Synthetic Methods

DOI: 10.1002/anie.201404218

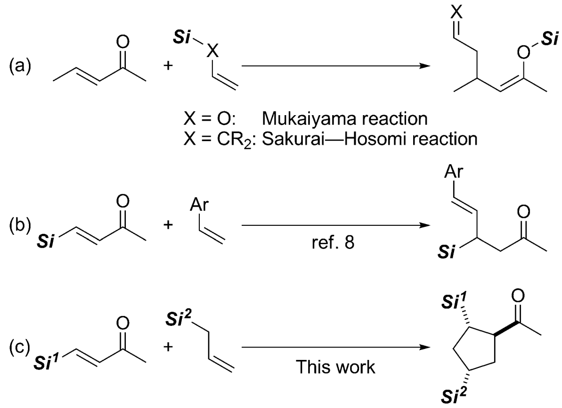
Stereoselective Construction of 1,3-Disilylcyclopentane Derivatives by Scandium-Catalyzed [3+2] Cycloaddition of Allylsilanes to β-Silylenones**

Kazuhiro Okamoto, Eisuke Tamura, and Kouichi Ohe**

Abstract: *The Sc(OTf)$_3$-catalyzed [3+2] cycloaddition of allylsilanes to β-silyl-α,β-unsaturated ketones (β-silylenones) has been developed to form five-membered syn-1,3-disilylketones diastereoselectively through the rearrangement of the silicon substituents on the allylsilane. Stabilization of the carbocation intermediates by a double silicon effect plays a key role in directing the course of the reaction to favor the [3+2] cycloaddition pathway over simple allylation.*

Multisubstituted cyclopentane derivatives with defined configurations constitute key structural motifs in many biologically active compounds, such as prostaglandins[1] and carbafuranose derivatives,[2] and their stereoselective synthesis is therefore of clear importance. Among the methods available for the stereoselective construction of cyclopentane rings, intermolecular [3+2] cycloaddition reactions are one of the most direct and efficient methods. For example, palladium- or nickel-catalyzed cycloaddition of trimethylenemethane precursors as 1,3-dipoles has been widely used for decades.[3] However, in contrast to these transition-metal-catalyzed processes, the $TiCl_4$-mediated [3+2] cycloaddition reaction involving allenylsilanes as the three-carbon unit proceeds with rearrangement of the silicon substituents.[4] This type of reaction has been expanded by Knölker and others to include the use of allylsilanes as the three-carbon unit.[5] However, the development of catalytic methods for [3+2] cycloaddition reactions has not yet been extensively studied.

Our research interest has focused on the acid-catalyzed reactions of simple alkenes with unsaturated carbonyl compounds bearing silicon substituents at the appropriate position. Although various methods involving the use of silicon-substituted alkenes, such as allylsilanes or silyl enol ethers, have been reported since their discovery by Mukaiyama[6] and Sakurai and Hosomi[7] in the 1970s (Scheme 1 a), the effect of silicon substitution at electron-deficient alkenes has seldom been studied. We recently reported the acid-catalyzed conjugate addition of styrene derivatives to β-silylenones, in which the silicon substitution effect plays a crucial role in the selective alkenylation (Scheme 1 b).[8] Herein, we report the reaction of allylsilanes with β-silylenones catalyzed by Lewis acid, which leads to the selective formation of cyclopentane rings bearing two silicon substituents (Scheme 1 c).



Scheme 1. Lewis acid mediated addition reactions of alkenes to β-silylenones.

As a result of optimization trials, scandium triflate $Sc(OTf)_3$ was found to be the best catalyst for the [3+2] cycloaddition of allyltrimethylsilane (**2a**) to β-silylenone **1a**, with cycloadduct **3a** being obtained in 60% yield (Table 1, entry 1). Under these conditions, the conjugate allylation product **4a** was formed as a byproduct in only 12% yield. Significantly, no [3+2] cycloadduct was observed when the reaction was performed under the same conditions with other enones bearing a methyl, isopropyl, or *tert*-butyl group at the β-position (entries 2–4). The use of other triflate salts of transition-metal or main-group metals, such as indium, gallium, or bismuth, led to lower yields of cycloadduct **3a** than obtained with scandium (entries 5–7).[8] Trimethylsilyl triflate (Me_3SiOTf) and triflic acid (HOTf) both showed very low catalytic activity, which is in contrast to the reported direct alkenylation reaction (entries 8 and 9).[9,10] Surprisingly, the product selectivity changed dramatically with the use of a stoichiometric amount of titanium chloride ($TiCl_4$); under these conditions, allylation product **4a** was obtained as the major product in 76% yield (entry 10).

The optimized conditions established for the present [3+2] cycloaddition reaction could be applied to a range of β-silylenones **1a** and **1e**–**l**, and allylsilanes **2a**–**f**, possessing a variety of silicon substituents such as Me_3Si, Et_3Si, $PhMe_2Si$,

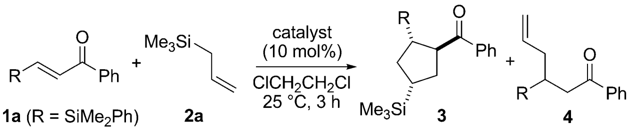
---

[*] Dr. K. Okamoto, E. Tamura, Prof. Dr. K. Ohe
Department of Energy and Hydrocarbon Chemistry
Graduate School of Engineering, Kyoto University
Katsura, Nishikyo-ku, Kyoto 615-8510 (Japan)
E-mail: kokamoto@scl.kyoto-u.ac.jp
ohe@scl.kyoto-u.ac.jp
Homepage: http://www.ehcc.kyoto-u.ac.jp/eh31/home/index-j.html

[**] This work was supported partly by JSPS KAKENHI Grant Number 26410119.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404218.

Table 1: Lewis acid catalyzed reaction of enones **1a–d** with allyltrimethylsilane (**2a**).[a]

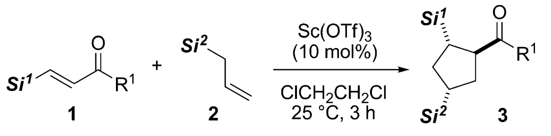


1a (R = SiMe$_2$Ph)
1b (R = Me)
1c (R = *i*-Pr)
1d (R = *t*-Bu)

Entry	Enone	Catalyst	Conv. 1 [%][b]	Yield 3 [%][b]	4 [%][b]
1	**1a**	Sc(OTf)$_3$	100	74 (60)[c]	12
2	**1b**	Sc(OTf)$_3$	46	0	12
3	**1c**	Sc(OTf)$_3$	0	0	0
4	**1d**	Sc(OTf)$_3$	0	0	0
5	**1a**	In(OTf)$_3$	100	45	16
6		Ga(OTf)$_3$	100	38	32
7		Bi(OTf)$_3$	100	7	0
8		Me$_3$SiOTf	5	0	5
9		HOTf	5	0	5
10		TiCl$_4$ (1.0 equiv)	100	19	81 (76)[c]

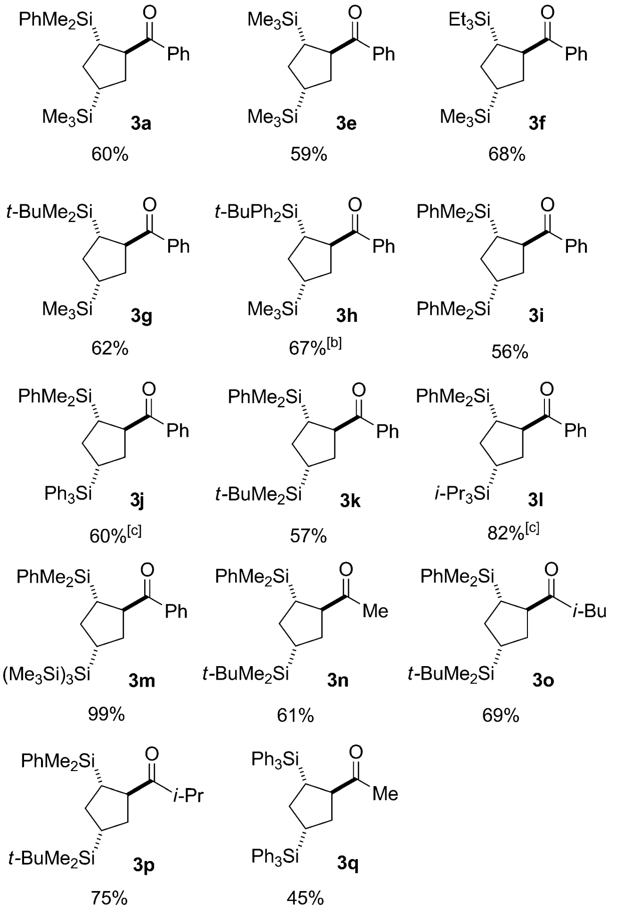
[a] Reaction conditions: enone **1** (0.20 mmol), allylsilane **2a** (0.60 mmol), and Sc(OTf)$_3$ (20 μmol) in ClCH$_2$CH$_2$Cl (1.5 mL) at 25 °C for 3 h. Cycloadduct **3** was obtained as a single diastereomer, the relative conformation of which is shown. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product.

Table 2: Sc(OTf)$_3$-catalyzed [3+2] cycloaddition reaction of enone **1** with allylsilane **2**.[a]



1a (***Si*** ^{1} = SiMe$_2$Ph, R^1 = Ph)
1e (***Si*** ^{1} = SiMe$_3$, R^1 = Ph)
1f (***Si*** ^{1} = SiEt$_3$, R^1 = Ph)
1g (***Si*** ^{1} = SiMe$_2$(*t*-Bu), R^1 = Ph)
1h (***Si*** ^{1} = SiPh$_2$(*t*-Bu), R^1 = Ph)
1i (***Si*** ^{1} = SiMe$_2$Ph, R^1 = Me)
1j (***Si*** ^{1} = SiMe$_2$Ph, R^1 = *i*-Bu)
1k (***Si*** ^{1} = SiMe$_2$Ph, R^1 = *i*-Pr)
1l (***Si*** ^{1} = SiPh$_3$, R^1 = Me)

2a (***Si*** ^{2} = SiMe$_3$)
2b (***Si*** ^{2} = SiMe$_2$Ph)
2c (***Si*** ^{2} = SiPh$_3$)
2d (***Si*** ^{2} = SiMe$_2$(*t*-Bu))
2e (***Si*** ^{2} = Si(*i*-Pr)$_3$)
2f (***Si*** ^{2} = Si(SiMe$_3$)$_3$)



3a 60%
3e 59%
3f 68%
3g 62%
3h 67%[b]
3i 56%
3j 60%[c]
3k 57%
3l 82%[c]
3m 99%
3n 61%
3o 69%
3p 75%
3q 45%

[a] Reaction conditions: enone **1** (0.20 mmol), allylsilane **2** (0.60 mmol), and Sc(OTf)$_3$ (20 μmol) in ClCH$_2$CH$_2$Cl (1.5 mL) at 25 °C for 3 h. Yields of isolated product are shown. The products were obtained as a single diastereoisomer. [b] The reaction time was 6 h. [c] In(OTf)$_3$ was used instead of Sc(OTf)$_3$.

Ph$_3$Si, *t*BuMe$_2$Si, *t*BuPh$_2$Si, *i*Pr$_3$Si, and (Me$_3$Si)$_3$Si (Table 2). When allyltriisopropylsilane was used, indium triflate [In(OTf)$_3$] worked as a better catalyst than Sc(OTf)$_3$, affording the product **3l** in 82% yield. The reaction with allylsilane **2f**, bearing a super silyl [Si(SiMe$_3$)$_3$] group, afforded the cycloadduct **3m** almost quantitatively (99% yield). Along with phenyl ketones, methyl, isobutyl, and isopropyl ketones were also applicable, giving the expected products **3n–q**.[11]

The relative configuration of the cycloadducts was determined by X-ray crystallographic analysis of product **3q**, which bears two Ph$_3$Si groups.[12] The crystal structure showed that the two silicon substituents are in a *cis* configuration, whereas the carbonyl group is *trans* to the two silicon substituents (Figure 1).

The selectivity of the reaction with respect to the formation of cycloadducts and allylation products can be explained by assuming that cationic intermediates are positive induction from the silicon substituents (Scheme 2). First, the carbonyl group of β-silylenone **1**, activated by Sc(OTf)$_3$ acting as a Lewis acid, undergoes nucleophilic attack from the C–C double bond of allylsilane **2** to form intermediate **A** (Scheme 2a). This intermediate then undergoes cycloaddition after silyl migration through transition state **B** to give **3** as a single diastereoisomer. The conjugate allylation reaction

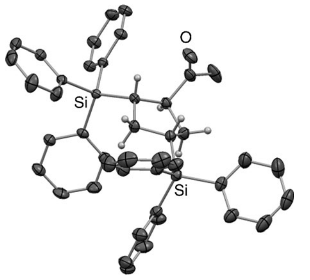
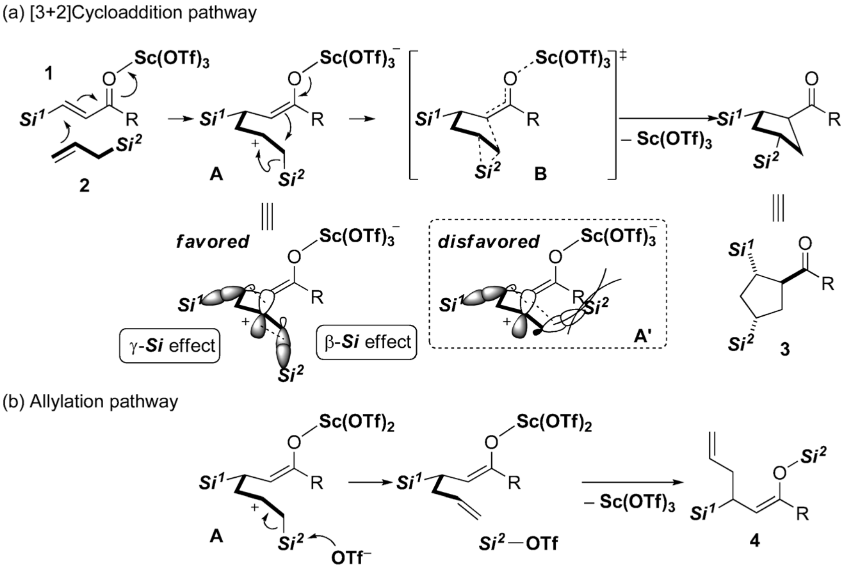


Figure 1. ORTEP of **3q**. Ellipsoids are set to 50% probability; a solvent atom and all hydrogen atoms except for those attached to the five-membered ring are omitted for clarity.

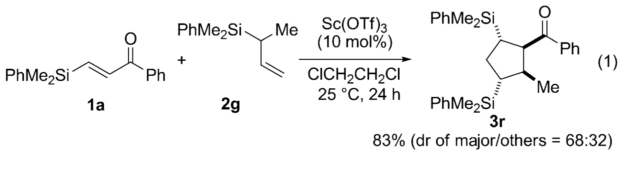


Scheme 2. Proposed origin of the diastereoselectivity and product selectivity based on a plausible reaction pathway.

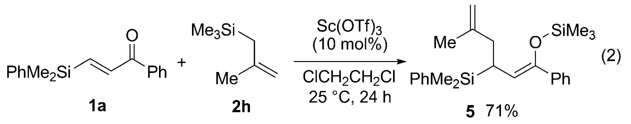
would also be expected to proceed through intermediate **A**; however, in this case, the counteranion of the Lewis acid catalyst attacks the silyl group *Si*^{2}, which is followed by elimination of the catalyst to afford the corresponding silyl enol ether (Scheme 2b).

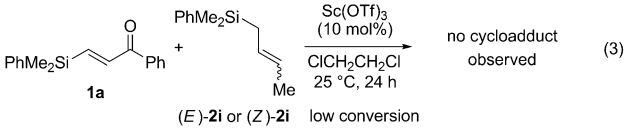
Carbocation **A** is stabilized by the β-silicon effect (usually observed in the acid-catalyzed reaction of allylsilanes)[13] from silyl group *Si*^{2}, derived from the allylsilane **2**, and by the γ-silicon effect from silyl group *Si*^{1}, derived from silylenone **1**.[14–17] Therefore, the carbocation moiety and the scandium enolate are close to each other in space at the most stabilized conformation of intermediate **A**, resulting in an acceleration of the subsequent cycloaddition step as a result of the reduced activation barrier. Thus, the origin of the product selectivity observed in the [3+2] cycloaddition is probably the stabilization of transition state **B**, which leads to cycloaddition involving the transfer of silyl group *Si*^{2}.[18] The high diastereoselectivity can also be explained by comparing the stability of intermediate **A** with another possible intermediate **A′** that is disfavored by the steric interaction between the silyl group *Si*^{2} and the enolate moiety.

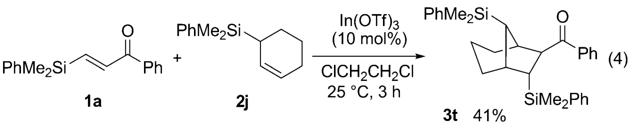
To extend the scope of the reaction further and obtain other substituted five-membered cycloadducts, the reaction of substituted allylsilanes was examined. The $Sc(OTf)_3$-catalyzed reaction of α-methylated allylsilane **2g** with silylenone **1a** proceeded well to afford the corresponding 1,2,3,4-tetrasubstituted five-membered product **3r** as a mixture of diastereoisomers [Eq. (1); 83% yield; d.r. of major isomer/others = 68:32].[19] However, β-methylated allylsilane **2h** also reacted under identical conditions to give the conjugate allylation product **5** in 71% yield, without formation of the [3+2] cycloadduct [Eq. (2)]. The reactivities of γ-methylated allylsilanes (*E*)- and (*Z*)-**2i** were very low, and no cycloadduct was observed in the reaction mixture [Eq. (3)]. The reaction of cyclic allylsilane **2j** proceeded with $In(OTf)_3$ as catalyst to provide cycloadduct **3t** as a single diastereoisomer incorporating the bicyclo[3.2.1]octane backbone [Eq. (4)].



Cycloadducts bearing two silyl substituents with a single relative configuration could be readily transformed stereospecifically into cyclopentanes bearing two or three functional groups. Cycloadduct **3i**, bearing two identical silyl groups ($SiMe_2Ph$), readily underwent protonolysis with fluoroboric acid ($HBF_4{\cdot}OEt_2$, 10 equiv) to form bis(fluorosilyl)cyclopentane **6** exclusively (Table 3, entry 1). Further transformation proceeded under the standard conditions of Tamao–Fleming oxidation[20] to give the corresponding *syn*-1,3-diol **8** as a single diastereoisomer in 62% yield. To our surprise, monofluorinated compound **7** was quantitatively obtained when **3i** was treated with a reduced amount of $HBF_4{\cdot}OEt_2$ (2.5 equiv) at lower temperature for a shortened reaction time (entry 2).[21] Oxidation of **7** gave mono-ol **9** in 91% yield, with the phenyldimethylsilyl group remaining unaffected.

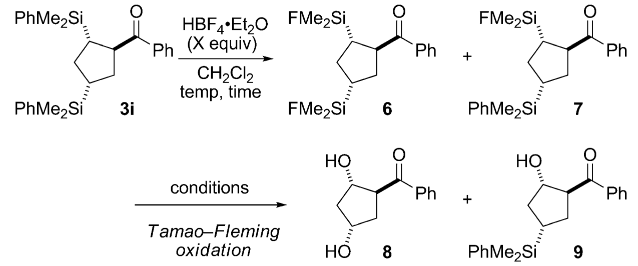






To summarize, we have developed a diastereoselective, $Sc(OTf)_3$-catalyzed [3+2] cycloaddition of allylsilanes with β-silylenones that affords multisubstituted five-membered products in good yields. The reaction proceeds under mild conditions, and a range of silyl substituents are suitable. Compared with previous systems in which only bulky silyl groups could be used,[5,10] the finding that even less hindered

Table 3: Selective transformations of disilane **3i** including Tamao-Fleming oxidation.



Entry	X	*T*, *t*	Conditions[a]	**6**/**7**[b]	Yield	
					8 [%]	**9** [%]
1	10.0	25 °C, 12 h	A	100/0	62	0
2	2.5	0 °C, 30 min	B	0/100	0	91

[a] Conditions A: KHF_2 (4.0 equiv), 30% H_2O_2 aq. (24 equiv), DMF, 60 °C, 7 h. Conditions B: KF (2.0 equiv), $KHCO_3$ (10 equiv), 30% H_2O_2 aq. (12 equiv), THF/MeOH, RT, 4 h. [b] Determined by ^{1}H NMR spectroscopy.

silyl groups such as the trimethylsilyl group can cause the selective cycloaddition is a particular advantage of the current system. The double silicon stabilization effect efficiently enhanced the reactivity towards cycloaddition, resulting in the suppression of conjugate allylation byproduct formation. The highly selective oxidation of two identical silyl substituents at different positions is significant because it allows the two substituents to be converted into different functional groups that can be independently used for subsequent derivatization. Further investigations into the synthetic application of this reaction toward the construction of biologically active compounds as well as the development of an enantioselective version of the reaction are in progress.

Received: April 11, 2014
Revised: May 23, 2014
Published online: July 25, 2014

Keywords: cycloaddition · diastereoselectivity · homogeneous catalysis · scandium · silicon

---

[1] For reviews, see: a) P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533; b) S. Das, S. Chandrasekhar, J. S. Yadav, R. Gree, *Chem. Rev.* **2007**, *107*, 3286.

[2] For a review, see: O. Arjona, A. M. Gómez, J. C. López, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919.

[3] For reviews, see: a) B. M. Trost, *Angew. Chem.* **1986**, *98*, 1; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1; b) P. Binger, H. M. Büch, *Top. Curr. Chem.* **1987**, *135*, 77; c) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; d) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213; e) I. Nakamura, Y. Yamamoto, *Adv. Synth. Catal.* **2002**, *344*, 111.

[4] a) R. L. Danheiser, D. J. Carini, A. Basak, *J. Am. Chem. Soc.* **1981**, *103*, 1604; b) R. L. Danheiser, D. J. Carini, D. M. Fink, A. Basak, *Tetrahedron* **1983**, *39*, 935; c) R. L. Danheiser, D. M. Fink, *Tetrahedron Lett.* **1985**, *26*, 2513; d) R. L. Danheiser, C. A. Kwasigroch, Y.-M. Tsai, *J. Am. Chem. Soc.* **1985**, *107*, 7233; e) R. L. Danheiser, D. M. Fink, Y.-M. Tsai, *Org. Synth.* **1988**, *66*, 8; f) D. A. Becker, R. L. Danheiser, *J. Am. Chem. Soc.* **1989**, *111*, 389; g) R. L. Danheiser, E. J. Stoner, H. Koyama, D. S. Yamashita, C. A. Klade, *J. Am. Chem. Soc.* **1989**, *111*, 4407; h) R. L. Danheiser, B. R. Dixon, R. W. Gleason, *J. Org. Chem.* **1992**, *57*, 6094; i) R. L. Danheiser, T. Takahashi, B. Bertók, B. R. Dixon, *Tetrahedron Lett.* **1993**, *34*, 3845.

[5] a) H.-J. Knölker, P. G. Jones, J.-B. Pannek, *Synlett* **1990**, 429; b) H.-J. Knölker, N. Foitzik, R. Graf, J.-B. Pannek, *Tetrahedron* **1993**, *44*, 9955; c) H.-J. Knölker, N. Foitzik, H. Goesmann, R. Graf, P. G. Jones, G. Wanzl, *Chem. Eur. J.* **1997**, *3*, 538; d) H.-J. Knölker, *J. Prakt. Chem.* **1997**, *339*, 304; e) T. Akiyama, M. Yamanaka, *Tetrahedron Lett.* **1998**, *39*, 7885; f) A. W. Schmidt, H.-J. Knölker, *Synlett* **2010**, 2207.

[6] For a pioneering report, see: K. Saigo, M. Osaki, T. Mukaiyama, *Chem. Lett.* **1976**, 163.

[7] For pioneering reports, see: a) A. Hosomi, H. Sakurai, *Tetrahedron Lett.* **1976**, *17*, 1296; b) A. Hosomi, H. Sakurai, *J. Am. Chem. Soc.* **1977**, *99*, 1673.

[8] Other triflate salts, such as $Cu(OTf)_2$, $Y(OTf)_3$, $La(OTf)_3$, and $Yb(OTf)_3$, did not catalyze the reaction at all.

[9] K. Okamoto, E. Tamura, K. Ohe, *Angew. Chem.* **2013**, *125*, 10833; *Angew. Chem. Int. Ed.* **2013**, *52*, 10639.

[10] This result is in sharp contrast to $HNTf_2$-catalyzed [3+2] and [2+2] cycloaddition reactions of allylsilanes reported by Takasu, Ihara, et al. See: K. Takasu, N. Hosokawa, K. Inanaga, M. Ihara, *Tetrahedron Lett.* **2006**, *47*, 6053.

[11] β,β-Disubstituted or α,α-disubstituted silylenones were not successful under the present reaction conditions. β-Silylenal was too reactive to form the corresponding [3+2] cycloadduct selectively. β-Silylenoate was not reactive at all.

[12] CCDC 996695 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] For reviews on hyperconjugation involving the β-silicon effect, see: a) J. B. Lambert, Y. Zhao, R. W. Emblidge, L. A. Salvador, X. Liu, J.-H. So, E. C. Chelius, *Acc. Chem. Res.* **1999**, *32*, 183; b) I. V. Alabugin, K. M. Gilmore, P. W. Peterson, *WIREs Comput. Mol. Sci.* **2011**, *1*, 109.

[14] For mechanistic studies on the γ-silicon effect, see: a) V. J. Shiner, Jr., M. W. Ensinger, G. S. Kriz, *J. Am. Chem. Soc.* **1986**, *108*, 842; b) V. J. Shiner, Jr., M. W. Ensinger, R. D. Rutkowske, *J. Am. Chem. Soc.* **1987**, *109*, 804; c) C. A. Grob, P. Sawlewicz, *Tetrahedron Lett.* **1987**, *28*, 951; d) C. A. Grob, M. Gründel, P. Sawlewicz, *Helv. Chim. Acta* **1988**, *71*, 1502; e) W. Kirmse, F. Söllenböhmer, *J. Am. Chem. Soc.* **1989**, *111*, 4127; f) J. B. Lambert, *Tetrahedron* **1990**, *46*, 2677; g) J. B. Lambert, S. M. Ciro, *J. Org. Chem.* **1996**, *61*, 1940; h) A. J. Green, T. Pigdon, J. M. White, J. Yamen, *J. Org. Chem.* **1998**, *63*, 3943; i) T. Nakashima, R. Fujiyama, M. Fujio, Y. Tsuno, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 741.

[15] For synthetic studies using the γ-silicon effect, see: a) H. Sakurai, T. Imai, A. Hosomi, *Tetrahedron Lett.* **1977**, *18*, 4045; b) Y. Hatanaka, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 719; c) K. Masuya, K. Tanino, I. Kuwajima, *Synlett* **1999**, 647; d) M. Ogasawara, A. Okada, H. Murakami, S. Watanabe, Y. Ge, T. Takahashi, *Org. Lett.* **2009**, *11*, 4240.

[16] For studies on the γ-effect of other elements, see: M. Sugawara, J. Yoshida, *J. Org. Chem.* **2000**, *65*, 3135.

[17] The observation that steric hindrance of the β-alkyl substituents in enone **1** resulted in a lower yield of the product (Table 1, entries 1–4) supports the idea of an electronic interaction from the β-substituents.

[18] In the $TiCl_4$-mediated reaction, both the very low catalytic activity and the selectivity toward allylation occurred because the high oxophilicity of titanium disallows the catalytic conversion, and because the higher nucleophilicity of the chloride anion enhances the allylation pathway.

[19] The relative configuration of the major diastereoisomer of product **3r** was determined based on NMR spectroscopic analysis of the derivatized product (see the Supporting Information for details).

[20] a) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694; b) K. Tamao, M. Kumada, K. Maeda, *Tetrahedron Lett.* **1984**, *25*, 321; c) I. Fleming, R. Henning, H. Plaut, *J. Chem. Soc. Chem. Commun.* **1984**, 29; d) I. Fleming, R. Henning, D. C. Parker, H. E. Plaut, P. E. Sanderson, *J. Chem. Soc. Chem. Commun.* **1995**, 317; e) Review: G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599.

[21] Because primary protonation might occur at the carbonyl oxygen, protonation of the silylarene closer to the carbonyl group might be strongly accelerated (as illustrated right).