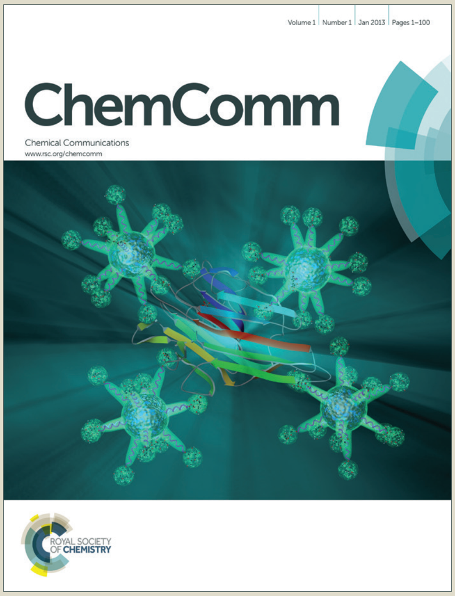
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name RSCPublishing

COMMUNICATION

Copper-Catalyzed Hiyama Cross-Coupling Using Vinylsilanes and Benzylic Electrophiles

Cite this: DOI: 10.1039/x0xx00000x

L. Cornelissen,[a] V. Cirriez,[a] S. Vercruysse[a] and O. Riant[a]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

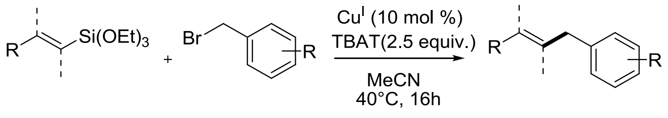
Allylbenzene derivatives are ubiquitous frameworks in organic chemistry. Herein is described an efficient copper-catalyzed cross-coupling reaction using vinylsilanes and benzyl bromides, leading to the synthesis of allylbenzenes. This methodology allows the use of *cis*, *trans* and 1,1'-disubstituted 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 on 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 Hiyama[3] and Hiyama-Denmark[4] reactions have proven useful in many cases. More recently, Tsubouchi and Takeda proposed a copper-catalyzed reaction between an alkenylsilane and various C(sp^3) electrophiles, promoted by the intramolecular coordination of an alkoxide.[5]

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 it 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.

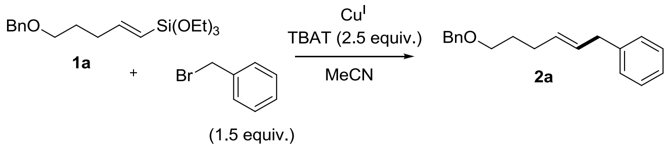
These encouraging results led us to apply this copper-catalyzed transformation on more challenging substrates such as benzylic electrophiles. Herein is described an efficient method to synthetize allybenzenes from readily available vinylalkoxysilanes [10-13] (Scheme 1). This methodology uses low copper loadings, requires no ligands, and uses TBAT (Tetrabutylammonium difluorotriphenylsilicate) as an activating agent.



Scheme 1. Copper-catalyzed benzylation of vinylsilanes.

The optimization started with similar conditions as previously reported, leading to a promising 70 % conversion[14] of the model vinylsilane (**1a**) to the desired product (**2a**) (Table 1, Entry 1). The remaining 30 % were identified as dimers and protodesilylated alkene. 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 well as the use of CuTC (copper(I) thiophenecarboxylate). 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 catalyst, the cationic copper(I) Cu[MeCN]$_4$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) of 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 result. 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).

Table 1. Initial experiments.

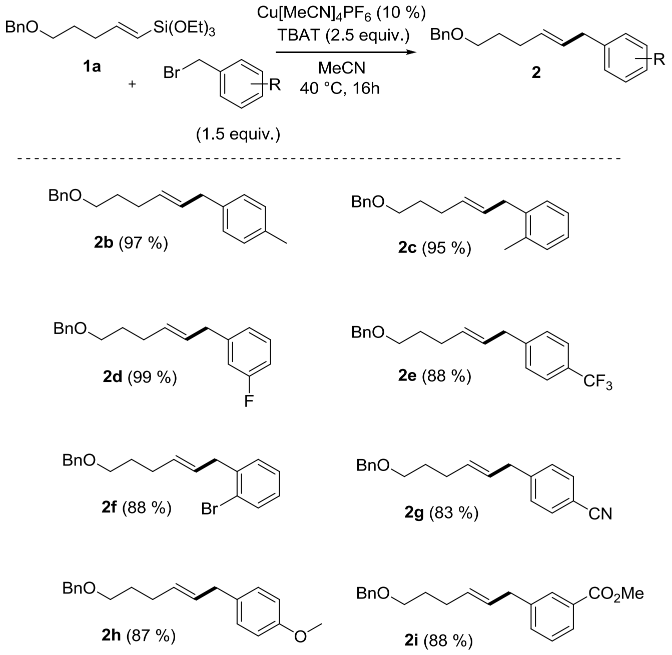


Entry	Cu^{I} salt	Reaction time/ Temperature	Conversion$^{a)}$
1	CuI (20%)	16h/r.t.	70
2	IPrCu(dbm) (20%)	16h/r.t.	61
3	CuTC (20%)	16h/r.t.	73
4	CuF(PPh)$_3$.2MeOH (20%)	16h/r.t.	60
5	Cu(MeCN)$_4$PF$_6$ (20%)	16h/r.t.	84
6	Cu(MeCN)$_4$PF$_6$ (10%)	16h/r.t.	93 (80$^{b)}$)
7	Cu(MeCN)$_4$PF$_6$ (10%)	32h/r.t.	91 (88$^{b)}$)
8	**Cu(MeCN)$_4$PF$_6$ (10%)**	**16h/40°C**	**92 (91$^{b)}$)**
9	Cu(MeCN)$_4$PF$_6$ (5%)	16h/40°C	76

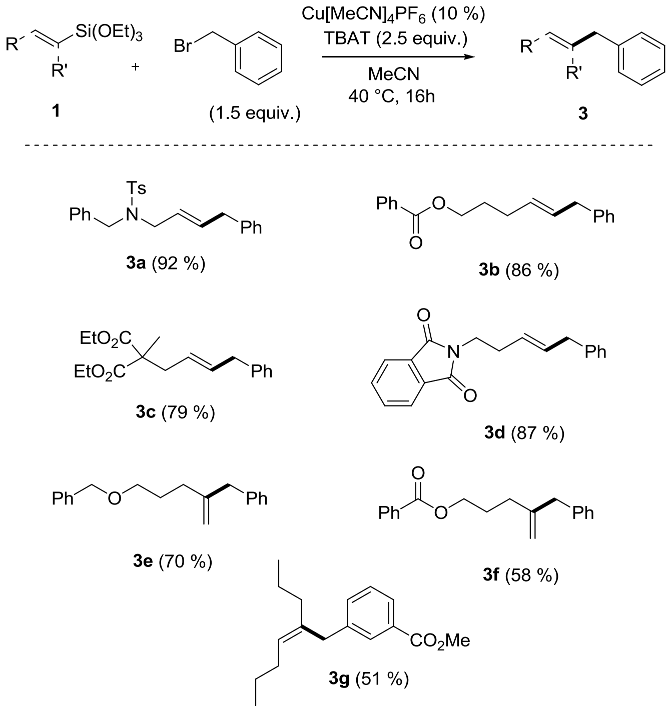
a) Determined by analysis of the crude mixture by ^{1}H NMR.
b) Isolated yield.

With optimal conditions in our hands (Table 1, Entry 9), 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 on the *ortho* position seems to have little impact on the reaction as shown by (**2c**). Fluorinated aromatics 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 with palladium-based catalysts. Yield of the reaction using electron-poor nitrile (**2g**) dropped to 83 % yield. This drop was not a surprise since a small part of TBAT reacted with the *p*-cynaobenzyl bromide to give the corresponding benzylic fluoride. Electron-rich anisole (**2h**) proceeded as well as the ester-substituted (**2i**) in 87 % and 88 % yield respectively. No addition of the vinylsilane on the carbonyl was observed. It must be noted that although electron-poor allylbenzenes tend to easily isomerize 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 about 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 allybenzenes are present in the natural world, very few methods exists to synthetize them. Benzyl and benzoyl protected 1,1-disubstituted alkenes (**3e**) and (**3f**) were synthetized in 70 % and 58 % yield 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.

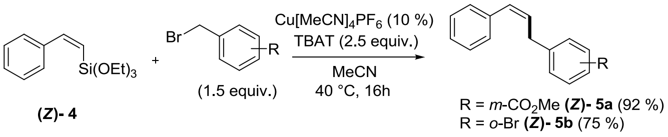


Scheme 2. Electrophile scope. Isolated yields are given between brackets.



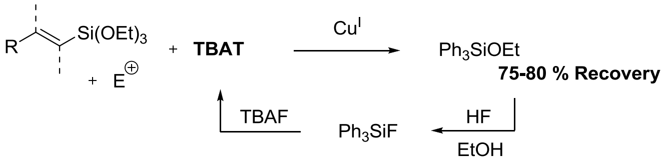
Scheme 3. Vinylsilane scope. Isolated yields are given between brackets.

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 straightfully 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 synthetize by conventional alkyne reductions and palladium cross-coupling reactions because of the sensitivity of the halide. In both cases, no isomerization into an (*E*)-alkene happened and full retention of stereochemistry was observed.



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

In order to tackle the problem of cost linked to the use of TBAT as an activating agent, efficient recycling is required. Upon reaction, 75 to 80 % of the TBAT-derivative ethoxytriphenylsilane 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.



Scheme 5. Recyclability of the activating agent TBAT.

Conclusions

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 a 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-couplings are in progress and will be reported in due time.

Financial support from the Fonds de la Recherche Scientifique (FRS-FNRS), the Fonds pour la formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA), and the Université catholique de Louvain is gratefully acknowledged.

Notes and references

[a] Institute of Condensed Matter and Nanosciences, Molecules, Solids and Reactivity (IMCN/MOST) – Université catholique de Louvain
Place Louis Pasteur 1, bte L4.01.02, 1348 Louvain-la-Neuve, Belgium
E-mail: Olivier.riant@uclouvain.be
http://www.uclouvain.be/en-201510.html

† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 I. Fleming, A. Barbero and D. Walter, Chem. Rev. 1997, **97**, 2063; M. J. Curtis-Long and Y. Aye, *Chem. Eur. J.*, 2009, **15**, 5402.
2 H. F. Sore, W. R. J. D. Galloway and D. R. Spring *Chem. Soc. Rev.*, 2012, **41**, 1845.
3 Y. Nakao and T. Hiyama, *Chem. Soc. Rev.*, 2011, **40**, 4893 and references cited therein.
4 S. E. Denmark and J. D. Baird, *Chem. Eur. J.*, 2006, **12**, 4954 and references cited therein.
5 A. Tsubouchi, D. Muramatsu and T. Takeda *Angew. Chem. Int. Ed.*, 2013, **52**, 12719.
6 For some representative examples see : C. Conti, L. P. Monaco and N. Desideri, *Bioorg. Med. Chem.*, 2011, **19**, 7357; S. Ahmed, S. Hettwer, J. W. Vrijbloed, C. Farina and H. Allgeier (NEUROTUNE A.G.), Neurotrypsin Inhibitors, WO 2012059442 (A2), 2012; B. C. Gonzalez, S. C. Sanchez, D. A. Sedes and R. B. Blanco (UNIV. SANTIAGO COMPOSTELA), Ester Derivatives as Competitive Inhibitors of Type II Dehydroquinase Enzyme, WO 2010146125 (A1), 2010; M. Bruncko, X. Song, H. Ding, Z.-F. Tao and A. Kunzer (ABBOTT LAB.), 7-Nonsubstituted Indole MCL-1 Inhibitors, WO 2008130970 (A1), 2008; E. Barbanti, O. Veneroni, F. Thaler, R. Pellicciari, L. Benatti and P. Salvati (NEWRON PHARM. S.P.A.), Alpha-aminoamide Derivatives Useful in the Treatment of Lower Urinary Tract Disorders, EP 1557166 (A1).
7 B. Liégault, J.-L. Renaud and C. Bruneau, *Chem. Soc. Rev*., 2008, **37**, 290 and references cited therein; **Si + Pd cat.** : D. Srimani, A. Bej and A.Sarkar, *J. Org. Chem*., 2010, **75**, 4296.
8 For some examples see : **Al and Zr + Ni cat.** : B. H. Lipshutz, G. Bülow, R. F. Lowe and K. L. Stevens, *Tetrahedron*, 1996, **52**, 7265; **Zn + Ni cat.** : M. Piber, A. E. Jensen, M. Rottländer and P. Knochel, *Org. Lett.*, 1999, **1**, 1323; **B + Ni cat.** : P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni and M. P. Watson, *J. Am. Chem. Soc.*, 2013, **135**, 280 ; D. M. Shacklady-McAtee, K. M. Roberts, C. H. Basch, Y.-G. Song and M. P. Watson, *Tetrahedron*, 2014, **70**, 4257; **Heck reaction + Ni cat.** : R. Matsubara, A. C. Gutierrez, and T. F. Jamison, *J. Am. Chem. Soc*., 2011, **133**, 19020 ; E. A. Standley and T. F. Jamison, *J. Am. Chem. Soc.*, 2013, **135**, 1585.
9 L. Cornelissen, S. Vercruysse, A. Sanhadji and O. Riant, *Eur. J. Org. Chem.*, **2014**, 35-38.
10 For some reviews about vinylsilane synthesis, see : D. S. W. Lim and E. A. Anderson, *Synthesis*, 2012, **44**, 983; b) A. Barbero and F. J. Pulido, *Acc. Chem. Res.*, 2004, **37**, 817.
11 Synthesis of β-(E)-vinylalkoxysilanes : a) G. Berthon-Gelloz, J.-M. Schumers, G. De Bo and I. E. Markó, *J. Org. Chem*., 2008, 73, 4190; b) G. De Bo, G. Berthon- Gelloz, B. Tinant and I. E. Markó, *Organometallics*, 2006, **25**, 1881; c) S. Dierick and I. E. Markó, personal communications.
12 Synthesis of α-vinylalkoxysilanes : B. M. Trost and Z. T. Ball, *J. Am. Chem. Soc*. 2005, **127**, 17644.

13 Synthesis of β-(Z)-vinylalkoxysilanes : J. W. Faller and D. G. D'Alliessi, *Organometallics*, 2002, **21**, 1743.

14 By conversion, we mean the specific transformation of the vinylsilane into the desired product (and not the amount of starting material consumed). By analysis of the crude ^{1}H NMR, a comparison of the unchanging benzyl signal with the different other signals allowed us to quickly quantify the conversion of the vinylsilane into the desired product.

15 C. Eaborn, *J. Chem. Soc.*, 1952, 2846.

16 C. J. Handy, Y.-F. Lam and P. DeShong, *J. Org. Chem.*, 2000, **65**, 3542.