aryl chloride tested gave lower yields (TON = 15) under these mild conditions (Scheme 2).

The simple catalyst preparation and use of widely available commercial reagents seemed to lend itself to a rapid cross-coupling procedure using microwave heating. Microwave-assisted cross-coupling reactions are currently making a significant impact in organic synthesis as high yields can be produced within minutes.[8] However, there does not appear to be any report of microwave-accelerated Hiyama cross-coupling.

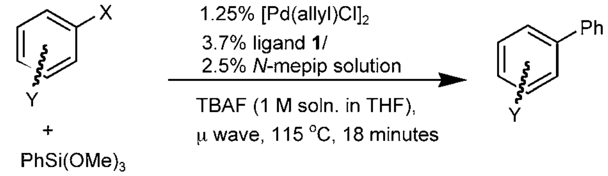


Scheme 1. *In situ* synthesis of the palladium catalyst, and its application in the Suzuki cross-coupling reaction.



Scheme 2. Hiyama reaction under conventional conditions.

The results presented in Tables 1 and 2 show that microwaves do indeed show a pronounced accelerating effect on Hiyama cross-couplings (Scheme 3). Table 1 shows the effect of different additives and catalysts in this reaction. The substrate *meta*-chlorofluorobenzene was subjected to cross-coupling using a variety of activation methods (Entries 1 to 5). The results show that the use of 1.25% $[Pd(allyl)Cl)]_2$/3.75% ligand **1**/*N*-mepip and an excess of TBAF as activator are the best conditions (at present) for this cross-coupling process. The use of unmodified $[Pd(OAc)_2]$ or a combination of the electron-donating, bulky, bidentate phosphine dtbpx (bis-di-*tert*-butylphosphinoxylene) with $[Pd(OAc)_2]$ gave very low conversions to the desired product (Entries 6 and 7). An initial attempt to carry out the reactions of an activated aryl bromide with $PhSi(OMe)_3$ using $[Pd(OAc)_2/PPh_3]$ as catalyst also proved unsuccessful, providing mainly reduced arene products (Table 1; Entry 8). The use of the catalyst derived from ligand **1** appears to be significant in obtaining the desired products.



Scheme 3. Microwave-assisted Hiyama reaction.

The reactions of an activated and deactivated aryl bromide with $PhSi(OMe)_3$ (Table 2; Entries 2 and 3) are complete within sixteen minutes at 105–115 °C. The activated aryl chlorides shown also give the desired biaryl with high yields on a similar time scale (Table 2; Entries 1 and 5). The side products from these reactions (if any) are small amounts of the reduced arene. Microwave heating seems to be especially well suited to cross-coupling reactions: it is noteworthy that although the reaction temperature is significantly above the boiling point of THF, these are moderate temperatures for a cross-coupling of aryl chlorides, and would be compatible with mildly heat sensitive functionality. Thus, we have opted for slightly longer reactions times, but with milder conditions than some microwave-accelerated re-

Table 1. Microwave-accelerated cross-coupling of aryl halides with PhSi(OMe)$_3$: influence of catalysts and additives.[a]

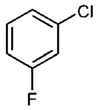
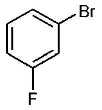
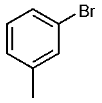
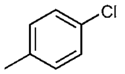
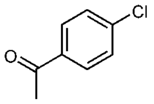
Entry	Substrate	Catalyst	Promoter	Conversion (GC Yield) [%]
1	3-chlorofluorobenzene	1.25% *in situ* catalyst from ligand **1**	TBAF	>99 (95)[b]
2	3-chlorofluorobenzene	0.4% *in situ* catalyst from ligand **1**	TBAF	58 (58)[c]
3	3-chlorofluorobenzene	1.25% *in situ* catalyst from ligand **1**	0.1 equiv. TBAF	<10 (<10)[c]
4	3-chlorofluorobenzene	1.25% *in situ* catalyst from ligand **1**	CsF	25 (25)[c]
5	3-chlorofluorobenzene	1.25% *in situ* catalyst from ligand **1**	K$_3$PO$_4$	40 (0)[b]
6	3-chlorofluorobenzene	2.5% [Pd(OAc)$_2$]	TBAF	<10 (<10)[c]
7	3-chlorofluorobenzene	2.5% [Pd(OAc)$_2$], 4% dtbpx	TBAF	<10 (<10)[c]
8	3-bromobenzonitrile	2.5% [Pd(OAc)$_2$], 5% PPh$_3$	TBAF	>95 (<10)[b]

[a] Reaction conditions: 115 °C, 2 min warm-up time, 16 min hold-time; power controlled by temperature and pressure setting (~60–80 Watt). Conversions refer to starting material consumed, yields refer to conversion to desired biaryl as determined by GCMS and ^{19}F NMR where appropriate.

[b] Remaining mass balance is reduced arene.

[c] Remaining mass is starting material (3-chlorofluorobenzene).

Table 2. Microwave accelerated cross-coupling of aryl halides with PhSi(OMe)$_3$.[a]

Entry	Substrate	Conversion (GC Yield) [%]
1		>99 (95)[b]
2		>99 (90)[b]
3		>99 (>95)
4		>99 (trace)[c]
5		>99 (90)[b]

[a] Reaction conditions: 115 °C, 2 min warm-up time, 16 min hold-time; power controlled by temperature and pressure setting (~60–80 Watt). Reactions were run with 1.25% catalyst derived from [Pd(allyl)Cl)]$_2$ and ligand **1**, using 3 equivalents of TBAF solution in THF as promoter. Conversions refer to starting material consumed, yields refer to conversion to desired biaryl as determined by GCMS and ^{19}F NMR where appropriate.

[b] Remaining mass balance is reduced arene.

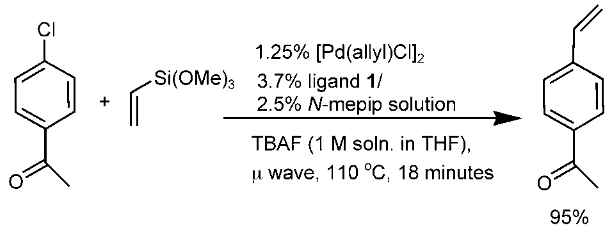
[c] Complex mixture including reduced arene as major product.

actions, which are often conducted above 150 °C. One limitation of this methodology seems to be cross-coupling of deactivated aryl chlorides as illustrated by 4-chlorotoluene (Table 2; Entry 4). The aryl chloride was converted into a mixture of biphenyl, benzene, toluene, 4-tolyltoluene and the desired product. Nonetheless, these results suggest that microwave-assisted Hiyama cross-coupling could be a very useful methodology in laboratory-scale synthesis.

The repeated failure of unactivated aryl chlorides to participate in organosilicon cross-coupling warrants further discussion: there are now several reports in the literature in which Suzuki, Negishi and Kumada coupling reactions take place with substrates such as 4-chlorotoluene (also compare Schemes 1 and 2). The contrasting results with organosilicon nucleophiles suggest one of the following:

a) the organosilicon compounds retard oxidative addition of aryl chlorides to palladium(0) species;
b) transmetallation of the organosilicon species is rate limiting and that the nature of the aryl substituents in the electrophile (and [Pd(L)Ar(Cl)] intermediate) has an effect on this process;
c) transmetallation and oxidative addition are finely balanced in the catalytic cycle, and if oxidative addition and transmetallation are slow, a pathway for catalyst degradation exists which lowers the overall productivity of the reaction;
d) a final alternative is that the organosilicon cross-coupling does not proceed through the commonly accepted cross-coupling mechanism; mechanistic studies to shed light on this intriguing reactivity are underway.

One of the useful applications of Stille and Hiyama cross-coupling is the synthesis of arylalkenes. A procedure used to produce styrene derivatives requires relatively mild conditions in order to prevent polymerisation of the products. It was pleasing to find that *para*-chloroacetophenone could be smoothly coupled with vinyltrimethoxysiloxane within 18 minutes at 110 °C using the new microwave procedure (Scheme 4). This product was isolated in pure form (95%) simply by pouring the black reaction mixture onto a pad of silica and eluting with petroleum ether/ether (4 : 1) to give a colourless solution of the desired alkene, which can be washed with water to remove water-soluble impurities. This preliminary result suggests that the cheapest, most convenient and environmentally benign method to prepare arylalkenes on research scale could prove to be the microwave-assisted procedure being developed here. In both styrene and biaryl syntheses, the ability of some aryl chlorides to undergo cross-coupling is significant as there are many more aryl chloride electrophiles commercially available and at a fraction of the cost of aryl bromides.



Scheme 4. Synthesis of a styrene derivative.

Conclusion

In summary, the first examples of microwave-assisted Hiyama cross-coupling reactions are reported. The microwaves have an amazing effect on the rate of this normally sluggish reaction. The reaction times (normally 24–48 hours in refluxing DMF) and catalyst loading have been reduced significantly compared to using conventional heating. At just 105–115 °C, high yields of biaryl can be produced in under twenty minutes. A new *in situ* ligand and catalyst synthesis has been developed that can be prepared prior to each cross-coupling reaction, or stored as the crude ligand **1**/*N*-mepip solution. Using this catalyst, activated aryl chlorides can also be coupled with $PhSi(OMe)_3$ and vinyl-$Si(OMe)_3$ within minutes under microwave heating. The procedures are very easy to carry out and therefore should find application in organic syntheses. Further studies to thoroughly evaluate the scope of Hiyama cross-coupling under both conventional and microwave heating will be carried out in due course and reported in a full paper. Mechanistic studies to gain better understanding of the fundamental steps of this reaction and optimal phosphine ligand are also underway.

Experimental Section

General Remarks

Reactions were carried out under a nitrogen atmosphere in 10-mL sealable glass tubes (available from CEM) in a CEM discover microwave apparatus. The power used was varied automatically in order to maintain the desired temperature within the specified pressure limit (250 psi). The reactions were stirred and carried out using the CEM cooling function which prevents overheating of the reaction mixture and provides more microwave radiation for a given temperature. ^{19}F and $^{19}F\{^1H\}$ NMR spectroscopy was carried out using a Bruker Advance 300 in conventional solvents using C_6D_6 as an internal standard. The reactions were monitored using a Hewlett Packard GC-MS machine equipped with an MDN-35 fused silica capillary column (30 m, 0.25 mm I. D.; 0.25 μm film). Temperature programme: 50 °C (2 min) up to 130 °C at 20 °C min^{-1}; hold 2 min; up to 230 °C (6 min). Spilt ratio = 100:1. $[Pd(Cl)(allyl)]_2$ was a generous gift from Johnson Matthey. *N*-Methylpiperazine, chlorodicyclohexylphosphine, and the aryl halides were obtained from Aldrich Chemical Company and used as received. Tetrabutylammonium fluoride (1 M solution in THF), $PhSi(OMe)_3$, and $C_2H_3Si(OMe)_3$ were obtained from Lancaster Chemical Company and used as received.

Hiyama Cross-Coupling using *in situ* Ligand-Catalyst Synthesis; Preparation of 3-fluorophenylbenzene, Typical Procedure

A dry Schlenk flask equipped with a rubber septum was evacuated and purged with nitrogen two or three times prior to the addition of dry toluene (60 mL), *N*-methylpiperazine (0.210 mL, 0.189 g, 1.895 mmol) and then triethylamine (0.194 mL, 0.141 g, 1.389 mmol). Neat dicyclohexylchlorophosphine (0.294 g, 1.263 mmol) was added dropwise to this solution *via* a syringe. This suspension was stirred overnight and then left to settle giving a solution of ~6 mg of ligand/mL concentration. This can then be used directly in reaction mixtures or transferred to a Young's flask *via* syringe and stored as a solution for several weeks under a dry nitrogen atmosphere. The purity of the ligand can be checked by $^{31}P\{^1H\}$ NMR if required ($\delta_P = 75.8$ ppm).

A microwave tube containing allylpalladium chloride dimer (5.0 mg, 1.367×10^{-5} mol, 1.25 mol %), 1-chloro-3-fluorobenzene (0.117 mL, 0.143 g, 1.09 mmol), and a magnetic stirring bar was then placed under an inert atmosphere before the addition of the ligand solution (2 mL of 6 $mg \cdot mL^{-1}$ solution, ~3.7 mol %) using a syringe. $PhSi(OMe)_3$ (0.408 mL, 043 g, 2.186 mmol) and a THF solution of TBAF (4.3 mL of 1 M solution) were then added to the microwave tube using a syringe. This microwave vessel was then heated at 115 °C for 16 min (with 2 minutes warm-up time). Yield and conversion for the reactions carried out using fluoroarylbenzenes were determined by ^{19}F NMR (C_6D_6, internal standard) [$\delta_{product} = -113.0$ ppm; ($\delta_{reactant} = -110$ ppm)]. It is noted, however, that the reduced arene product also comes at a similar chemical shift to the product, so a close inspection of the expanded spectrum is required. The conversion and yield of these reactions were also checked by GC-MS for accuracy. In all cases there was good agreement between NMR and GC results. Yields and conversion for the other aryl chlorides were determined by GC-MS using naphthalene as internal standard.

Acknowledgements

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