

Stereoselective Synthesis of Disubstituted Butadienes via Copper-Mediated Coupling of Alkenyl Silanes

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Received 7 April 2011

Abstract: A strategy is described for the stereoselective synthesis of substituted (*E*)-, (*Z*)-, and α -disubstituted butadienes from terminal alkynes by the copper-mediated coupling of geometrically-defined alkenyl silanes. Proof-of-concept results that demonstrate the feasibility of this approach are presented.

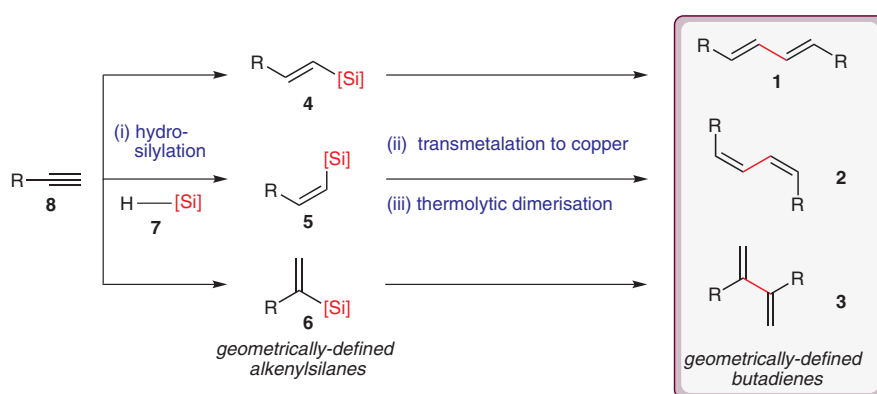
Key words: copper, coupling, diversity-oriented synthesis, butadienes, hydrosilylation

Conjugated polyene systems are a commonly encountered structural feature in natural products¹ and some optical materials;² consequently the development of methods to access such bonding arrangements in a stereoselective fashion has attracted interest amongst synthetic chemists.³ Herein we outline a strategy for the regio- and stereoselective synthesis of (*E*)-, (*Z*)-, and α -disubstituted butadienes from a common terminal alkyne precursor. Such chemistries could offer an efficient means of rapidly achieving structural diversification from a common starting material; as such, they could also be exploited in reagent-based diversity-oriented synthesis (DOS) pathways.^{4,5}

In line with our group's continued interest in copper-based methods for carbon–carbon bond construction⁶ we were interested in exploring the thermolytic dimerisation of geometrically-defined alkenylcopper species as a route towards the desired *E*-, *Z*-, and α -substituted butadiene architectures (**1–3**, Scheme 1). It was envisaged that such copper species could be accessed by transmetalation from suitable geometrically-defined alkenylmetal precursors

(or latent functional equivalents), which could ideally be selectively generated from a common alkyne starting material. We were interested in examining the use of alkenylsilanes (of the general form **4–6**) in this context: there are a number of reactions that seemingly involve silicon–copper transmetalations,⁷ and a range of catalytic methods have been developed for the stereoselective hydrosilylation of (terminal) alkynes, allowing the formation of *E*-, *Z*-, and α -isomers in a controllable fashion.⁸ Thus if an alkenyl silane moiety capable of undergoing stereospecific transmetalation to copper could be identified, it may be possible to effect the stereoselective formation of geometrically-defined alkenylsilanes **4–6** containing this moiety (by hydrosilylation using the parent silane **7**, Scheme 1) and convert these into the corresponding alkenylcopper species for subsequent coupling. Overall, it was envisaged that this sequence could provide access to all possible *E*-, *Z*-, and α -disubstituted butadiene isomers **1–3** from a common terminal alkyne precursor **8**. In this letter we present proof-of-concept results that demonstrate the feasibility of this approach.

Our synthetic strategy was dependent upon the identification of (*E*)-, (*Z*)-, and α -alkenylsilane precursors that could be readily prepared with geometrical control and undergo stereospecific transmetalation to copper under mild conditions. Ideally, all desired geometrical isomers of such alkenylsilanes could be generated by hydrosilylation from the same starting material through variation in the catalyst employed. Yoshida et al. have reported that



Scheme 1 Outline of our strategy for the stereoselective synthesis of disubstituted butadienes via the homocoupling of alkenylsilanes

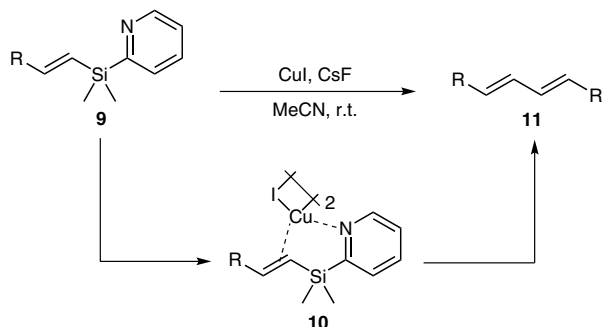
SYNLETT 2011, No. 15, pp 2140–2144

Advanced online publication: 31.08.2011

DOI: 10.1055/s-0030-1261150; Art ID: D10711ST

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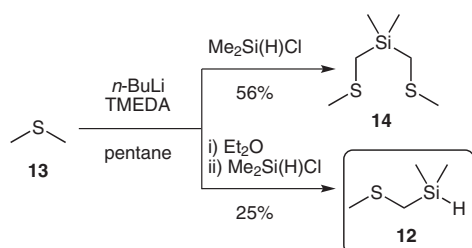
alkenyl(2-pyridyl)dimethylsilanes **9** can bind to copper(I) in a bidentate fashion, presumably through the pyridine lone pair and alkene π system, to form isolable complexes such as **10** (Scheme 2).⁹



Scheme 2 Silicon–copper transmetalation using alkenyl-(2-pyridyl)dimethylsilanes **9** as described by Yoshida et al.⁹

Treatment of these complexes with caesium fluoride results in the formation of *E*-symmetrical butadienes of the general form **11**, presumably via silicon–copper transmetalation followed by the thermolysis of the alkenylcopper species thus formed.⁹ This coordination-driven transmetalation offers an appealing mechanism for achieving stereospecific silicon–copper exchange. However, the 2-pyridylsilanes have some significant drawbacks: the preparation of 2-pyridyldimethylsilane is low-yielding, and the silane is obtained in high purity only after multiple distillations, and while catalytic *E*-selective hydrosilylation of terminal alkynes with 2-pyridyl(dimethyl)silane has been shown to proceed in good yield,¹⁰ *Z*- and α -selective hydrosilylations with 2-pyridyl(dimethyl)silane have not been reported; in the authors' hands preliminary attempts at effecting these reactions gave none of the desired products. Alternative silanes bearing metal-coordinating functionality were therefore sought.

Our focus turned towards the use of alkenylsilanes bearing a thioether moiety which we envisaged would be capable of interacting with copper in a similar fashion to the pyridyl group present in Yoshida's silane **9**. Towards this end we initially targeted the synthesis of thioether-functionalised (*E*)-silane **12** (Scheme 3). We first investigated the reaction of methylthiomethylithium [prepared by the treatment of dimethylsulfide (**13**) with *n*-BuLi and TMEDA] with dimethylchlorosilane. Unfortunately, the only identifiable product obtained was the silane **14**.¹¹



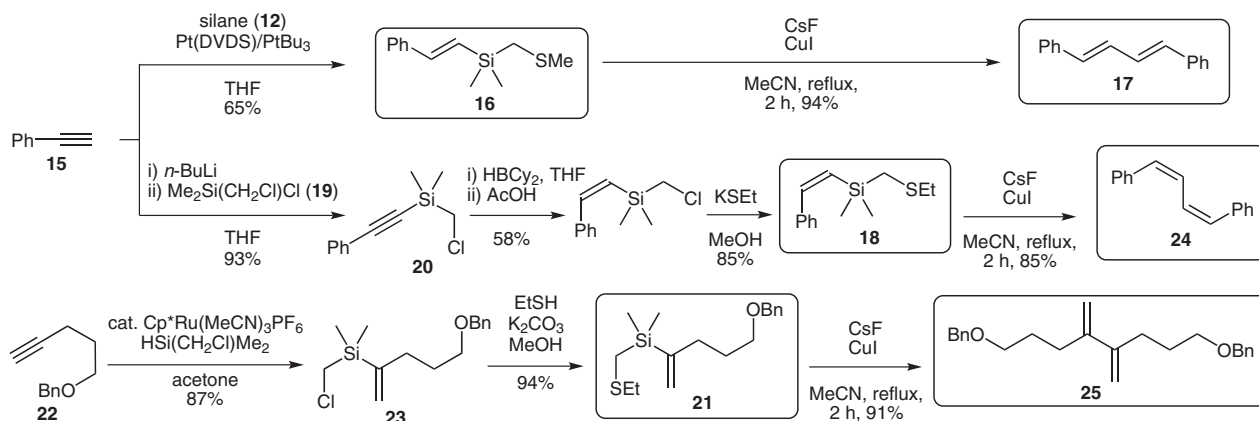
Scheme 3 Preparation of (methylthiomethyl)dimethylsilane **12**

When the methylthiomethylithium was treated with diethyl ether prior to addition of the chlorosilane, the desired product **12** was obtained in an unoptimised 25% yield (Scheme 3).⁸

With silane **12** in hand, stereoselective hydrosilylation of phenylacetylene (**15**) proceeded smoothly to give (*E*)-alkenylsilane **16** with excellent geometrical selectivity (Scheme 4). Treatment of **16** with caesium fluoride and copper(I) iodide in acetonitrile at reflux provided the desired (*E*)-butadiene **17** as the sole isolated product in an excellent yield (Scheme 4). There was no evidence in the ¹H NMR of the crude product material for any *Z*- or α -substituted products suggesting that both the silicon–copper transmetalation and thermolytic coupling processes proceed with retention of the double-bond geometry present in the starting silane.

This result was considered sufficiently promising to merit further investigation of thioether-substituted silanes. The *Z*-selective hydrosilylation of phenylacetylene (**15**) with silane **12** was therefore investigated. Unfortunately, neither Chang's¹² nor Hiyama's¹³ catalysts furnished the desired compound with useful selectivity; the former system gave a 1:1:0.45 mixture of the *E*-, *Z*-, and 1,1-disubstituted isomers, while the latter gave very little conversion. A thioether-functionalised (*Z*)-alkenyl silane **18** was ultimately obtained via a two-step sequence. Silylation of the lithium acetylide of phenylacetylene (**15**) with chlorosilane **19** generated chloride **20**. Hydroboration and protodeborylation with acetic acid followed by chloride displacement with potassium ethanethiolate in methanol furnished the silane **18** (Scheme 4). Attempts to access the corresponding α -substituted silane from phenylacetylene (**15**) were unsuccessful. Therefore an alternative α -substituted silane bearing the thioether moiety was desired so that the general behaviour of the α -species under the coupling reaction conditions could be examined. Thus the α -substituted alkenylsilane **21** was prepared by a two-step sequence. Hydrosilylation of the known alkyne **22** with chloromethyldimethylsilane, promoted by Trost's catalyst,^{8d} furnished an inseparable mixture of the α - and (*Z*)-alkenylsilanes **23**. As with **20**, displacement with potassium ethanethiolate proceeded smoothly, and **21** could be isolated in a geometrically pure form in good yield after purification by column chromatography (Scheme 4). Copper-mediated oxidative homocoupling of thioether-functionalised (*Z*)- and α -alkenylsilanes **18** and **21** in acetonitrile was sluggish at room temperature, but furnished the desired butadienes **24** and **25**, respectively, in good yields at a concentration of 0.2 M when heated at reflux (Scheme 4); as was the case with the corresponding *E*-isomer **17**, the sole observable byproduct was desilylated starting material. Importantly, the geometry of the starting silylalkenes was retained in the products; there is no evidence of isomerisation during the transmetalation and subsequent coupling.¹⁴

In an attempt to better delineate the progress of these coupling reactions the interactions of the (*E*)-, (*Z*)-, and α -silanes **16**, **18**, and **21** with copper(I) salts were studied by

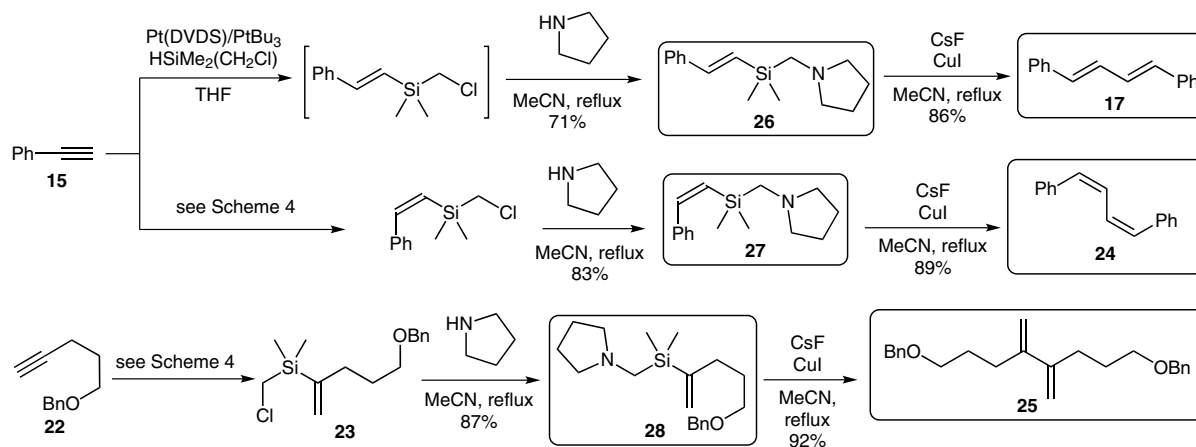


Scheme 4 Preparation of geometrically-defined thioether-substituted alkenyl silanes and their subsequent homocoupling to furnish (*E*)-, (*Z*)-, and α -substituted butadienes

^1H NMR (Table 1). The spectra of the free ligands were recorded in appropriate solvents and compared to those obtained in the presence of one equivalent of a copper salt.¹⁵ When **16** was treated with one equivalent of the cationic copper(I) species $\text{Cu}(\text{MeCN})_4\text{PF}_6$ in $\text{CH}_2\text{Cl}_2\text{-}d_2$, significant changes in the spectrum were observed, with large decreases in the chemical shifts of the alkenyl protons in the complexed material relative to the free ligand and smaller increases in the chemical shift of the protons of the thioether moiety (Table 1, entry 1). These data are consistent with the binding of copper to both the alkene and the thioether.¹⁶ Similar changes in the chemical shifts of the alkenyl protons were observed with the *Z*- and α -configured silanes **18** and **21** in the presence of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ in $\text{CH}_2\text{Cl}_2\text{-}d_2$, suggesting that these too are capable of binding to copper (Table 1, entries 2 and 3). A control experiment was performed using (*E*)-(styryl)triethylsilane, which lacks coordinating functionality besides the alkene; its spectrum in $\text{CH}_2\text{Cl}_2\text{-}d_2$ was essentially unchanged on adding one equivalent of $\text{Cu}(\text{MeCN})_4\text{PF}_6$, which suggests that silylalkenes alone are not capable of binding to copper(I) in the same way as are the thioether-substituted alkenylsilanes **16**, **18**, and **21**.

To assess the effect of using a more strongly coordinating alkenylsilane on the transmetalation process, (*E*)-, (*Z*)-,

and α -alkenylsilanes **26–28**, respectively, bearing a pendant tertiary amine, were prepared with high levels of geometrical selectivity (Scheme 5). As with the thioether-functionalised silanes, these species all underwent transmetalation to copper and oxidative dimerisation to yield the corresponding butadienes in good yields (Scheme 5). NMR analysis of their complexes with copper showed similar changes in chemical shift to those observed with the thioether-functionalised silanes; however, with the more strongly coordinating pyrrolidine group, the changes in chemical shift were observed in acetonitrile as well as in dichloromethane (Table 1, entries 4–6). In spite of this, the yields obtained for the thermolytic dimerisation with the amine-functionalised silanes did not differ significantly from those obtained with the thioether-functionalised species (Scheme 5). Once again there was no evidence in the ^1H NMR spectra of the crude product materials for any undesired geometrical isomers of the products, suggesting that both the silicon–copper transmetalation and thermolytic coupling processes proceed with retention of the double-bond geometry present in the starting silane. Hence, both the amine-functionalised silanes **26–28** and those bearing pendant thioethers **16**, **18**, and **21** satisfy the requirements for an alkenylmetal precursor that is readily prepared with geometrical control



Scheme 5 Preparation of geometrically-defined pyrrolidine-functionalised alkenyl silanes and their subsequent homocoupling to furnish (*E*)-, (*Z*)-, and α -substituted butadienes.

Table 1 Studying the Interactions of Thioether- and Amine-Functionalised Alkenylsilanes with Cu(I) by ^1H NMR Spectroscopy^a

Entry	Substrate	Proton	$\Delta\delta_{\text{H}}$ (ppm)
1 ^b		1	-0.2
		2	-0.7
		3	+0.2
		4	+0.2
16			
2 ^b		1	NA ^d
		2	-0.7
		3	+0.1
		4	+0.3
18			
3 ^b		1	-0.3
		2	-0.4
		3	+0.3
		4	+0.3
X = (CH ₂) ₃ OBn			
21			
4 ^c		1	-0.2
		2	-0.4
		3	+0.2
		4	+0.2
26			
5 ^c		1	-0.3
		2	-0.4
		3	+0.3
		4	+0.2
X = (CH ₂) ₃ OBn			
28			
6 ^c		1	-0.3
		2	-0.3
		3	+0.2
		4	+0.2
27			

^a Values in the column $\Delta\delta_{\text{H}}$ indicate the observed difference in the chemical shift of the proton of interest in the copper-complexed species relative to that of the free ligand in the same solvent at the same concentration; negative values indicate that the shift in the complex is less than that in the free ligand; 20 mg substrate in 0.75 mL of solvent with 1 equiv of Cu(I) salt relative to substrate in all cases.

^b Conditions: $\text{Cu}(\text{MeCN})_4\text{PF}_6$, CH_2Cl_2 .

^c Conditions: CuI , MeCN .

^d NA = not applicable. The signal of this proton is coincident with those of the aromatic ring in the copper complex and, consequently, $\Delta\delta_{\text{H}}$ could not be determined.

and undergoes transmetalation to copper under mild conditions.

In conclusion, we have described a strategy for the stereoselective synthesis of substituted *E*-, *Z*-, and α -disubstituted butadienes from terminal alkynes by the copper-mediated coupling of geometrically-defined alkenyl silanes. Ideally, we envisage generating the required silanes from a common alkyne starting material by hydrosilyla-

tion with a given silane using different conditions. Thus far this remains an unmet goal, and studies towards this end are ongoing. Nevertheless, proof-of-concept results demonstrate the general feasibility of our approach: (*E*)-, (*Z*)-, and α -alkenyl silane intermediates containing chelating amine and thioether functionalities could be formed with excellent regio- and stereoselectivity, and they could be transformed to the corresponding (*E*)-, (*Z*)-, and α -butadienes upon heating in the presence of copper(I) iodide without loss of selectivity and in good yields. Experimental observations and NMR studies are consistent with a process involving transmetalation from the alkenyl silane to form a neutral organocopper species followed by thermolytic dimerisation to yield the coupled product. This strategy potentially offers an efficient means of achieving molecular diversification from common alkyne starting materials (through variation of the reagents employed); as such, it may prove valuable in branching, reagent-based DOS pathways.¹ Furthermore, we anticipate that these new methodologies could prove valuable in a wider synthetic context, with potentially broad applications in target-oriented synthesis (e.g., the synthesis of natural products and pharmaceutical agents). The scope of the methodologies described herein is currently being explored and developed further, and its application to the preparation of structurally diverse small-molecule collections will be reported in due course.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (11) Compound **14** was presumably formed by displacement of both the chloride and the hydride from the chlorosilane. This can be rationalised as follows: suppose that lithiation of **13** proceeds to completion. In the absence of other Lewis basic donors, it might be expected that the sulfur atom of one lithiated molecule of **13** will coordinate to the lithium of another. When the chlorosilane is added, it will be attacked by the organolithium to form **12**; however, as there will be one or more molecules of the organolithium still coordinated to the sulfur atom of the newly formed **12**, intra-aggregate transfer of the organic group of this coordinated organolithium to the proximal silicon atom may be more rapid than an intermolecular on a second molecule of the chlorosilane. If this was the case, it was reasoned that the addition of a more strongly coordinating solvent (Et_2O) should reduce the extent to which the organolithium is complexed by the thioether, and might thus prevent this second attack.
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- (14) If either CsF or CuI are omitted from the reaction mixtures, no coupled product is observed; with extended reaction times (48 h), partial desilylation of the starting material is observed if CsF is present but not CuI.
- (15) Interestingly, while CuI in MeCN together with CsF promotes complete conversion of the (*E*)-silane **16** (Scheme 4), the addition of 1 equiv of CuI did not induce any change in the spectrum of **16** in MeCN- d_3 .
- (16) Since thioethers are almost pure σ -donors, with no vacant low-energy orbitals suitable for metal–ligand back bonding, donation of the lone pair of sulfur to the metal might be expected to decrease the electron density at (and thus deshield) the carbons proximal to the sulfur atom, resulting in the observed increase in the chemical shift of their attached protons. Unlike the thioether, the alkene has a low-energy π^* orbital suitable for metal–ligand back bonding, and so back donation from the metal to the alkene might account for the observed decrease in the chemical shift of the alkenyl protons in the presence of copper.