Synthetic Methods

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Copper(II)-Catalyzed Silylation of Activated Alkynes in Water: Diastereodivergent Access to *E*- or *Z*-β-Silyl-α,β-Unsaturated Carbonyl and Carboxyl Compounds**

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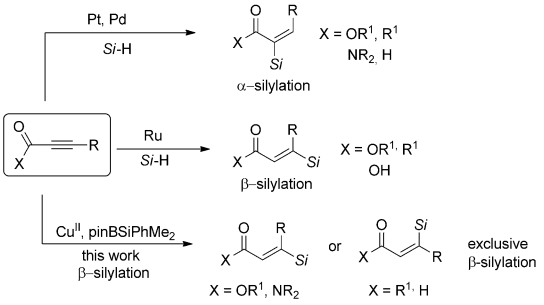
Abstract: *Copper(II)-catalyzed silylation of substituted alkynylcarbonyl compounds was investigated. Through the activation of $Me_2PhSiBpin$ in water at room temperature and open atmosphere, vinylsilanes conjugated to carbonyl groups are synthesized in high yield. A surprising diastereodivergent access to olefin geometry was discovered using a silyl conjugate addition strategy: aldehydes and ketones were Z selective while esters and amides were exclusively transformed into the E products.*

Vinylsilanes are versatile building blocks in organic synthesis because of their utility in diverse types of chemical transformations such as C–C bond formation in the Hiyama coupling, oxidation to a carbonyl with the Tamao–Fleming reaction, and alkene formation by protodesilylation.[1] Owing to their stability, low toxicity, and affordability, methods for the preparation of organosilicon compounds have received increased attention.[2] Transition-metal-catalyzed regioselective hydrosilylation of alkynes provides the most straighforward and atom economical access to vinylsilanes.[3] Synthesis of substituted vinylsilanes conjugated to carbonyl groups is challenging because of the difficulty in controlling the regio- (α versus β) and stereoselectivity (*E* versus *Z*) of products (Scheme 1).[4] Platinum-[5] and palladium-catalyzed[6] hydrosilylation of alkynyl carbonyl compounds affording vinylsilanes with excellent regioselectivity, where the silicon group is transfered to the α position of the carbonyl, have been developed.[7] In contrast, ruthenium-catalyzed hydrosilylation methods generate the complementary β-silyl-α,β-unsaturated carbonyl products with excellent *Z* selectivity.[8] Most recently, Molander and co-workers reported a copper(I)-catalyzed conjugate silylation method using disilane reagents to yield β-silyl-α,β-unsaturated esters in varying yields and modest *E*/*Z* selectivity.[9] Hence, there is a paucity of methods capable of providing products with the necessary regioselectivity towards β silylation and selectivity with regards to olefin geometry. Furthermore, to the best of our knowledge, there are no examples of amides or aldehydes which have been employed as substrates in these reactions.



Scheme 1. Strategies toward carbonyl conjugated vinylsilanes.

Given that a mild method with broad substrate scope, functional-group tolerance, and high stereoselectivity is currently lacking, and our interest in copper-catalyzed boryl[10] and silyl[11] conjugate addition,[12] we sought to develop a process to address these shortcomings. In particular, we employ commercially available $Me_2PhSiBpin$[13] as the silicon source, which was recently used by Loh and co-workers in the synthesis of linear and branched vinylsilanes.[14] Herein, we report a copper(II)-catalyzed conjugate addition of substituted alkynyl carbonyls to generate the corresponding β-silylated products. Surprisingly, the method furnishes a substrate-controlled diastereodivergent access to stereoisomeric products: aldehydes selectively afford *Z* olefins whereas esters and amides exclusively generate the *E*-alkene geometry. The protocol offers several practical advantages. Firstly, it utilizes a catalytic amount of redox-stable and inexpensive transition metal, a copper(II) source, which is resistant to oxidation. Copper(I) sources require special handling which includes either Schlenk techniques or use of a glovebox. Secondly, the reaction is insensitive to moisture and provides a green chemistry process which utilizes water as the solvent. Finally, the method is mild and proceeds when open to the atmosphere at room temperature within 2–4 h.

We initiated our investigations by examining the appropriate base additive which can activate a B–Si bond (Table 1). We previously demonstrated that 4-picoline was sufficiently effective in acting as a Brønsted base to activate a nucleophilic water molecule towards $Me_2PhSiBpin$ and chemoselectively transfer silicon to α,β-unsaturated carbonyl compounds in the presence of catalytic amounts of copper(II).[11] An important aspect of our studies is the generation of a water-stable, nucleophilic Cu–Si intermediate to initiate silyl transfer to the β-carbon atom. A screen of bases confirmed that most organic and inorganic bases efficiently catalyzed the conversion of 2-octyn-1-al (**1b**) into (*E*)- and (*Z*)-**2b** within 2 hours

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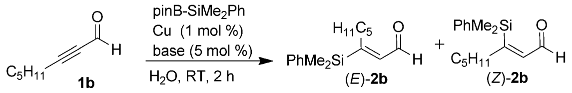
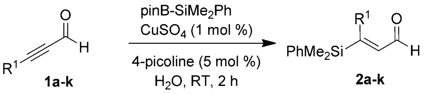
Table 1: Screening of base additives and copper source.[a]

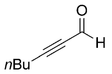
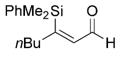
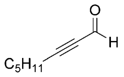
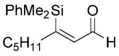
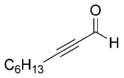
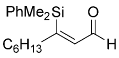
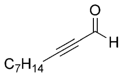
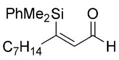
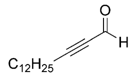
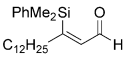
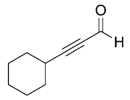
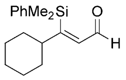
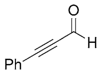
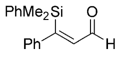
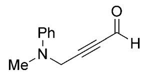
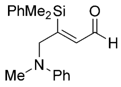
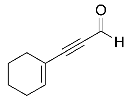
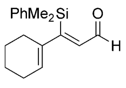
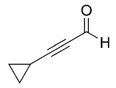
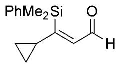


Entry	Base	Copper source	Conv. [%][b]	*E*/*Z*[c]
1	4-picoline	$CuSO_4$	97	9:91
2	pyridine	$CuSO_4$	98	9:91
3	DBU	$CuSO_4$	> 99	22:78
4	TEA	$CuSO_4$	97	30:70
5	NaO*t*Bu	$CuSO_4$	> 99	22:78
6	NaOH	$CuSO_4$	> 99	26:74
7	KOAc	$CuSO_4$	69	25:75
8	none	$CuSO_4$	trace	–
9	4-picoline	none	n.r.	–
10	4-picoline	$Cu(OAc)_2$	> 99	11:89
11	4-picoline	$Cu(BF_4)_2$	> 99	10:90
12	4-picoline	$CuCl_2$	> 99	10:90

[a] General procedure: Base (5 mol%), 2-octyn-1-al (1 equiv), $Me_2PhSiBpin$ (1.5 equiv), and 1 mL of 0.325 mg mL^{-1} $CuSO_4$ solution were mixed at RT for 2 h. [b] Conversion values determined by ^1H NMR analysis of the crude reaction mixture. [c] Determined by ^1H NMR analysis of the crude reaction mixture. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, n.r. = no reaction.

Table 2: Silyl conjugate addition to substituted acetylenic aldehydes.[a]



Entry	Substrate	Product		Yield[b] [%]	*E*/*Z*[c]
1			**2a**	74[d]	11:89
2			**2b**	97	5:95
3			**2c**	93	10:90
4			**2d**	95	11:89
5			**2e**	98	9:91
6			**2f**	86	12:88
7			**2g**	51[e]	19:81
8			**2h**	60	2:98
9			**2i**	84	14:86
10			**2j**	90	8:92

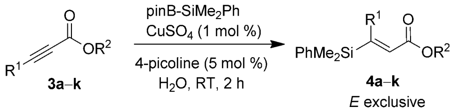
[a] General procedure: 4-picoline (5 mol%), substrate (1.0 equiv), $Me_2PhSiBpin$ (1.5 equiv), and 1 mL of 1.30 mg mL^{-1} $CuSO_4$ solution are mixed at RT for 2 h. Each reaction is an average of at least two experiments. [b] Yield of isolated product. [c] Ratio determined by ^1H NMR analysis and assignment by nOe experiments; see the Supporting Information for details. [d] 1.1 equiv of $Me_2PhSiBpin$ was used. [e] Competing 1,2-addition product was observed. Ratio of 1,4-versus 1,2-addition product was 2:1.

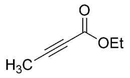
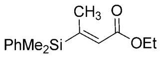
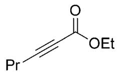
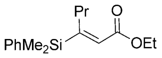
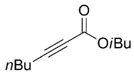
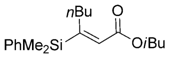
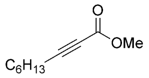
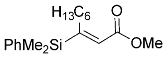
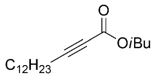
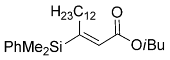
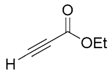
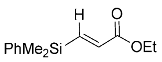
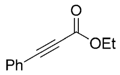
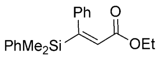
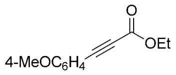
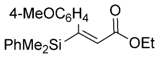
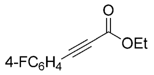
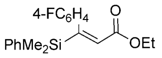
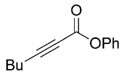
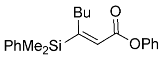
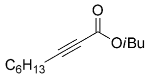
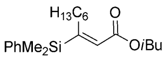
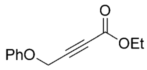
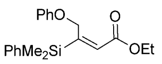
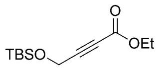
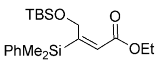
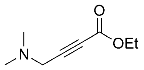
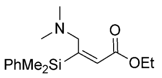
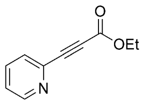
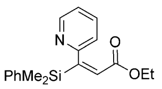
(entries 1–7). However, 4-picoline and pyridine preferentially afforded **2b** in greater than 97% conversion with 9:91 *E*/*Z* ratio. Surprisingly, the *Z* geometry of the double bond observed is contrary to that of a copper(I)-catalyzed addition to acetylenic esters recently reported by Iannazzo and Molander.[15] The double-bond geometry was unambiguously assigned by nuclear Overhauser effect (nOe) experiments (see the Supporting Information for details). In addition, exclusive formation of the β-silylated product was observed. Control experiments suggest both amine and copper were required for this reaction to proceed (entries 8–9). Finally, investigations on copper reagents indicate a number of copper(II) sources efficiently afford (*Z*)-**2b** in excellent conversion and selectivity (entries 10–12).

With optimized reaction conditions established, we investigated the scope of the silyl conjugate addition reaction with aldehydes (Table 2). Use of 1.1 equivalents of $Me_2PhSiBpin$ afforded the product **2a** in 74% yield with 11:89 *E*/*Z* selectivity (entry 1). As the aldehyde starting material was not fully consumed in the reaction, the equivalency of $Me_2PhSiBpin$ was increased to 1.5 in subsequent reactions. Thus, alkynyl aldehydes with alkyl substituents, ranging from a short pentyl to a much longer dodecyl chain, on the β-carbon atom were efficiently transformed into the corresponding vinyl silanes (**2b–e**) in excellent yield (up to 98%) and in up to 5:95 *E*/*Z* selectivity (entries 2–5). A more sterically encumbered cyclohexyl group was also an efficient substrate (entry 6), but a phenyl substituent suffered from a competing 1,2-addition to afford **2g** in 51% yield (entry 7).[16] To explore functional-group tolerance of the reaction conditions, the propargyl amine **1h** was converted into the desired product in almost complete *Z* selectivity (entry 8). Additionally, the α,β,γ,δ-unsaturated ynal **1i** specifically reacted on the β-carbon atom to afford **2i** in 84% yield despite possible competing δ- and 1,2-addition (entry 9). Finally, cyclopropylacrylaldehyde efficiently underwent the reaction in excellent yield and selectivity, thus affording the β-silylated product **2j** (entry 10).

With an efficient method for accessing *Z* silylenals developed, we directed our efforts towards investigating the reaction outcome with esters (Table 3). Treatment of the butynoate ethylester **3a** with 1.1 equivalents of $Me_2PhSiBpin$, catalytic amounts of copper sulfate, and 4-picoline in water at room temperature and open to the atmosphere, provided the desired vinylsilane **4a** in 95% yield (entry 1). To our delight, a single isomer was exclusively formed and nOe studies (see the Supporting Information for details) unambiguously assigned the alkene geometry as *E*, which is in sharp contrast to the stereochemistry described for aldehydes. To determine whether the switch in olefin geometry in the product was general, substrates with varying substituents on the ester and alkyne functionalities were investigated. Substrates with increasingly larger alkyl substituents on the β-carbon atom generated the corresponding products in excellent yields with exclusive *E* selectivity (entries 2–5). Indeed, a hydrophobic dodecyl chain on the β-carbon atom efficiently afforded the vinyl silane (*E*)-**4e** in 96% yield. Even though hydrogen on the β-carbon atom in ethyl propiolate generated **4f** in a slightly lower yield (entry 6), aryl substituents were also effective substrates. For example, a phenyl group resulted in 98% yield and 100% *E* selectivity (entry 7). Both electron-donating and electron-withdrawing groups on the aryl ring were tolerated and afforded the desired products in excellent yields and selectivity (entries 8 and 9). The nature of the ester functionality has negligible impact on the reaction yield (compare entries 3 and 4 versus entries 10 and 11). Methyl, ethyl, isobutyl, and phenyl esters underwent the silylation reaction efficiently. Furthermore, no evidence of ester hydrolysis was observed even with phenyl ester (entry 10). To investigate the functional-group tolerance of the protocol, substrates bearing heteroatoms were subjected to the reaction conditions. For example, a propargyl ether with phenyl or silicon protecting groups (TBS) were tolerated and efficiently converted into the corresponding products **4l** and **4m** in 87 and 89% yield, respectively (entries 12 and 13). Interestingly, coordinating groups were also good substrates and did not affect the regio- and stereochemistry of the reaction. Tertiary amine and pyridine moieties exclusively gave *E* products in moderate to good yields (entries 14 and 15).

Table 3: Silyl conjugate addition to substituted acetylenic esters.[a]

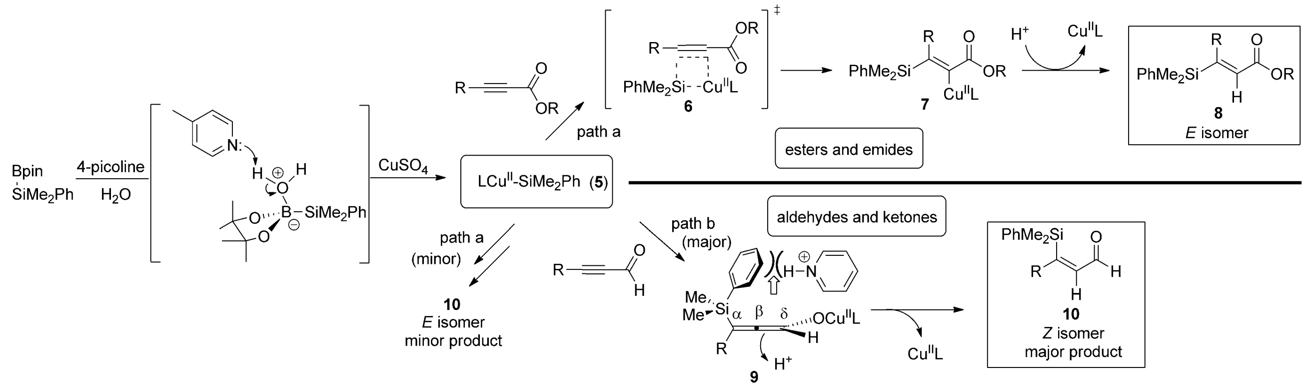


Entry	Substrate	Product		Yield[b] [%]
1			**4a**	95
2			**4b**	83
3			**4c**	92
4			**4d**	93
5			**4e**	96
6			**4f**	57
7			**4g**	98
8			**4h**	89
9			**4i**	99
10			**4j**	94
11			**4k**	95
12			**4l**	87
13			**4m**	89
14			**4n**	50
15			**4o**	74[c,d]

[a] General procedure: 4-picoline (5 mol%), substrate (1.0 equiv), Me$_2$PhSiBpin (1.1 equiv), and 1 mL of 1.30 mg mL^{-1} CuSO$_4$ solution are mixed at RT for 2 h. Each reaction is an average of at least two experiments. [b] Yield of isolated product. [c] Reaction run for 5 h. [d] Yield as determined by NMR spectroscopy; product and starting material were chromatographically inseparable. TBS = *tert*-butyldimethylsilyl.

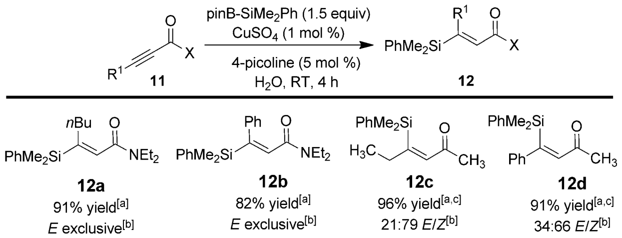
We were intrigued by the change in the stereochemical outcome of the reaction based on the identity of the carbonyl. A key difference between these substrates is the nature of the electron-withdrawing ability of the carbonyl groups. A proposed mechanism and origin of stereoselectivity observed is shown in Scheme 2. A nucleophilic silylcopper species (**5**) is generated by water-mediated activation of the Si–B bond and subsequent transmetalation.[10d,11] In the case of α,β-acetylenic esters, silylcupration across the triple bond (**6**) occurs in a *syn* fashion to afford the intermediate **7** (path a). Protonation affords the (*E*)-β-silyl-α,β-unsaturated ester **8** as well as turns over the copper(II) catalyst. In this particular case, a formal 1,4-conjugate addition is disfavored because of electron donation to the carbonyl group from the ester moiety. In contrast, when more-electron-deficient aldehydes are used, addition of **6** may proceed through two possible pathways: 1) a *syn* addition in a similar path to that observed with esters (path a), thus generating the *E* isomer as a minor product, and 2) a competing 1,4-conjugate addition (path b) which leads to the allenolate intermediate copper(II) complex **9**. Because the substituents on the α- and δ-positions of **9** are orthogonal, protonation occurs on the site opposite the sterically encumbered dimethylphenylsilyl group to provide the *Z* isomer **10** as the major product. A similar mechanism has been proposed with trimethylgermyl copper addition to alkynyl esters, that is, protonation occurs from the side opposite a bulky trimethylgermanium group.[17]

To test this hypothesis, carbonyl groups with better electron-donating substituents, such α,β-alkynyl amides,



Scheme 2. Proposed mechanism and origin of diastereoselectivity.

were subjected to the reaction conditions. To our delight, amides bearing either a butyl (**11a**) or phenyl (**11b**) moiety on the alkyne provided the products **12a,b** in excellent yields with exclusive *E* configuration (Scheme 3). As predicted, substrates with intermediate carbonyl electrophilicity (i.e., between aldehydes and esters), such as the α,β-unsaturated ketones **11c,d**, afforded a mixture of isomers but with a slight perference for the *Z* alkene (**12c,d**).



Scheme 3. Silyl conjugate addition to amides and ketones. [a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Reaction was performed with 1.1 equiv $Me_2PhSiBpin$ for 2 h.

In summary, we have reported the first example of a copper(II)-catalyzed hydrosilylation of α,β-alkynyl carbonyl compounds. The mild method is a convenient and operationally simple protocol which affords β-silyl-α,β-unsaturated carbonyl compounds with excellent substrate control of diastereoselectivity. Notably, aldehydes and ketones are selectively converted into *Z*-isomeric products while esters and amides generate the complementary *E* isomers. The developed reaction offers environmentally friendly reaction conditions which utilize water as the solvent and catalytic amounts of metal. The present method provides access to otherwise difficult intermediates, and hence, is of synthetic value. Further investigation towards extension of the method with more complex systems is underway.

Experimental Section

General procedure: In a 1 dram vial, α,β-acetylenic carbonyl (1.0 equiv), 4-picoline (0.05 equiv), $Me_2PhSiBpin$ (1.1 or 1.5 equiv), and 1 mL of 1.3 mg mL^{-1} $CuSO_4$ stock solution (0.01 equiv) were vigorously stirred together. The reaction was quenched with 1 mL of hexanes as followed by TLC. The aqueous layer was extracted 3 × with hexanes. The combined hexanes layer was back extracted 5 × with water and then dried over sodium sulfate. Silica gel chromatography was used to purify the product.

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[1] a) M. A. Brook, *Silicon in Organic*, *Organometallic*, *and Polymer Chemistry*, Wiley, New York, **2000**; b) W. T. Chang, R. C. Smith, C. S. Regens, A. D. Bailey, N. S. Werner, S. E. Denmark, *Cross-Coupling with Organosilicon Compounds*, Wiley, Hoboken, **2011**.

[2] D. S. W. Lim, E. A. Anderson, *Synthesis* **2012**, *44*, 983 – 1010.

[3] For recent reviews, see: a) B. M. Trost, Z. T. Ball, *Synthesis* **2005**, 853 – 887; b) B. Marciniec, H. Maciejewski, C. Pietraszuk, P. Pawluc, *Hydrosilylation: A Comprehensive Review on Recent Advances*, *Vol. 1* (Ed.: B. Marciniec), Springer, Berlin, **2009**, pp. 53 – 158.

[4] a) B. H. Lipshutz, N. Tanaka, B. R. Taft, C.-T. Lee, *Org. Lett.* **2006**, *8*, 1963 – 1966; b) T. Fujiwara, K. Sawabe, T. Takeda, *Tetrahedron* **1997**, *53*, 8349 – 8370; c) I. Ojima, E. Vidal, M. Tzamarioudaki, I. Matsuda, *J. Am. Chem. Soc.* **1995**, *117*, 6797 – 6798; d) I. Ojima, R. J. Donovan, M. Eguchi, W. R. Shay, P. Ingallina, A. Korda, Q. Zeng, *Tetrahedron* **1993**, *49*, 5431 – 5444; e) L. A. Aronica, S. Terreni, A. M. Caporusso, P. Salvadori, *Eur. J. Org. Chem.* **2001**, 4321 – 4329; f) P. Pawluć, *Catal. Commun.* **2012**, *23*, 10 – 13; g) A. Barbero, P. Cuadrado, I. Fleming, A. M. Gonzalez, F. J. Pulido, A. Sanchez, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1525 – 1532; h) I. Fleming, T. W. Newton, V. Sabin, F. Zammattio, *Tetrahedron* **1992**, *48*, 7793 – 7802; i) I. Fleming, E. Marangon, C. Roni, M. G. Russell, S. T. Chamudis, *Can. J. Chem.* **2004**, *82*, 325 – 332; j) I. Fleming, E. Marangon, C. Roni, M. G. Russell, S. T. Chamudis, *Chem. Commun.* **2003**, 200 – 201; k) T. Harada, S. Imanaka, Y. Ohyama, Y. Matsuda, A. Oku, *Tetrahedron Lett.* **1992**, *33*, 5807 – 5810; l) S. E. Gibson, G. J. Tustin, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2427 – 2432; m) J. R. Hwu, C. H. Chen, C. I. Hsu, A. R. Das, Y. C. Li, L. C. Lin, *Org. Lett.* **2008**, *10*, 1913 – 1916.

[5] a) D. A. Rooke, E. M. Ferreira, *J. Am. Chem. Soc.* **2010**, *132*, 11926 – 11928; b) D. A. Rooke, E. M. Ferreira, *Angew. Chem.* **2012**, *124*, 3279 – 3284; *Angew. Chem. Int. Ed.* **2012**, *51*, 3225 – 3230.

[6] Y. Sumida, T. Kato, S. Yoshida, T. Hosoya, *Org. Lett.* **2012**, *14*, 1552–1555.

[7] Lewis-acid-mediated hydrosilylations of propiolate esters to provide both α and β adducts have been reported. Y. Liu, S. Yamazaki, S. Yamabe, *J. Org. Chem.* **2004**, *69*, 556–561.

[8] a) B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655; b) B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2004**, *126*, 13942–13944.

[9] L. Iannazzo, G. A. Molander, *Eur. J. Org. Chem.* **2012**, 4923–4926.

[10] a) M. Gao, S. B. Thorpe, W. L. Santos, *Org. Lett.* **2009**, *11*, 3478–3481; b) M. Gao, S. B. Thorpe, C. Kleeberg, C. Slebodnick, T. B. Marder, W. L. Santos, *J. Org. Chem.* **2011**, *76*, 3997–4007; c) S. B. Thorpe, X. Guo, W. L. Santos, *Chem. Commun.* **2011**, *47*, 424–426; d) S. B. Thorpe, J. A. Calderone, W. L. Santos, *Org. Lett.* **2012**.

[11] J. A. Calderone, W. L. Santos, *Org. Lett.* **2012**, *14*, 2090–2093.

[12] For silyl conjugate addition approach using $Me_2PhSiBpin$ to access β-silyl carbonyl derivatives, see: a) C. Walter, G. Auer, M. Oestreich, *Angew. Chem.* **2006**, *118*, 5803–5805; *Angew. Chem. Int. Ed.* **2006**, *45*, 5675–5677; b) C. Walter, M. Oestreich, *Angew. Chem.* **2008**, *120*, 3878–3880; *Angew. Chem. Int. Ed.* **2008**, *47*, 3818–3820; c) C. Walter, R. Fröhlich, M. Oestreich, *Tetrahedron* **2009**, *65*, 5513–5520; d) E. Hartmann, M. Oestreich, *Angew. Chem.* **2010**, *122*, 6331–6334; *Angew. Chem. Int. Ed.* **2010**, *49*, 6195–6198; e) K. S. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900; f) K. S. Lee, H. Wu, F. Haeffner, A. H. Hoveyda, *Organometallics* **2012**, *31*, 7823–7826; g) J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7712–7715; h) V. Pace, J. P. Rae, H. Y. Harb, D. J. Procter, *Chem. Commun.* **2013**, *49*, 5150–5152; i) I. Ibrahem, S. Santoro, F. Himo, A. Córdova, *Adv. Synth. Catal.* **2011**, *353*, 245–252; j) A. Welle, J. Petrignet, B. Tinant, J. Wouters, O. Riant, *Chem. Eur. J.* **2010**, *16*, 10980–10983; k) H. Y. Harb, K. D. Collins, J. V. G. Altur, S. Bowker, L. Campbell, D. J. Procter, *Org. Lett.* **2010**, *12*, 5446–5449.

[13] Synthesis: a) M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **2000**, *19*, 4647–4649; Authoritative reviews: b) M. Oestreich, E. Hartmann, M. Mewald, *Chem. Rev.* **2013**, *113*, 402–441; c) T. Ohmura, M. Suginome, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29–49.

[14] P. Wang, X.-L. Yeo, T.-P. Loh, *J. Am. Chem. Soc.* **2011**, *133*, 1254–1256.

[15] L. Iannazzo, G. A. Molander, *Eur. J. Org. Chem.* **2012**, 4923–4926.

[16] 1,2-Addition of silicon to aldehydes have been reported. For details, see: a) V. Cirriez, C. Rasson, T. Hermant, J. Petrignet, J. Díaz Álvarez, K. Robeyns, O. Riant, *Angew. Chem.* **2013**, *125*, 1829–1832; *Angew. Chem. Int. Ed.* **2013**, *52*, 1785–1788; b) C. Kleeberg, E. Feldmann, E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Eur. J.* **2011**, *17*, 13538–13543; c) D. J. Vyas, R. Frohlich, M. Oestreich, *Org. Lett.* **2011**, *13*, 2094–2097.

[17] E. Piers, R. M. Lemieux, *Organometallics* **1998**, *17*, 4213–4217.