CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201200431

Palladium-Catalysed Cross-Coupling of Vinyldisiloxanes with Benzylic and Allylic Halides and Sulfonates

Elizabeth C. Frye,[a] Cornelius J. O'Connor,[a] David G. Twigg,[a] Bryony Elbert,[a] Luca Laraia,[a, c] David G. Hulcoop,[b] Ashok R. Venkitaraman,[c] and David R. Spring*[a]

Abstract: The Hiyama cross-coupling reaction is a powerful method for carbon–carbon bond formation. To date, the substrate scope of this reaction has predominantly been limited to sp^2–sp^2 coupling reactions. Herein, the palladium-catalysed Hiyama type cross-coupling of vinyldisiloxanes with benzylic and allylic bromides, chlorides, tosylates and mesylates is reported. A wide variety of functional groups were tolerated, and the synthetic utility of the methodology was exemplified through the efficient total synthesis of the cytotoxic natural product bussealin A. In addition, the antiproliferative ability of bussealin A was evaluated in two cancer-cell lines.

Keywords: C–C coupling · cytotoxicity · cross-coupling · palladium · synthetic methods

Introduction

In 2010, Professors Richard Heck, Ei-chi Negishi and Akira Suzuki were awarded the Nobel Prize for chemistry, for their work developing palladium-catalysed cross-coupling reactions in organic synthesis. Carbon–carbon bond-forming reactions are widely used in both academia and industry for the synthesis of new medicines, agrochemicals and synthetic materials for the electronics industry.[1] Organotin (Stille),[2] organoboron (Suzuki–Miyaura),[3] organozinc (Negishi)[4] and Grignard reagents (Tamau–Kumada–Corriu)[5] are well-established organometallics employed in transition-metal cross-couplings. Because of their low toxicity, high chemical stability and ease of synthesis, organosilanes have emerged in recent years as an attractive alternative to the conventional reagents for cross-coupling reactions.[6] Some natural products, which have been synthesised by using Hiyama type coupling reactions, are shown in Figure 1.

Pioneering work by Hiyama and Hatanaka established the cross-coupling of organosilanes with aryl and vinyl halides through activation of the Si–C bond by using fluoride to facilitate transmetalation.[7] Subsequently, Denmark, Baird, and Regens developed base-activated silanolate cross-couplings, which precluded the requirement for fluoride activation.[8] To date, substrate scope has been predominantly limited to sp^2–sp^2 cross-couplings[8] and a paucity of examples of cross-couplings of organosilanes with sp^3 halides (or equivalents thereof).[9] The first example was reported by Hiyama and co-workers in 1991, who effected the cross-coupling of fluoride activated allyltrifluorosilanes with cinnamyl acetate in the presence of a palladium catalyst.[9a] The reaction was performed in a sealed tube at elevated temperature and provided the product in 54% yield.

Later, Fu and co-workers reported the cross-coupling of fluoride activated aromatic alkoxysilanes with alkyl bromides and iodides.[9b] The choice of palladium catalyst and

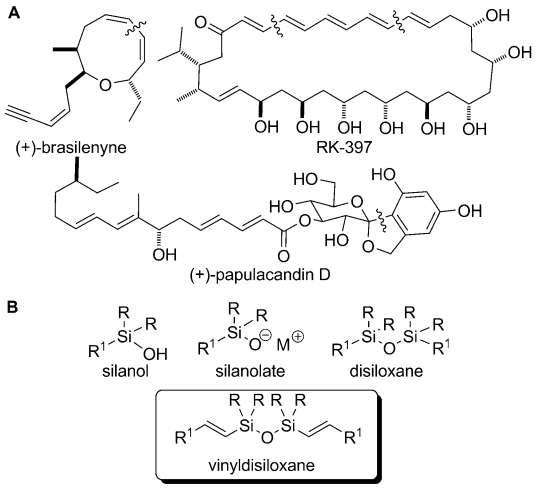


Figure 1. a) Natural products synthesised by using Hiyama type couplings;[11] b) examples of different siloxane functionality used in cross-coupling reactions.

[a] E. C. Frye, Dr. C. J. O'Connor, D. G. Twigg, B. Elbert, L. Laraia, Dr. D. R. Spring
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
Fax: (+44)-1223-336362
E-mail: spring@ch.cam.ac.uk

[b] Dr. D. G. Hulcoop
GlaxoSmithKline
Gunnelswood Road, Stevenage (UK)

[c] L. Laraia, Prof. A. R. Venkitaraman
MRC Hutchison/Cancer Cell Unit
Addenbrookes Hospital, Hills Road, Cambridge (UK)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200431.

phosphine ligand had a dramatic effect on the reaction yield with palladium dibromide and bis-*tert*-butylmethyl phosphine proving optimal to effect the transformation. In 2007, the Fu laboratory disclosed the cross-coupling of fluorinated aromatic silanes with activated and unactivated secondary alkyl halides by using a nickel–norephedrine catalytic system.[9c] In addition, Fu and colleagues later described a very elegant asymmetric cross-coupling of alkoxysilanes with racemic α-bromo esters, using a chiral nickel–diamine catalytic complex.[10] To expand the scope of existing cross-coupling methodology to incorporate a wider variety of sp^3 substrates, we sought to develop a protocol for the efficient, regio- and stereoselective Hiyama type cross-coupling of vinyldisiloxanes with benzylic and allylic alkyl halides.

An on-going area of interest within our research group is the use of disiloxanes as masked silanols in cross-coupling reactions.[12] Disiloxanes have been shown to exist in equilibrium with silanolate species when activated, and we have harnessed this phenomenon for the development of both fluoride-activated and fluoride-free cross-coupling reactions between a variety of aromatic- and vinyldisiloxanes with aryl and heteroaryl halides.[12] In a detailed mechanistic study of the fluoride-activated reaction between silanols or their masked equivalents with aromatic halides, Denmark demonstrated that regardless of the organosilicon starting material, the species that participates in the transmetalation step is thought to be a fluoride-activated disiloxane.[13] Unlike silanols and silanolates, disiloxanes display enhanced stability, present good levels of functional-group tolerance and, therefore, offer significant advantages over other organosilane coupling agents in the context of multistep synthesis.[12a,14]

Results and Discussion

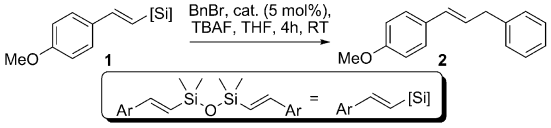
Our study began with the reaction between vinyldisiloxane **1** (which can be easily synthesized through the hydosilylation of *para*-ethynylanisole)[12a] and benzyl bromide in the presence of a range of palladium catalysts (Table 1) and a source of fluoride to activate the disiloxane species. A wide variety of palladium catalysts proved effective at catalysing the reaction to some degree with $[Pd_2(dba)_3]$ and $[allylPdCl]_2$ (APC) proving optimal (Table 1, entries 6 and 8). The activation of the disiloxane species was accomplished by using Lewis base catalysis. Several bases were investigated including KO*t*Bu in *t*BuOH, but tetrabutylammonium fluoride (TBAF) proved most effective. Highest yields were obtained when 3.0 equivalents of TBAF were used.

The effect of temperature on the reaction was also studied. No appreciable difference was observed in yield when the reaction was performed at 0 °C or at room temperature, but significantly lower temperatures did result in a decrease in yield. The optimum concentration for the reaction was determined to be 0.5 M.

By using our optimized reaction conditions (TBAF, 3.0 equiv; APC, 5 mol%, 0.5 M; 4 h; RT), the desired compound **2** was formed in 83% yield as a single isomer (Table 1, entry 8). The reactions were performed by using 1.0 equivalent of vinyldisiloxane and 1.5 equivalents of halide. Since both vinyl groups in a single disiloxane molecule are transferred, this corresponds so a slight excess of disiloxane, which ensures the reaction goes to completion. Next, we focused on determining whether other benzylic halides and indeed halide equivalents could be effectively cross-coupled by using the same conditions. Fortunately, in addition to bromide substrates, benzylic chlorides, tosylates and mesylates underwent clean conversion to the corresponding product **2**, all in good yield (Table 2, entries 1–3).

To determine the scope of the reaction, vinyldisiloxane **1** was reacted with a number of commercially available benzylic halides (Table 2). Gratifyingly, the electronic nature of the halide substrate did not significantly affect the outcome of the reaction: electron rich (Table 2, entry 8), neutral (Table 2, entry 1) and deficient (Table 2, entry 6) benzylic halides underwent facile conversion to their corresponding products all in good yield. In general, yields were higher for *meta*- and *para*-substituted benzylic halides (Table 2, entries 7 and 8) than more sterically hindered *ortho*-substituted substrates (Table 2, entries 4 and 9). The reaction was also successfully carried out with heteroaromatic substrates (Table 2, entries 10 and 11), which demonstrated the potential applicability of this reaction for the synthesis of natural products or pharmaceuticals. Pleasingly, a wide variety of functional groups were tolerated. Entry 9 from Table 2 demonstrated the selectivity profile of the reaction, in which no cross-coupling was observed between the sp^2 halide and the disiloxane. In addition, the secondary halide, benzhydryl chloride, was effectively cross-coupled in excellent yield, although the more sterically demanding trityl chloride proved beyond the orbit of this methodology. Unfortunately, the methodology could not be extended to the cross-coupling of benzylic halides containing beta hydrogens, for example, 1-bromo-1-phenyl ethane.

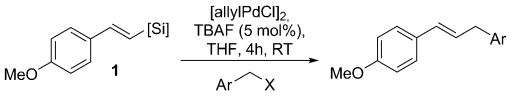
Table 1. Optimisation of cross-coupling reaction.

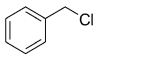
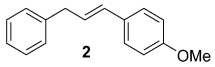
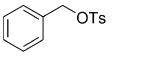
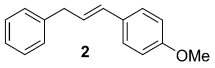
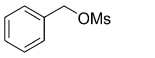
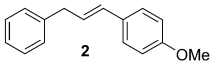
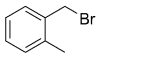
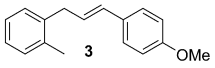
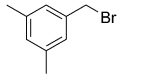
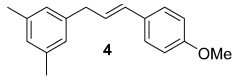
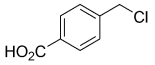
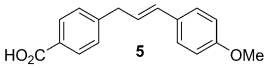
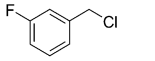
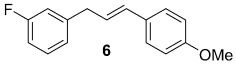
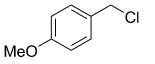
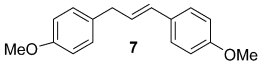
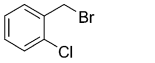
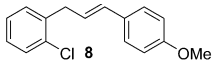
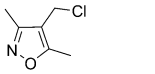
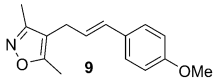
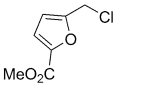
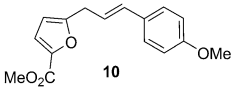
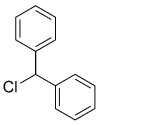
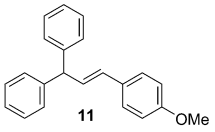
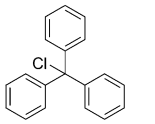
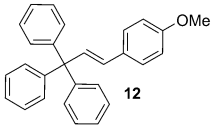


	Catalyst	TBAF [equiv]	Yield[a,b] [%]
1	$PdCl_2(MeCN)_2$	3.0	52
2	$Pd(PPh_3)_4$	3.0	15
3	$Pd(OAc)_2$	3.0	76
4	$PdCl_2$	3.0	19
5	$Pd(PPh_3)_2Cl_2$	3.0	19
6	$Pd_2(dba)_3$	3.0	82
7	$Pd(dba)_2$	3.0	77
8	$[allylPdCl]_2$	3.0	83
9	$[allylPdCl]_2$	1.0	68
10	$[allylPdCl]_2$	0.2	19

[a] Reactions were performed by using disiloxane (1.0 equiv) and alkyl halide (1.5 equiv). [b] Isolated yield after column chromatography.

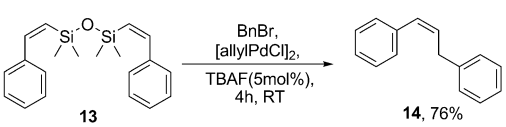
Table 2. Hiyama type cross-coupling of vinyldisiloxanes with benzylic halides and sulfonates.



	Ar X	Product	Yield[a] [%]
1			88
2			86
3			79
4			50
5			70
6			70
7			84
8			87
9			64
10			85
11			67
12			85
13			0

[a] Isolated yield after column chromatography.

Pleasingly the cross-coupling reaction could also be performed by using *Z*-vinyldisiloxanes (Scheme 1). However, a small degree of isomerization was observed; approximately 6% (relative ratio) of the *E*-benzylstyrene could be seen in the ^{1}H NMR spectrum of the crude reaction mixture. Fortunately, this unwanted side product could be removed by column chromatography, and the geometrically pure *Z*-benzylstyrene (**14**) was isolated in good yield (76%).



Scheme 1. Cross-coupling of *Z*-vinyldisiloxane with benzyl bromide.

The cross-coupling of more challenging allylic substrates was also investigated. The effective cross-coupling of allylic halides with vinyldisiloxanes would enable the formation of skipped dienes, an important motif present in a plethora of natural products (Figure 2). The presence of a hydrogen atom in the beta position should allow the possibility of β-hydride elimination upon oxidative addition of the halide; however, when a variety of allylic halides were subjected to the reaction conditions, none of the corresponding allenic products were observed. The scope of this methodology was investigated by cross-coupling a range of vinyldisiloxanes with an array of allyl halides (Table 3). In general, yields for the reaction were typically good-to-excellent, with only the amino-containing disiloxane (Table 3, entry 6) giving the desired diene in moderate yield, which could be attributed to a competing amino-substitution reaction.

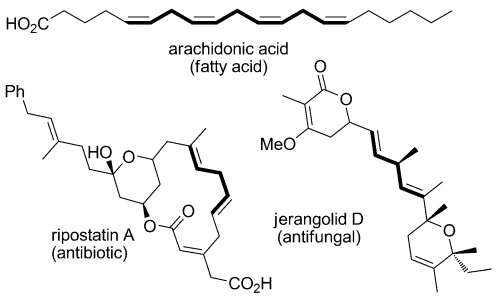
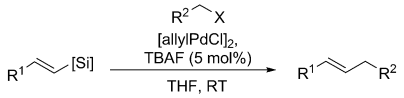


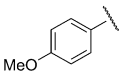
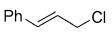
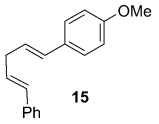
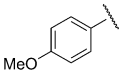
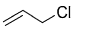
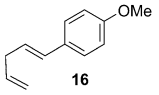
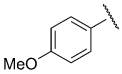
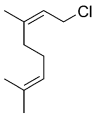
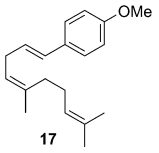
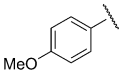
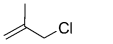
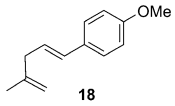
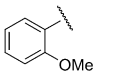
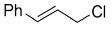
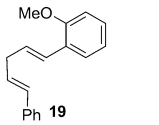
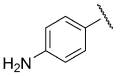
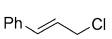
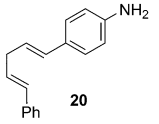
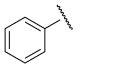
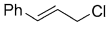
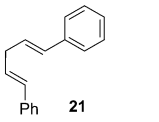
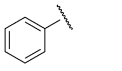
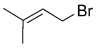
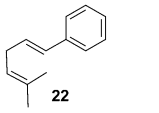
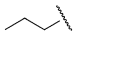
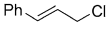
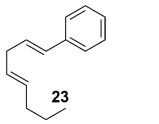
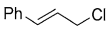
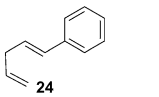
Figure 2. Three examples of natural-products-containing the "skipped diene" motif: a) arachidonic acid, a common fatty acid;[15a] b) ripostatin A, an antibiotic that targets eubacterial RNA polymerase;[15b] and c) jerangolid D, a potent antifungal agent.[15c]

The possibility of cross-coupling non-aromatic vinyldisiloxanes using this methodology was also investigated. Gratifyingly, both alkyl substituted and terminal vinyldisiloxanes were also tolerated as cross-coupling partners (Table 3, entries 9 and 10). All of the reported yields correspond to geometrically pure products. However, small quantities (<5%) of isomeric products could be observed, if prolonged reaction times were used.

A possible mechanism for the reaction is shown in Scheme 2. We suggest that the underlying mechanism follows the usual sequence of oxidative addition to a coordinatively unsaturated palladium complex **26**, followed by transmetalation with a fluoride-activated disiloxane species **27**[13] and subsequent reductive elimination to give the coupled product. Although a detailed mechanistic study is beyond the scope of this report, we tentatively propose that the similar reactivity displayed by bromides, chlorides, tosylates and mesylates in this reaction indicate that oxidative addition is rapid, and that either transmetalation or reductive elimination is the rate-determining step. In a detailed mechanistic study of the fluoride-activated cross-coupling of alkenylsila-

Table 3. Cross-coupling of vinyldisiloxanes with allylic halides.

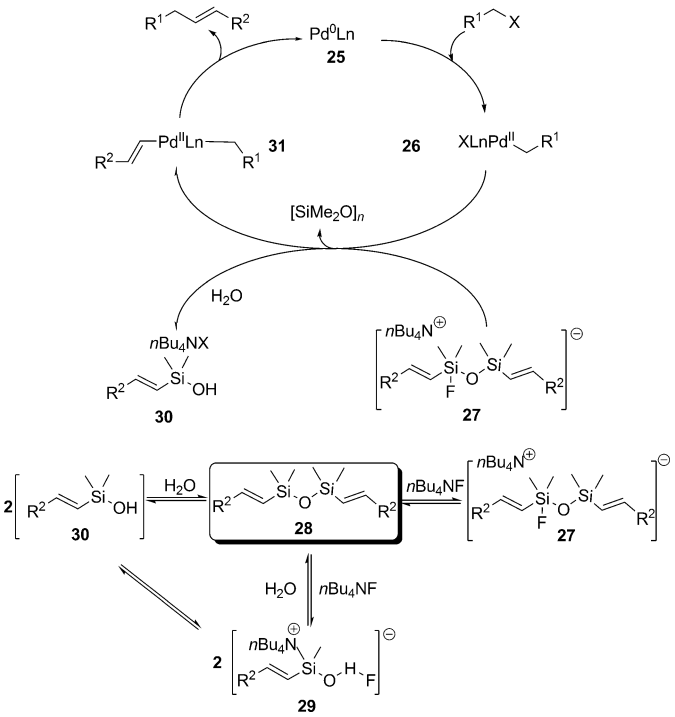


	R^1	R^2X	Product	Yield[a] [%]
1			 **15**	88
2			 **16**	64
3			 **17**	80
4			 **18**	72
5			 **19**	88
6			 **20**	35
7			 **21**	73
8			 **22**	53
9			 **23**	89
10	H		 **24**	90

[a] Isolated yield after column chromatography.

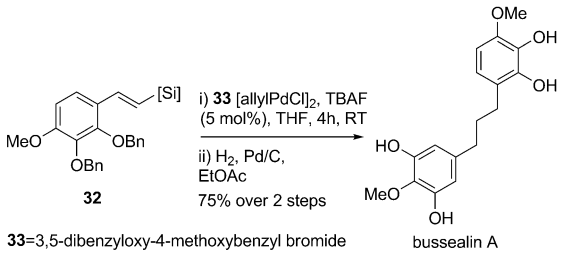
nols with aryl iodides, Denmark reported a correlation between the rate of the reaction and silanol concentration, which supported transmetalation as the turnover-limiting step in the transformation, as is the case in the cross-coupling of organostannanes. It is therefore possible that transmetalation is similarly turnover limiting in the cross-coupling of vinyldisiloxanes with benzylic and allylic halides and sulfonates.

This methodology represents a new approach for the synthesis of 1,3-diphenylpropene derivatives and offers significant advantages over alternative methods, which are often blighted by the formation of isomeric compounds. For example, separate reports by Chen et al.[16] and Fernández et al.,[17] both of which employed Friedel–Crafts methodology to synthesize this class of compound, document significant isomeric contamination (up to 20% in some cases). In addition, the mild reaction conditions and high functional-group tolerance represent a notable improvement over analogous Suzuki type methodology, which demand elevated temperatures (50–80°C)[18] and extended reaction times on occasion.[19]



Scheme 2. Possible mechanism for the Hiyama type cross-coupling of vinyl disiloxanes with benzylic and allylic halides and sulfonates.

To further demonstrate the potential utility of this methodology, we sought to synthesize the cytotoxic natural product bussealin A—an extract of the endemic Malagasy plant *Bussea sakalava*.[20] Therefore, we carried out the cross-coupling of disiloxane **32** with benzylic bromide **33** (Scheme 3). The cross-coupling reaction proceeded in good yield, and reduction of the resulting olefin gave the desired product quantitatively.



Scheme 3. Total synthesis of bussealin A.

Polyphenolic compounds are employed in a variety of diverse functional roles in biological systems, from providing resistance against bacterial[21] and viral[22] infections, to protecting against DNA-damaging solar radiation.[23] In addition, diphenylpropyl polyphenolic compounds and derivatives thereof have exhibited anti-inflammatory,[24] antifungal,[25] antivascular[26] and antiadipogenic activities.[27] We therefore sought to further characterize the biological activity of bussealin A by testing its ability to inhibit the proliferation of an osteosarcoma-cell line (U2OS) and an adenocarcinomic human alveolar basal epithelial cell line (A549) by using a sulforhodamine B (SRB) assay.[28] It was shown to inhibit the proliferation of both cell lines with moderate potency, with half maximal inhibitory concentration (IC_{50}) values of 17 μM (U2OS) and 52 μM (A549). Bussealin A has previously been shown to display antiproliferative activity against the human ovarian-cancer-cell line A2780 (IC_{50} = 36 μM).[20] Bussealin A was also screened for its ability to arrest U2OS cells in mitosis by using a high-content screening approach (HCA). By treating U2OS cells with compounds for 24 h and staining with a phosphohistone H3 antibody, cells arrested in mitosis can be detected. Although no significant increase in mitotic cells was observed, clear signs of cytotoxicity were observed despite the short timeframe (Figure 3).

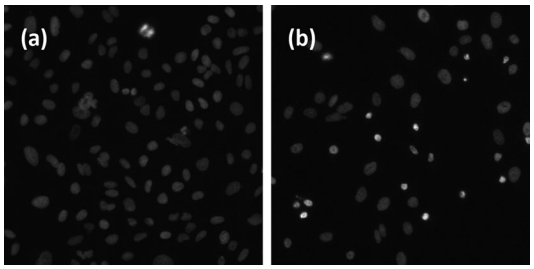


Figure 3. U2OS stained with DNA marker Hoechst: a) control, b) treated with 60 μM bussealin A.

Conclusion

To summarize, we have developed a new procedure for the effective cross-coupling of vinyldisiloxanes with benzylic and allylic halides and sulfonates. The reaction proceeds under mild conditions and tolerates a wide variety of functional groups. The procedures described herein offer a new, cost-effective, operationally simple and robust method for the preparation of a wide variety of 1,3-diphenylpropenes and skipped dienes under mild conditions. Currently, we are utilizing this approach for the synthesis of functionally diverse small molecules,[29] the anti-mitotic activity of which will be assessed by using HCA as part of our chemical genetic-screening program.[30]

Experimental Section

General experimental procedure for the Hiyama type cross-coupling of vinyldisiloxanes with alkyl halides: A solution of TBAF (3.0 equiv, 1.0 M in THF) was added to a mixture of disiloxane **1** (1.0 equiv, 120 mg, 0.30 mmol), benzyl bromide (1.5 equiv, 77 mg, 0.45 mmol) and $[allylPdCl]_2$ (5 mol%). The reaction mixture was stirred at RT for 4 h. The mixture was then filtered through a small layer of SiO_2, eluted with ethyl acetate, and the solvent was removed in vacuo. The crude material was purified by flash-column chromatography (petroleum ether/ethyl acetate 100:0 to 99:1) providing the desired product **2** as a colourless oil (84 mg, 0.37 mmol, 83%). R_f = 0.21 (SiO_2; petroleum ether/ethyl acetate 49:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (2H, d, J = 9.0 Hz, C-(OCH_3)CHC*H*), 7.33–7.28 (5H, m, Ar–CH), 6.84 (2H, d, J = 9.0 Hz, C-(OCH_3)C*H*), 6.41 (1H, d, J = 15.5 Hz, C*H*=$CHCH_2$), 6.22 (1H, dt, J = 15.5 Hz, 7.0 Hz, CH=C*H*CH_2), 3.80 (3H, s, OCH_3), 3.54 ppm (2H, d, J = 7.0 Hz, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8 (*C*(OCH_3)), 140.4 (Ar–C), 130.4 (*C*H=$CHCH_2$), 130.3 (Ar–C(OCH_3)CHC*H*C), 128.7 (Ar–CH), 128.5 (Ar–CH), 127.2 (Ar–CH), 127.1 (Ar–CH), 126.1 (CH=C*H*CH_3), 113.9 (C(OCH_3)*C*H), 55.3 (OCH_3), 39.3 ppm (CH_2); IR (neat): $\tilde{\nu}_{max}$ = 3027 (w, C–H), 2956 (w, C–H), 2907 (w, C–H), 2834 (w, C–H), 1606 (s, C=C), 1578 (w, C=C), 1509 (s, C=C), 1494 cm^{-1} (m, C=C). This data is consistent with that previously reported.[31] Experimental details and characterization data are provided in the Supporting Information.

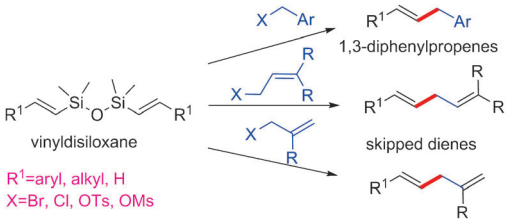
Acknowledgements

The authors thank GlaxoSmithKline and the EU, EPSRC, BBSRC, MRC, Cancer Research UK, Wellcome Trust and Frances and Augustus Newman Foundation for funding.

[1] J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710.
[2] a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; b) P. Espinet, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 4804–4839; *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734.
[3] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
[4] a) V. B. Phapale, D. J. Cardenas, *Chem. Soc. Rev.* **2009**, *38*, 1598–1607; b) E.-i. Negishi, M. Qian, F. Zeng, L. Anastasia, D. Babinski, *Org. Lett.* **2003**, *5*, 1597–1600; c) J. A. Casares, P. Espinet, B. Fuentes, G. Salas, *J. Am. Chem. Soc.* **2007**, *129*, 3508–3509.
[5] a) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144; b) T. Kohei, *J. Organomet. Chem.* **2002**, *653*, 23–26; c) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.
[6] a) S. E. Denmark, *J. Org. Chem.* **2009**, *74*, 2915–2927; b) H. F. Sore, W. R. J. D. Galloway, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 1845–1866; c) Y. Nakao, T. Hiyama, *Chem. Soc. Rev.* **2011**, *40*, 4893–4901.
[7] a) Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918–920; b) Y. Hatanaka, T. Hiyama, *Synlett* **1991**, *12*, 845–853.
[8] a) S. E. Denmark, J. D. Baird, *Chem. Eur. J.* **2006**, *12*, 4954–4963; b) S. E. Denmark, C. S. Regens, *Acc. Chem. Res.* **2008**, *41*, 1486–1499.
[9] a) Y. Hatanaka, Y. Ebina, T. Hiyama, *J. Am. Chem. Soc.* **1991**, *113*, 7075–7076; b) J.-Y. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 5616–5617; c) N. A. Strotman, S. Sommer, G. C. Fu, *Angew. Chem.* **2007**, *119*, 3626–3628; *Angew. Chem. Int. Ed.* **2007**, *46*, 3556–3558.
[10] X. Dai, N. A. Strotman, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303.
[11] a) S. E. Denmark, S.-M. Yang, *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440; b) S. E. Denmark, S.-M. Yang, *J. Am. Chem. Soc.* **2002**, *124*, 15196–15197; c) S. E. Denmark, S. Fujimori, *J. Am. Chem. Soc.* **2005**, *127*, 8971–8973; d) S. E. Denmark, C. S. Regens, T. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2774–2776; e) S. E. Denmark, J. H. C.

Liu, *Angew. Chem.* **2010**, *122*, 3040–3049; *Angew. Chem. Int. Ed.* **2010**, *49*, 2978–2986.
[12] a) H. F. Sore, C. M. Boehner, S. J. F. MacDonald, D. Norton, D. J. Fox, D. R. Spring, *Org. Biomol. Chem.* **2009**, *7*, 1068–1072; b) C. M. Boehner, E. C. Frye, K. M. G. O'Connell, W. R. J. D. Galloway, H. F. Sore, P. G. Dominguez, D. Norton, D. G. Hulcoop, M. Owen, G. Turner, C. Crawford, H. Horsley, D. R. Spring, *Chem. Eur. J.* **2011**, *17*, 13230–13239; c) H. F. Sore, D. T. Blackwell, S. J. F. MacDonald, D. R. Spring, *Org. Lett.* **2010**, *12*, 2806–2809; d) H. F. Sore, C. M. Boehner, L. Laraia, P. Logoteta, C. Prestinari, M. Scott, K. Williams, W. R. J. D. Galloway, D. R. Spring, *Org. Biomol. Chem.* **2011**, *9*, 504–515.
[13] S. E. Denmark, R. F. Sweis, D. Wehrli, *J. Am. Chem. Soc.* **2004**, *126*, 4865–4875.
[14] a) S. E. Denmark, C. R. Butler, *J. Am. Chem. Soc.* **2008**, *130*, 3690–3704; b) W. Prukała, *Synlett* **2008**, 3026–3030.
[15] a) A. I. Rachlin, N. Wasyliw, M. W. Goldberg, *J. Org. Chem.* **1961**, *26*, 2688–2693; b) H. Irschik, H. Augustiniak, K. Gerth, G. Hofle, H. Reichenbach, *J. Antibiot.* **1995**, *48*, 787–792; c) J. Pospíšil, I. E. Markó, *J. Am. Chem. Soc.* **2007**, *129*, 3516–3517.
[16] G.-Q. Chen, Z.-J. Xu, S. L.-F. Chan, C.-Y. Zhou, C.-M. Che, *Synlett* **2011**, 2713–2718.
[17] I. Fernández, R. Hermatschweiler, F. Breher, P. S. Pregosin, L. F. Veiros, M. J. Calhorda, *Angew. Chem.* **2006**, *118*, 6535–6540; *Angew. Chem. Int. Ed.* **2006**, *45*, 6386–6391.
[18] a) S. M. Sarkar, Y. Uozumi, Y. M. A. Yamada, *Angew. Chem. Int. Ed.* **2011**, *50*, 9437–9441; b) H. Tsukamoto, T. Uchiyama, T. Suzuki, Y. Kondo, *Org. Biomol. Chem.* **2008**, *6*, 3005–3013.
[19] a) O. Giorgio, *Tetrahedron Lett.* **2003**, *44*, 4311–4314; b) R. Kuwano, M. Yokogi, *Org. Lett.* **2005**, *7*, 945–947.
[20] E. Pan, L. Harinantenaina, P. J. Brodie, J. S. Miller, M. W. Callmander, S. Rakotonandrasana, E. Rakotobe, V. E. Rasamison, D. G. I. Kingston, *J. Nat. Prod.* **2010**, *73*, 1792–1795.
[21] K. Funatogawa, S. Hayashi, H. Shimomura, T. Yoshida, T. Hatano, H. Ito, Y. Hirai, *Microbiol. Immunol.* **2004**, *48*, 251–261.
[22] N. Vilhelmova, R. Jacquet, S. Quideau, A. Stoyanova, A. S. Galabov, *Antiviral Res.* **2011**, *89*, 174–181.
[23] S. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, *Angew. Chem.* **2011**, *123*, 610–646; *Angew. Chem. Int. Ed.* **2011**, *50*, 586–621.
[24] C.-R. Su, Y.-C. Shen, P.-C. Kuo, Y.-L. Leu, A. G. Damu, Y.-H. Wang, T.-S. Wu, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6155–6160.
[25] N. P. Lopes, M. J. Kato, M. Yoshida, *Phytochemistry* **1999**, *51*, 29–33.
[26] S. Ducki, D. Rennison, M. Woo, A. Kendall, J. F. D. Chabert, A. T. McGown, N. J. Lawrence, *Bioorg. Med. Chem.* **2009**, *17*, 7698–7710.
[27] U. J. Youn, Y. S. Lee, H. Jeong, J. Lee, J.-W. Nam, Y. J. Lee, E. S. Hwang, J.-H. Lee, D. Lee, S. S. Kang, E.-K. Seo, *J. Nat. Prod.* **2009**, *72*, 1895–1898.
[28] V. Vichai, K. Kirtikara, *Nat. Protoc.* **2006**, *1*, 1112–1116.
[29] a) D. R. Spring, *Org. Biomol. Chem.* **2003**, *1*, 3867–3870; b) W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Chem. Commun.* **2009**, 2446–2462; c) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 80; d) C. J. O'Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc Rev.* **2012**, *41*, 4444–4456.
[30] a) C. J. O'Connor, L. Laraia, D. R. Spring, *Chem. Soc. Rev.* **2011**, *40*, 4332–4345; b) S. Zheng, L. Laraia, C. J. O'Connor, D. Sorrell, Y. S. Tan, Z. Xu, A. R. Venkitaraman, W. Wu, D. R. Spring, *Org. Biomol. Chem.* **2012**, *10*, 2590–2593.
[31] Y. Shen, J. Yao, *J. Org. Chem.* **1996**, *61*, 8659–8661.

Received: February 9, 2012
Published online: ■■ ▮▮, 0000



The Hiyama type cross-coupling of aryl and alkyl vinyldisiloxanes with activated alkyl halides and pseudohalides is reported. This methodology is an important expansion of current methods for Csp^2–Csp^3 bond formation (see scheme). The synthetic utility of the methodology is exemplified in the total synthesis of the natural product bussealin A. In addition, the antiproliferative ability of bussealin A was evaluated in two cancer-cell lines.

Cross-Coupling

*E. C. Frye, C. J. O'Connor, D. G. Twigg, B. Elbert, L. Laraia, D. G. Hulcoop, A. R. Venkitaraman, D. R. Spring** ..... ▮▮▮▮–▮▮▮▮

Palladium-Catalysed Cross-Coupling of Vinyldisiloxanes with Benzylic and Allylic Halides and Sulfonates