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Aryl–Aryl Bond Formation by the Fluoride-Free Cross-Coupling of Aryldisiloxanes with Aryl Bromides

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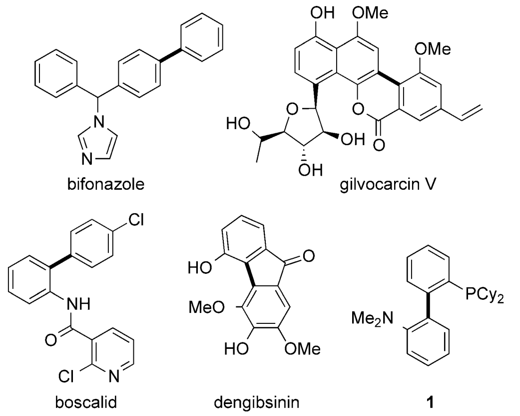
Abstract: The prevalence of the biaryl structural motif in biologically interesting and synthetically important molecules has inspired considerable interest in the development of methods for aryl–aryl bond formation. Herein we describe a novel strategy for this process involving the fluoride-free, palladium-catalysed cross-coupling of readily accessible aryldisiloxanes and aryl bromides. Using a statistical-based optimisation process, preparatively useful reaction conditions were formulated to allow the cross-coupling of a wide range of different substrates. This methodology represents an attractive, cost-efficient, flexible and robust alternative to the traditional transition-metal-catalysed routes typically used to generate molecules containing the privileged biaryl scaffold.

Keywords: biaryls · C–C coupling · cross coupling · silicon · synthetic methods

Introduction

The importance of the biaryl structural motif in chemistry is exemplified by its presence in a large number of biologically active and functional molecules, including natural products, pharmaceutical agents, catalysts and ligands (Scheme 1).[1,2] Consequently the development of methods for aryl–aryl bond construction has attracted immense interest amongst synthetic chemists.[1–3] Transition-metal-catalysed cross-coupling between a organometallic compound and an organic halide or pseudo-halide represents the most widely utilised strategy for biaryl bond formation.[1,2] Numerous organometallic species have been utilized as suitable cross-coupling partners, with organotin (Stille) and organoboron reagents (Suzuki) being the most significant in terms of synthetic utility.[1]



Scheme 1. Some examples of biologically interesting molecules that contain biaryl systems. Bifonazole and boscalid have broad-spectrum activity against fungal strains,[4,5] gilvocarcin V is known to have antitumour activity[6] and fluorenone-based natural and synthetic compounds such as dengibsinin are of pharmaceutical interest.[7] Biaryl phosphane ligands such as **1** are widely employed in palladium-catalyzed amination reactions.[8] In all cases, the biaryl bond is highlighted in bold

Despite the undoubted value of such "traditional" cross-coupling protocols in organic synthesis, there are drawbacks associated with them; for example, the toxicity of organostannanes and their by-products and difficulties associated with preparation and purification of some organoboron reagents.[9–11] Consequently, there is continuing interest in the development of novel coupling procedures for the formation of biaryl bonds (and carbon–carbon bonds in general) that utilise alternative organometallic coupling species and con-

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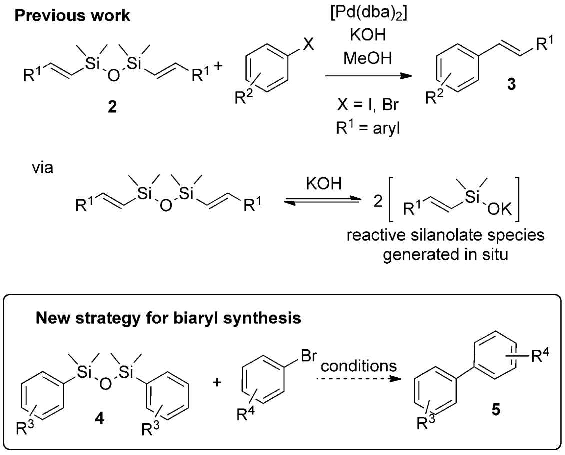
ditions. In this context, the use of organosilicon reagents in palladium-catalysed cross-coupling has attracted the attention of synthetic chemists.[12–16] Organosilicon reagents have a number of unique advantages over other organometallic species including low toxicity, high stability, low molecular weight and ease of introduction into various substrates.[12,13,15]

Seminal studies by Hiyama and Hatanaka established that a range of alkenyl-, alkynyl and allyltrimethylsilanes could undergo palladium-catalysed cross-coupling with aryl, vinyl and allyl halides through activation of the silicon–carbon bond with fluoride ions to facilitate transmetallation.[17] Since these pioneering works, significant advances in the cross-coupling of organosilicon reagents have been made that have extended the scope and generality of this method greatly. In the context of biaryl synthesis, numerous organosilane species have been successfully employed as aryl donors in fluoride-activated cross-coupling reactions with aryl halides.[18,19] However, there are several significant drawbacks associated with the use of fluoride including the cost of fluoride sources, the corrosive effects of such compounds and its incompatibility with many functional groups, particularly silicon protecting groups, which are ubiquitously employed in organic synthesis.[11,12,18] Consequently, the development of protocols that allow efficient coupling of aryl silicon species with aryl halides under fluoride-free conditions has attracted significant interest. For example, a variety of bases have been shown to act as effective activators of silicon-based reagents.[20–28] In 2000, Hiyama and co-workers described the fluoride-free palladium-catalysed cross-coupling of organosilanol species with a variety of iodoarenes in the presence of stoichiometric Ag_2O as an activator.[29] Over the last decade, the field of organosilanol-based cross-coupling has developed rapidly, with significant practical and theoretical contributions being made by Denmark and co-workers.[11,12,14,18,30] These researchers have reported that aromatic and heteroaromatic silanol species and pre-formed silanolate salts can be cross-coupled with a range of aromatic and heteroaromatic halides to form biaryl derivatives; the reactive species in such processes has been shown to be the corresponding silanolate, which in the case of silanols, is generated in situ in the presence of a base.[11] Despite the undoubted utility of these protocols for the formation of biaryl bonds, the high levels of reactivity exhibited by silanol(ate)s can hinder their progression through multistep syntheses.[31,32] Consequently, complex synthetic sequences incorporating silanol-based cross-coupling reactions are inherently inflexible in the sense that the relevant silcon functionality cannot be installed at an early stage in the synthesis due to an incompatibility with other functionality or reagents. In an effort to address this issue, various "masked" forms of alkenyl- and aryl silanol(ate)s have been developed and utilised to forge new carbon-carbon bonds.[16,32] Such species are (ideally) stable to a wide range of reaction conditions but can be selectively unmasked or "activated" in situ under specific conditions to reveal the desired reactivate silanol in preparation for the subsequent coupling reaction.[16] The majority of work on masked silanol(ate)s has focused upon vinylation, either under fluoride-activated[33–40] or fluoride free conditions;[30,41] though there are some examples of biaryl synthesis using masked silanol(ate)s, most require fluoride activation[42,43]

A continuing area of interest within our research group is the use of disiloxanes as masked silanols in cross-coupling reactions.[31,32] Disiloxanes have been shown to exist in equilibrium with the corresponding silanolate species under basic conditions (Scheme 2).[18,30,31] We have previously exploited this phenomenon for the development of operationally simple protocols for the base-induced cross-coupling of a range of aryl substituted vinyldisloxanes **2** with aryl and heteroaryl iodides and bromides under fluoride-free conditions, providing access to (*E*)-stilbene derivatives **3** in good to excellent yields with excellent levels of geometric purity (Scheme 2).[31,32] Disiloxanes offer the advantage of increased stability relative to silanol(ate)s and therefore have the potential to be carried through multi-step synthesis, which could offer new disconnection strategies in the synthesis of complex molecular systems.[31,32] In addition, the use of disiloxanes is more atom efficient compared to alternative "masked" silanols, which have been more commonly employed.[31,32]



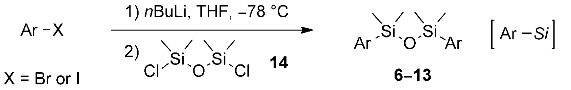
Scheme 2. Palladium-catalyzed, base-induced fluoride-free cross-coupling of disiloxanes. $[Pd(dba)_2]$ = bis(dibenzylideneacetone)palladium(0).

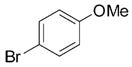
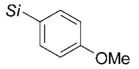
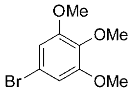
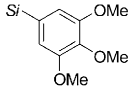
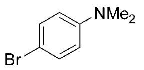
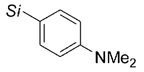
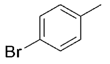
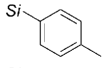
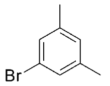
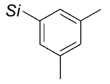
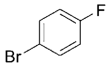
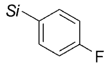
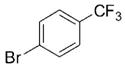
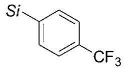
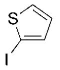
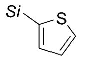
We envisaged expanding the scope of our disiloxane-based coupling strategy to include aryldisiloxanes **4**, with the aim of developing a novel, robust methodology of broad synthetic utility and generality for the preparation of substituted biaryl systems **5**. Herein we report upon the successful realisation of this goal. Using statistical-based methods to expedite the optimisation process, preparatively useful reaction conditions were formulated that allow for the base-mediated, palladium-catalysed, fluoride-free cross-coupling of a wide range of readily prepared aryldisiloxanes **4** and commercially available aryl bromides. These methods represent attractive, cost-efficient alternatives to the transition-metal-catalysed routes typically used to generate molecules containing the privileged biaryl scaffold.

Results and Discussion

Preparation of disiloxanes: To comprehensively explore aryl–aryl coupling employing aryldisiloxanes, a range of these species, varying in both steric and electronic properties, were required. Towards this end, aryldisiloxanes **6**–**13** were synthesised from the appropriately substituted aryl halide derivatives through halogen–lithium exchange and trapping with chlorodisiloxane **14** (Table 1). Pleasingly, both electron-rich and electron-poor aryl bromides readily participated in the reaction and yields of the desired products were typically good to excellent.

Table 1. Synthesis of aryldisiloxanes using aryl lithium reagents.[a]

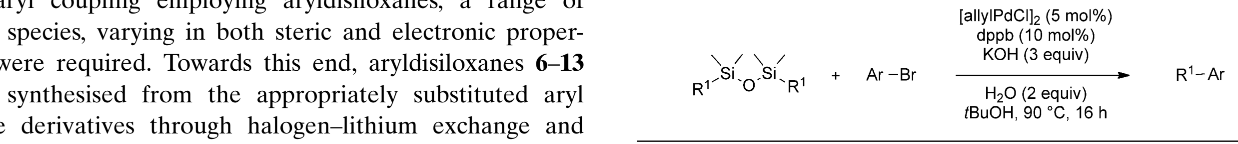


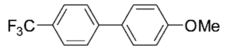
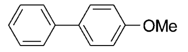
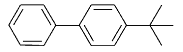
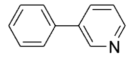
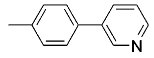
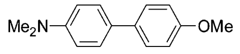
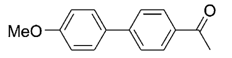
Entry	Ar–X	Product		Yield [%][b]
1			**6**	96
2			**7**	94
3			**8**	75
4			**9**	96
5			**10**	81
6			**11**	65
7			**12**	76
8			**13**	82

[a] General conditions: aryl halide (2.1 equiv), *n*BuLi (2.0 equiv) disiloxane (1.0 equiv). [b] Yield of product isolated after purification by flash column chromatography.

Preliminary studies on biaryl formation using aryldisiloxanes: With a range of aryldisloxanes in hand, their behaviour in palladium-catalysed base-mediated cross-coupling reactions with aryl bromides was investigated. Initially, the use of reaction conditions we had previously developed for the cross-coupling of vinyldisiloxanes with aryl halides were investigated; bis(dibenzylideneacetone)palladium(0) ([Pd(dba)$_2$]), KOH, MeOH.[31,32] However, these conditions were found to be ineffective for the cross-coupling of aryldisiloxanes with aryl halides (data not shown). The cross-coupling of aryl(dimethyl)silanols with aryl halides has been reported.[18] Inspired by these observations, we examined the use of related reaction conditions for the cross-coupling of aryldisiloxanes (Table 2). However, the results of this initial study were disappointing; in several cases it did not prove possible to isolate the desired biaryl product, and, in the limited number of examples in which this could be achieved, the isolated yields were typically low; homocoupled aryl bromide and dehalogenated material were also observed as significant by-products. Significant optimisation of the reaction conditions was required to realise our goal of developing a synthetically useful protocol of broad generality for the cross-coupling of aryldisiloxanes with aromatic halides.

Table 2. Base-induced cross-coupling of aryldisiloxanes.[a]

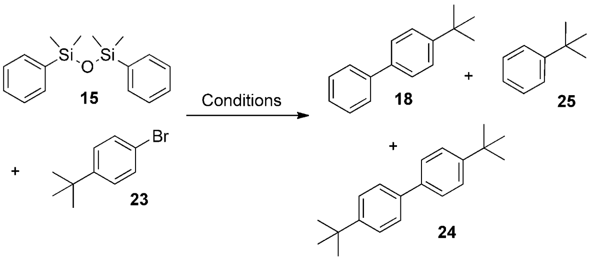


Entry	Disiloxane	Product		Yield[b] [%]
1	**12**		**16**	NA
2	**15**[e]		**17**	detected[c]
3	**15**[e]		**18**	27[d]
4	**15**[e]		**19**	detected[c]
5	**9**		**20**	28
6	**8**		**21**	detected[c]
7	**6**		**22**	11

[a] General conditions: disiloxane (1.0 equiv), aryl bromide (1.5 equiv). [b] Yield of product isolated after purification by flash column chromatography. Yield based upon aryl bromide. [c] Product mass was detected in LCMS spectrum of the crude reaction mixture but could not be isolated. [d] Product yield determined by ^{1}H NMR spectroscopic analysis of the isolated mixture of **17** and the corresponding homocoupled product after flash column chromatography. NA = no evidence for formation of the desired product by LCMS and ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] **15** = 1,1,3,3-tetramethyl-1,3-bis(phenyl)disiloxane (R^1 = Ph; commercially available).

Reaction optimisation is traditionally carried out by a "one-factor-at-a-time-approach", in which the effect of one particular experimental variable (factor) is assessed by keeping all other conditions constant, then this factor is held at its optimum setting and a different factor is examined, and so on.[44] The preliminary study outlined above suggested that cross-coupling reactions involving aryldisiloxanes are affected by many variables; thus a traditional systematic optimisation process would be expected to be an extremely lengthy endeavour.[44] In addition, optimisation using a traditional approach is known to provide only a partial exploration of the overall "reaction space" (the full range of all the variables and all possible combinations of the variables) as any interactions between the variables are not considered; thus a true reaction optimum may not be found.[44,45] We therefore sought to optimise the reaction conditions for the cross-coupling of aryldisiloxanes by using an alternative strategy based on a statistical-based process, centred around the application of a Design of Experiment (DoE) protocol. DoE is a statistical tool used for experimental design and the optimisation of continuous variables (i.e., number of equivalents of given reagent, concentration of a given reagent, temperature, reaction time).[45] In the context of reaction optimisation, use of DoE gives more precise information about the reaction process (including knowledge about the interaction(s) between different reaction variables) and a fuller examination of the reaction space from fewer experiments than that achieved using a traditional one-factor-at-a-time-approach.[44–46] DoE thus offers the opportunity to achieve a better understanding and control of a given reaction process.[44,45] DoE was developed specifically to look at large problems with many variables and interactions.[46] Given that cross-coupling using aryldisiloxanes appeared to be a complex process, with several variables influencing the outcome of the reaction (see above), we believed that optimisation using a DoE strategy would be advantageous.

Determination of the discrete variables for the DoE study using an experimental design method: Before the DoE analysis could be carried out a specific set of discrete variables (i.e., the exact types of reaction components such as base, solvent and ligand) needed to be defined. The preliminary investigations into the cross-coupling of aryldisiloxanes had provided reaction conditions with limited substrate scope which only gave the desired biaryl products in low yields (see above). These conditions were thus deemed to be unsuitable for use as a starting point for the DoE study. To find a refined set of reaction components the reaction between disiloxane **15** and 4-bromo-*tert*-butylbenzene (**23**) to produce **18** was examined (Scheme 3; this substrate pair was also used as the "model" reaction in the subsequent DoE analysis[47]). The effects of various discrete variables (different bases, solvents and ligands) upon the reaction profile was investigated, with experiments based upon a balanced sub-set of potential combinations forming a categorical screening design rather than a traditional one-variable-at-a-time approach to: 1) cover a larger area of the reaction space than in previous investigations and 2) arrive at the desired conditions in a reduced number of experiments. Improving the yield of the desired biaryl product **18** was an obvious objective for the optimisation process. Related objectives included increasing the consumption of aryl bromide **23** and reducing the amount of homocoupled material **24** generated during such reactions.



Scheme 3. Model substrate pair used in studies to determine discrete variables for the DoE analysis.

The variables in this initial screening design included the choice of ligand, base, solvent and the presence/absence of H_2O.[48] The palladium source used in all cases was chosen to be $[allylPdCl]_2$ as Denmark and Ober had previously demonstrated its utility in the cross-coupling of aryl silanol(ate)s.[18] Overall eight solvents, eight bases, and 16 ligands were included (see the Supporting Information). A complete set of all variable combinations, incorporating the presence/absence of water would lead to 2048 experiments. However, by using the screening design the number of experiments was reduced to 68 (including four control replicates), while still retaining good information on the suitability of the variables in the cross-coupling process. The responses in the first screening design were defined as the amount (in% yield) of product **18**, aryl bromide **23**, homocoupled product **24** and dehalogenated starting material **25**. These were determined through HPLC analysis of the crude reaction mixtures. More detailed information on this screening experiment is provided in the Supporting Information. Ultimately, the reaction components (discrete variables) selected as the starting point for use in the DoE were: KOH (base), *t*BuOH (solvent), $P(tBu)_3$ (ligand) in the presence of H_2O.

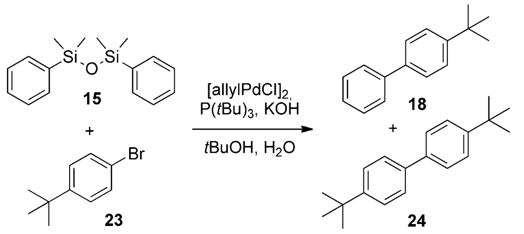
Optimisation of continuous variables using a DoE protocol: The DoE analysis involved a series of experiments which analysed the effects of the continuous variables associated with the reaction process; that is, the ranges of the reaction components already identified (e.g. number of equivalents of a specified reagent) and other variables such as reaction time, reaction temperature, and so on. The ranges (high and low levels) of the reaction variables chosen as the starting point for the DoE study were:[49]

Base:	KOH, 1–10 equivalents
Catalyst:	$[allylPdCl]_2$: 2–10 mol %
H_2O:	0–20 equivalents
Temperature:	70–90 °C
Time:	3–10 h

A key goal of this study was the development of a process that was competitive with the existing cross-coupling procedures. Thus, an operationally simple protocol with relatively mild reaction conditions and a broad substrate scope which proceeded efficiently at low catalyst loading was desired; these criteria guided the choice of upper limits for base, reaction temperature, time and catalyst loading.

Initially a two-level factorial design with additional centre points was carried out.[50] The responses in this DoE analysis were defined as the amount (in% yield) of product **18** and

Table 3. Details of experiments performed in two-level factorial design.[a]



Run[b]	KOH [equiv]	H_2O [equiv]	Cat [mol %][c]	T [°C][d]	t [h][e]	Yield [%][f] Pr (18)	HC (24)
1	1.0	0	2.0	70	10	22	4
2	5.5	10.0	6.0	80	6.5	70	12
3	5.5	10.0	6.0	80	6.5	71	12
4	10.0	20.0	10.0	70	3	69	10
5	1.0	20.0	2.0	90	10	13	3
6	10.0	0	10.0	90	3	22	14
7	1.0	20.0	2.0	70	3	9	1
8	10.0	20.0	10.0	90	10	71	13
9	1.0	0	2.0	90	3	25	6
10	10.0	0	10.0	70	10	25	13
11	10.0	20.0	2.0	70	10	16	3
12	1.0	0	10.0	90	10	16	3
13	1.0	20.0	10.0	70	10	16	3
14	10.0	0	2.0	90	10	3	2
15	10.0	0	2.0	70	3	1	1
16	10.0	20.0	2.0	90	3	16	2
17	1.0	20.0	10.0	90	3	12	3
18	1.0	0	10.0	70	3	23	3

[a] General reaction conditions: disiloxane **15** (1.0 equiv), 4-bromo-*tert*-butylbenzene (**23**) (1.8 equiv), Pd/P(tBu)$_3$ 1:1. [b] run = run order (computationally randomised order, in which experiments are performed). [c] Cat = catalyst ([allylPdCl]$_2$). [d] T = temperature [e] t = time; h = hours. [f] Pr = product **18**, HC = homocoupled product **24**. Yields (based upon aryl bromide) determined through HPLC diode array (UV-trace) analysis of the crude reaction mixtures relative to the IS (1,1′-biphenyl-4-methanol).

homocoupled product **24.** The screening experiment was set up using a statistical software package[51] and consisted of a set of 18 reactions (Table 3). The responses were determined through HPLC analysis of the crude reaction (see the Supporting Information).

The effect of the various factors, including interacting factors, upon the yields of the desired product **18** and homocoupled material **24** were represented in a graphical fashion in the form of main factor or interaction graphs and additionally as 3D-graphs (see the Supporting Information).

Significant factors affecting the product formation were found to be catalyst, base and H_2O. In addition, the following interaction effects were also found to be significant: base–H_2O, base–catalyst, catalyst–H_2O and time–temperature. There was also a smaller, negative interaction between catalyst and temperature. The identification of these interaction effects demonstrates the superiority of the DoE compared to a one-factor-at-a-time approach for reaction optimisation, which does not take into account any interdependency of factors.[50] Further analysis indicated that the best results in terms of yield of the desired product **18** should be achieved when all of these three factors were at their highest factor level. For example, the interaction between base and catalyst and its effect upon desired product formation could be represented in a 2D and 3D plots, which clearly indicate that the use of high equivalents of H_2O, high levels of base and catalyst loading should lead to a high product yield (Figure 1 and Figure 2). The effect of temperature and time proved to be only marginal.

The data gathered from the experimental design indicated that the most important factor affecting the yield of the undesired homocoupled material **24** was the interdependence of base and catalyst. The analysis suggested that low catalyst loading together with low amount of base should lead to a reduced yield of this undesired material. However, these conditions would be expected to lead to an inferior yield of the desired cross-coupled material **18**. Thus the aim of discovering reaction conditions which would provide the desired product **18** in a high yield whilst minimising the quantity of homocoupled material **24** formed had not been realised by this two-level factorial design. Clearly, further analysis of the reaction process was required.

In all the interaction graphs for both **18** and **24**, in which the remaining factors (i.e., those not involved in the interaction under analysis) were set to their centre point values, the centre point design points (corresponding to the actual performed experiments) were elevated relative to the interaction lines (i.e., corresponded to a higher yield of the desired product **18**). That is, the centre points gave yields of **18** which were above the values predicted

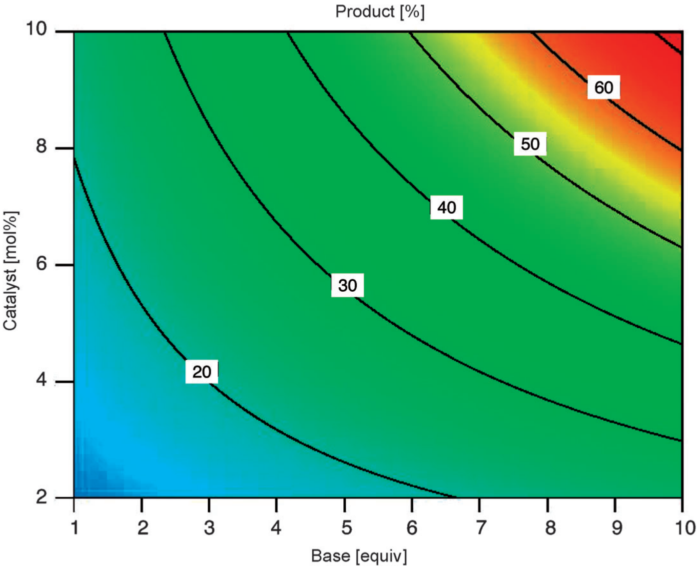


Figure 1. 2D Contour graph of the interaction of base and catalyst: Base is displayed on the X axis, catalyst on the Y axis. The product (**18**) formation for the experimental space is represented in graduated colour shading, from blue (low yield) to bright red (high yield) and the contour lines displaying the product yield. Equivalents of H_2O is set to high factor level (20.0 equiv), and time and temperature are set at their centre point values.

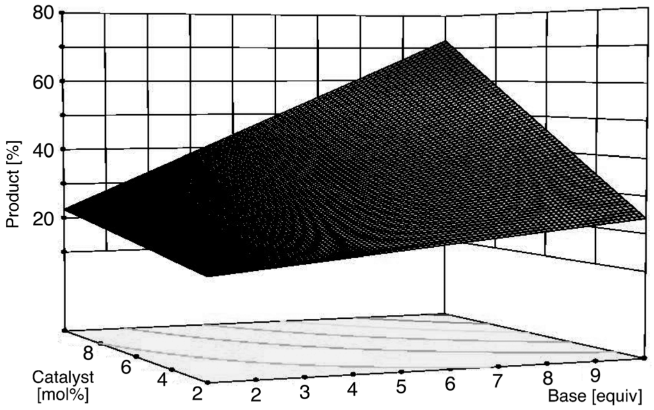


Figure 2. 3D view of the interaction of base and catalyst: Base is displayed on the X axis, catalyst on the Y axis. The product (**18**) formation for the experimental space is displayed on the Z axis; H_2O equivalents are set to high level (20.0 equiv), time and temperature are set at their centre point values (6.5 h, 80° C).

by the computational model. This phenomenon suggested considerable "curvature" in the experimental space for the formation of the desired cross-coupled product **18** and the homocoupled material **24**, which indicated that the linear assumptions made in the two-level factorial model were not descriptive of the real response surfaces.[50] To model the real reaction system with a higher degree of accuracy, a more detailed study involving the examination of nonlinear terms was carried out with the design points (experiments) chosen according to a central composite design (CCD).[50]

A CCD involves experiments at extra positions of the design space relative to a two-level factorial design to investigate the area around the centre points in the response area.[50] The variables examined in this second study were base, catalyst and water; all at the initial levels used in the two-level factorial study.[52] CCD screening was set up using a statistical software package.[51] Overall the experimental design consisted of a total of 20 reactions. The responses chosen were the yield of the desired product **18** as well as the yield of the undesired homocoupled material **24**, which were determined through HPLC analysis of the reaction mixtures. The effects of base–catalyst, base–water and catalyst–water interactions upon the product formation could be visualised in form of 2D contour plots and 3D response surface plots. These graphs showed a gradual increase in yield of the desired product **18** with increasing amounts of the three main factors (base, catalyst, H_2O), with the optimum within this selected experimental space positioned at the highest explored level of all these factors (Figure 3). As suggested by the two-level factorial design, the formation of homocoupled product **24** is favoured by high catalyst loading and high concentration of base. Unfortunately, these are the conditions suggested to be necessary for a high yield of the desired product **18**. Overall, a better knowledge of the experimental space around the centre point region was gained by the non-linear response surface study, which showed a gradual increase in the yield of the desired product **18** towards a small plateau at the end of the design space; that is, at a high level of each factor (and the data indicated that further improvements in the yield of **18** could be obtained with increases in the value of the main factors, that is, base, catalyst, H_2O).[53]

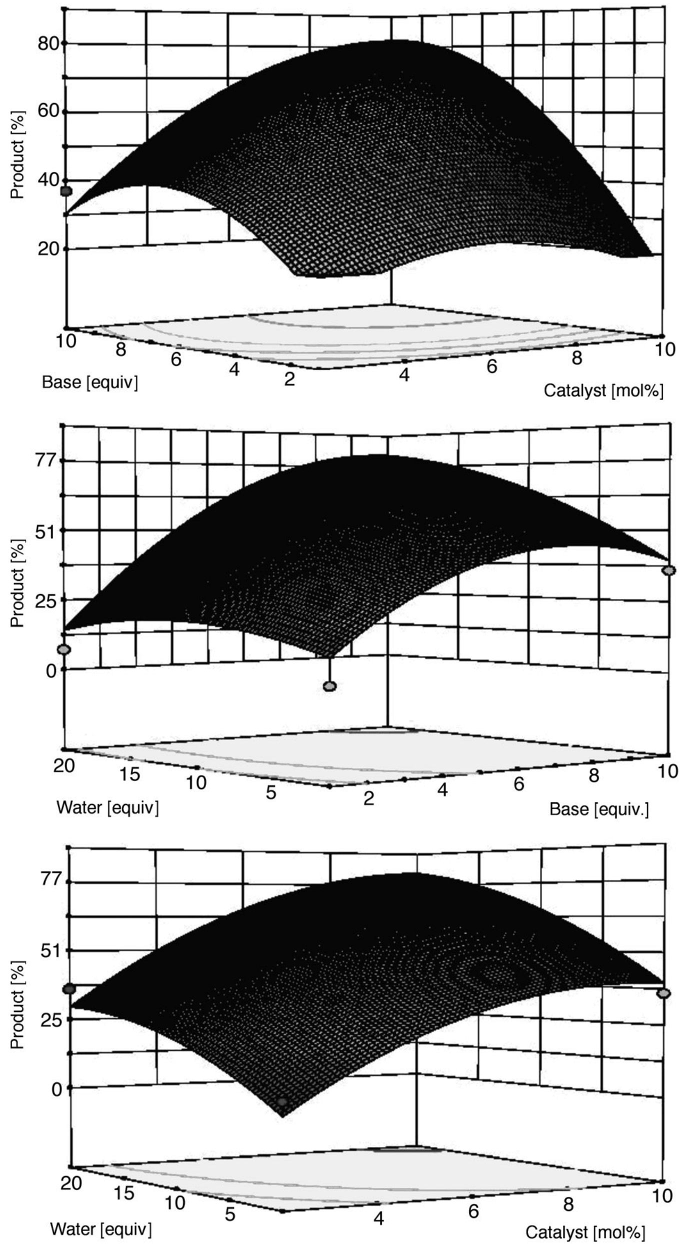
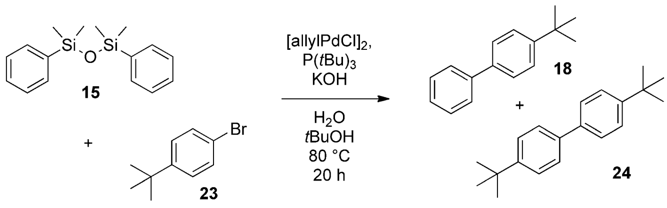


Figure 3. Upper: 3D response surface plot with catalyst loading displayed on the X-axis, equiv of base on the Y axis and yield of **18** (%) on the Z axis; Middle: 3D response surface plot with equiv of base displayed on the X axis, equivalents of H_2O on the Y axis and yield of **18** (%) on the Z axis; Bottom: 3D response surface plot with catalyst loading displayed on the X axis, equiv of H_2O on the Y axis and yield of **18** (%) on the Z axis. Actual point(s) included in the design space (that is, points corresponding to actual performed experiments) that deviated significantly from the computationally derived model are indicated by solid point(s).

Determination of a final set of reaction conditions using a multiple response optimisation process: In an attempt to reduce the amount of base (10 equivalents) and, perhaps more significantly, the catalyst loading (10 mol %), a multiple response optimisation was performed.[51] Values of the reagents (in this case KOH, H_2O and $[allylPdCl]_2$) within defined limits, which were predicted to fulfil desired outcomes (in this case, a high yield of the cross-coupled product **18** together with a low yield of homocoupled product **24**) were suggested by the statistical software.[51] The computational analysis predicted that only reaction conditions with a catalyst loading ≥ 7 mol % would furnish the desired product **18** in greater than 70 % yield. Five examples of these computationally generated suggestions were selected and the reactions performed (Table 4). In terms of maximising both the yield of **18** and the ratio of **18:24** whilst reducing the amount of catalyst and base used, the best conditions employed seven equivalents of base and seven mol % of catalyst (Table 4, entry 4). An additional increase in yield of the desired product **18** was obtained when the amount of aryl bromide (4-bromo-*tert*-butylbenzene) was increased to 2.5 equivalents (Table 4, entry 6). Thus the optimised set of reaction components for the cross-coupling of **15** and **23** were determined to be: $[allylPdCl]_2$ (7.0 mol %), $P(tBu)_3$ (28.0 mol %), KOH (7.0 equivalents), H_2O (20.0 equivalents) and *t*BuOH at 80 °C with a reaction time of 20 h.

Table 4. Investigation of five computationally generated reaction solutions.[a]



Entry	H_2O [equiv]	KOH [equiv]	$[allylPdCl]_2$ [mol %]	Ratio P/HC[b]	Yield [%][c]
1	19	7	8	1:0.15	52
2	20	9	8	1:0.17	48
3	20	10	9	1:0.21	43
4	20	7	7	1:0.15	50
5	20	8	8	1:0.15	47
6[d]	20	7	7	1:0.16	59

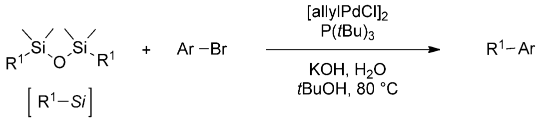
[a] General reaction conditions: disiloxane **14** (1 equiv), 4-bromo-*tert*-butylbenzene (**23**) (1.8 equiv),Pd/ligand 1:2. [b] P = desired product **18**, HC = homocoupled product **24**; ratio determined by the analysis of ^{1}H NMR spectra of a mixture of **18** and **24** obtained after flash column chromatography. [c] Isolated product yield of **18** after flash column chromatography (based upon aryl bromide). [d] 2.5 equiv of 4-bromo-*tert*-butylbenzene (**23**) used, yield based upon disiloxane (assuming 1 equiv disiloxane gives 2 equiv active silanolate).

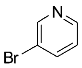
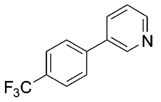
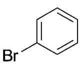
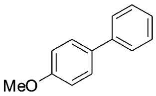
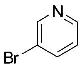
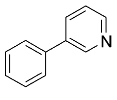
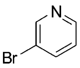
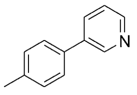
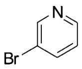
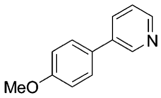
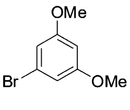
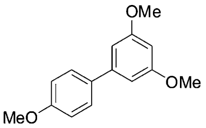
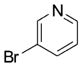
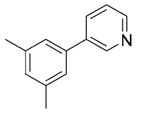
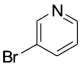
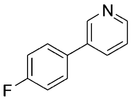
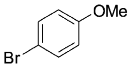
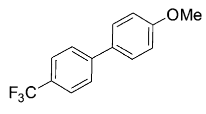
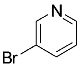
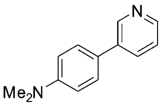
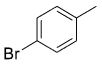
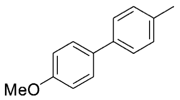
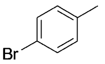
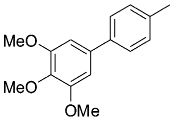
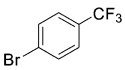
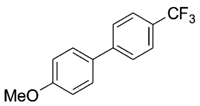
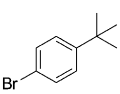
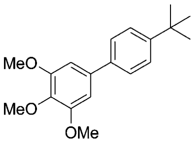
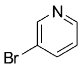
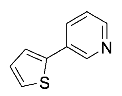
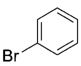
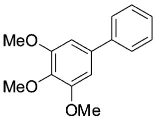
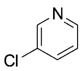
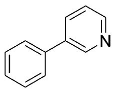
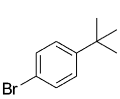
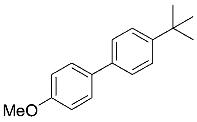
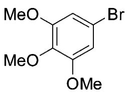
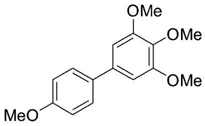
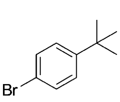
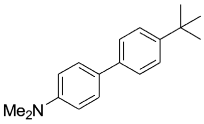
Exploring the substrate scope of the cross-coupling of aryldisiloxanes: Gratifyingly, the DoE-optimised reaction conditions were found to be applicable to the cross-coupling of a wide range of substituted aryldisiloxanes and aryl bromides (Table 5). These included compounds **16**, **17** and **19**, which could not be previously accessed (Table 5, entries 2 5, 9, 11 and 12), highlighting the expanded substrate scope offered by the newly developed protocols. In addition, biaryls **16** and **19** could be accessed by using both appropriate substrate combinations (Table 5, entries 5 and 7, and 2 and 9, respectively) in comparable yields, which demonstrates the flexibility of this cross-coupling strategy and is encouraging for its future application in complex molecule synthesis. As anticipated, the most frequently observed side product was homocoupled material resulting from the self-condensation of the aryl bromide component. The new methodology also proved suitable for the reaction of heteroaryldisiloxane **13** (Table 5, entry 8) as well as aryl chlorides (formation of **19**, Table 5, entry 9). This last result is particularly appealing, because aryl chlorides are lower cost and more widely available than aryl bromides.[54] Overall, the substrate scope offered by this methodology is large, allowing rapid access to a variety of biaryl products.

Conclusion

Herein we have described the development of methodology for biaryl synthesis based upon the palladium-catalysed, base-induced, fluoride-free cross-coupling of aryl bromides with aryldisiloxanes. Preliminary studies demonstrated that such reactions were dependent upon many interacting factors. Thus a statistical-based optimisation approach was adopted, which centre upon the use of a DoE method to more fully examine the reaction space and expedite the development of robust reaction conditions. By this process, the factors most affecting the yield of the desired cross-coupled product were identified as catalyst loading, the amount of base and the concentration of H_2O. Preparatively useful reaction conditions were formulated that allow for the cross-coupling of a wide range of readily accessible aryl bromides and electronically different aryldisiloxanes. Preliminary results indicate that it should be possible to expand the scope of this disiloxane-based cross-coupling strategy to encompass the use of heteroaromatic and aryl chloride coupling partners. Further studies towards this end are ongoing, together with investigations into the application of this methodology in multi-step synthesis. Overall, the procedures described herein offer novel, cost-effective, operationally simple and robust alternatives for the preparation of a wide range of substituted biaryl systems. Some notable features of this cross-coupling strategy in comparison with more "traditional" approaches include ease of disiloxane synthesis and purification (compared with the preparation of organoboranes), low toxicity of disiloxanes and their by-products (compared with organostannanes), increased functional group tolerance in comparison with silanol(ate)s (that could offer new disconnection strategies in the synthesis of complex molecular systems) and increased atom efficiency compared with more commonly employed "masked" silanol species. As such we anticipate that this general cross-coupling strategy could prove valuable in a wide synthetic context, with potentially broad applications in both target- and diversity-oriented synthesis.[55,56]

Table 5. Cross-coupling of aryldisiloxanes.



Entry	R^1–Si	Ar–X	Product		Yield [%][f]	Entry	R^1–Si	Ar–X	Product		Yield [%][f]
1[a]	**12**			**33**	41	11[b]	**1**			**17**	68
2[a]	**15**			**19**	53 (57[c])	12[b]	**11**			**31**	74
3[d]	**6**			**25**	63	13[b]	**6**			**32**	48
4[a]	**10**			**34**	38	14[b]	**11**			**33**	63
5[a]	**12**			**16**	51	15[d]	**8**			**34**	70
6[a]	**6**			**28**	72	16[d]	**7**			**35**	88
7[a]	**6**			**16**	49	17[d]	**7**			**36**	69
8[a]	**13**			**29**	24	18[e]	**7**			**37**	63
9[a]	**15**			**19**	29	19[d]	**6**			**38**	50
10[b]	**7**			**30**	62	20[d]	**8**			**39**	52

[a] Reagents as indicated, disiloxane (1.0 equiv), aryl halide (2.5 equiv), $[allylPdCl]_2$ (7.0 mol %), P(tBu)$_3$ (28.0 mol %), KOH (7.0 equiv), H_2O (20.0 equiv), tBuOH, 80 °C, 20 h. [b] $[allylPdCl]_2$ (10.0 mol %), P(tBu)$_3$ (40.0 mol %). [c] NEt_3 additive. [d] disiloxane (1.0 equiv), aryl halide (1.5 equiv), $[allylPdCl]_2$ (5.0 mol %), dppb (10.0 mol %), KOH (3.0 equiv), H_2O (2 equiv). [e] $[allylPdCl]_2$ (10.0 mol %), dppb (20.0 mol %). [f] Isolated yield of product after purification by flash column chromatography. For conditions [a] and [b] yields are based upon disiloxane (assuming 1 equiv disiloxane gives 2 equiv active silanolate). For conditions [d] yields are based upon aryl bromide. dppb = 1,4-bis(diphenylphosphino)butane.

Experimental Section

Details regarding the statistical processes described in this report and practical experimental procedures and characterisation data for compounds synthesised is provided in the Supporting Information.

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[48] It had previously been noted that the presence of H_2O was advantageous in reactions involving the cross-coupling of silanols, probably due to a shifting of the aryldisiloxane equilibrium to towards the reactive silanolate species (see Ref. [18]). However, in combination with other solvents or bases water could have detrimental effects upon the cross-coupling reaction. Therefore the presence of water was included as one of the variables.
[49] In a DoE, the ranges of the factors to be investigated (defining the covered experimental space) should be sufficiently wide so as to ensure that the optimum is residing within the experimental space studied, but not so large that experiments become impractical (e.g., an extremely long reaction time) or indeed, that the overall process yields optimised values for a given reaction component that are undesirable (e.g., a very large catalyst loading). See Ref. [50].
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sired product **18**, we decided to keep the initial factor levels for the CCD analysis, as an increased amount of these factors, particularly base and catalyst, would limit the attractiveness of the methodology. Rather, we hoped to discover an optimum within the constraints of the design space, with base and catalyst levels lower than their highest levels.

[53] Such conditions also favour formation of the undesired homocoupled material **24**. Indeed, from these analyses it appears that this process cannot be "decoupled" from formation of the desired product to any great extent; that is, the yield of undesired homocoupled material **24** cannot be minimised without negatively impacting upon the yield of the desired product **18**.

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