Palladium-catalysed synthesis of aryl-alkyl ethers using alkoxysilanes as nucleophiles†

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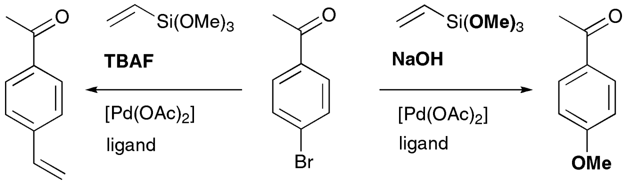
Changing the activator from tetrabutyl ammonium fluoride (TBAF) to sodium hydroxide unexpectedly switches the catalytic pathway of the Hiyama coupling reaction of vinyl trialkoxysilanes with aryl bromides into a Pd catalysed C–O bond forming reaction; if the correct conditions are used, high yields of aryl-alkyl ethers are observed. In addition, coupling between readily available tetraalkoxysilanes and aryl bromides can also be realised with NaOH or TBAF activation. The reactions take place in only 20 minutes if microwave heating is employed.

Introduction

Aryl ethers are a widespread motif in a wide range of natural products, pharmaceuticals, agrochemicals and organic materials, and consequently there has been a considerable amount of research into their synthesis.[1] Nucleophilic aromatic substitution reactions can be a useful procedure for electron deficient aryl chlorides and fluorides under basic conditions. The Cu-promoted Ullman ether synthesis can be a useful method but is limited to certain reactive substrates and only takes place in high boiling polar solvents.[2] Palladium-catalysed C–O bond forming reactions potentially have several advantages, including high functional group tolerance, the use of common, relatively benign solvents, and the use of some less-reactive aryl halide electrophiles under mild conditions. However, in contrast to Pd-catalysed C–N bond forming reactions, developments in Pd-catalysed C–O bond formation have been slow, with many limitations still to overcome. The Pd-catalysed synthesis of diaryl ethers using phenols as nucleophiles has been improved markedly providing that specific bi-aryl phosphines are used.[3] Good results have also been readily obtained using tertiary alkoxides as nucleophiles,[3f] since Pd-tertiary alkoxides cannot undergo β-hydride elimination during the catalytic cycle. A sustained effort has seen some examples of effective cross-coupling to give aryl-alkyl ethers with specific aryl halide substrates, but no general method has been discovered to date, making this one of the least developed Pd-catalysed cross-coupling reactions. Iron-catalysed ether synthesis using aryl iodides is an important recent discovery, but needs significant further research to extend the reaction to aryl bromides and chlorides under mild conditions.[4,2d] In this paper, we report an alternative method for Pd-catalysed ether formation that makes use of alkoxysilanes and an activator.

Results and discussion

The background to this serendipitous discovery was a project focused on developing genuinely practical conditions for the arylation of alkenyl trialkoxysilanes.[5] Although we have observed quite efficient reactions between certain aryl chlorides using TBAF as activator,[5e,f] swapping TBAF for other activators had a highly negative effect on the yield of aryl alkene. When vinyl trimethoxysilane was used in combination with sodium hydroxide as activator, the methoxy group of vinyl trimethoxysilane was unexpectedly coupled to the aryl halide to give an aryl-methyl ether in moderate yield (Scheme 1). This type of reactivity has not, to the best of our knowledge, been reported before. Our efforts were therefore focused on investigating if reaction conditions could be devised that allowed a high-yielding ether synthesis.



Scheme 1

A ligand screen[6] revealed that this reaction is highly sensitive to ligand structure. Electron-donating, larger bite angle diphosphines seem to perform best, and the commercially available ligand, 1-di-*tert*-butylphosphino-1′-diphenylphosphino-ferrocene (dtbdppf), was selected for further development. A study on the effect of Pd precursor, and the L/Pd ratio demonstrated that $Pd(OAc)_2$ in combination with two equivalents of the ligand gave the best results. A solvent screen (see ESI†) demonstrated that useful yields could be obtained using toluene as solvent, which is cheaper and of lower environmental impact than THF. The reaction takes place very conveniently in a short time using microwave heating, but in many of the cases studied, good yields could still be obtained using conventional heating. Experiments in which the NaOH to silane ratio was varied revealed that the reaction is sensitive to this parameter, although for the model reaction used in Table 1, a variety of ratios between 1 and 2.5 gave good results. The control experiments of reaction without catalyst, or with $[Pd(OAc)_2]$ used without ligand did not give any significant amounts of product with any of the substrates described here. For

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Table 1 Effect of different pre-catalysts and conditions on the coupling reaction of vinyl trimethoxysilane with *para*-bromoacetophenone

Entry	Pd pre-catalyst	Ligand (mol%)	Temp. / °C	Conversion to methyl ether (%)[a]
1	$Pd(OAc)_2$	PPh_3 (2)	75	16
2	$Pd(OAc)_2$	PCy_3 (2)	75	10
3	$Pd(OAc)_2$	S-Phos (2)	75	8
4	$Pd(OAc)_2$	dppe (1)	75	16
5	$Pd(OAc)_2$	dppb (1)	75	9
6	$Pd(OAc)_2$	dcype (1)	75	21
7	$Pd(OAc)_2$	dppf (1)	75	20
8	$Pd(OAc)_2$	dippf (1)	75	38
9	$Pd(OAc)_2$	dtbdppf (1)	75	42
10	$Pd(OTfac)_2$	dtbdppf (1)	75	9
11	$Pd(dba)_2$	dtbdppf (1)	75	17
12	$Pd(OAc)_2$	dtbdppf (3)	75	29
13	$Pd(OAc)_2$	dtbdppf (2)	75	59
14[b]	$Pd(OAc)_2$	dtbdppf (2)	105	77
15[b]	$Pd(OAc)_2$	dtbdppf (2)	75	80
16[bc]	$Pd(OAc)_2$	dtbdppf (2)	130	84
17[d]	$Pd(OAc)_2$	dtbdppf (2)	120	95
18[be]	$Pd(OAc)_2$	dtbdppf (2)	105	85
19[d]	none	none	120	0
20[d]	$Pd(OAc)_2$	none	120	0

[a] *Reagents and conditions*: 1 mol% Pd precursor, ligand as described in column 3, 1.5 equiv. vinyl trimethoxysilane, 2.5 equiv. NaOH unless otherwise indicated, 0.5 mmol *p*-xylene internal standard, stirred at the temperature indicated in THF for 16 hours unless otherwise indicated. [b] Toluene used as solvent at temperature indicated. [c] Reaction carried out in a sealed tube; 74% yield after chromatography. [d] Toluene used as solvent and microwave heating for 20 minutes. [e] 1.25 equiv. of NaOH, 8 hours reaction time.

comparison, sodium methoxide did not give any ether product under these reaction conditions.

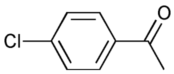
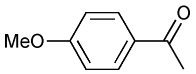
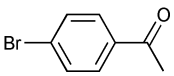
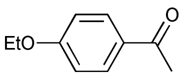
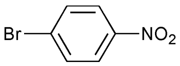
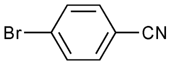
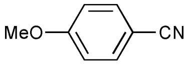
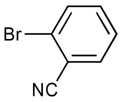
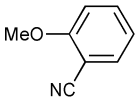
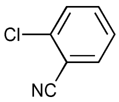
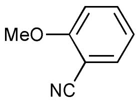
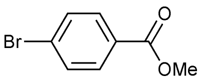
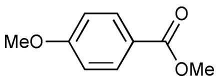
Our working hypothesis is that the hydroxide, once in solution binds to Si to form a hypervalent silicon species that can transfer alkoxide to palladium, or alternatively gradually release alkoxides as the reaction proceeded. We felt that this alternative method could potentially be adapted for synthetic use, and therefore a number of other aryl halides were investigated under these reactions conditions. It was therefore pleasing to find that the reaction can indeed be extended to other aryl halides, including the activated aryl chlorides in Table 2, entries 1 and 6.

The reactions shown do generally proceed well under the original conditions, but can also be carried out in only 20 minutes if microwave heating is used at 120 °C.

Vinyl trimethoxy- and vinyl triethoxysilanes are actually cheap fine chemicals and thus could be developed as nucleophiles for the synthesis of methyl and ethyl ethers. However, for this discovery to have a broader impact in the synthesis of aryl-alkyl ethers the reactions needed to be extended to readily available tetraalkoxysilanes; we were therefore delighted to find that simple tetraalkoxysilanes would also undergo this reaction (even more) readily. Choosing the appropriate alkoxysilanes allowed for the transfer of ethoxy, *n*-propoxy and *n*-butoxy groups to aryl halides using the new method (Scheme 2 and Table 3). The use of TBAF has also been investigated as an alternative activator for the tetraalkoxysilanes, and in some cases, improved results have been obtained (Table 3, entries 6–9).

In these studies using these relatively unoptimised conditions and simple commercially available diphosphine ligands, we have found that several aryl halides gave lower yielding reactions using both the vinyl trialkoxysilanes or tetraalkoxysilane nucleophiles. For example, *p*-dimethylamino-bromobenzene gave predominantly starting material with some reduced arene, whereas *o*-chloro-anisole, a very deactivated substrate, returned only

Table 2 Coupling of vinyl trimethoxysilane or vinyl triethoxysilane with aryl halides[a]

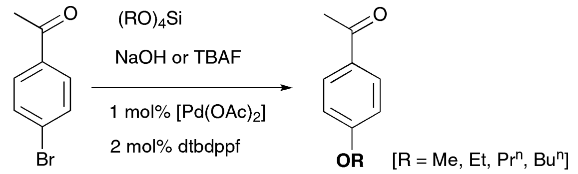
Entry	Aryl halide	Product	Conversion [yield] (%)
1			84 [74]
2			85 [77]
3			81 [80][b]
4			76 [73][c]
5			84 [74]
6			86 [72]
7			75 [66][d]

[a] *Reagents and conditions*: 1 mol% Pd precursor, 2 mol% dtbdppf as ligand, 1.5 equiv. vinyl trimethoxysilane, 1.25 equiv. NaOH unless otherwise indicated, 0.5 mmol *p*-xylene internal standard, stirred at 120 °C in toluene using microwave heating for 20 min. Conversions are product calibrated against internal standard, yields refer to pure compounds after chromatography. [b] 84% yield if heated at reflux in toluene for 16 hours (oil bath). [c] 86% yield if heated at reflux in toluene for 16 hours (oil bath). [d] 2.0 equiv. of vinyl trimethoxysilane.

Table 3 Pd-catalysed C–O bond formation between a variety of silanes and *para*-bromoacetophenone

Entry	Silane	Activator[a]	Conversion [yield] (%)
1	$Si(OMe)_4$	NaOH	80 [72]
2	$Si(OMe)_4$	TBAF	78
3	$Si(OEt)_3H$	NaOH	82 [73]
4	$Si(OEt)_4$	NaOH	79 [67]
5	$Si(OEt)_4$	TBAF	68[b]
6	$Si(OPr^n)_4$	NaOH	70 [65]
7	$Si(OPr^n)_4$	TBAF	80
8	$Si(OBu^n)_4$	NaOH	50 [42]
9	$Si(OBu^n)_4$	TBAF	86 [73]

[a] *Reagents and conditions*: 1 mol% Pd precursor, 2 mol% dtbdppf as ligand, 1.5 equiv. tetraalkoxysilane, 1.25 equiv. NaOH or 3 equiv. of TBAF. 0.5 mmol *p*-xylene as internal standard, stirred in refluxing toluene for 16 hours. Conversions are product calibrated against internal standard, yields refer to pure compounds after chromatography. [b] The coupling of $Si(OEt)_4$ with *p*-bromonitrobenzene also gave a high isolated yield (81%) using TBAF conditions in toluene.



Scheme 2

starting material. Tetraisopropoxysilane and alkoxysilanes derived from tertiary alcohols have proven rather unreactive in these first studies; a contrast to the latter being easier nucleophiles[3f] in the direct reaction that possibly reflects that some of these reactions are limited by slow transmetalation using these relatively bulky catalysts.[7] This reflects that a more in-depth study developing new catalysts for this new variant of C–O coupling is required before it is truly general in scope. The results described here suggest considerable potential for using alkoxysilanes as oxygen nucleophiles, and given that the contrasting reactivity patterns (*e.g.* in the preferred choice of catalyst) were seen to the direct coupling of alcohols, the new procedure may prove to be complementary to the existing methodology.[8]

Conclusions

In conclusion, the unexpected observation of alkoxy transfer from vinyl trimethoxysilane in a Hiyama reaction is reported along with the development into a procedure for Pd-catalysed C–O bond formation. These results suggest that optimal ligands are electron-donating bidentate ligands and that it is possible to couple to a range of activated bromides and chlorides. It has also been established that more widely available tetraalkoxysilanes can also be coupled using either NaOH or TBAF activation. Although this catalytic process is still in the early stages of development, it is hoped that the use of custom-designed diphosphine ligands could lead to quite a general process that may find a niche where direct coupling of alcohols under basic conditions is not successful. Further studies will also concentrate on elucidating if direct Si–OR to Pd reactions occur or if the hypervalent silanes serve to release low concentrations of alkoxide as the reaction proceeds. Given that alkoxysilanes are widely available, and sometimes produced as intermediates in synthesis, the results reported here could lead to useful procedures in the synthesis of ethers.

Experimental

For full details, see ESI†: general procedure for reactions using normal heating. The aryl halide (1 mmol) was added to a flame-dried Schlenk tube containing a stirrer bead, followed by the silyl-ether (1.5 mmol), *p*-xylene (0.5 mmol, 62 μL) and dry, degassed toluene (5 mL). A ^1H NMR spectra of this solution was taken to calibrate the internal standard. To this, $Pd(OAc)_2$ (0.0023 g, 0.1 mmol, 1 mol%), dtbdppf (0.0102 g, 0.2 mmol, 2 mol%) and powdered NaOH (0.05 g, 1.25 mmol) were added to the tube that was then sealed, flushed with nitrogen or argon and heated to reflux (or other temperatures) for the time specified. The reactions were analysed by ^1H NMR and GCMS. The products were isolated by removal of solvent followed by column chromatography (SiO_2) using hexane–diethyl ethers as eluent.

Microwave heating conditions

The aryl halide (1 mmol) was added to a flame dried Schlenk tube containing a stirrer bead, followed by the silyl-ether (1.5 mmol), *p*-xylene (0.5 mmol, 62 μL) and dry, degassed toluene (5 mL). A ^1H NMR spectra of this solution was taken to calibrate the internal standard. This was then added *via* syringe to $Pd(OAc)_2$ (0.0023 g, 0.1 mmol, 1 mol%), dtbdppf (0.0102 g, 0.2 mmol, 2 mol%) and powdered NaOH (0.05 g, 1.25 mmol) (or TBAF, 3 equiv.), in a dry microwave tube flushed with nitrogen or argon. The reaction mixture was heated by microwave irradiation at 120 °C for 20 minutes, with analysis and isolation carried out as above.

Acknowledgements

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