Synthetic Methods

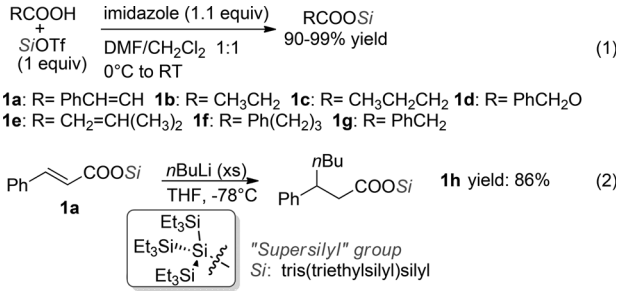
DOI: 10.1002/ange.201300102

The Supersilyl Group as a Carboxylic Acid Protecting Group: Application to Highly Stereoselective Aldol and Mannich Reactions**

*Jiajing Tan, Matsujiro Akakura, and Hisashi Yamamoto**

Historically, silyl groups have rarely been utilized as a protecting group for carboxylic acids in organic synthesis, as the Si–O bonds are too labile even under mild reaction conditions.[1,2] Similarly, the employment of silyl esters in synthetically useful organic transformations has also been underrepresented.[1,2] As part of our continuing studies on the tris(trialkylsilyl)silyl (supersilyl) group, we have developed the supersilyl directed aldol reactions of β-siloxymethyl ketones and cascade Mukaiyama aldol reactions, which enabled the rapid assembly of polyol motifs and expedient synthesis of polyketide natural products.[3] The supersilyl group, with unique electronic properties and large steric bulk, has been discovered to play a crucial role in obtaining high yields and selectivities.[3] Encouraged especially by the stability and steric encumbrance of supersilyl ether motifs, we reasoned that the supersilyl group might be able to offer the necessary robustness for silyl esters as it is well-known that the stability of silyl esters, like that of silyl ethers, parallels the steric bulk of the silyl group.[1] Herein, we are glad to report our initial efforts toward the low stability problems of silyl esters described above: 1) the use of supersilyl group as a highly effective carboxyl protection group; and 2) the exemplificative application of supersilyl esters as stable synthetic equivalents of carboxylic acids in highly stereoselective aldol and Mannich reactions.

The installation of the supersilyl group could be simply achieved by treatment of carboxylic acids with tris(triethylsilyl)silyl triflate (generated in situ by mixing the silane with triflic acid) in the presence of imidazole [Scheme 1, Eq. (1)].[4] It is worth mentioning that the obtained silyl esters are UV-active owing to the supersilyl group (allowing for straightforward TLC analysis even when the R group is aliphatic)[5] and stable for purification by chromatography. Our preliminary efforts made to evaluate the stabilities of supersilyl esters toward various reagents implied that the model substrate **1f** is stable to excess MeMgBr, *n*BuLi, DIBAL-H, and LiHMDS (Table 1).[6,7] Like most known carboxyl protecting groups,



Scheme 1. Supersilyl ester synthesis and the 1,4-addition reaction.

this silyl group failed to offer protection against MeLi owing to the rapid formation of methylated silane. Remarkably, treating **1a** with *n*BuLi at −78 °C only led to the conjugate addition product **1g** while the carboxyl group remained intact [Eq. (2)].[8] These results clearly showed that the supersilyl group confers extraordinary protection upon the carboxyl functionality. Such unprecedented stability of silyl esters may offer a high degree of synthetic flexibility and even an exciting possibility for new synthetic strategies, which thus prompted us to explore their applications in organic transformations.

Table 1: Investigation of the stability of supersilyl esters.

Reagents	**1f** (0.1 M)
MeMgBr (2 equiv)	No nucleophilic attack and silane methylation observed (−78 °C to RT)
MeLi (2 equiv)	Rapid formation of methylated silane observed at −78 °C
DIBAL-H (2 equiv)	No reduction of carboxyl functionality observed (−78 °C to RT)
LiHMDS (2 equiv)	No decomposition and deprotonation observed (−78 °C to RT)
*n*BuLi (2 equiv)	No nucleophilic attack and silane alkylation observed Enolate formation observed (−78 °C to −20 °C)

[a] DIBAL-H = diisobutylaluminum hydride, HDMS = hexamethyldisilazide.

Even though the carboxyl moiety is well-protected by the supersilyl group, deprotonation at the α-position is still effective. Reaction of **1b** with *n*BuLi at −78 °C followed by quenching with D_2O gave the deuterium-substituted product in quantitative yield with more than 95% deuterium incorporation.[7] This promising result led us to first investigate the reactivity of stable supersilyl ester enolates. Undoubtedly, one of the most straightforward strategies for synthesizing β-amino/hydroxy carboxylic acid derivatives is the stereoselective aldol[9,10] or Mannich[11,12] reaction of metal enolates with aldehydes or imines, respectively. As these compounds are

[*] J.-J. Tan, Prof. Dr. H. Yamamoto
Department of Chemistry, The University of Chicago
5735 South Ellis Avenue, Chicago, IL 60637 (USA)
E-mail: yamamoto@uchicago.edu
Prof. Dr. H. Yamamoto
Molecular Catalyst Research Center, Chubu University
1200 Matsumoto, Kasugai 487-8501 (Japan)
Prof. Dr. M. Akakura
Department of Chemistry, Aichi University of Education (Japan)

[**] Support of this work was provided by the NIH (P50 GM086 145-01). J.J.T. is grateful for fruitful discussions with Dr. B. J. Albert, Dr. Y. Yosuke, Dr. S. Hirashima, P. B. Brady, and Prof. S. A. Kozmin.
Supersilyl = tris(triethylsilyl)silyl.

privileged structural motifs for biologically active molecules and natural products, such as peptides[13] (dolastatin D) and polyketides[14] (erythromycin A), the development of alternative synthetic methods is still highly desirable (Figure 1). Notably, the employment of silyl groups as carboxylic acid donor groups in stereoselective metal enolate C–C bond formation reactions has never been explored to date.

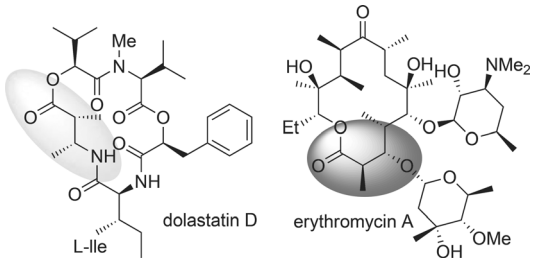
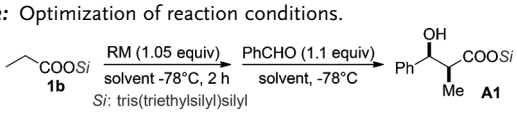


Figure 1. Dolastatin D and erythromycin A.

To our delight, the model reaction of the lithium enolate of **1b** and benzaldehyde in THF gave **A1** with good yield and *syn* selectivity (Table 2, entry 1). Other bases, including LDA,

Table 2: Optimization of reaction conditions.



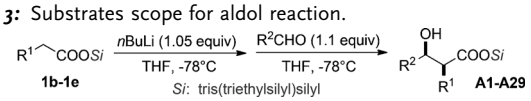
Entry	Reagent[b]	Solvent	Yield [%][a]	*syn*/*anti*[c]
1	*n*BuLi	THF	90	95:5
2	LDA	THF	60	80:20
3	LiHMDS	THF	N.R.	N.D.
4	KHMDS	THF	N.R.	N.D.
5	*t*BuLi	THF	90	95:5
6	*n*BuMgCl	THF	N.R.	N.D.
7	*n*BuLi	Et_2O	20	75:25
8	*n*BuLi	Toluene	trace	N.D.
9	*n*BuLi/TMEDA	THF	85	84:16
10	*n*BuLi/HMPA	THF	82	33:67
11[d]	*n*BuLi	THF	trace	N. D.
12[e]	*n*BuLi	THF	91	75:25
13[f]	*n*BuLi	THF	86	99:1

[a] Yield of isolated product. [b] LDA = lithium diisopropylamide, HDMS = hexamethyldisilazide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, HMPA = hexamethylphosphoramide. [c] Determined by ^{1}H NMR of crude products. [d] The triisopropylsilyl (TIPS) group was used. [e] Temperature: −40 °C. [f] Lithiation time: 24 h.

LiHMDS, *t*BuLi, KHMDS, and *n*BuMgCl were also screened; only the *t*BuLi offered comparable results (entries 2–6).[15] Switching the solvent to toluene or diethyl ether proved to be detrimental to the yield and selectivity, implying the importance of THF coordination to lithium (entries 7–8). A decreased or even reversed selectivity was observed when TMEDA or HMPA was employed as the additive (entries 9–10). The control experiment with the TIPS group gave only trace amounts of the aldol product while the rest of starting materials decomposed at −78 °C (entry 11). Further optimization revealed that raising the temperature to −40 °C failed to improve the results (entry 12). Despite careful screening, increasing lithiation time was finally found to be critical for obtaining high *syn* selectivity (entry 13).[7]

A variety of substrates were then investigated under the optimized reaction conditions (Table 3). The aromatic aldehydes with both electron donating and withdrawing groups,

Table 3: Substrates scope for aldol reaction.



Entry	R^1	R^2	Yield [%][a]	*Syn*:*anti*[b]
1	Me	Ph	86	99:1
2	Me	2-MeC_6H_4	75	99:1
3	Me	2-FC_6H_4	74	99:1
4	Me	3-MeC_6H_4	86	99:1
5	Me	3-$MeOC_6H_4$	83	99:1
6	Me	3-BrC_6H_4	90	99:1
7	Me	4-MeC_6H_4	95	99:1
8	Me	4-FC_6H_4	89	99:1
9	Me	4-BrC_6H_4	87	99:1
10	Me	4-$CF_3C_6H_4$	77	99:1
11	Me	4-$MeOC_6H_4$	89	99:1
12	Me	*t*-butyl	90	97:3
13	Me	ethyl	88	95:5
14	Me	cyclopropyl	87	97:3
15	Me	*c*-hexyl	90	99:1
16	Me	*n*-C_7H_{15}	86	98:2
17	Me	cinnamyl	93	99:1
18	Me	phenylacetylenyl	85	95:5
19	Me	$BnOCH_2$	90	92:8
20	Me	1-naphthyl	70	98:2
21	Me	2-naphthyl	83	99:1
22	Me	2-furyl	70	99:1
23	Me	2-thienyl	79	99:1
24	Me	*N*-tosylindol-3-yl	65	99:1
25	Me	acetophenone	66	95:5
26	Et	Ph	85	97:3
27	BnO	Ph	80	90:10
28	Allyl	Ph	72	90:10
29	Bn	Ph	86	86:14

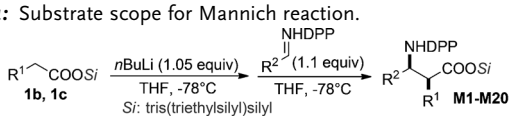
[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy of the crude products.

possessing various substitution patterns on the phenyl ring, gave the aldol products with good yields and selectivities (entries 1–11). Subjection of the aliphatic aldehydes to standard conditions also provided the desired products in excellent selectivities (entries 12–16). Furthermore, conjugated aldehydes were suitable substrates to solely give 1,2-addition products (entries 17 and 18). When the α-oxygenated aldehyde was examined, the aldol reaction proceeded effectively to give the polyol product in 90% yield and 95:5 *syn* selectivity (entry 19). Aldehydes bearing either heterocycles or naphthyl rings were also well-tolerated, delivering aldol products with slightly lower yields (entries 20–24). Essentially, the acetophenone was used as the electrophile, which led to the product with contiguous tertiary and quaternary carbon centers (entry 25). Further exploration of silyl esters **1b**–**1e** with diverse R^1 groups also provided the aldol products with good *syn* selectivities (entry 26–28). Even

1g, with a bulky benzyl substituent, could be deprotonated to form the stable enolate, giving the desired product with moderate stereoselectivity (entry 29).

Next, the Mannich reactions with various *N*-diphenylphosphinyl (*N*-DPP) imines were evaluated (Table 4).[7] In all reactions of the aromatic imines, excellent stereoselectivities

Table 4: Substrate scope for Mannich reaction.

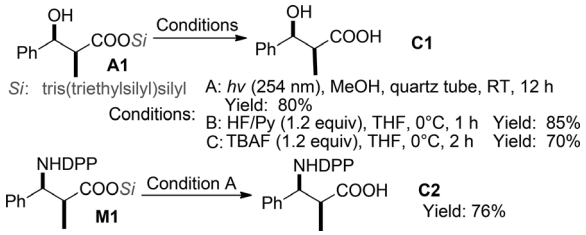


Entry	R^1	R^2	Yield [%][a]	*syn*/*anti*[b]
1	Me	Ph	88	99:1
2	Me	2-MeC_6H_4	83	99:1
3	Me	2-FC_6H_4	70	97:3
4	Me	3-MeC_6H_4	79	99:1
5	Me	3-$MeOC_6H_4$	78	99:1
6	Me	3-BrC_6H_4	91	99:1
7	Me	4-MeC_6H_4	77	98:2
8	Me	4-$CF_3C_6H_4$	85	99:1
9	Me	4-BrC_6H_4	89	99:1
10	Me	4-$MeOC_6H_4$	81	98:2
11	Me	cinnamyl	89	97:3
12	Me	phenylacetylenyl	75	91:9
13	Me	isopropyl	79	93:7
14	Me	cyclopropyl	80	97:3
15	Me	*tert*-butyl	92	95:5
16	Me	1-naphthyl	68	99:1
17	Me	2-naphthyl	87	99:1
18	Me	2-furyl	80	97:3
19	Me	2-thienyl	72	99:1
20	Et	Ph	80	97:3

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy of the crude products.

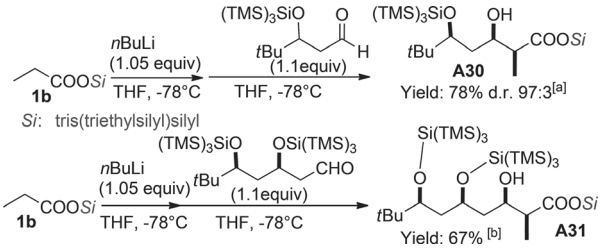
were achieved, while both electron-donating and -withdrawing groups had little impact (entries 1–10). The reactions of conjugated imines exclusively gave the 1,2-addition products (entries 11–12). Aliphatic imines with and without enolizable α-hydrogen atoms all reacted with silyl ester enolates effectively (entries 13–15). For imines bearing naphthyl rings, the Mannich reactions all occurred with high selectivities (entries 16 and 17). Notably, heteroaryl-substituted amino acids, widely present in molecules with promising biological activities, could be constructed by this procedure in excellent stereoselectivities from heteroaromatic imines, such as furyl imines and thienyl imines (entries 18 and 19).[13] Reaction of **1c** also gave the desired β-aminosilyl ester product with high *syn* selectivity (entry 20).

To address the synthetic utility of this procedure, desilylation methods were studied. Along with commonly used fluoride methods (TBAF, HF/Py) for the removal of silyl groups, an environmentally friendly photodesilylation condition was established.[16] Simple exposure of the supersilyl esters to 254 nm light from UV lamps for laboratory use could remove this unique silyl group in high efficiency (Scheme 2). Given the significance of polyketides in medicinal chemistry,[14] we recognized another attractive prospect might be the rapid synthesis of polyketide subunits with carboxyl function-



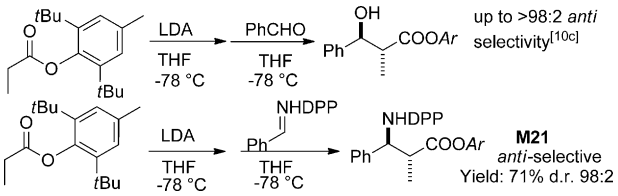
Scheme 2. Deprotection methods.

alities. β-Siloxy aldehydes obtained by cascade Mukaiyama aldol reactions[3a] were thus used to react with these silyl ester enolates, providing the desired polyketide analogues in good yields and selectivities (Scheme 3).



Scheme 3. Rapid synthesis of polyketide subunits. [a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Yields for the major diastereomer. d.r. could not be determined by the ^{1}H NMR analysis.

Finally, the bulky aryl ester reported by Heathcock et al.[10c,e] were examined for the Mannich reaction. The *anti* product was obtained instead. Therefore, we concluded that our method is a complementary approach, favouring *syn*-selective products for aldol and Mannich reactions. With a more advantageous deprotection procedure, this method is also expected to be as broadly utilized in natural product synthesis as Heathcock's method (Scheme 4).



Scheme 4. *anti*-Selective aldol and Mannich reaction of esters.

To shed light on the mechanism, DFT calculations were carried out to unveil the configuration of supersilyl ester enolates (Figure 2).[7] Computation results suggested that the solvated *Z*-enolate of **1b** is more stable than its solvated *E*-enolate. Three THF molecules were coordinated to the lithium center. Based on the observed stereochemical information of aldol products, the sense of induction could not be rationalized by invoking the six-membered Zimmerman–Traxler-type transition state as suggested for the similar addition of ester enolates to aldehydes.[10c,17] Instead, the observed *syn* selectivity might originate from an *anti*-clinal

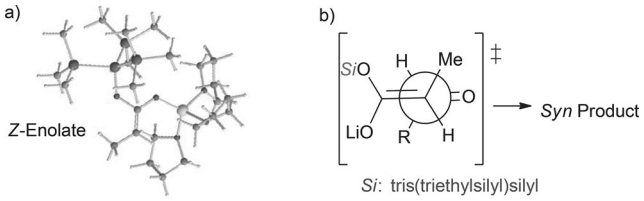


Figure 2. a) Calculated *Z*-enolate configuration and b) proposed transition state.

open transition state where the smallest aldehydic hydrogen is oriented over the bulky silyl group to minimize serious steric interactions.[18,19] Low diastereoselectivity obtained by the addition of HMPA might be the result of the destabilization of solvated enolates through the replacement of coordinated THF molecules.

In summary, we have introduced the application of the supersilyl group as an effective carboxyl protection group. The exceptional properties of the supersilyl group enabled it to outperform typical carboxyl protecting groups, especially for protection against the organometallic reagents. Moreover, supersilyl esters with outstanding stabilities were used as the innovative synthetic equivalents of carboxylic acids for the first time in highly stereoselective aldol and Mannich reactions, which allowed for the rapid synthesis of α-branched β-amino/hydroxy carboxylic acid derivatives in uniformly good yields and diastereoselectivities. The value of this method has been highlighted by the efficient photodeprotection procedure and its applications in rapid synthesis of polyketide subunits. This new supersilyl carboxyl protection group is expected to be of broad utilities in organic synthesis. Future work will focus on discovering new reactivity of supersilyl esters.

Received: January 6, 2013
Revised: March 27, 2013
Published online: May 29, 2013

Keywords: aldol reactions · carboxy groups · Mannich reaction · photodeprotection · protecting groups

[1] a) P. Kocienski, *Protecting Groups*, 3rd ed., Thieme, Stuttgart, **2005**; b) P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley-Interscience, New York, **2007**.

[2] a) E. J. Corey, C. U. Kim, *J. Org. Chem.* **1973**, *38*, 1233; b) A. Iwasaki, Y. Kondo, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 10238; c) H. Liang, L. Hu, E. J. Corey, *Org. Lett.* **2011**, *13*, 4120.

[3] a) M. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48; b) M. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 2762; c) M. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 1580; d) B. J. Albert, H. Yamamoto, *Angew. Chem.* **2010**, *122*, 2807; *Angew. Chem. Int. Ed.* **2010**, *49*, 2747; e) Y. Yamaoka, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5354; f) B. J. Albert, Y. Yamaoka, H. Yamamoto, *Angew. Chem.* **2011**, *123*, 2658; *Angew. Chem. Int. Ed.* **2011**, *50*, 2610; g) J. Saadi, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 14248; h) P. B. Brady, H. Yamamoto, *Angew. Chem.* **2012**, *124*, 1978; *Angew. Chem. Int. Ed.* **2012**, *51*, 1942.

[4] a) E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190; b) R. Tacke, H. Lange, *Chem. Ber.* **1983**, *116*, 3685.

[5] a) B. G. Ramsey, *J. Organomet. Chem.* **1974**, *67*, C67.

[6] a) T. Hashimoto, T. Takagaki, H. Kimura, K. Maruoka, *Chem. Asian J.* **2011**, *6*, 1936; b) M. Bellassoued, J. Grugler, N. Lensen, A. Catheline, *J. Org. Chem.* **2002**, *67*, 5611; c) R. J. P. Corriu, G. F. Lanneau, M. Perrot, *Tetrahedron Lett.* **1987**, *28*, 3841; d) G. L. Larson, M. Ortiz, M. Rodriguez de Roca, *Synth. Commun.* **1981**, *11*, 583.

[7] For details, see the Supporting Information.

[8] M. P. Cooke, Jr., *J. Org. Chem.* **1986**, *51*, 1637.

[9] a) D. A. Evans, J. V. Nelson, T. R. Taber, *Topics in Stereochemistry*, *Vol. 13* (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1982**, p. 1; b) C. H. Heathcock, *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison), Academic Press, New York, **1984**, chap. 2; c) C. H. Heathcock, *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 181; d) R. Mahrwald, *Modern Aldol Reactions*, *Vol. 1–2*, Wiley-VCH, Weinheim, **2004**; e) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600.

[10] a) C. T. Buse, C. H. Heathcock, *J. Am. Chem. Soc.* **1977**, *99*, 8109; b) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, J. Lampe, *J. Org. Chem.* **1980**, *45*, 1066; c) M. C. Pirrung, C. H. Heathcock, *J. Org. Chem.* **1980**, *45*, 1727; d) C. H. Heathcock, J. P. Hagen, E. T. Jarvi, M. C. Pirrung, S. D. Young, *J. Am. Chem. Soc.* **1981**, *103*, 4972; e) C. H. Heathcock, M. C. Pirrung, S. Montgomery, H. J. Lampe, *Tetrahedron* **1981**, *37*, 4087; f) C. H. Heathcock, M. C. Pirrung, S. D. Young, J. P. Hagen, E. T. Jarvi, U. Badertscher, H.-P. Marki, S. H. Montgomery, *J. Am. Chem. Soc.* **1984**, *106*, 8161; g) J. L. García Ruano, D. Barros, M. C. Maestro, R. Araya-Maturana, J. Fischer, *J. Org. Chem.* **1996**, *61*, 9462; h) D. J. Dixon, S. V. Ley, A. Polara, T. D. Sheppard, *Org. Lett.* **2001**, *3*, 3749; i) D. A. Evans, G. Helmchen, M. Rueping, *Asymmetric Synthesis-The Essentials M. Christmann*, *Vol. 3* (Ed.: S. Brase), Wiley-VCH, Weinheim, **2007**; j) G. L. Khatik, V. Kumar, V. A. Nair, *Org. Lett.* **2012**, *14*, 2442.

[11] a) E. F. Kleinmann, *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Flemming), Pergamon, New York, **1991**, chap. 4.1; b) M. Arend, B. Westerman, N. Risch, *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; c) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; d) S. Denmark, O. J.-C. Nicaise, *Comprehensive Asymmetric Catalysis*, *Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamomoto), Springer, Berlin, **1999**, p. 93; e) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797; f) J. M. M. Verkade, L. J. C. VanHemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29.

[12] a) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060; b) S. Saito, K. Hatanaka, H. Yamamoto, *Org. Lett.* **2000**, *2*, 1891; c) C. Palomo, M. Oiarbide, A. Landa, M. C. Gonzalez-Rego, J. M. Garcia, A. Gonzalez, J. M. Odriozola, M. Martin-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, *124*, 8637; d) F. A. Davis, J. Deng, *Org. Lett.* **2004**, *6*, 2789; e) S. Hata, M. Iguchi, T. Iwasawa, K. Yamada, K. Tomioka, *Org. Lett.* **2004**, *6*, 1721; f) H. Morimoto, S. H. Wiedemann, A. Yamaguchi, S. Harada, Z. Chen, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2006**, *118*, 3218; *Angew. Chem. Int. Ed.* **2006**, *45*, 3146; g) E. A. Tiong, J. L. Gleason, *Org. Lett.* **2009**, *11*, 1725; h) F. Colpaert, S. Mangelinckx, N. De Kimpe, *Org. Lett.* **2010**, *12*, 1904.

[13] a) F. V. Nussbaum, P. Spiteller, *Highlights in Bioorganic Chemistry: Methods and Application* (Eds.: C. Schmuck, H. Wennemers), Wiley-VCH, Weinheim, **2003**, p. 63; b) G. Lelais, D. Seebach, *Biopolymers* **2004**, *76*, 206; c) A. Kuhl, M. G. Hahn, M. Dumic, J. Mittendorf, *Amino Acids* **2005**, *29*, 89.

[14] a) S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021; b) J. Rohr, *Angew. Chem.* **2000**, *112*, 2967; *Angew. Chem. Int. Ed.* **2000**, *39*, 2847; c) A. M. P. Koskinen, K. Karisalmi, *Chem. Soc. Rev.* **2005**,

34, 677; d) C. Hertweck, *Angew. Chem.* **2009**, *121*, 4782; *Angew. Chem. Int. Ed.* **2009**, *48*, 4688; e) S. Pal, *Tetrahedron* **2006**, *62*, 3171.

[15] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Amsterdam, **2002**; c) W. I. I. Bakker, P. L. Wong, V. Snieckus, J. M. Warrington, L. Barriault in *e-EROS* (Ed.: L. A. Paquette), Wiley, New York, **2004**.

[16] a) V. N. Rajasekharan Pillai, *Synthesis* **1980**, 1; b) M. C. Pirrung, Y. R. Lee, *J. Org. Chem.* **1993**, *58*, 6961; c) M. A. Brook, S. Balduzzi, M. Mohamed, C. Gottardo, *Tetrahedron* **1999**, *55*, 10027; d) P. Klán, M. Zabadal, D. Heger, *Org. Lett.* **2000**, *2*, 1569; e) M. C. Pirrung, L. Fallon, J. Zhu, Y. R. Lee, *J. Am. Chem. Soc.* **2001**, *123*, 3638; f) R. S. Givens, P. G. Conrad II, A. L. Yousef, J.-I. Lee, *Photoremovable Protecting Groups in CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed. (Ed.: W. M. Horspool), CRC Press: Boca Raton, Florida, **2003**, chap. 69, p. 1.

[17] a) H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920; b) J. E. Dubois, J. F. Fort, *Tetrahedron* **1972**, *28*, 1653; c) J. E. Dubois, J. F. Fort, *Tetrahedron* **1972**, *28*, 1665; d) J. E. Dubois, P. C. R. Fellman, *Acad. Sci.* **1972**, *274*, 1307; e) J. E. Dubois, P. Fellman, *Tetrahedron Lett.* **1975**, *16*, 1225.

[18] This model could be used to rationalize the unique *syn* selectivity for Mannich reaction. However, the observed *syn*-selectivity could possibly originate from a cyclic- or twist-boat TS. For references, see: a) S. E. Denmark, B. R. Henke, *J. Am. Chem. Soc.* **1991**, *113*, 2177; b) R. W. Hoffmann, K. Ditrich, S. Froech, *Tetrahedron* **1985**, *41*, 5517.

[19] D. R. Williams, A. F. Donnell, D. C. Kammler, *Heterocycles* **2004**, *62*, 167.

