ORGANIC LETTERS

2010
Vol. 12, No. 12
2806−2809

Diversity-Oriented Synthesis of Disubstituted Alkenes Using Masked Silanols

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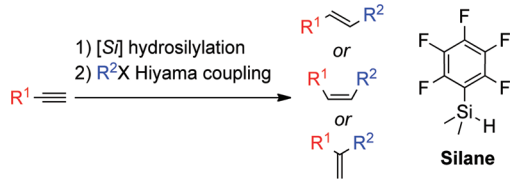
Received April 19, 2010

ABSTRACT



The regio- and stereoselective synthesis and subsequent Hiyama cross coupling of pentafluorophenyldimethylvinylsilanes has been developed, thus providing a convenient and robust method for the diversity-oriented synthesis of (*E*)-, (*Z*)- and α-disubstituted alkenes from terminal alkynes. Pentafluorophenyldimethylvinylsilanes undergo cross-coupling reactions with excellent selectivity and in good yields, offering an attractive alternative to existing masked silanols.

Diversity-oriented synthesis (DOS) is an efficient method for the synthesis of structurally diverse compounds by variation of the core molecular scaffold and stereochemistry.[1] In this context, the development of functional group methodologies of broad synthetic utility that allow the regio- and stereoselective synthesis of (*E*)-, (*Z*)- and α-disubstituted alkenes from a single common precursor would be valuable. Such chemistries could be exploited in reagent-based branching pathways to facilitate rapid structural diversification from a common functionalized starting material, increasing molecular diversity and generating products suitable for further modification and diversification. Herein, we report the development of a methodology for the synthesis of all viable disubstituted alkene isomers from terminal alkynes.

The synthesis of disubstituted alkenes from terminal alkynes can be achieved via hydrometalation and subsequent palladium catalyzed cross coupling; however, poor stereospecificity in the hydrometalation and/or loss of double-bond geometry on cross coupling as well as poor reagent stability and toxicity remain ongoing issues.[2,3] To address this synthetic problem, numerous catalysts have been developed for the synthesis of vinylorganosilyl species stereospecifically.[3] Additionally, in more recent years, the development of organosilicon reagents as effective coupling nucleophiles has aroused interest, particularly because of their greater stability, mild cross-coupling conditions, and low toxicity compared to other organometallic nucleophiles.[4,5]

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(3) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, *6*, 853.

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10.1021/ol100895d
Published on Web 05/21/2010

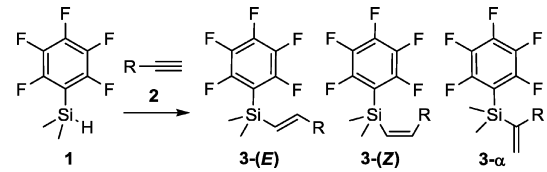
After extensive research by Denmark et al., the potential of organosilanols to cross couple under base activation was realized and subsequently exploited to great effect.[6] Since these fundamental discoveries, a variety of masked silanols have been developed offering the advantage of increased stability relative to the silanol, thus providing the potential to modify and carry the silyl species through multiple steps.[7] It was anticipated that development of pentafluorophenyldimethylvinylsilanes as masked silanols would allow for further elaboration prior to cross coupling and/or their direct application in the selective synthesis of all possible geometric isomers of disubstituted alkenes.[8] We envisaged that such methodology would prove to be a valuable advance with potential applications in both target- and diversity-oriented synthesis.

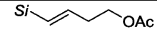
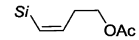
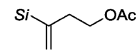
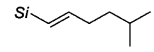
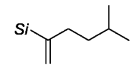
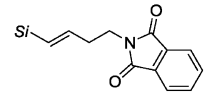
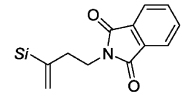
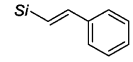
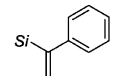
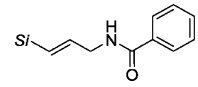
Early attempts by Brennan and Gilman to develop the hydrosilylation of terminal alkynes with pentafluorophenyldimethylsilane (**1**) suffered from poor regioselectivity, with mixtures of α- and *β*-vinylsilanes being produced when H_2PtCl_6 was employed as the catalyst.[9] Advances in the Pt-catalyzed hydrosilylation of terminal alkynes has led to the exclusive synthesis of (*E*)-*β*-vinylsilanes with a variety of silanes, when the organically soluble ($^tBu_3P$)Pt(DVDS) complex was used.[10,7h] Application of the Pt complex to the hydrosilylation of terminal alkynes with silane **1** resulted in excellent selectivity: only the (*E*)-isomer was observed by ^1H NMR analysis of the crude reaction mixture (Table 1, entries 1, 4, 6, and 8). Significantly, further modification of the vinylsilane (**3**) was possible prior to cross coupling, building upon the diversity (Table 1, entry 10).

Historically, generation of the (*Z*)-*β*-vinylsilanes by stereoselective hydrosilylation of terminal alkynes has proven to be a more complex and difficult task than formation of the corresponding thermodynamically favored (*E*)-*β*-vinylsilanes.[3] Accordingly, the synthesis of **3-(*Z*)** was more challenging. Rh-, Ir- and Ru-based catalysts were all explored. The Ru complex, RuHCl(CO)(PCy_3), developed by Ozawa,[11] was the most promising, producing **3-(*Z*)** with reasonable selectivity and in a modest yield (Table 1, entry 2). Alternative strategies were investigated for the exclusive synthesis of the (*Z*)-isomer.

Markovnikov addition of silanes across terminal alkynes has been achieved with excellent regioselectivity using the cationic cyclopentadienylruthenium complex, [Cp*Ru(MeCN)$_3$]PF_6.[12] Pleasingly, treatment of silane **1** with a range of terminal alkynes produced the α-isomer exclusively, when catalyzed by the Ru complex (Table 1, entries 3, 5, and 7). Interestingly, in order to drive the reaction

Table 1. Hydrosilylation of Terminal Alkynes (**2**) Using Pentafluorophenyldimethylsilane (**1**)



entry	method[a]	product	(*E*):(*Z*):α[b]	yield (%)[c]
1	A		>98% (*E*)	66
2	B		19:68:13	48
3	C		>98% α	89
4	A		>98% (*E*)	97
5	C		>98% α	98
6	A		>98% (*E*)	86
7	C		>98% α	99
8	A		>98% (*E*)	89
9[d]	C		>98% α	86
10	D		>98% (*E*)	68

[a] Reaction conditions: (A) silane (1 equiv), alkyne (1.1 equiv), ($^tBu_3P$)Pt(DVDS) (0.1 mol %), toluene, 0 °C to rt; (B) silane (1 equiv), alkyne (1 equiv), RhHCl(CO)(PCy_3)$_2$ (5 mol %), DCM, rt; (C) silane (1.05 equiv), alkyne (1 equiv), [Cp*Ru(MeCN)$_3$]PF_6 (1 mol %), DCM, 0 °C to rt; (D) (i) silane (1 equiv), propargyl amine (1 equiv), ($^tBu_3P$)Pt(DVDS) (0.1 mol %), toluene, 0 °C to rt, (ii) benzoyl chloride (1.2 equiv), triethylamine (1.2 equiv), THF, 0 °C. [b] Determined by ^1H NMR spectroscopy [c] Isolated yield. [d] 10 mol % catalyst used.

(5) (a) Denmark, S. E. *J. Org. Chem.* **2009**, *74*, 2915. (b) Denmark, S. E.; Baird, J. D. *Chem.—Eur. J.* **2006**, *12*, 4954.

(6) (a) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486. (b) Denmark, S. E.; Sweis, R. *Acc. Chem. Res.* **2002**, *35*, 835. (c) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439.

(7) Examples of masked silanols: (a) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, 2491. (b) Denmark, S. E. *J. Org. Chem.* **2009**, *74*, 2915. (c) Denmark, S. E.; Baird, J. D. *Chem.—Eur. J.* **2006**, *12*, 4954. (d) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (e) Sore, H. F.; Boehner, C. M.; MacDonald, S. J. F.; Norton, D.; Fox, D. J.; Spring, D. R. *Org. Biomol. Chem.* **2009**, *7*, 1068. (f) Prukala, W. *Synlett* **2008**, *19*, 3026. (g) Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 3690. (h) Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073. (i) Anderson, J. C.; Munday, R. H. *J. Org. Chem.* **2004**, *69*, 8971. (j) Anderson, J. C.; Anguille, S.; Bailey, R. *Chem. Commun.* **2002**, *18*, 2018. (k) Denmark, S. E.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2007**, *129*, 3737. (l) Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895. (m) Itami, K.; Mitsudo, K.; Nokami, T.; Kamei, T.; Koike, T.; Yoshida, J.-i. *J. Organomet. Chem.* **2002**, *653*, 105. (n) Itami, K.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (o) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, *31*, 138.

(8) It was anticipated that the lower pK_a (pentafluorobenzene pK_a = 25) of the pentafluorophenyl group relative to existing "masked silanols" would faciliate its deprotection and subsequent participation in the regio- and stereoselective cross coupling under mild conditions.

(9) Brennan, T.; Gilman, H. *J. Organomet. Chem.* **1969**, *16*, 63.

(10) Chandra, G.; Lo, P. Y.; Hitchcock, P. B.; Lappert, M. F. *Organometallics* **1987**, *6*, 191.

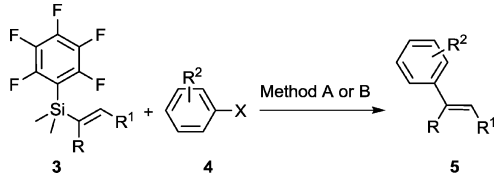
(11) Ozawa, F.; Katayama, H.; Taniguchi, K.; Kobayashi, M.; Sagawa, T.; Minami, T. *J. Organomet. Chem.* **2002**, *645*, 192.

(12) (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726.

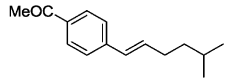
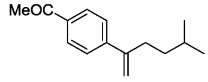
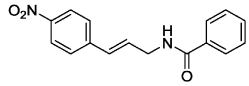
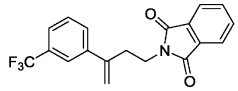
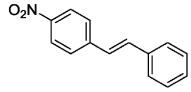
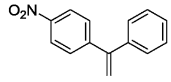
to completion with the more sterically demanding phenylacetylene, an increased catalyst loading was required; however, excellent selectivity was maintained at the higher catalyst loading (Table 1, entry 9).

With the regio- and stereoselective synthesis of **3-(*E*)** and **3-α** vinylsilanes established, their effectiveness at cross coupling under mild reaction conditions and with retention of configurations was examined. Two alternative methods of activation were explored. Initial investigation into the base activated cross coupling of vinylsilanes looked promising, with good yields and excellent selectivity for the *ipso*-subsituted product (direct substitution of the C−Si bond with no regioisomerization) being obtained when the aryl-substituted (*E*)-vinylsilane was reacted (Table 2, entry 5).

Table 2. Hiyama Cross Coupling of (*E*)- and α-Vinylsilanes



3 **4** **5**

entry	R^2	A/B[a]	product	yield (%)[b]
1	4-COMe	A		91
2	4-COMe	A		87
3	4-NO_2	A		85
4	3-CF_3	A		99
5	4-NO_2	B		75
6	4-NO_2	A		86

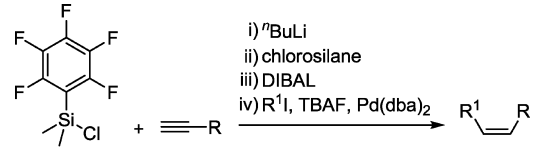
[a] Reaction conditions: (A) vinylsilane (1 equiv), aryl iodide (0.75 equiv), TBAF (2 equiv), $Pd(dba)_2$ (5 mol %), THF, rt; (B) vinylsilane (1 equiv), aryl iodide (0.75 equiv), KOH (3 equiv), $Pd(dba)_2$ (2.5 mol %), MeOH, rt. [b] Isolated yield of isomerically pure material.

However, on expanding the substrate scope of the vinylsilane, loss of selectivity was observed under base activation conditions when aryl-substituted α-vinylsilanes or alkyl-substituted vinylsilanes were reacted. The nature of the substituent and the double-bond orientation were both highly influential on the successful outcome of the base-activated reaction. Pleasingly, on switching the activation source to fluoride, improved selectivity for the *ipso*-subsituted product was observed. Aryl- and alkyl-substituted (*E*)- and α-vinylsilanes readily participated in cross coupling with aryl iodides yielding the desired disubstituted double bonds with complete retention of configuration (Table 2, enteries 1−4 and 6).[13]

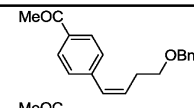
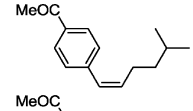
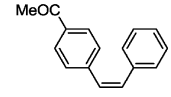
The different stereochemical outcomes observed when cross-coupling vinylsilanes (**3**) under base or fluoride activation indicate that these methods proceed through alternative mechanisms. The fluoride activation pathway is believed to proceed via a pentacoordinate silicate intermediate,[14] whereas under base activation a tetracoordinate transition state involving a covalent Pd−O−Si bond has been reported.[5,15] It is reasonable to conclude that the fluoride activation pathway appears to be less susceptible to steric or electronic changes in the vinylsilane, consequently leading to a higher proportion of the desired *ipso*-substituted product.

Synthesis of **3-(*Z*)** via hydrosilylation with silane **1** and terminal alkynes (**2**) was met with limited success; consequently, an alternative approach involving the synthesis and subsequent reduction of the alkynylsilane was investigated. A variety of alkynes were successfully deprotonated with ^{n}BuLi and treated with the commerically available chlorosilane **6** forming the corresponding alkynylsilanes in excellent yields. A number of reduction conditions were explored, some protocols led to over reduction forming the alkane and/or mixtures of isomers being observed. In an approach similar to those of Panek[16] and Anderson,[7i] it was found that treatment of the alkynylsilanes with diisopropylaluminium hydride produced the respective (*Z*)-vinylsilanes in good yields and selectivity. Telescoping the synthesis of the alkynylsilane, reduction, and subsequent cross coupling ultimately produced the desired (*Z*)-disubstituted alkenes **5-(*Z*)** with excellent geometrical purity and in an overall good combined yield for the four steps (Table 3).

Table 3. Synthesis of (*Z*)-Alkenes[a]

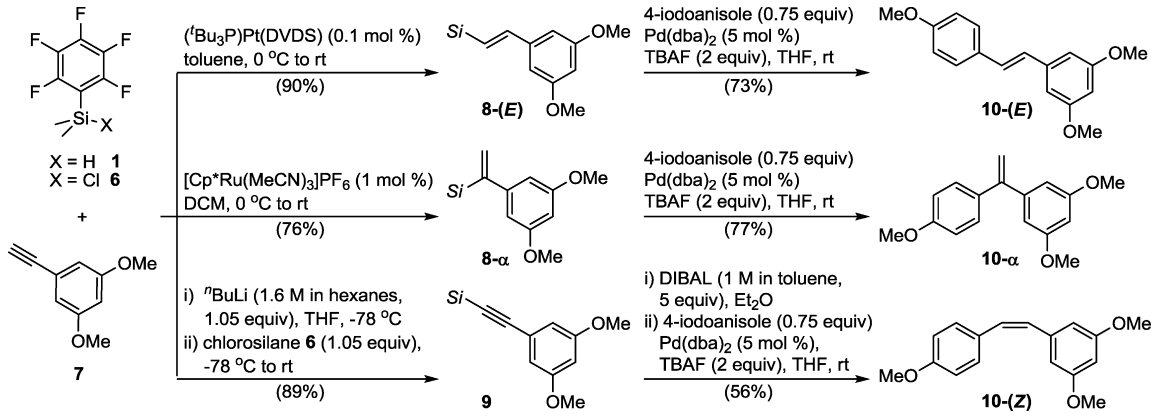


6 (step ii) **2** **5-(*Z*)**

entry	alkyne R	product	yield (%)[b]
1	$(CH_2)_2OBn$		66
2	$(CH_2)_2CH(CH_3)_2$		79
3	Ph		70

[a] Reaction procedure: (i) alkyne (1 equiv), ^{n}BuLi (1.6 M in hexanes, 1.05 equiv), THF, −78 °C, (ii) chlorosilane (1.05 equiv), −78 °C to rt, work up, (iii) DIBAL (1 M in toluene, 5 equiv), Et_2O, 0 °C, (iv) aryl iodide (0.75 equiv), TBAF (2 equiv), $Pd(dba)_2$ (5 mol %), THF, rt. [b] Isolated yield of isomerically pure material (combined yield over four steps).

Scheme 1. Synthesis of Resveratrol Analogues



To display the utility of the newly developed methodology in a DOS context, all geometric isomers of trimethoxyreservatrol were synthesized from the same commercially available terminal alkyne and aryl halide (Scheme 1). Resveratrol and its analogues show a range of therapeutic activities including cardiovascular prevention, anti-inflammatory and anticancer properties.[17] Synthesis of the intermediate silanes proceeded smoothly via either hydrosilylation or nucleophilic substitution of the chlorosilane. On subjecting the intermediate silanes to fluoride-induced cross coupling (with prior reduction for the (*Z*)-isomer), excellent selectivity was achieved and the corresponding (*E*)-, α-, and (*Z*)-disubstituted alkenes were isolated in good yields.

In summary, a convienent and versatile method has been developed for the synthesis of (*E*)-, (*Z*)-, or α-disubsituted alkenes from terminal alkynes utilizing pentafluorophenyldimethylsilyl intermediates. The vinylsilane intermediates were formed with excellent regio- and stereoselectivity and under the appropriate conditions were transformed into the corresponding alkenes without loss of selectivity. Such chemistries thus provide an efficient means of achieving molecular diversification from common alkyne starting materials (through variation of the reagents employed); as such, these methods are expected to prove valuable in branching, reagent-based DOS pathways. These methods are currently being used in the preparation of structurally diverse small molecule collections. Furthermore, we anticipate that these new methodologies will prove valuable in a wider synthetic context, with potentially broad applications in the synthesis of natural products and pharmaceutical agents. In addition, this work contributes to the ongoing development of silicon cross coupling as a viable and practical alternative to existing strategies.

Acknowledgment. We are grateful to the EPSRC, BBSRC, and GlaxoSmithKline for their generous financial support.

Supporting Information Available: General experimental procedures, characterization of synthesized compounds, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100895D

(13) Aryl bromides cross couple in comparable yields.

(14) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865.
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