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Abstract

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Copper-catalyzed Hiyama cross-coupling using vinylsilanes and benzylic electrophiles†

L. Cornelissen, V. Cirriez, S. Verduyck and O. Riant*

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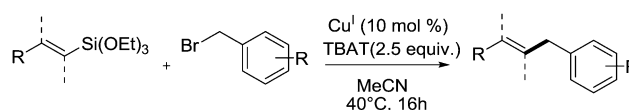
Allylbenzene derivatives are ubiquitous frameworks in organic chemistry. Herein is described an efficient copper-catalyzed cross-coupling reaction using vinylsilanes and benzyl bromides, leading to the synthesis of allylbenzenes. This methodology allows the use of *cis*, *trans* and 1,1'-disubstituted vinylsilanes as well as a large number of sensitive moieties.

Vinylsilane-based cross-coupling reactions have emerged as a powerful and versatile tool to introduce insaturations in complex organic frameworks.¹ The low toxicity, low cost, ready availability and high chemical stability of silylated molecules led to the development of various palladium-based cross-coupling reactions.² Namely, the Hiyama³ and Hiyama–Denmark⁴ reactions have proven to be useful in many cases. More recently, Tsubouchi and Takeda proposed a copper-catalyzed reaction between an alkenylsilane and various C(sp³) electrophiles, promoted by the intramolecular coordination of an alkoxide.⁵

The coupling of a vinyl-metal and a benzylic electrophile leads to the formation of allylbenzene derivatives. Allylbenzenes are ubiquitous in organic chemistry, especially as pharmacologically active molecules.⁶ The relative instability of allylbenzenes, due to the prompt isomerization of the alkene into a styrene, makes efficient procedures quite rare, compared to other cross-coupling products. Although the more common ways to synthesize allylbenzenes require palladium catalysts,⁷ non-noble metal catalysis emerged.⁸

Our group recently developed an efficient copper-catalyzed methodology to synthesize 1,4-dienes from vinylsilanes.⁹ This very mild method proved to be compatible with many functional groups ranging from halides to aldehydes.

These encouraging results led us to apply this copper-catalyzed transformation to more challenging substrates such

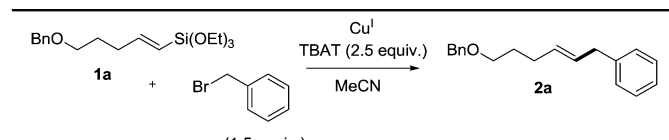


Scheme 1 Copper-catalyzed benzylation of vinylsilanes.

as benzylic electrophiles. Herein is described an efficient method to synthesize allylbenzenes from readily available vinylalkoxysilanes^{10–13} (Scheme 1). This methodology uses low copper loadings, requires no ligands, and uses TBAT (tetrabutylammonium difluorotriphenylsilicate) as an activating agent.

The optimization started under similar conditions as previously reported, leading to a promising 70% conversion¹⁴ of the model vinylsilane (**1a**) to the desired product (**2a**) (Table 1, entry 1). The remaining 30% was identified as dimers and protodesilylated alkenes. Importantly, no isomerization of the alkene into a styrene was observed. Other common copper(I) sources were then evaluated. The bulkiness of the NHC IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) ligand reduced the conversion (Table 1, entry 2), as did the use of CuTC (copper(I) thiophenecarboxylate).

Table 1 Initial experiments



Entry	Cu ^I salt	Reaction time/ temperature	Conversion ^a
1	CuI (20%)	16 h/r.t.	70
2	IPrCu(dbm) (20%)	16 h/r.t.	61
3	CuTC (20%)	16 h/r.t.	73
4	CuF(PPh) ₃ ·2MeOH (20%)	16 h/r.t.	60
5	Cu(MeCN) ₄ PF ₆ (20%)	16 h/r.t.	84
6	Cu(MeCN) ₄ PF ₆ (10%)	16 h/r.t.	93 (80 ^b)
7	Cu(MeCN) ₄ PF ₆ (10%)	32 h/r.t.	91 (88 ^b)
8	Cu(MeCN) ₄ PF ₆ (10%)	16 h/40 °C	92 (91 ^b)
9	Cu(MeCN) ₄ PF ₆ (5%)	16 h/40 °C	76

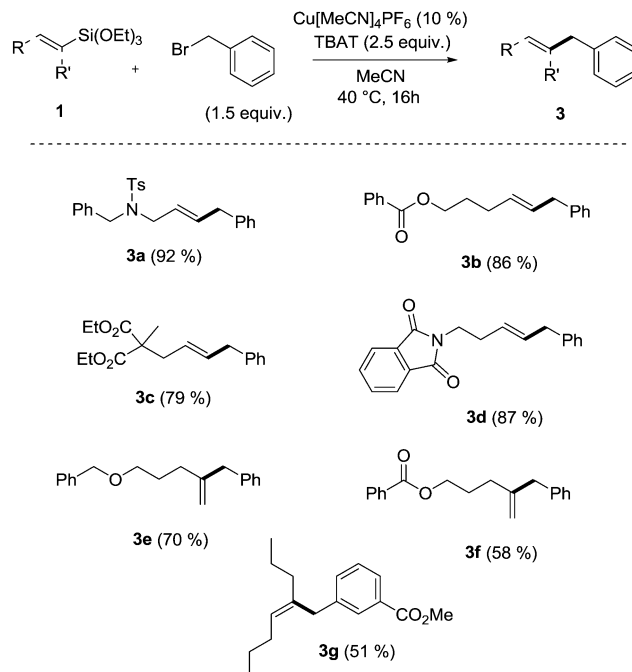
^a Determined by analysis of the crude mixture by ¹H NMR. ^b Isolated yield.

Institute of Condensed Matter and Nanosciences, Molecules, Solids and Reactivity (IMCN/MOST) – Université catholique de Louvain, Place Louis Pasteur 1, bte LA.01.02, 1348 Louvain-la-Neuve, Belgium. E-mail: Olivier.riant@uclouvain.be; Web: <http://www.uclouvain.be/en-201510.html>

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The presence of methanol in the copper(I) fluoride catalyst led to the protodesilylation of the vinylsilane, hence reducing the conversion to 60% (Table 1, entry 4). Still using 20% of the catalyst, cationic copper(I) $\text{Cu}[\text{MeCN}]_4\text{PF}_6$ led to the best conversion of 84% (Table 1, entry 5). Reducing the copper loading to 10% led to an improvement (Table 1, entry 6) in the conversion. The isolated yield however, was surprisingly low compared to the conversion. This might indicate an incomplete reaction, as the activated silicate is lost during the work-up. Longer reaction time indeed improved the yield to 88% (Table 1, entry 7). To our delight, gently heating the solution to 40 °C overnight gave the best results. The desired product (**2a**) was obtained in 91% isolated yield (Table 1, entry 8). However, it was not possible to further reduce the catalytic loading without loss of conversion (Table 1, entry 9).

With optimal conditions in hand (Table 1, entry 8), model vinylsilane (**1a**) was coupled with various benzylic electrophiles (Scheme 2) in order to determine the scope of the reaction. The presence of a methyl in the *para* position gave the desired product (**2b**) in excellent yield. Bulkiness at the *ortho* position seems to have little impact on the reaction, as shown by (**2c**). Fluorinated aromatic groups were tolerated, as shown by (**2d**) and the trifluoromethylated (**2e**). Interestingly, brominated (**2f**) gave the cross-coupling product in 88% yield, without any degradation of the aromatic bromine, as would be expected for palladium-based catalysts. Yield of the reaction using electron-poor nitrile (**2g**) dropped to 83%. This drop was not a surprise since a small part of TBAT reacted with the *p*-cyanobenzyl bromide to give the corresponding benzylic fluoride. Electron-rich anisole (**2h**) as well as the ester-substituted (**2i**) proceeded in 87% and 88% yields, respectively. No addition of the vinylsilane on the carbonyl was observed. It must be noted that although electron-poor allylbenzenes tend to easily isomerize

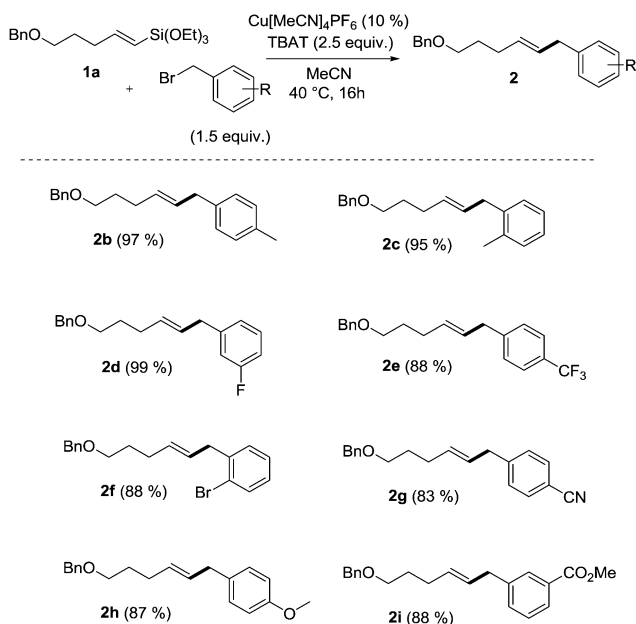


Scheme 3 Vinylsilane scope. Isolated yields are given within brackets.

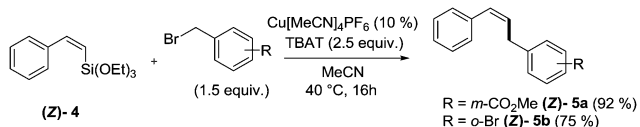
because of the very acidic allylbenzyl hydrogen, no styrene derivatives were observed at any moment. Globally, all of the desired products were obtained in high yields, ranging from electron-rich, electron-poor and hindered substrates, leading to a large array of different allylbenzenes.

Various vinylsilanes were benzylated under our optimal conditions (Scheme 3) to collect information on the limitations of this methodology. β -(*E*)-Vinylsilanes bearing a tosylamine or a benzoyl group gave the desired products (**3a**) and (**3b**) in excellent yields. The more hindered and chelating malonate (**3c**) resulted in a slight drop in yield. Phthalimide (**3d**) was fully tolerated in 87% yield. Although 1,1-disubstituted allylbenzenes are present in the natural world, very few methods exist to synthesize them. Benzyl and benzoyl protected 1,1-disubstituted alkenes (**3e**) and (**3f**) were synthesized in 70% and 58% yields, respectively, which is acceptable considering the bulkiness of such vinylsilanes. (*Z*)-Trisubstituted alkene (**3g**) was obtained in 51% yield, confirming that steric hindrances might have a negative effect on the reactivity of the vinylsilanes. Overall, all of the β -(*E*)-vinylsilanes led to high yields, no matter how sensitive the functional groups were, while other more bulky vinylsilanes led to reduced yields.

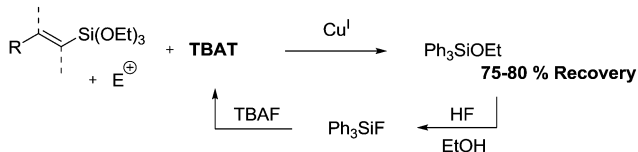
The synthesis of (*Z*)-alkenes deserves special attention since very few practical methods exist to obtain such substrates. β -(*Z*)-Vinylsilane **Z**-(**4**) was obtained directly from phenylacetylene according to Faller *et al.*¹³ It was benzylated with the *meta*-methylester substituted benzyl bromide to form the desired product **Z**-(**5a**) in an excellent 92% yield (Scheme 4). The presence of a bromide in the *ortho* position gave the desired product **Z**-(**5b**) in 75% yield. Such a compound would be very tedious to synthesize by conventional alkyne reductions and palladium cross-coupling reactions because of the sensitivity of



Scheme 2 Electrophile scope. Isolated yields are given within brackets.



Scheme 4 Benzylation of a β -(Z)-vinylsilane with full retention of stereochemistry.



Scheme 5 Recyclability of the activating agent TBAT.

the halides. In both cases, no isomerization into an (*E*)-alkene occurred and full retention of stereochemistry was observed.

In order to tackle the problem of cost linked to the use of TBAT as an activating agent, efficient recycling was required. Upon reaction, 75 to 80% of the TBAT-derivative ethoxytri-phenylsilane could be recovered by chromatographic separation (Scheme 5). As shown in the literature, treatment of the latter with hydrogen fluoride in ethanol,¹⁵ followed by crystallization with tetrabutylammonium fluoride (TBAF)¹⁶ allows an efficient recyclability of the fluorinating agent.

An efficient copper-catalyzed Hiyama-type reaction was described. Allylbenzenes were synthesized from vinylsilanes in good yields by using benzylic bromides. A broad range of electrophiles were functionalized in high yields. No isomerization of the resulting alkene into a styrene was observed, even when using electron-poor benzyl bromides. *cis*, *trans* and 1,1'-Disubstituted alkenes were obtained, with full retention of stereochemistry. Various sensitive moieties were tolerated, including halides, esters and nitriles. Finally, it was shown that TBAT (tetrabutylammonium difluorotriphenylsilicate) could be employed as a recyclable activating agent. Further studies concerning other copper-catalyzed cross-coupling reactions are in progress and will be reported in due time.

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