

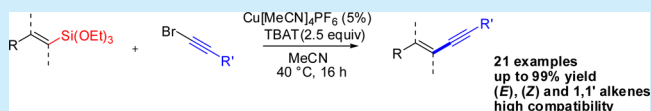
Copper-Catalyzed Cross-Coupling of Vinylsiloxanes with Bromoalkynes: Synthesis of Enynes

Loïc Cornelissen, Maxime Lefrancq, and Olivier Riant*

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

S Supporting Information

ABSTRACT: Enynes are versatile building blocks in organic synthesis. A copper-catalyzed Hiyama-type cross-coupling of vinylsiloxanes with bromoalkynes is presented. This mild and efficient method led to the formation of various sensitive enynes. The use of *cis*, *trans*, and 1,1'-disubstituted vinylsiloxanes was allowed, and full retention of stereochemistry was observed. Sensitive groups such as halides, unsaturated ketones, and aldehydes were fully tolerated.



Silicon-based cross-coupling reactions are extremely powerful tools for the introduction of new C–C bonds in complex organic frameworks.¹ The ready availability, low cost, and high chemical stability of silylated molecules led to the development of several palladium-based cross-couplings.² The well-known Hiyama³ and Hiyama–Denmark⁴ reactions are indeed now widely used in organic synthesis. More recently, copper-based vinylsilane transformations started to emerge. Takeda et al.'s work regarding the formation of vinylcopper(I) species via Brook-like silyl migrations⁵ proved the feasibility of such alternative methods. Enantioselective transfers of vinylsilanes to aldehydes⁶ and unsaturated ketones⁷ were proposed by Shibasaki and Hoveyda respectively, by the use of chiral copper(I) complexes. Aryl and heteroaryl silanes could be coupled with aryl and heteroaryl iodides in a copper-catalyzed reaction, as recently shown by Giri et al.⁸

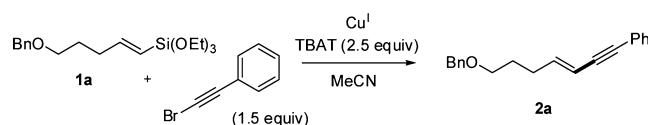
Enynes are conjugated alkynes with high importance in organic chemistry and synthesis.⁹ This ubiquitous building block is present in natural products, pharmacologically active molecules, agrochemicals, and materials for optics and electronics. The most common way to access enynes relies on the palladium-catalyzed Sonogashira reaction¹⁰ and is based on a nucleophilic alkyne coupled with an electrophilic vinyl moiety. Although scarcely developed, a complementary approach relies on the use of nucleophilic vinyl moieties and electrophilic alkynes.¹¹

Our group recently published a mild and efficient copper-catalyzed method to synthesize 1,4-dienes from vinylsiloxanes.¹² These first encouraging results led us to extend this method toward the synthesis of enynes. Herein is described a very mild ligandless copper-catalyzed cross-coupling of readily available vinylsiloxanes^{13–15} and bromoalkynes. This umpolung-type of approach compared to the classic Sonogashira reaction uses TBAT (tetrabutylammonium difluorotriphenylsilicate) as an activating agent and uses a low catalyst loading.

We started our experiments using similar conditions as reported in our allylation procedure. The transformation of vinylsiloxane **1a** into enyne **2a** was studied in acetonitrile, using

2.5 equiv of TBAT as the activating agent (Table 1). To our surprise, our first trial using 10% of Cu(MeCN)₄PF₆ as a

Table 1. Initial Optimization for the Coupling of 1a with (Bromoethynyl)benzene^a



entry	Cu ^I salt	reaction time/temp	yield (%) ^b
1	Cu(MeCN) ₄ PF ₆ (10%)	16 h/rt	93
2	Cu(MeCN) ₄ PF ₆ (10%)	16 h/40 °C	96
3	Cu(MeCN) ₄ PF ₆ (5%)	16 h/40 °C	97
4	Cu(MeCN) ₄ PF ₆ (2%)	16 h/40 °C	91
5	/	16 h/40 °C	/

^aReactions were run on a 0.2 mmol scale in 1 mL of acetonitrile.

^bYield of the isolated product.

catalyst during 16 h at room temperature led to an impressive 93% isolated yield (entry 1). The reaction was pushed to completion by gently heating the solution to 40 °C (entry 2).

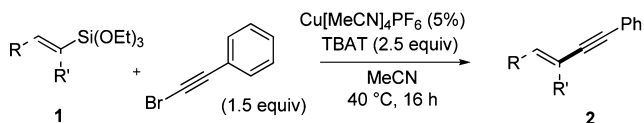
Reducing the catalytic loading to 5% of copper(I) led to an almost quantitative 97% yield (entry 3). Reducing the loading to 2% started to have a negative impact on the reactivity (entry 4), resulting in an incomplete reaction. The absence of copper(I) led to no conversion at all (entry 5). Other activating agents were screened, only to show that TBAT was the only one able to promote the reaction with high yields.¹⁶ Although not particularly atom economic, TBAT is transformed into Ph₃SiOEt upon reaction. Ph₃SiOEt can be easily recovered and transformed into TBAT again,¹⁷ meaning an overall loss of *n*Bu₄NF (TBAF).

Received: April 20, 2014

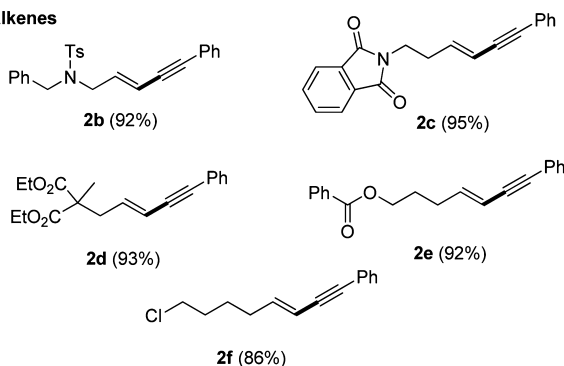
Published: May 12, 2014

With optimal conditions in hands, the functional group compatibility of the vinylsiloxane reagent was then evaluated (Scheme 1).

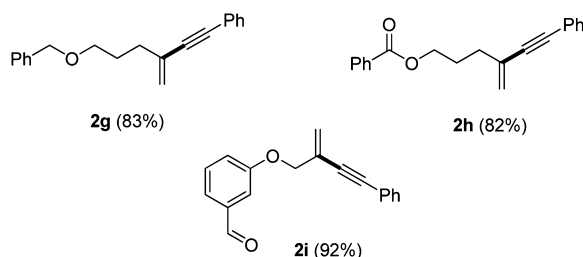
Scheme 1. Evaluation of the Compatibility of Various Vinylsiloxanes and (Bromoethynyl)Benzene^a



(E)-alkenes



1,1'-disubstituted alkenes

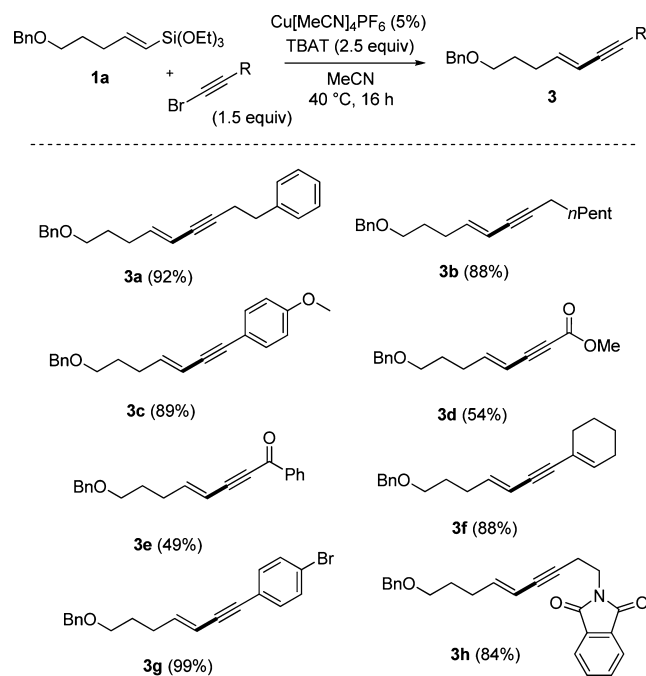


^aIsolated yields are given in parentheses.

Nitrogen-containing enynes such as tosylamine **2b** and phthalimide **2c** were synthesized in excellent yields. Diethyl malonate **2d** was tolerated with an almost quantitative yield, regardless of its hindrance and coordinating ability. The presence of leaving groups on the nucleophilic precursor was evaluated with ester **2e** and chloride **2f** which both gave excellent yields. 1,1'-Disubstituted enynes are known to be relatively tedious to synthesize.¹⁸ α -Vinylsiloxanes were synthesized according to the Trost and Ball method¹⁴ with good α/β selectivities, ranging from 84:16 to 92:8.¹⁹ The mixtures of isomers were coupled to give the corresponding enynes with full retention of stereo- and regiochemistry. Benzyl **2g** and benzoyl **2h** were indeed obtained in good yields. Furthermore, nucleophile sensitive functions such as aldehydes were fully tolerated and **2i** was obtained in 92% yield, emphasizing the very mild nature of this reaction.

The electrophile scope was also evaluated by varying the alkyne moiety (Scheme 2). β -(E)-Vinylsiloxane **1a** was employed as a robust model during the whole screening. Alkane chains attached to the alkyne gave very good yields, as shown by **3a** and **3b**. The reduced reactivity of electron-rich bromoalkynes was not a problem, *p*-OMe **3c** being obtained in 89% yield. On the other hand, electron-poor alkynes such as **3d** and **3e**, known to be poorly reactive substrates in the

Scheme 2. Electrophile Scope Using Model Vinylsiloxane **1a**^a

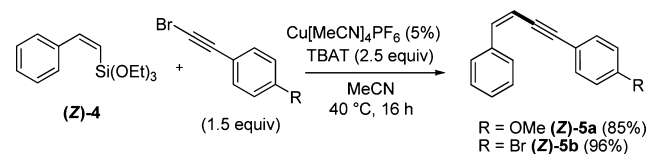


^aIsolated yields are given in parentheses.

Sonogashira reaction,²⁰ only gave moderate yields. It appears that the starting bromoalkynes were not stable enough in the reaction media, leading to a prompt degradation. No addition of the vinylsiloxane to the carbonyl was observed in any case. Polyenes structures could be synthesized in good yields, according to **3f**. This kind of pattern is present in several natural products²¹ and could eventually lead to very interesting (E)-(Z)-(E)-conjugated alkenes²² by a (Z)-selective reduction of the triple bond. While difficult to obtain by conventional palladium-catalyzed reactions, bromide **3g** was synthesized quantitatively. The presence of a leaving group close to the reactive center of the electrophile was also tolerated, as shown by **3h**.

The synthesis of (Z)-alkenes remains a constant challenge in organic chemistry. β -(Z)-Vinylsiloxane (**Z**)-**4** was obtained straightforwardly from phenylacetylene with excellent selectivity using the Faller et al. method (Scheme 3).¹⁵ Electron-rich

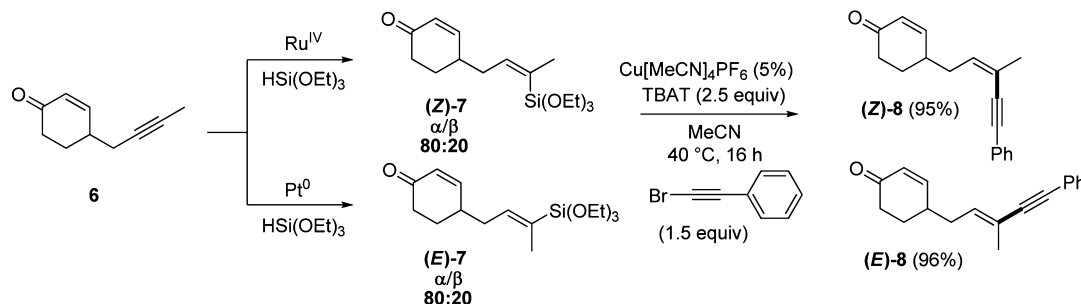
Scheme 3. Synthesis of (Z)-Enynes^a



^aIsolated yields are given in parentheses.

(Z)-**5a** was formed in 85% yield, with full retention of the stereochemistry. The more challenging bromide (Z)-**5b** was also obtained in a quantitative yield. Such a compound would be hard to synthesize by other means and can be further functionalized to reach much more valuable compounds.

One of the advantages of using vinylsilanes as nucleophilic precursors is the large choice of very efficient hydrosilylation catalysts, leading to a large range of isomers. In order to

Scheme 4. Stereodivergent Synthesis of Polysubstituted Enynes^a

^aIsolated yields are given in parentheses.

illustrate this point, internal alkyne **6** was used to propose a stereodivergent synthesis of trisubstituted enynes (Scheme 4). (*Z*)-**7** was obtained by the method of Trost and Ball,¹⁴ with an α/β selectivity of 80:20. The isomers could not be separated, and the mixture was coupled with (bromoethynyl)benzene under our optimal conditions. Trisubstituted enyne (*Z*)-**8** was obtained with the same ratio of isomers in excellent yield. Vinylsiloxane (*E*)-**7** was synthesized using an *N*-heterocyclic platinum(0) carbene catalyst¹³ with an α/β selectivity of 80:20. The isomers could be separated, and pure (*E*)-**7** was coupled under the same conditions as before. (*E*)-**8** was obtained almost quantitatively with full retention of stereochemistry. Although being known to be quite sensitive toward organocopper species, no addition onto the electron-deficient double bond was ever observed.

In conclusion, a mild and efficient copper-catalyzed cross-coupling of vinylsiloxanes with bromoalkynes was presented. Various *cis*, *trans*, and 1,1'-disubstituted vinylsiloxanes were transformed into enynes with full retention of stereochemistry. The presence of sensitive groups such as bromides, ketones, and aldehydes were fully tolerated, emphasizing the very soft nature of the reaction. Finally, a stereodivergent synthesis of trisubstituted enynes was proposed, using different hydro-silylation metal catalysts. Further studies concerning copper-catalyzed transformations of vinylsilanes are underway and will be reported in due time.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Olivier.riant@uclouvain.be.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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. We wish to warmly thank Dr. Christophe Meyer (ESPCI Paris) and Pr. Fabrice Chemla (UPMC Paris) for useful advices and encouragements throughout this work.

■ REFERENCES

- (1) (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2193. (b) Curtis-Long, M. J.; Aye, Y. *Chem.—Eur. J.* **2009**, *15*, 5402–5416.
- (2) Sore, H. F.; Galloway, W. R. J. D.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 1845–1866.
- (3) Nakao, Y.; Hiyama, T. *Chem. Soc. Rev.* **2011**, *40*, 4893–4901 and references cited therein.
- (4) Denmark, S. E.; Baird, J. D. *Chem.—Eur. J.* **2006**, *12*, 4954–4963 and references cited therein.
- (5) (a) Taguchi, H.; Miyashita, H.; Tsubouchi, A.; Takeda, T. *Chem. Commun.* **2002**, 2218–2219. (b) Tsubouchi, A.; Onishi, K.; Takeda, T. *J. Am. Chem. Soc.* **2006**, *128*, 14268–14269. (c) Tsubouchi, A.; Matsuda, H.; Kira, T.; Takeda, T. *Chem. Lett.* **2009**, *38*, 1180–1181. (d) Tsubouchi, A.; Enatsu, S.; Kanno, R.; Takeda, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7089–7091. (e) Tsubouchi, A.; Muramatsu, D.; Takeda, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12719–12722.
- (6) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138–4139.
- (7) Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455–4462.
- (8) Gurung, S. K.; Thapa, S.; Vangala, A. S.; Giri, R. *Org. Lett.* **2013**, *15*, 5378–5381.
- (9) (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922. (b) Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*; Elsevier: Oxford, 2004. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017.
- (10) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871.
- (11) For some representative examples, see: (a) Commerçon, A.; Normant, J. F.; Villieras, J. *Tetrahedron* **1980**, *36*, 1215–1221. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980. (c) Beaudet, I.; Parrain, J.-L.; Quintard, J.-P. *Tetrahedron Lett.* **1992**, *33*, 3647–3650. (d) Sorg, A.; Brückner, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4523–4526. (e) Hoshi, M.; Kawamura, N.; Shirakawa, K. *Synthesis* **2006**, 1961–1970. (f) Wang, S.; Wang, M.; Wang, L.; Wang, B.; Li, P.; Yang, J. *Tetrahedron* **2011**, *67*, 4800–4806.
- (12) Cornelissen, L.; Vercruyse, S.; Sanhadji, A.; Riant, O. *Eur. J. Org. Chem.* **2014**, 35–38.
- (13) Synthesis of β -(*E*)-vinylsiloxanes: (a) Berthon-Gelloz, G.; Schumers, J.-M.; De Bo, G.; Markó, I. E. *J. Org. Chem.* **2008**, *73*, 4190–4197. (b) De Bo, G.; Berthon-Gelloz, G.; Tinant, B.; Markó, I. E. *Organometallics* **2006**, *25*, 1881–1890. (c) Dierick, S.; Markó, I. E. Personal communications with their permission.
- (14) Synthesis of α -vinylsiloxanes: Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655.
- (15) Synthesis of β -(*Z*)-vinylsiloxanes: Faller, J. W.; D'Alliessi, D. G. *Organometallics* **2002**, *21*, 1743–1746.
- (16) See the Supporting Information for more details about the activating agents survey.
- (17) (a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167. (b) Handy, C. J.; Lam, Y.-F.; DeShong, P. *J. Org. Chem.* **2000**, *65*, 3542–3543.

(18) (a) Thongsornkleeb, C.; Danhaiser, R. L. *J. Org. Chem.* **2005**, *70*, 2364. (b) Xu, H.-D.; Zhang, R.-W.; Li, X.; Huang, S.; Tang, W.; Hu, W.-H. *Org. Lett.* **2013**, *15*, 840–843.

(19) Details about the α/β selectivities are present in the Supporting Information.

(20) (a) Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111–3113. (b) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597–1600.

(21) For some representative examples, see: (a) Bohlmann, F.; Thefeld, W.; Zdero, C. *Chem. Ber.* **1970**, *103*, 2245–2251. (b) Taniguchi, M.; Uchio, Y.; Yasumoto, K.; Kusumi, T.; Ooi, T. *Chem. Pharm. Bull.* **2008**, *56*, 378–382. (c) Akiyama, T.; Takada, K.; Oikawa, T.; Matsuura, N.; Ise, Y.; Okada, S.; Matsunaga, S. *Tetrahedron* **2013**, *69*, 6560–6564.

(22) Organ, M. G.; Ghasemi, H. *J. Org. Chem.* **2004**, *69*, 695–700.