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A robust method for the Hiyama-type coupling of arylsiloxanes and disiloxanes with aryl halides

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Abstract

Palladium catalysed Hiyama-type coupling of aryl disiloxanes or aryl silanols with aryl halides in the presence of stoichiometric silver(I) oxide and catalytic TBAF allows the rapid preparation of biaryls in moderate to high yield under mild thermal or microwave irradiation conditions.

Recent developments in the field of palladium catalysed cross-coupling reactions of organosilanes (Hiyama couplings) from the laboratories of Denmark and Hiyama amongst others have resulted in the emergence of valuable alternatives to the more commonly used Suzuki cross-coupling reactions.[1–9] The organosilicon group can be introduced using a wide variety of methods to provide compounds possessing a high degree of functionality. The reagents required to introduce the organosilicon functionality are generally available in bulk and are inexpensive. Alkene dimethylsilanols, dimethylsiloxanes and tetramethyldisiloxanes give the desired products in good to excellent yields under a variety of cross-coupling conditions. Although there are some excellent protocols available, there is no one universal cross-coupling procedure which works well for aryldimethylsilanols, dimethylsiloxanes and tetramethyldisiloxanes. Hiyama and co-workers[8] have developed a silver(I) oxide mediated reaction for coupling aryl dimethylsilanols with aryl iodides; however, the reaction fails when aryl bromides are employed. They have also demonstrated that cross-coupling of such species fails when TBAF is used as an activator in place of silver(I) oxide. In this case, the dimethylsilanol condenses in situ to give the 1,3-di(aryl)-1,1,3,3-tetramethyldisiloxane, which is not a competent cross-coupling partner under the reaction conditions. Denmark and Ober[9] observed that di(aryl)-1,1,3,3-tetramethyldisiloxanes fail to react under their standard cross-coupling conditions, which work very well for dimethylsilanols, using cesium carbonate as the base. Additional water in the reaction mixture gives the desired product in low yield, while the use of cesium hydroxide in place of cesium carbonate results in a higher yield but at the expense of competing homocoupling and reduced functional group compatibility.

A variety of dimethylsilanols, dimethylsiloxanes and tetramethyldisiloxanes have recently become commercially available through several catalog suppliers[10] making the reagents readily accessible. With this in mind, we thought it timely to re-investigate the arylsilicon cross-coupling reaction with a view to developing a general, high yielding and practically expedient reaction protocol, which would hopefully address the shortcomings of existing methodologies.

Herein, we report a mild and efficient method for the cross-coupling of aryl silanols, silanes and disiloxanes with aryl iodides and aryl bromides, using palladium tetrakistriphenylphosphine, relatively inexpensive silver(I) oxide[11] and catalytic quantities of tetra-*n*-butylammonium fluoride

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(TBAF), which gives good conversion to the desired products after only 30 min for most cases and does not lead to the formation of homocoupled by-products.

Examination of the conditions applied previously by other groups[2–9] led to the selection of a set of hybrid conditions in which the effect of different fluoride sources in addition to silver(I) oxide was explored (Scheme 1 and Table 1).

For the reaction of phenyldimethylsilanol with 4-iodoacetophenone, improved conversions were observed when using palladium tetrakistriphenylphosphine and silver(I) oxide in combination with tetra-*n*-butyl ammonium fluoride (TBAF) or tetra-*n*-butylammonium difluorotriphenyl silicate (TBAT) as activators (Table 1, entries 3 and 5). Furthermore, when catalytic amounts of the fluoride source were used, the conversion to product was found to be greatly enhanced (Table 1, entries 6 and 7) with TBAT giving the best results. Clearly, the addition of a fluoride source leads to increased reactivity allowing for the significantly reduced reaction times to be employed. Whilst some mechanistic aspects of the coupling reaction have been discussed previously,[8,9] the combination of silver(I) oxide and fluoride may behave differently to either additive alone. Further mechanistic analysis will be required to determine the role of fluoride in this reaction, and indeed why the use of catalytic quantities is beneficial.

A further observation was that under these reaction conditions, no homocoupled side products were detected, which is in contrast to the literature observations where the addition of fluoride or base (in the absence of silver(I) oxide) can lead to varying amounts of homocoupling.[5,9] Conducting the reactions under thermal conditions in pressure tubes resulted in similar reaction profiles and yields to those observed when using microwave irradiation.

The utility of these reaction conditions was further demonstrated for a range of aryl halides as shown in Table 2, enabling the formation of the desired biaryl products in good to excellent isolated yields. Applying these conditions to the reaction of 4-bromoacetophenone gave a 38% conversion after 30 min (Table 2, entry 8). This result is in contrast to the use of silver(I) oxide alone, which fails to give significant cross-coupling when aryl bromides are employed.[8]

As a wider array of aryl bromide building blocks is commercially available compared to aryl iodides, we thought it useful to optimise the procedure further. A screen of the reaction conditions varying the additive, solvent and palladium species for the cross-coupling of phenyldimethylsilanol with 4-bromoacetophenone was conducted (see Scheme 2, Tables 3 and 4). The results confirmed silver(I) oxide as the additive of choice (Table 3, entry 1), giving a 35% conversion in THF, although the use of silver(I) sulfate gave a similar reaction profile and conversion of 33% (Table 3, entry 12).

When the solvent was altered to 1,4-dioxane or *N*,*N*-dimethylformamide, conversions increased to 48% and 46%, respectively (Table 4, entries 3 and 7), whereas altering the palladium species to palladium(II) acetate bis-triphenylphosphine gave a conversion of 67% (Table 4, entry 13). Under the optimised conditions (1 equiv Ag_2O, 0.12 equiv TBAF, 5 mol % $Pd(OAc)_2(PPh_3)_2$, 1,4-dioxane), after 6 h of heating, the conversion increased to 80% resulting in a 67% isolated yield of 4-phenylacetophenone. This result demonstrates that it is feasible to employ aryl bromides in place of iodide; however, longer reaction

Table 1
Fluoride source screen for 4-iodoacetophenone coupling using 1 equiv Ag_2O and 5 mol %$Pd(PPh_3)_4$ in THF

Entry	Additive	Time	Temp(°C)	Conv.[a] (%)
1	—	18 h	70	47
2	—	30 min	70	14
3	1 equiv TBAF	30 min	70	56
4	1 equiv TBAF	30 min	120	66
5	1 equiv TBAT	30 min	70	88
6	0.12 equiv TBAF	30 min	70	81
7	0.12 equiv TBAT	30 min	70	94

[a] Conversion calculated from product peak versus4-iodoacetophenone peak in the LCMS UV trace after 30 min microwave irradiation using a CEM Explorer focused reactor.

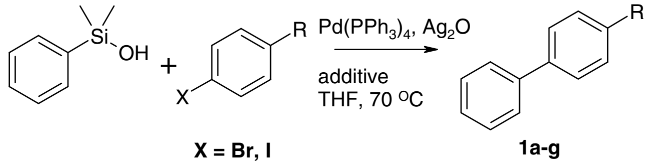
Table 2
Phenyldimethylsilanol coupling with aryl halides

Entry	R	X	Product	Yield[a] (%)
1	COMe	I	**1a**	98 (75)[b]
2	NO_2	I	**1b**	78
3	Me	I	**1c**	100
4	OMe	I	**1d**	85
5	NH_2	I	**1e**	52
6	CF_3	I	**1f**	86
7	5-Iodoindole[c]	I	**1g**	50
8	COMe	Br	**1a**	38

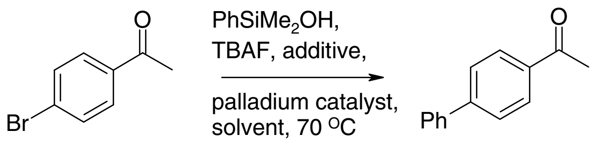
[a] Isolated yield from reactions carried out on 0.25 mmol scale with 1 equiv Ag_2O, 1.2 equiv silanol, 5 mol % $Pd(PPh_3)_4$ and 0.12 equiv TBAT (tetra-*n*-butylammonium difluorotriphenyl silicate) in THF with heating for 30 min under thermal conditions.

[b] Yield in brackets using TBAF as the fluoride source.

[c] 5-Iodoindole coupling partner not pendant R group.



Scheme 1.



Scheme 2. For conversions see Tables 3 and 4.

Table 3
Varying the additive in THF with $Pd(PPh_3)_4$

Entry	Additive	Conv.[a] (%)	Entry	Additive	Conv.[a] (%)
1	Ag_2O	35	7	Me_3SiOK	0
2	$CsCO_3$	0	8	BaO	0
3	K_2CO_3	0	9	CuI	0
4	NaO^tBu	0	10	$PhCO_2Ag$	0
5	$AgNO_3$	13	11	Ag_2CO_3	26
6	DIPEA	0	12	Ag_2SO_4	33

[a] Conversion calculated from product peak versus4-iodoacetophenone peak in the LCMS UV trace after 30 min microwave irradiation. Thermal conditions gave similar results.

Table 4
Varying the solvent and palladium catalyst[a]

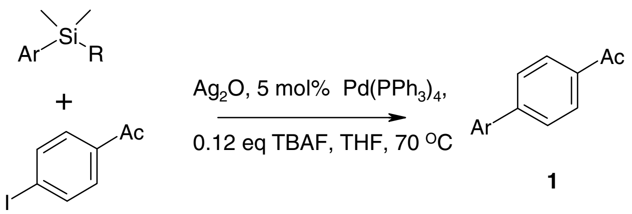
Entry	Solvent	Catalyst	Conv.[b] (%)
1	THF	$Pd(PPh_3)_4$	38
2	Bu_2O	$Pd(PPh_3)_4$	0
3	1,4-Dioxane	$Pd(PPh_3)_4$	48
4	Toluene	$Pd(PPh_3)_4$	17
5	DCM	$Pd(PPh_3)_4$	8
6	MeCN	$Pd(PPh_3)_4$	22
7	DMF	$Pd(PPh_3)_4$	46
8	Water	$Pd(PPh_3)_4$	7
9	1,4-Dioxane	$PdCl_2(PPh_3)_2$	0
10	1,4-Dioxane	$PdSO_4(PPh_3)_2$	6
11	1,4-Dioxane	allyl-$PdCl(PPh_3)_2$	42
12	1,4-Dioxane	$Pd(dba)_2(PPh_3)_2$	32
13	1,4-Dioxane	$Pd(OAc)_2(PPh_3)_2$	67

[a] Reactions carried out on 0.2 mmol scale with 5 mol % catalyst, 0.12 equivTBAF (1 Min THF), 1 equivAg_2O and 1.2 equiv phenyldimethylsilanolfor 30 min under thermal conditions.

[b] Conversion calculated from product peak versus4-iodoacetophenone peak in the LCMS UV trace.

times are generally required to achieve similar levels of conversion.

The next phase of the investigation was to determine whether other silicon reagents could be used in place of the more traditional aryldimethylsilanol for the coupling with 4-iodoacetophenone (Scheme 3, Table 5). For these reactions, we switched to using TBAF as the activator. A drawback of using TBAT is that it can act as a phenyl group donor, which leads to the formation of trace amounts of side products in reactions where silanols other than phenyldimethylsilanol are used.[12] This is not the case for TBAF and thus our preference was to use this as the activating agent.



Scheme 3.

Table 5
Coupling of 4-iodoacetophenone with a range of aromatic silicon reagents

Entry	Ar	R	Yield[a] (%)
1	C_6H_5	OH	75
2	C_6H_5	OMe	73
3	C_6H_5	ONa	0
4	C_6H_5	$OSiMe_2Ph$	88

[a] Isolated yield from the reactions carried out on a 0.2 mmol scale with 1.2 equivsilicon reagent, 1 equivAg_2O, 0.12 equivTBAF (1 Min THF) and 5 mol %$Pd(PPh_3)_4$ for 30 min under thermal conditions.

The use of the methyl ether derivative of phenyldimethylsilanol was well tolerated giving a similar result to the silanol, although the sodium salt gave no cross-coupling using these conditions (Table 5, entries 2 and 3).

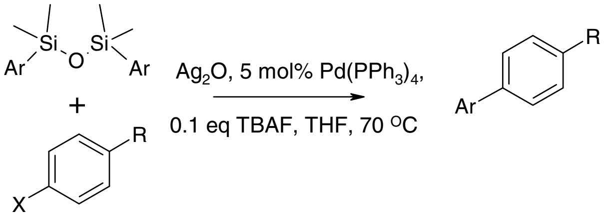
Of significant interest was the reaction of 1,3-diphenyl-1,1,3,3-tetramethyl-disiloxane which gave an 88% yield of the desired biaryl product (Table 5, entry 4). This was particularly intriguing as the formation of a dimeric species previously presumed to be the disiloxane had been observed as a side reaction when phenyldimethylsilanol was used. The exact nature of this side product has not yet been determined. This result is significant as other literature methods employing silver(I) oxide alone or base fail to give good levels of conversion to the desired cross-coupled product.[8,9] As the disiloxane species could in theory be capable of donating both of its aryl groups during the cross-coupling reaction, experiments were conducted with reduced equivalents of this reagent. The reaction using 0.5 equiv of the disiloxane resulted in the formation of the biaryl product in 47% yield. This would suggest that the enhanced yield when using 1.2 equiv of the reagent (Table 5, entry 4) was as a result of having two aryl groups available for the reaction. This observation is consistent with a recent example of the reaction of hexaarylcyclotrisiloxanes in Hiyama-type cross-couplings reported by Endo et al.[5]

The reproducibility of these reactions was found to be highly dependent on the quality of the Pd catalyst and the TBAF source. TBAF was employed as a solution in THF, which needed to be refrigerated on storage to avoid loss of activity in the reaction. The TBAF solution contained trace quantities of water (~5 wt %) which may be important for the reaction;[13] however, this was not explored as part of the current study.

To demonstrate the utility of this new methodology, the coupling of differing aryl iodides and bromides with various disiloxanes was examined (Scheme 4, Table 6).

The phenyl disiloxane reacted well with both electron rich and electron poor aryl iodides (Table 6, entries 1–3) to give the desired products in excellent yield. As expected the aryl bromides gave reduced yields when compared to the iodides after the same reaction period although *p*-nitro bromobenzene (Table 6, entry 6) proved to be an exception suggesting that electron deficient bromides are good coupling partners for this type of reaction.

The presence of electron donating groups on the disiloxane resulted in lower yields under these reaction conditions



Scheme 4.

Table 6
Disiloxane couplings

Entry	Ar	X	R	Product	Yield[a] (%)
1	C_6H_5	I	COMe	**1a**	77
2	C_6H_5	I	OMe	**1d**	96
3	C_6H_5	I	NO_2	**1b**	85
4	C_6H_5	Br	COMe	**1a**	55[b]
5	C_6H_5	Br	OMe	**1d**	31[b]
6	C_6H_5	Br	NO_2	**1b**	92[b]
7	4-(MeO)C_6H_4	I	COMe	**2a**	26[c]
8	4-MeC_6H_4	I	COMe	**3a**	59[c]
9	4-ClC_6H_4	I	COMe	**4a**	37[c]
10	2-Thiophene	I	COMe	**5a**	38 (49)[d]

[a] Isolated yield from reactions carried out on a 1.0 mmol scale with 1.5 equivsilicon reagent, 0.1 equivTBAF (1 Min THF) and 5 mol %Pd(PPh_3)$_4$ for 60 min under thermal conditions.

[b] Aryl bromide couplings performed in 1,4-dioxane.

[c] Reactions heated for 18 h.

[d] Bracketed yield when the reaction was heated at 90 °C.

(Table 6, entries 7 and 9), with longer heating times required to achieve moderate conversions.

In conclusion, we have developed new reaction conditions which enable the cross-coupling of a range of aryl silicon reagents with aryl iodides or bromides.[14] Under mild conditions and shortened reaction times, only 30 min in many cases, the desired biaryl products are afforded in good yield with no evidence of competing homocoupling occurring. More significantly, we have demonstrated the utility of this methodology for the coupling of aryl disiloxanes, which are simple to prepare and unlike their silanol equivalents are not sensitive to trace amounts of acids and bases. With the recent increase in commercial availability of aryl silicon reagents, this methodology offers a valuable alternative to traditional methods for biaryl formation such as Suzuki and Stille couplings.

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10. Suppliers include Advanced Molecular Technologies, Alfa Aesar, Sigma–Aldrich and Wako.
11. A typical price for silver(I) oxide is £10 for 1 g from Sigma–Aldrich.
12. TBAT has previously been reported as a phenyl source see: McElroy, W. T.; Deshong, P. *Org. Lett.* **2003**, *5*, 4779–4782.
13. See Ref. 9 for a discussion on the role of water in similar base mediated reactions.
14. *Example procedure—thermal reaction*: To 1 mmol aryl iodide and 1 mmol silver(I) oxide in 7.5 ml anhydrous THF were added 1.5 mmol 1,1,3,3-tetramethyl 1,3-diphenyl disiloxane, 0.05 mmol tetrakis(triphenylphosphine) palladium(0) and 0.1 mmol tetrabutylammonium fluoride (1 M in THF). The resulting suspension was stirred in a pressure tube at 70 °C for 1 h. The reaction was then filtered and washed with EtOAc and then to the resulting filtrate was added 1.5 g of silica, and the resultant suspension was concentrated to give the silicated crude product, which was purified by column chromatography (heptane + 0–5% EtOAc). Selected example: 4-acetylbiphenyl (**1a**), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.5 (s, 3H), 7.30–7.35 (m, 1H), 7.35–7.41 (m, 2H), 7.50 (d, $J = 8.1$ Hz, 2H), 7.54 (d, $J = 6.6$ Hz, 2H), 7.90 (d, $J = 6.6$ Hz, 2H); *m/z* 197.16 $(M+H)^+$. *Example procedure—msicrowave reaction*: To 1 mmol aryl iodide and 1 mmol silver(I) oxide in 7.5 ml anhydrous THF were added 1.5 mmol 1,1,3,3-tetramethyl 1,3-diphenyl disiloxane, 0.05 mmol tetrakis(triphenylphosphine) palladium(0) and 0.1 mmol tetrabutylammonium fluoride (1 M in THF). The microwave tube was sealed and placed in the microwave cavity of a CEM Explorer. The tube was irradiated with microwave energy for 30 min maintaining a temperature of 70 °C. Work-up was conducted as for the thermal example.