



Improved Hiyama cross-coupling reactions using HOMSi[®] reagents: a novel application of a palladacycle

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ABSTRACT

Various parameters in the Hiyama cross-coupling reaction of HOMSi[®] reagents with ethyl bromobenzoate were studied. These included solvent, ligand, palladium source, and added water. DMF and THF were found to be excellent solvents. Palladium chloride was found to be the best palladium source and no added water was required. The use of tri-*o*-tolylphosphine as the ligand proved to be particularly effective.

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Our interest in the silicon-mediated coupling reaction known as the Hiyama reaction has developed as a parallel to the much studied and extremely useful boron-mediated Suzuki reaction.^{2–8} The Suzuki reaction relies on the generation of a tetrasubstituted boron-intermediate that is able to transfer a ligand to palladium. The palladium complex formed then undergoes reductive elimination to form the desired C–C coupled products. Many of the properties of boron that contribute to the great success of the Suzuki reaction are also present in the chemistry of silicon in the Hiyama reaction. The Hiyama reaction is a silicon-mediated palladium-catalyzed coupling reaction that has developed enormously from its advent to the current day.^{9–37} Silicon-mediated coupling chemistry has some notable advantages that warrant its further development. Firstly, there is a broad and growing range of silicon reagents commercially available. Secondly, silicon is the second most abundant element on Earth, whereas boron has limited supplies.³⁸

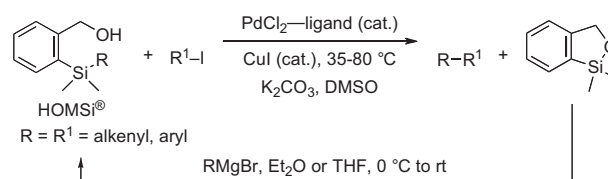
Hiyama et al.^{39,40} introduced carefully designed silicon reagents, the alkenyl, and aryl[(2-hydroxymethyl)phenyl]dimethyl silanes (HOMSi[®]).¹ A key design feature of the HOMSi[®] reagents is the presence of two aryl groups on the silicon in many cases. In other cases, the two relevant substituents are aryl and vinyl. There is no evidence in either situation that the hydroxymethyl aryl group transmetalates to palladium in preference to the introduced aryl or vinyl substituent.^{41,42} Presumably, this is due to the bidentate nature of the hydroxymethylaryl ligand at the point of

transmetalation. These reagents incorporate an intramolecular hydroxy group for silicon activation under basic conditions, they are readily prepared and recyclable (Scheme 1).

Hiyama and others have recognized these couplings have a number of parameters that should be optimized for best reaction. Also the reactions have alternative modes that can enhance the range of applications. Despite a number of papers reporting further work on the Hiyama reaction since the disclosure of the HOMSi[®] reagents,^{43,39,44–47,42,48} there is still much work to be done in optimizing their use, reaction conditions, and in exploiting different reagents and coupling modes including the development of copper-free reactions.⁴⁹

We herein report our preliminary results from our first foray into this exciting field of silicon mediated Hiyama coupling chemistry using HOMSi[®] reagents.

In this Letter, a number of Hiyama reaction parameters for some exemplary aryl substrates were investigated. These parameters include the presence of water, alternative solvents, ligands, and palladium catalyst.



Scheme 1. HOMSi[®] reagent coupling and recycling.

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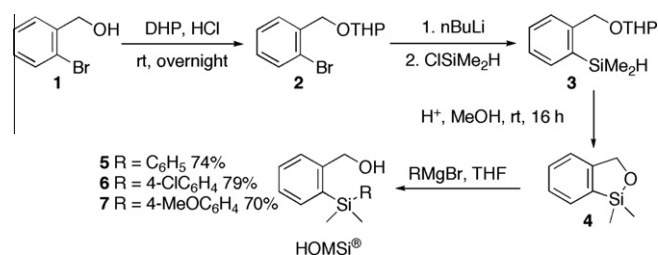
HOMSi[®] reagents have a number of important attributes including good functional group compatibility, reactions can be performed under fluoride-free conditions, the organosilicon 'by-product' can be recycled if required and the cross-coupling reactions can be turned 'OFF' by the use of suitable protecting groups on the 2-hydroxymethyl group.

The HOMSi[®] reagents required for the coupling reactions can be prepared by standard protocols (Scheme 2)⁴⁴ or purchased from commercial sources.⁵⁰ 2-Bromobenzyl alcohol **1** was protected as its tetrahydropyran ether **2** using dihydropyran and hydrochloric acid. Metal-halogen exchange with *n*-butyllithium gave the aryl anion, which reacted with chlorodimethylsilane to give the dimethylsilane **3**. Under acidic conditions the THP ether was hydrolyzed and cyclization of the alcohol gave 2-oxa-1-silaindan (**4**). This 2-oxa-1-silaindan is the central intermediate for the formation of HOMSi[®] reagents. In the current study bromobenzene, 4-chlorobromobenzene and 4-methoxybromobenzene were each converted into the corresponding Grignard reagent and on reaction with 2-oxa-1-silaindan (**4**) gave HOMSi[®] reagents **5**, **6**, and **7**, respectively.

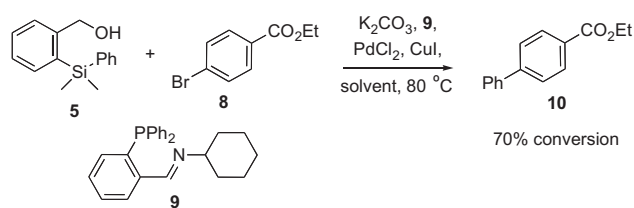
An initial Hiyama coupling (Scheme 3) was performed to establish a baseline result for the reaction (Table 1, entry 1). This coupling reaction was designed to be close to established general conditions for the Hiyama coupling.⁴⁴ The coupling partners **5** and **8** were mixed with potassium carbonate, cuprous iodide, and palladium(II) chloride in dry DMSO. An amount of water (1.5 equiv) and the iminophosphine ligand **9**, often employed by Hiyama, were added. The reaction was heated at 80 °C for 15 h and work-up gave a 70% conversion to product **10**. This result was determined by the comparison of the integrations of two ¹H NMR signals. Ethyl 4-bromobenzoate (starting material) displayed a doublet at 7.87 ppm, while the biphenyl product **10** showed a unique doublet at 8.12 ppm in the ¹H NMR spectra.

Early HOMSi[®] coupling reactions employed solvents such as DMSO^{45,51} and THF.^{40,39,42} Later, the use of DMF was also reported.^{47,51} Notably, when DMSO was the solvent it was not always clear whether water (adventitious or added) was included or not.⁴⁵ The effect of water on the reaction needed to be considered and also a broader range of solvents examined. Accordingly, the first variations (Table 1, entries 2–4) had different amounts of water included. The initial reaction (entry 1) included 1.5 equiv of water. The 2 equiv used in entry 2 had no effect (71% conversion) compared to entry 1. But amounts of water above this caused a significant decrease in the reaction conversion (entries 3 and 4). In the case of entry 4 (20 equiv H₂O) it is notable that the reaction was still occurring; however, only 21% conversion was observed. Small amounts of water (2 equiv or less) do not interfere with this process to a great extent, but do have the effect of improving the solubility of the base K₂CO₃ needed to deprotonate the HOMSi[®] reagent and this positive effect gives higher conversions.

Substitution of DMSO/H₂O for DMF gave a small improvement in conversion (Table 1, entry 5, 75% conversion). It should be noted that the DMF used was a commercial sample that was not specifi-



Scheme 2. HOMSi[®] reagent preparation.



Scheme 3. Benchmark Hiyama coupling.

Table 1

Hiyama cross-coupling reaction^a varying the solvent

Entry	Solvent	Time (h)	Conversion ^b (%)
1	DMSO/1.5 equiv H ₂ O	15	65–70
2	DMSO/2.0 equiv H ₂ O	15	71
3	DMSO/4.0 equiv H ₂ O	15	50
4	DMSO/20 equiv H ₂ O	15	21
5	DMF ^c	15	75
6	THF ^{c,d}	15	77
7	1,4-Dioxane ^c	45	58
8	Toluene ^c	15	9
9	MeOH ^d	15	0

^a Reaction as depicted in Scheme 3 using a mixture of **5** (1 equiv), ethyl 4-bromobenzoate (0.84 equiv), ligand **9** (0.03 equiv) and PdCl₂ (0.025 equiv).

^b % Conversion was determined by comparison of the integrations of the signals at 7.87 ppm for the starting material **8** and 8.12 ppm for the product **10** in the ¹H NMR spectra.

^c No added water.

^d Reaction performed at 65–66 °C.

cally dried prior to use and may contain a small amount of adventitious water. The ethereal solvent THF (Table 1, entry 7) was similarly effective (77% conversion) even though this reaction occurred at a lower temperature (66 °C). However, the reaction seemed to be much slower when the related solvent 1,4-dioxane was used; there was a marked improvement in conversion at the longer reaction time (Table 1, entry 7, 45 h, 58% conversion).

Conversion was markedly decreased when toluene was used (Table 1, entry 10). This is thought to be due to the lower solubility of the reagents in this solvent. The protic solvent, methanol (Table 1, entry 11) afforded no reaction. Presumably, methanol behaves much like water in excess and interferes with the reaction, particularly with ligand exchange processes.

Further work on the use of different solvents is suggested by these results. Ideal solvents seem to be DMF and THF. Inclusion of a small amount of water is also convenient but the question remains if this might also be replaced effectively by a small amount of an alcohol such as methanol, ethanol or 2-propanol which might still improve potassium carbonate solubility but have less propensity to interfere in other reaction processes. The useful improvement in conversion by including water might also be unnecessary if a more effective, organic soluble base was implemented instead of potassium carbonate.

In the next phase of study, the palladium ligand was considered. A broad range of different substances have been used as the palladium ligand in Hiyama reactions (Fig. 1). Hiyama's studies have found that in general the more sterically bulky ligands give higher cross-coupling yields.^{41,42} Two of the better ligands being **9**^{30,32,44,45} and RuPhos.^{47,50}

Ligand **9** was available in our laboratory and its use was a convenient point of comparison. To our delight it was found that the *o*-tolyl phosphine ligand **11** gave conversion >90% (Table 2, entry 9) and this was significantly better than reactions employing **9** as ligand. In addition, its isomer, the *p*-tolyl phosphine **12** gave lower conversion (Table 2, entry 8) under the same reaction conditions.

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