Vinylogous Aldol Reaction

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Disulfonimide-Catalyzed Asymmetric Vinylogous and Bisvinylogous Mukaiyama Aldol Reactions**

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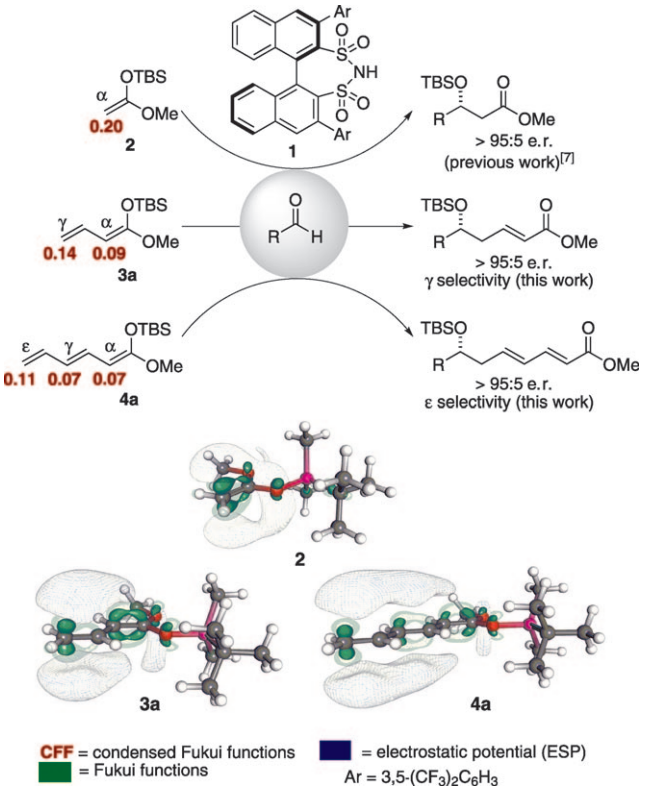
The term vinylogy, which describes a unique property of π systems where the electron density and reactivity is amplified along conjugated bonds, was proposed 75 years ago by Fuson.[1] The principle becomes particularly relevant in the context of the aldol reaction: While metal dienolates often furnish mixtures of α- and γ-addition products,[2] the corresponding dienolsilanes react with high selectivity at the remote γ position.[3] Asymmetric vinylogous Mukaiyama aldol reactions furnish structural subunits commonly occurring in natural products, as illustrated by the research groups of Carreira, Denmark, Kalesse, and others.[4] Several catalytic, asymmetric versions have been developed over the last few years.[5] However, general and highly stereoselective methods that tolerate a wide range of unactivated substrates are still needed. Moreover, bisvinylogous aldol additions, potentially furnishing α,β,γ,δ-unsaturated esters in a single step, have to our knowledge not been successfully developed to date.[6] Herein we report asymmetric vinylogous aldol additions, catalyzed by our recently introduced pre-Lewis acidic disulfonimide catalysts **1**.[7] We also describe the unprecedented extension of the Mukaiyama aldol addition towards a bisvinylogous ε-selective and highly enantioselective variant.

Initial computational studies revealed the expected reactivity trends of the extended ketene acetals (Scheme 1). DFT calculations for attack by an electrophile ($f^-(\boldsymbol{r})$) provided the corresponding condensed Fukui functions (CFF), and the electrostatic potentials (ESP).[8] The data obtained for nucleophiles of type **3** were in line with those previously reported, thus suggesting the reaction occurred preferentially in the γ position ($\alpha = 0.09$, $\gamma = 0.14$).[3f] Interestingly for nucleophiles of type **4**, compounds that have been obtained previously though never studied in terms of their application in aldol additions,[9] the calculations point to nucleophilic attack from the terminal position as well ($\alpha = 0.07$, $\gamma = 0.07$, $\varepsilon = 0.11$). However, the values for the different positions vary less than for nucleophiles of type **3**, possibly suggesting a less distinct selectivity. Furthermore, the nature of the aldehyde should also influence the outcome of the reaction.



Scheme 1. Reactivity and calculated nucleophilic properties of vinylogous nucleophiles for the Mukaiyama aldol reaction. The isosurfaces correspond to values of −0.025 a.u. (ESP) and 0.01 and 0.005 a.u. for Fukui functions. TBS = *tert*-butyldimethylsilyl.

Despite the advancements in the asymmetric catalysis of vinylogous Mukaiyama aldol reactions, organocatalytic systems proved to be more challenging to establish. Probably the best system to date was reported by Denmark and co-workers, who described the Lewis base activation of Lewis acids by utilizing chiral hexamethylphosphoramide (HMPA) derivatives in combination with $SiCl_4$.[10] However, even this method has its limitations, either in scope or reactivity, and requires stoichiometric amounts of the Lewis acid.

As a starting point for our experimental work we explored our chiral disulfonimide catalyst **1** in the reaction of 2-naphthaldehyde with crotonate-derived nucleophile **3a** in different solvents at different temperatures. These studies revealed that Et_2O at −78 °C was optimal (see the Supporting

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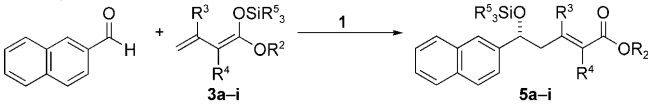
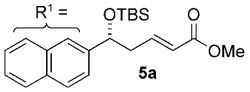
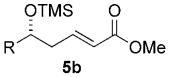
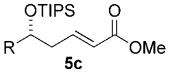
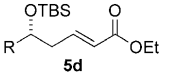
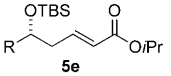
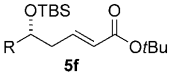
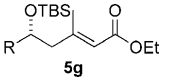
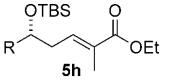
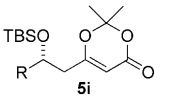
Information). The desired product was obtained in almost quantitative yield and γ selectivity, with an excellent e.r. value of 97:3 using 5 mol% of the catalyst. In line with previous studies,[11] the *E*/*Z* geometry of the starting dienolate had only a small influence on the stereochemical outcome of the reaction as shown in control experiments with the chromatographically separated geometrical isomers of **3a** (see the Supporting Information), and therefore **3a** was used as a mixture.

Next, we also explored other nucleophiles (see Table 1). Studying the influence of the silyl group and the ester substituent in nucleophiles **3b**–**3f** revealed that the silyl group had only a small influence on the reaction outcome, while the ester substituent proved to be important in terms of reactivity. The methyl ester showed high reactivity and delivered products in high yields, while increasing the ester bulkiness, for example, with a *tert*-butyl group, significantly reduced the yields (Table 1, entries 4–6).

Table 1: Nucleophile scope of the disulfonimide-catalyzed vinylogous Mukaiyama aldol reaction.[a]



Entry	Product	Yield [%]	e.r.[b]
1	 **5a**	96	97:3[c]
2	 **5b**	67[d]	96:4
3	 **5c**	73	95:5
4	 **5d**	71	96:4
5	 **5e**	61[e]	95:5
6	 **5f**	30[e]	94:6
7	 **5g**	60[d]	94:6
8	 **5h**	78	81:19
9	 **5i**	80	92:8[f]

[a] Typical reaction conditions: 0.2 mmol of aldehyde, 0.3 mmol of corresponding nucleophile **3**, and 5 mol% of **1** were stirred in Et_2O [0.2 M] for 3 days at −78°C; the yields refer to isolated products. [b] Determined by HPLC on a chiral stationary phase. [c] γ/α ratio > 50:1 determined by GC-MS analysis. [d] In these cases small amounts of side product evident by TLC led to decreased yields of the isolated product. [e] Starting material recovered. [f] The absolute stereochemistry of **5i** was assigned by optical rotation measurements and comparison with literature values. The other compounds were assigned following analogy (see the Supporting Information). TIPS = triisopropylsilyl.

The introduction of substituents, such as in nucleophiles **3g**–**3i**, revealed that a substituent in the β position is well tolerated (Table 1, entries 7 and 9). A substituent in the α position furnished the product with somewhat decreased enantioselectivity (Table 1, entry 8), a trend that complements the Denmark approach, where α substituents are better tolerated than β substituents.[10b] Ketene acetal **3i**, a preferred and especially reactive substrate in previous studies,[5] also gave the product with decreased enantioselectivity.

The reaction of nucleophile **3a** with different aldehydes was also explored (Table 2). In general, electron-rich or -neutral aromatic aldehydes provide superior results, but electron-poor aromatic substrates still enable the reaction to occur with promising enantioselectivities and yields for products not accessible by previous methods. Branched and unbranched aliphatic aldehydes can be utilized as well; however, the products are obtained with lower enantioselectivities and yields.

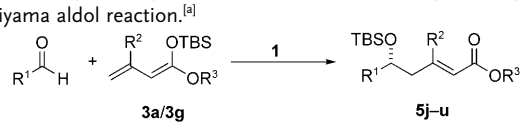
After demonstrating the suitability of our catalytic system for asymmetric vinylogous Mukaiyama aldol reactions, we turned our focus on the previously unexplored bisvinylogous version. The products that are potentially accessible by this method can otherwise only be synthesized directly by using aluminum-mediated mixed crossed aldol condensations of aldehydes with conjugated esters, as shown by Yamamoto and co-workers.[12] The required ketene acetal nucleophiles **4** are easily accessible as *E*/*Z* mixtures from inexpensive sorbic acid derivatives, which are naturally occurring bulk chemicals.[13]

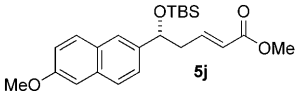
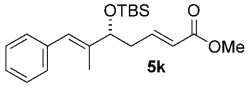
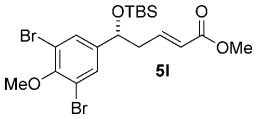
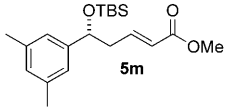
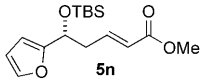
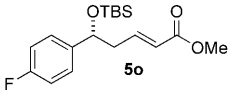
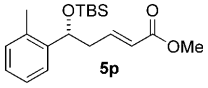
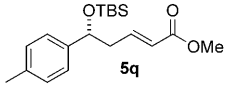
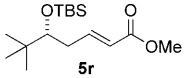
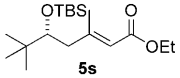
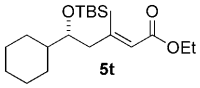
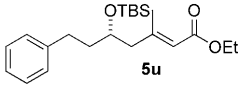
We were pleased to find that compound **4a** reacted smoothly under the same reaction conditions evaluated for its congener **3a** with various aldehydes in good conversions and high enantioselectivity (Table 3). To the best of our knowledge, this is the first report of a regio-, highly enantio-, and ε-selective vinylogous Mukaiyama aldol reaction of double vinylogous silyl ketene acetals with aldehydes.

As predicted by our DFT calculations, the terminal, ε selectivity proved to be less distinct in these transformations. For example, product **6a** was obtained in a ε/α ratio of 5:1. The γ product remained entirely undetectable as proven spectroscopically by analyses of the ^1H, ^{13}C, DEPT-135, and ^1H-^1H-COSY spectra (see the Supporting Information). The data also confirmed an all-*E*-configuration of ε product **6a**. While pronounced structural and electronic variations of the aldehyde were tolerated, the moderate ε/α ratio proved to be true for other substrates as well, thus diminishing the yields of the isolated products somewhat.

Our catalyst system was particularly suited for aromatic and cinnamaldehyde derivatives, with the desired products obtained in high enantioselectivities and good yields. Aliphatic aldehydes, such as pivaldehyde, could be used, which led to the product with promising regioselectivity and yield, but poor enantioselectivity. The introduction of a methyl group to the silyl enol ether, as in nucleophile **4b** (Table 3, entries 10 and 11) gave products with good enantioselectivites but somewhat lower yields.

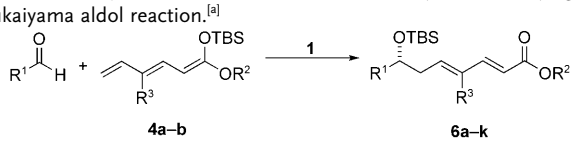
Table 2: Aldehyde scope of the disulfonimide-catalyzed vinylogous Mukaiyama aldol reaction.[a]

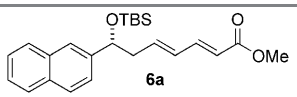
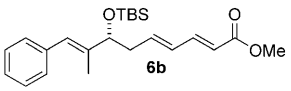
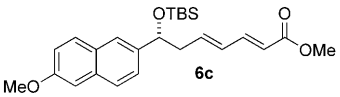
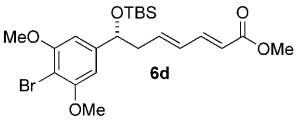
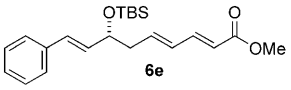
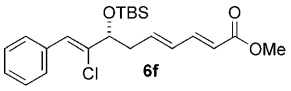
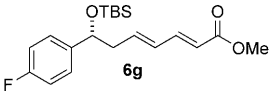
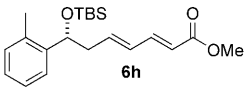
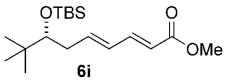
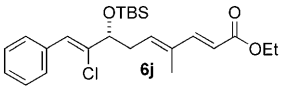
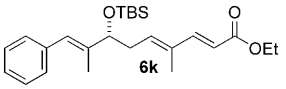


Entry	Product	Yield [%]	e.r.[b]
1	 **5j**	80	98:2[c]
2	 **5k**	89	92:8[c]
3	 **5l**	67	93:7[c]
4	 **5m**	81	96:4[c]
5	 **5n**	76	84:16
6	 **5o**	65	82:18
7	 **5p**	80	78:22
8	 **5q**	61	81:19
9	 **5r**	62	61:39
10	 **5s**	65	65:35
11	 **5t**	45	72:28
12	 **5u**	33	72:28

[a] Experiments conducted under the conditions mentioned in Table 1; the yields refer to isolated products. [b] Determined by HPLC on a chiral stationary phase. [c] All γ/α ratios $>40:1$, as determined by GC-MS.

Table 3: Development of a disulfonimide-catalyzed bisvinylogous Mukaiyama aldol reaction.[a]

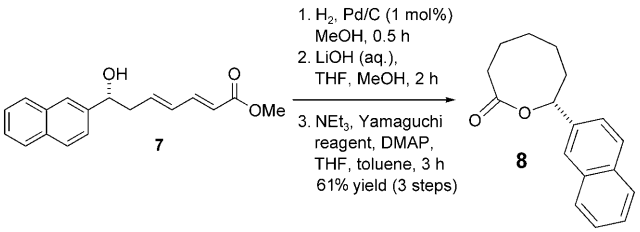


Entry	Product	Yield [%][b]	e.r.[c]	ε/α[d]
1	 **6a**	75	95:5	5:1
2	 **6b**	65	89:11	9:1
3	 **6c**	54	93:7	2:1
4	 **6d**	49[e]	91:9	5:1
5	 **6e**	46	87:13	8.4:1
6	 **6f**	57	96:4	7.7:1
7	 **6g**	37	81:19	1.2:1
8	 **6h**	42	76:24	1.4:1
9	 **6i**	47	54:46	3.2:1
10	 **6j**	55[f]	90:10	0.6:1
11	 **6k**	49	90:10	1.4:1

[a] Typical reaction conditions: 0.2 mmol of aldehyde, 0.3 mmol of corresponding nucleophile **4**, and 5 mol% of **1** were stirred in Et_2O [0.2 M] for 3 days at −78 °C. [b] The yields refer to isolated ε product. The side products were isolated and characterized by NMR spectroscopy where possible (see the Supporting Information). [c] Determined by HPLC on a chiral stationary phase. The stereochemistry was assigned by analogy. [d] Determined by integration of the ^{1}H NMR spectrum of the crude products or by GC-MS. [e] Starting material recovered: 70% conv. [f] Product **6j** was inseparable from a regioisomer by column chromatography and a virtually pure sample was obtained by preparative TLC.

Having α,β,γ,δ-unsaturated esters **6** readily available, we envisioned their implementation in a straightforward approach towards ζ-lactones (Scheme 2). This structural motif occurs in a variety of natural products,[14] and our bisvinylogous aldol products would be ideal starting points for their synthesis. Accordingly, deprotected product **7** was converted into lactone **8** in reasonable yield by a hydrogenation, ester cleavage, Yamaguchi lactonization sequence.[15]

In summary we have developed efficient and easily applicable, disulfonimide-catalyzed vinylogous and bisvinylogous Mukaiyama aldol additions. These extended aldolizations display good to excellent enantioselectivity and have a remarkably broad ketene acetal scope. Highly enantioselective catalytic asymmetric bisvinylogous aldol reactions of any type were previously unknown and, similar to the Mukaiyama aldol reaction itself and its vinylogous variation, offer excellent potential in natural product synthesis. Future



Scheme 2. Synthesis of eight-membered ring lactone **8**. DMAP = 4-dimethylaminopyridine.

studies aim at developing more generally applicable catalysts. With regard to the scope and applicability towards a wider range of electrophiles, an exact understanding of the mechanism is desirable, and is currently being investigated in our laboratories.

Experimental Section

A septum-capped vial with a stirring bar was charged with the corresponding aldehyde (0.2 mmol), catalyst **1** (5 mol%), and dry Et_2O (1 mL). The resulting mixture was cooled to −78 °C in an acetone/dry ice bath, before the silyl enolate (0.3 mmol) was added dropwise by syringe. The resulting reaction mixture was stirred at −78 °C for 3 days. A saturated $NaHCO_3$ solution (0.5 mL) was then added at −78 °C and the reaction mixture was allowed to reach room temperature. Subsequently, the reaction was diluted with Et_2O (25 mL) and dried with $MgSO_4$. The solvent was removed in vacuo and the resulting crude material purified by column chromatography on silica gel (hexanes/ethyl acetate 8:1) to afford the desired products as colorless oily liquids. For further details see the Supporting Information.

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[1] a) R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1 – 27; b) R. E. Christ, R. C. Fuson, *J. Am. Chem. Soc.* **1937**, *59*, 893 – 897.

[2] a) M. W. Rathke, D. Sullivan, *Tetrahedron Lett.* **1972**, *13*, 4249 – 4252; b) J. L. Herrmann, G. R. Kieczykowski, R. H. Schlessinger, *Tetrahedron Lett.* **1973**, *14*, 2433 – 2436.

[3] a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011 – 1014; b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503 – 7509; c) T. Mukaiyama, A. Ishida, *Chem. Lett.* **1975**, 319 – 322; for recent comprehensive studies see: d) G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929 – 1972; e) C. Palomo, M. Oiarbide, J. M. García, *Chem. Eur. J.* **2002**, *8*, 36 – 44; f) S. E. Denmark, J. R. Heemstra, G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760 – 4777; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682 – 4698; g) B. Schetter, R. Mahrwald, *Angew. Chem.* **2006**, *118*, 7668 – 7687; *Angew. Chem. Int. Ed.* **2006**, *45*, 7506 – 7525.

[4] a) M. Kalesse, J. Hassfeld, in *Asymmetric Synthesis—The Essentials*, 2nd ed. (Eds.: M. Christmann, S. Bräse), Wiley-VCH, Weinheim, **2008**, pp. 112 – 116; b) Y. Kim, R. A. Singer, E. M. Carreira, *Angew. Chem.* **1998**, *110*, 1321 – 1323; *Angew. Chem. Int. Ed.* **1998**, *37*, 1261 – 1263; c) M. Christmann, U. Bhatt, M. Quitschalle, E. Claus, M. Kalesse, *Angew. Chem.* **2000**, *112*, 4535 – 4538; *Angew. Chem. Int. Ed.* **2000**, *39*, 4364 – 4366; *Angew. Chem.* **2000**, *112*, 4535 – 4538; d) D. A. Evans, D. M. Fitch, T. E. Smith, V. J. Cee, *J. Am. Chem. Soc.* **2000**, *122*, 10033 – 10046; e) J. Hassfeld, M. Christmann, M. Kalesse, *Org. Lett.* **2001**, *3*, 3561 – 3564; f) J. Hassfeld, M. Kalesse, *Synlett* **2002**, 2007 – 2010; g) F. Liesener, M. Kalesse, *Synlett* **2005**, 2236 – 2238; h) I. Paterson, R. D. M. Davies, A. C. Heimann, R. Marquez, A. Meyer, *Org. Lett.* **2003**, *5*, 4477 – 4480; i) S. E. Denmark, S. Fujimori, *J. Am. Chem. Soc.* **2005**, *127*, 8971 – 8973; j) M. Yamaoka, Y. Fukatsu, A. Nakazaki, S. Kobayashi, *Tetrahedron Lett.* **2009**, *50*, 3849 – 3852; k) E. H. Sessions, P. A. Jacobi, *Org. Lett.* **2006**, *8*, 4125 – 4128.

[5] Selected examples: a) M. Sato, S. Sunami, Y. Sugita, C. Kaneko, *Chem. Pharm. Bull.* **1994**, *42*, 839 – 845; b) R. A. Singer, E. M. Carreira, *J. Am. Chem. Soc.* **1995**, *117*, 12360 – 12361; c) D. A. Evans, J. A. Murry, M. C. Kozlowksi, *J. Am. Chem. Soc.* **1996**, *118*, 5814 – 5815; d) J. Krüger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837 – 838; e) G. Bluet, J.-M. Campagne, *J. Org. Chem.* **2001**, *66*, 4293 – 4298; f) M. Christmann, M. Kalesse, *Tetrahedron Lett.* **2001**, *42*, 1269 – 1271; g) S. Onitsuka, Y. Matsuoka, R. Irie, T. Katsuki, *Chem. Lett.* **2003**, *32*, 974 – 975; h) V. B. Gondi, M. Gravel, V. H. Rawal, *Org. Lett.* **2005**, *7*, 5657 – 5660; i) S. Simsek, M. Horzella, M. Kalesse, *Org. Lett.* **2007**, *9*, 5637 – 5639; j) R. Villano, M. R. Acocella, A. Massa, L. Palombi, A. Scettri, *Tetrahedron Lett.* **2007**, *48*, 891 – 895; k) L. V. Heumann, G. E. Keck, *Org. Lett.* **2007**, *9*, 4275 – 4278; l) N. Zhu, B.-C. Ma, Y. Zhang, W. Wang, *Adv. Synth. Catal.* **2010**, *352*, 1291 – 1295.

[6] a) For an early example of a racemic $ZnCl_2$-mediated bisvinylogous aldol addition to acetals, see B. W. Domagalska, L. Skyper, K. A. Wilk, *Synthesis* **2001**, 2463 – 2469; b) during the preparation of this manuscript, attempts towards an asymmetric bisvinylogous Mukaiyama aldol addition were described by Denmark et al. in the context of the total synthesis of (+)-papulacandin D: S. E. Denmark, T. Kobayashi, C. S. Regens, *Tetrahedron* **2010**, *66*, 4745 – 4759.

[7] P. García-García, F. Lay, P. García-García, C. Rabalakos, B. List, *Angew. Chem.* **2009**, *121*, 4427 – 4430; *Angew. Chem. Int. Ed.* **2009**, *48*, 4363 – 4366; for further studies on the disulfonimide motif, see a) M. Treskow, J. Neudörfl, R. Giernoth, *Eur. J. Org. Chem.* **2009**, 3693 – 3697; b) H. He, L.-Y. Chen, W.-Y. Wong, W.-H. Chan, A. W. M. Lee, *Eur. J. Org. Chem.* **2010**, 4181 – 4184; c) A. Berkessel, P. Christ, N. Leconte, J.-M. Neudörfl, M. Schäfer, *Eur. J. Org. Chem.* **2010**, 5165 – 5170.

[8] For detailed descriptions of the DFT calculations see the Supporting Information and a) M. E. Beck, *J. Chem. Inf. Model.* **2005**, *45*, 273 – 282; b) M. E. Beck, M. Schindler, *Chem. Phys.* **2009**, *356*, 121 – 130.

[9] a) M. Ohno, K. Mori, S. Eguchi, *Tetrahedron Lett.* **1986**, *27*, 3381 – 3384; b) I. Fleming, J. Iqbal, E.-P. Krebs, *Tetrahedron* **1983**, *39*, 841 – 846; c) W. R. Hertler, T. V. Rajan Babu, D. W. Ovenall, G. S. Reddy, D. Y. Sogah, *J. Am. Chem. Soc.* **1988**, *110*, 5841 – 5853.

[10] a) S. E. Denmark, T. Wynn, G. L. Beutner, *J. Am. Chem. Soc.* **2002**, *124*, 13405 – 13407; b) S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800 – 7801.

[11] S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774 – 3789.

[12] S. Saito, M. Shiozawa, H. Yamamoto, *Angew. Chem.* **1999**, *111*, 1884 – 1886; *Angew. Chem. Int. Ed.* **1999**, *38*, 1769 – 1771.

[13] W. R. Hertler, G. S. Reddy, D. Y. Sogah, *J. Org. Chem.* **1988**, *53*, 3532 – 3539.

[14] For selected examples, see a) P. A. Horton, F. E. Koehn, R. E. Longley, O. J. McConnell, *J. Am. Chem. Soc.* **1994**, *116*, 6015 – 6016; b) E. Lee, H. Y. Song, J. W. Kang, D.-S. Kim, C.-K. Jung, J. M. Joo, *J. Am. Chem. Soc.* **2002**, *124*, 384 – 385; c) T.

Yoshimura, F. Yakushiji, S. Kondo, X. Wu, M. Shindo, K. Shishido, *Org. Lett.* **2006**, *8*, 475 – 478; d) Y. Seo, K. W. Cho, J.-R. Rho, J. Shin, B.-M. Kwon, S.-H. Bok, J.-I. Song, *Tetrahedron* **1996**, *52*, 10583 – 10596; e) J. E. Davoren, S. F. Martin, *J. Am. Chem. Soc.* **2007**, *129*, 510 – 511; f) A. Robinson, V. K. Aggarwal, *Angew. Chem.* **2010**, *122*, 6823 – 6825; *Angew. Chem. Int. Ed.* **2010**, *49*, 6673 – 6675.

[15] a) M. Yamaguchi, J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993; b) J. Mulzer, P. A. Mareski, J. Buschmann, P. Luger, *Synthesis* **1992**, 215 – 228.

