

Catalytic Enantioselective Inverse Electron Demand Hetero-Diels–Alder Reaction with Allylsilanes**

Yuki Matsumura, Takahiro Suzuki, Akira Sakakura,* and Kazuaki Ishihara*

Abstract: The first diastereo- and enantioselective inverse electron demand hetero-Diels–Alder reaction of β,γ -unsaturated α -ketoesters with allylsilanes is described. Chiral copper(II) catalysts successfully activate the β,γ -unsaturated α -ketoesters and promote the reaction with allylsilanes with excellent enantioselectivities. This process represents a new entry to chiral oxanes.

We have developed chiral copper(II) catalysts (**1**-CuX₂; Figure 1), which show higher catalytic activities than conventional bis(oxazoline)/copper(II) complexes in the enantioselective Diels–Alder reaction with acrylamides.^[1,2] The sulfonamide groups of **1** interact with the copper(II) cation

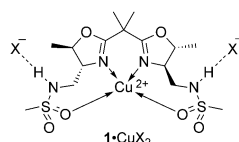
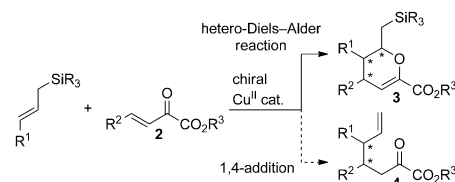


Figure 1. Chiral *n*-cation catalysts **1**-CuX₂.

(*n*-cation interaction), and results in high catalytic activity for a wide range of substrates and a high level of enantioselective induction.^[3] Thus, the *n*-cation catalysts may also be applicable to other asymmetric carbon–carbon bond-forming reactions of α,β -unsaturated carbonyl compounds. We report herein the first enantioselective hetero-Diels–Alder (HDA) reaction of β,γ -unsaturated α -ketoesters with allylsilanes.

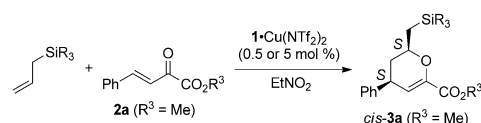
During the course of our extensive studies on **1**-CuX₂-catalyzed asymmetric carbon–carbon bond-forming reactions,



Scheme 1. HDA reaction versus 1,4-addition with allylsilanes.

we examined the reaction of the β,γ -unsaturated α -ketoesters **2** with allylsilanes (Scheme 1). Although β,γ -unsaturated α -ketoesters^[4,5] are good Michael acceptors, allylsilanes^[6] are less nucleophilic alkenes than vinyl ethers and silyl enol ethers.^[7] Therefore, strong Lewis acid catalysts are generally required to promote the reaction of allylsilanes. We expected that our *n*-cation catalysts would promote the reaction of the β,γ -unsaturated α -ketoesters **2** with allylsilanes to give the corresponding 1,4-adducts **4**. Indeed, the chiral complex **1**-Cu(NTf₂)₂ successfully catalyzed the reaction of **2a** with allyltrimethylsilane (Table 1). However, the reaction surprisingly gave the corresponding HDA adduct **3a** (65 % yield) with excellent enantioselectivity, along with a small amount of the 1,4-adduct **4a** (12 % yield, 27 % *ee*; entry 1). The absolute configuration of *cis*-**3a** (R = Me) was determined to be 2*S*,4*S* by X-ray crystallographic analysis after conversion into the amide with (*S*)- α -methyl-4-nitrobenzylamine.^[8] The asymmetric HDA reaction of carbonyl compounds is one of the most powerful methods for the construction of optically

Table 1: HDA reaction of **2a** with allylsilanes promoted by *n*-cation catalyst.^[a]



Entry	R	T [°C]	t [h]	Yield [%] ^[b] 3 a (4 a)	<i>cis/trans</i>	<i>ee</i> [%] ^[c]	
						<i>cis</i> - 3 a	<i>trans</i> - 3 a
1	Me	−20	14	65 (12)	75:25	98	99
2	Et	−20	2	57 (37)	61:39	98	99
3	<i>i</i> Pr	−20	25	83 (0)	54:46	81	68
4 ^[d]	Ph	RT	3	89 (0)	65:35	99	99
5 ^[d]	TMS	0	20	71 (0)	29:71	84	71

[a] Unless otherwise noted, the reaction of **2a** (0.2 mmol) and an allylsilane (5 equiv) was conducted in EtNO₂ (1 mL) in the presence of **1**-Cu(NTf₂)₂ (5 mol %). [b] Yield of isolated product **3a**. Data within parentheses represent the yield of **4a**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 2 equiv of allylsilane were used. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

[*] Y. Matsumura, T. Suzuki, Prof. Dr. K. Ishihara
Graduate School of Engineering, Nagoya University
Furo-cho, Chikusa, Nagoya 464-8603 (Japan)
E-mail: ishihara@cc.nagoya-u.ac.jp
Homepage: <http://www.nubio.nagoya-u.ac.jp/nubio4/index.htm>
Prof. Dr. A. Sakakura
Graduate School of Natural Science and Technology
Okayama University
3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530 (Japan)
E-mail: sakakura@okayama-u.ac.jp
Prof. Dr. K. Ishihara
Japan Science and Technology Agency (JST), CREST
Furo-cho, Chikusa, Nagoya 464-8603 (Japan)

[**] Financial support for this project was provided by JSPS.KAKENHI (23350039).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201402934>.

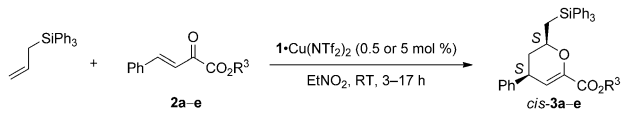
active heterocycles.^[9,10] Highly electron-rich alkenes such as vinyl ethers have been used as dienophiles for the asymmetric inverse electron demand HDA reaction of α,β -unsaturated carbonyl compounds. Very recently, the asymmetric inverse electron demand HDA reaction with simple alkenes was reported.^[19] To the best of our knowledge, this is the first successful example of the enantioselective inverse electron demand HDA reaction of β,γ -unsaturated α -ketoesters with allylsilanes.^[11–13]

Based on this promising result, we next examined the reactivities of various allylsilanes for the **1**-Cu(NTf₂)₂-catalyzed reaction of **2a** (R³ = Me). As a result, the use of sterically hindered allylsilanes such as allyltriisopropylsilane, allyltriphenylsilane, and allyltris(trimethylsilyl)silane suppressed the generation of **4a** and improved the yield of **3a**, although the diastereoselectivities were moderate (Table 1, entries 2–5). Allyltriphenylsilane gave the best result (entry 4).^[14] The major isomer **3a** (R = Ph) could be separated as a single isomer by chromatography on silica gel. Interestingly, the use of sterically hindered allyltris(trimethylsilyl)silane preferentially gave the corresponding *trans*-**3a** (entry 5). Notably, in contrast to the **1**-Cu(NTf₂)₂-catalyzed reaction (entry 4), the use of a conventional bis(oxazoline)-copper(II) complex, (S,S)-*t*Bu-bis(oxazoline)-Cu(NTf₂)₂, as a catalyst gave **3a** in only 51% yield with significant decomposition of **2a**, even after 17 hours at ambient temperature.

We propose here a mechanism for the present inverse electron demand HDA reaction with allylsilanes based on the absolute configuration of **3a** and our previous studies.^[2] The *n*-cation interaction would create an efficient asymmetric environment around the copper(II) cation and preferentially shield the C β -*Re* face of the coordinated **2a** (Figure 2b). Allyltriphenylsilane would approach the C β -*Si* face of **2a** via the *endo* transition state to give *cis* adducts as major products. The predominance of *endo* transition state can be explained in terms of a secondary orbital interaction between the

allylsilane HOMO and the β,γ -unsaturated α -ketoester LUMO^[15,16] (Figure 2a). Indeed, an achiral copper(II) catalyst also preferentially gave *cis*-**3a** (ca. 8:2).^[8] However, the steric repulsion between the sulfonamide group and the triphenylsilyl group decreases the *endo/exo* selectivity, which resulted in the moderate *cis/trans* ratio of the adducts. This consideration is consistent with the fact that the sterically less hindered allyltrimethylsilane showed good *cis* selectivity, while the sterically hindered allyltris(trimethylsilyl)silane preferentially gave *trans* adducts (Table 1).

Table 2: Effect of the ester moiety on the *cis/trans* selectivity.^[a]



Entry	2 (R ³)	Yield [%] ^[b]	<i>cis/trans</i>	<i>ee</i> [%] ^[c]	<i>cis</i> - 3 / <i>trans</i> - 3
1	2a (Me)	89	65:35	99	99
2	2b (<i>i</i> Pr)	89	80:20	95	92
3	2c [CH(<i>i</i> Pr) ₂]	99	89:11	96	99
4	2d [CH(<i>t</i> Bu) ₂]	99	90:10	99	99
5 ^[d]	2d [CH(<i>t</i> Bu) ₂]	99	90:10	97	96
6	2e (<i>t</i> Bu)	20 ^[e]	97:3 ^[e]	n.d.	n.d.

[a] Unless otherwise noted, the reaction of **2** (0.4 mmol) and an allylsilane (2 equiv) was conducted in EtNO₂ (2 mL) in the presence of **1**-Cu(NTf₂)₂ (5 mol%) at ambient temperature for 3–17 h. [b] Yield of isolated product **3**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction of **2d** (4 mmol) and allylsilane (2 equiv) was conducted in the presence of **1**-Cu(NTf₂)₂ (0.5 mol%) in EtNO₂ (4 mL). [e] Yield and *cis/trans* ratio of the corresponding carboxylic acid (R³ = H).

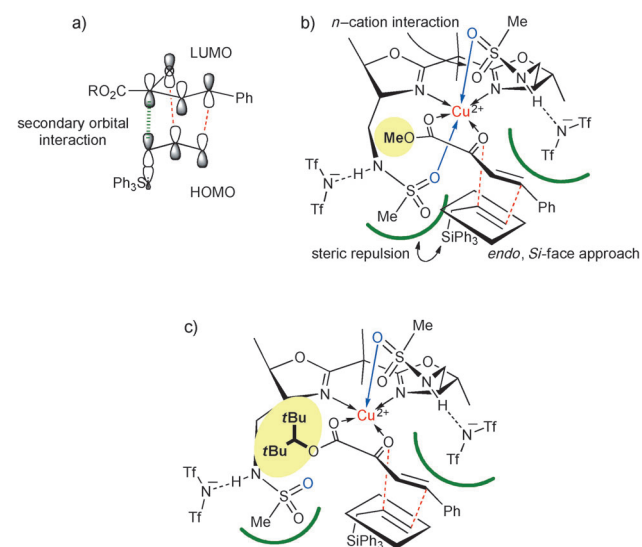


Figure 2. Proposed transition-state assembly for the **1**-Cu(NTf₂)₂-catalyzed HDA reaction of **2**.

To improve the *cis/trans* selectivity of the present HDA reaction, we next investigated the ester moiety of **2** (Table 2). As a result, we found that the use of **2** bearing a bulky R³ group improved the *cis/trans* ratio (entries 2–4). Especially, the use of a di(*tert*-butyl)methyl group gave the best results (entry 4). In contrast, the *tert*-butyl ester (**2e**) was unstable under the reaction conditions and gave the carboxylic acid derivatives of **3e** in low yield (20%), although the diastereoselectivity was high (*cis/trans* 97:3). The improved diastereoselectivity can be explained by the structure of the transition-state assembly (Figure 2c). The sterically hindered di(*tert*-butyl)methyl group of **2d** would make the sulfonamide group move toward the left back side. This change in conformation would release the steric repulsion between the sulfonamide group and the triphenylsilyl group to improve the diastereoselectivity. Only 0.5 mol% of **1**-Cu(NTf₂)₂ efficiently promoted the reaction of **2d** (4 mmol) to give the corresponding adduct **3d** in 99% yield with excellent selectivity (entry 5). The major *cis*-isomer of **3d** could be separated as a single isomer by chromatography on silica gel.

With the highly diastereo- and enantioselective reaction conditions in hand, we next explored the generality and scope of the present HDA reaction with allyltriphenylsilane. The reactions of the various β,γ -unsaturated α -ketoesters **2** were conducted in the presence of **1**-Cu(NTf₂)₂ (5 mol%) at –20 °C

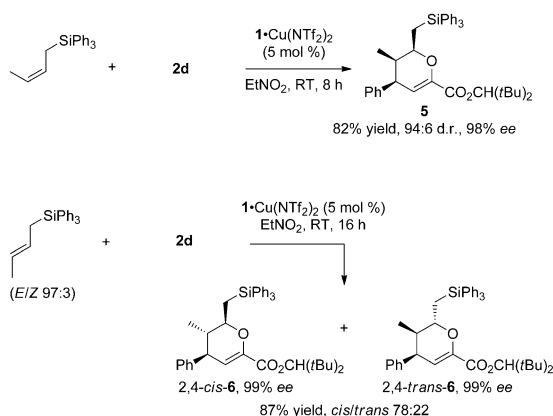
Table 3: Catalytic HDA reaction with allyltriphenylsilane.^[a]

Entry	2 (R ²)	Yield [%] ^[b]	cis/trans	ee [%] ^[c]
1	2 f (4-MeOC ₆ H ₄)	99	92:8	99
2 ^[d]	2 f (4-MeOC ₆ H ₄)	94	91:9	98
3	2 g (4-BrC ₆ H ₄)	97	91:9	99
4 ^[d]	2 g (4-BrC ₆ H ₄)	99	90:10	99
5	2 h (3-BrC ₆ H ₄)	98	90:10	99
6	2 i (2-BrC ₆ H ₄)	96	90:10	98
7	2 j (2-naphthyl)	98	91:9	99
8	2 k (N-acetyl-3-indolyl)	77	91:9	99
9	2 l [(E)-PhCH=CH]	86	90:10	99
10 ^[e]	2 m (Me)	99	92:8	99
11 ^[f]	2 n (iPr)	64	79:21	92

[a] The reaction of **2** (0.4 mmol) and allyltriphenylsilane (2 equiv) was conducted in EtNO₂ (2 mL) in the presence of **1**·Cu(NTf₂)₂ (5 mol %) at ambient temperature. [b] Yield of isolated product **3**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction of **2** (4 mmol) and allyltriphenylsilane (2 equiv) was conducted in EtNO₂ (4 mL) in the presence of **1**·Cu(NTf₂)₂ (0.5 mol %) at ambient temperature. [e] At -20 °C. [f] At 0 °C.

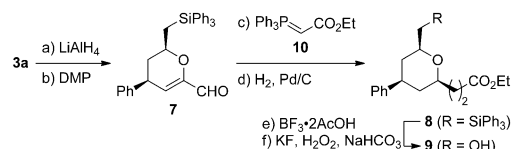
to ambient temperature (Table 3). As a result, **2 f–i**, bearing an electron-donating methoxy group or electron-withdrawing bromine group on the phenyl ring, were smoothly converted into the corresponding adducts **3 f–i** in almost quantitative yield with high diastereo- and enantioselectivity (entries 1–6). The use of only 0.5 mol % of **1**·Cu(NTf₂)₂ successfully gave excellent results (entries 2 and 4). The reaction of **2 j–n**, bearing a 2-naphthyl, *N*-acetyl-3-indolyl, cinnamyl, and alkyl group at the γ-position also gave the corresponding adducts **3 j–n** with high diastereo- and enantioselectivity (entries 7–11).

We next examined the enantioselective HDA reaction of **2 d** with *E*- and *Z*-crotyltriphenylsilanes catalyzed by **1**·Cu(NTf₂)₂ (Scheme 2). The reaction with *Z*-crotyltriphenylsilane gave the corresponding 2,4-*cis*-adduct **5** (82% yield) with excellent enantioselectivity (98% *ee*) and diastereoselectivity (94:6 d.r.). The configuration of *Z*-crotylsilane was com-


Scheme 2. HDA reaction with crotylsilanes.

pletely retained during the reaction. In the same way, the reaction with *E*-crotyltriphenylsilane gave a mixture of the corresponding 2,4-*cis*-adducts **6** (87% yield) with excellent enantioselectivity (99% *ee*) and good diastereoselectivity (78:22 d.r.). These results clearly indicated that the reaction proceeded through a concerted pathway.

The triphenylsilyl group in adduct **3 d** could be converted into a hydroxy group by the following reaction sequence (Scheme 3). Reduction of the ester group of **3 d** (99% *ee*) and subsequent Dess–Martin oxidation gave the aldehyde **7** in



Scheme 3. Oxidative conversion of a triphenylsilyl group: a) LiAlH₄ (5 equiv), THF, 0 °C, 85%; b) Dess–Martin periodinane (DMP; 1.1 equiv), EtOAc, RT, 99%; c) Ph₃P=CHCO₂Et (**10**, 1.1 equiv), THF, RT, 97%; d) H₂, 10% Pd/C (10% w/w), EtOAc, 50 °C, 94%; e) BF₃·2AcOH (10 equiv), CH₂Cl₂, reflux; f) KF (3 equiv), 30% aq. H₂O₂ (10 equiv), NaHCO₃ (1 equiv), MeOH/THF (1:1 v/v), reflux, 70% for two steps. THF = tetrahydrofuran.

84% yield. Wittig reaction of **7** with the ylide **10**^[17] followed by hydrogenation gave the ethyl ester **8** in 91% yield as a single isomer. Subsequent oxidative conversion^[18] of the triphenylsilyl group gave the hydroxycarboxylic ester **9** in 70% yield without any loss of enantiomeric excess (99% *ee*).

In conclusion, we have achieved the first diastereo- and enantioselective inverse electron demand HDA reaction of β,γ-unsaturated α-ketoesters with allylsilanes using *n*-cation catalysts. In contrast to the conventional inverse electron demand HDA reactions with vinyl ethers which give cyclic acetals, the present reaction represents a new entry to chiral oxanes, which can serve as useful building blocks.

Received: March 2, 2014

Revised: March 28, 2014

Published online: April 29, 2014

Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.

Keywords: asymmetric catalysis · copper · cycloaddition · heterocycles · Lewis acid

- [1] a) A. Sakakura, R. Kondo, Y. Matsumura, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2009**, *131*, 17762–17764; b) A. Sakakura, K. Ishihara, *Chem. Soc. Rev.* **2011**, *40*, 163–172.
- [2] For our contributions to π-cation catalysis, see: a) K. Ishihara, M. Fushimi, *Org. Lett.* **2006**, *8*, 1921–1923; b) K. Ishihara, M. Fushimi, M. Akakura, *Acc. Chem. Res.* **2007**, *40*, 1049–1055; c) K. Ishihara, M. Fushimi, *J. Am. Chem. Soc.* **2008**, *130*, 7532–7533; d) A. Sakakura, M. Hori, M. Fushimi, K. Ishihara, *J. Am. Chem. Soc.* **2010**, *132*, 15550–15552. See also Ref. [1b].
- [3] a) I. B. Seiple, S. Su, I. S. Young, A. Nakamura, J. Yamaguchi, L. Jørgensen, R. A. Rodriguez, D. P. O'Malley, T. Gaich, M. Köck, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 14710–14726; b) K.

- Orimoto, H. Oyama, Y. Namera, T. Niwa, M. Nakada, *Org. Lett.* **2013**, *15*, 768–771.
- [4] G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2013**, *113*, 5924–5988.
- [5] For selected recent reports of 1,4-additions to β,γ -unsaturated α -ketoesters, see: a) L. Gremaud, A. Alexakis, *Angew. Chem.* **2012**, *124*, 818–821; *Angew. Chem. Int. Ed.* **2012**, *51*, 794–797; b) Y.-F. Wang, K. Wang, W. Zhang, B.-B. Zhang, C.-X. Zhang, D.-Q. Xu, *Eur. J. Org. Chem.* **2012**, 3691–3696; c) L. Liu, H. Ma, Y. Xiao, F. Du, Z. Qin, N. Li, B. Fu, *Chem. Commun.* **2012**, 48, 9281–9283; d) R. Lu, W. Wei, J. Wang, S. Nie, X. Zhang, M. Yan, *Tetrahedron* **2012**, *68*, 9397–9404; e) J. Lee, D. Kim, *Bull. Korean Chem. Soc.* **2013**, *34*, 1619–1620; f) J. Duan, F. Cao, X. Wang, C. Ma, *Chem. Commun.* **2013**, 49, 1124–1126; g) Z. E. D. Cele, S. C. Sosibo, P. G. Andersson, H. G. Kruger, G. E. M. Maguire, T. Govender, *Tetrahedron: Asymmetry* **2013**, *24*, 191–195.
- [6] a) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293–1316; b) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2793; c) L. Chabaud, P. James, Y. Landais, *Eur. J. Org. Chem.* **2004**, 3173–3199.
- [7] a) J. Bartl, S. Steenken, H. Mayr, *J. Am. Chem. Soc.* **1991**, *113*, 7710–7716; b) J. Burfeindt, M. Patz, M. Müller, H. Mayr, *J. Am. Chem. Soc.* **1998**, *120*, 3629–3634; c) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–1821; d) H. A. Laub, H. Yamamoto, H. Mayr, *Org. Lett.* **2010**, *12*, 5206–5209.
- [8] See the Supporting Information for details.
- [9] a) S. M. Weinreb in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 401–449; b) D. L. Boger in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 451–512; c) H. Waldmann, *Synthesis* **1994**, 535–551; d) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, *32*, 605–613; e) K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702–3733; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588; f) K. A. Jørgensen, *Eur. J. Org. Chem.* **2004**, 2093–2102; g) H. Pellissier, *Tetrahedron* **2009**, *65*, 2839–2877; h) K. Ishihara, A. Sakakura in *Stereoselective Synthesis*, Vol. 3 (Ed.: P. A. Evans), Georg Thieme, Stuttgart, **2011**, pp. 67–123; i) H. Wang, Z. Xu, *Synlett* **2011**, 2907–2912; j) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515–5546.
- [10] For selected recent reports of asymmetric inverse electron demand HDA reactions of α,β -unsaturated carbonyl compounds with vinyl ethers, see: a) J. Kaeobamrung, M. C. Kozłowski, J. W. Bode, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20661–20665; b) S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 10650–10651; c) Z. Xu, L. Liu, K. Wheeler, H. Wang, *Angew. Chem.* **2011**, *123*, 3546–3550; *Angew. Chem. Int. Ed.* **2011**, *50*, 3484–3488; d) Y. Zhu, M. Xie, S. Dong, X. Zhao, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 8202–8208; e) J. Lv, L. Zhang, S. Hu, J.-P. Cheng, S. Luo, *Chem. Eur. J.* **2012**, *18*, 799–803; f) D. Sinha, S. Perera, J. C.-G. Zhao, *Chem. Eur. J.* **2013**, *19*, 6976–6979.
- [11] a) V. Nair, R. Dhanya, N. Vidya, S. Devipriya, *Synthesis* **2006**, 107–110; b) N. Shindoh, H. Tokuyama, K. Takasu, *Tetrahedron Lett.* **2007**, *48*, 4749–4753; c) N. Shindoh, H. Tokuyama, Y. Takemoto, K. Takasu, *J. Org. Chem.* **2008**, *73*, 7451–7456; d) J. Matsuo, S. Sasaki, T. Hoshikawa, H. Ishibashi, *Org. Lett.* **2009**, *11*, 3822–3825.
- [12] Y.-h. Lam, C. Bobbio, I. R. Cooper, V. Gouverneur, *Angew. Chem.* **2007**, *119*, 5198–5202; *Angew. Chem. Int. Ed.* **2007**, *46*, 5106–5110.
- [13] For selected recent reports of Diels–Alder reactions of silylated dienes, see: a) Y.-h. Lam, P. H.-Y. Cheong, J. M. B. Mata, S. J. Stanway, V. Gouverneur, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 1947–1957; b) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390; c) E. Vedejs, S. M. Duncan, *J. Org. Chem.* **2000**, *65*, 6073–6081.
- [14] Nitroethane was the most suitable solvent for the present reaction. The use of CH_2Cl_2 as a solvent for the reaction of **2a** ($\text{R} = \text{Ph}$) with allyltriphenylsilane decreased the reactivity (14 h, 78% yield) and selectivity (d.r. 45:55, *cis* isomer 89% *ee*, *trans* isomer 97% *ee*).
- [15] L.-R. Pan, T. Tokoroyama, *Tetrahedron Lett.* **1992**, *33*, 1469–1472.
- [16] Although we attribute the *cis* selectivity to the secondary orbital interaction, there is some controversy about the existence of secondary orbital interactions in pericyclic reactions. See: J. I. García, J. A. Mayoral, L. Salvatella, *Acc. Chem. Res.* **2000**, *33*, 658–664.
- [17] L. Rout, A. M. Harned, *Chem. Eur. J.* **2009**, *15*, 12926–12928.
- [18] a) G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599–7662; b) H.-J. Knölker, P. G. Jones, G. Wanzl, *Synlett* **1998**, 613–616.
- [19] J. Lv, L. Zhang, S. Luo, J.-P. Cheng, *Angew. Chem.* **2013**, *125*, 9968–9972; *Angew. Chem. Int. Ed.* **2013**, *52*, 9786–9790.