Selenenylation

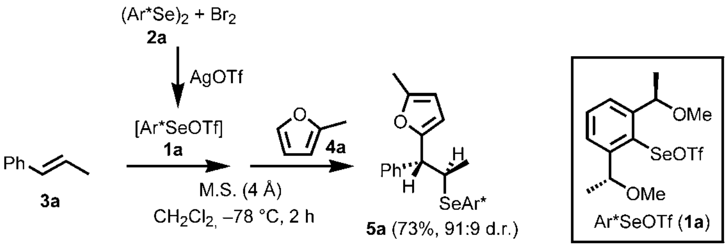
Asymmetric Carboselenenylation Reaction of Alkenes with Aromatic Compounds**

*Kazuki Okamoto, Yoshiaki Nishibayashi,**
*Sakae Uemura, and Akio Toshimitsu**

Asymmetric functionalization of simple alkenes is one of the most attractive subjects in organic synthesis. A variety of asymmetric reactions such as epoxidation,[1] dihydroxylation,[2] aminohydroxylation,[3] hydroboration,[4] hydrosilylation,[5] cyclopropanation,[6] and carbonylation[7] have been reported for the introduction of new functional groups into alkene substrates to produce optically active compounds. The stereoselective addition of electrophilic reagents to simple alkenes is another versatile approach to provide synthetically useful compounds that bear various functionalized groups.[8,9] Recently, electrophilic selenium reagents with optically active moieties have been successfully employed in a number of stereoselective additions to simple alkenes.[10] Typically, the stereoselective selenenylation of simple alkenes with heteroatom-centered nucleophiles such as alcohols, nitriles, oximes, and azides gave the corresponding functionalized organoselenium compounds with high diastereoselectivity.[11,12] In all cases, the selenenylation proceeds via chiral episelenonium ions as key intermediates, which then undergo a ring-opening reaction by nucleophilic attack.

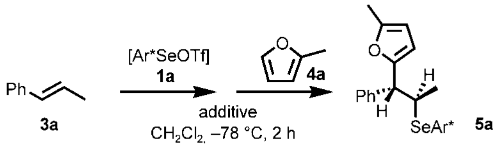
We recently reported the stereospecific reactions of chiral episelenonium ions generated from optically active (β-arylseleno)ethyl alcohols with carbon-centered nucleophiles such as alkenyl silyl ethers, trimethylsilyl cyanide, allyltrimethylsilane, and aromatic compounds.[13] This result prompted us to investigate the asymmetric carboselenenylation reaction of simple alkenes with carbon-centered nucleophiles. We describe herein the first example of the asymmetric carboselenenylation reaction of simple alkenes with aromatic compounds by using an optically active electrophilic selenium reagent.[14]

Treatment of an optically active areneselenenyl trifluoromethanesulfonate (triflate) **1a** (which is generated in situ from the reaction of a diaryl diselenide **2a** with bromine and silver triflate) with excess (*E*)-β-methylstyrene (**3a**) at −78 °C for 10 min in dichloromethane in the presence of molecular sieves (4 Å) and then with 2-methylfuran (**4a**) at −78 °C for 2 h gave 2-(1-phenyl-2-arylselenopropyl)-5-methylfuran (**5a**) in 73 % yield with 91:9 d.r. (Scheme 1). Typical results are shown in Table 1. The presence of the 4-Å molecular sieves is essential to obtain **5a** in high yields (Table 1, entries 1–3). In fact, in the absence of the 4-Å molecular sieves, the yield of **5a** decreased, with an increase in the amount of 1-phenyl-2-aryleselenopropanol (**6**) (Table 1, entry 4). The compound **6** is considered to be formed by nucleophilic attack of adventitious water at the episelenonium ion intermediate. The use of a smaller amount of **3a** decreased the yield of **5a**



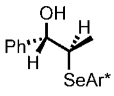
Scheme 1. Asymmetric carboselenenylation reaction of (*E*)-β-methylstyrene (**3a**) with 2-methylfuran (**4a**) by using an optically active electrophilic selenium reagent (**1a**). Tf = trifluoromethanesulfonyl.

Table 1: Asymmetric carboselenenylation reaction of (*E*)-β-methylstyrene (**3a**) with 2-methylfuran (**4a**) by using an optically active electrophilic selenium reagent (**1a**).[a]



Entry	**3a** [equiv]	Additive	Yield [%][b]	d.r.[c]
1	10	M.S. (4 Å) (300 mg)	73	91:9
2	10	M.S. (4 Å) (100 mg)	57	91:9
3	10	M.S. (3 Å) (100 mg)	50	91:9
4	10	–	41[d]	91:9
5	2	–	25[e]	91:9

[a] All the reactions of **3a** (2.00 mmol) with **4a** (1.00 mmol) by using **1a** (0.20 mmol) were carried out at −78 °C for 2 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. M.S. = molecular sieves. [d] 1-Phenyl-2-areneselenopropanol (**6**) was formed in 25 % yield. [e] 1-Phenyl-2-areneselenopropanol (**6**) was formed in 35 % yield.



6

---

[*] K. Okamoto, Dr. Y. Nishibayashi,[+] Prof. Emeritus Dr. S. Uemura
Department of Energy and Hydrocarbon Chemistry
Graduate School of Engineering
Kyoto University
Katsura, Nishikyo-ku, Kyoto, 615-8510 (Japan)
Fax: (+81) 75-383-2517
E-mail: ynishiba@scl.kyoto-u.ac.jp
Prof. Dr. A. Toshimitsu
International Innovation Center
Kyoto University
Sakyo-ku, Kyoto, 606-8501 (Japan)
Fax: (+81) 75-753-9174
E-mail: akiot@iic.kyoto-u.ac.jp

[+] Current address:
Institute of Engineering Innovation
School of Engineering, The University of Tokyo
Yayoi, Bunkyo-ku, Tokyo, 113-8656 (Japan)
Fax: (+81) 35-841-1175

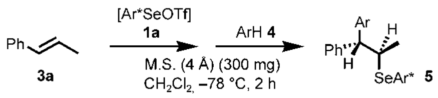
[**] This work was supported by a Grant-in-Aid for Scientific Research for Young Scientists (A) (No. 15685006) to Y.N. from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

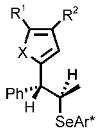
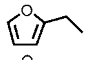
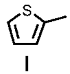
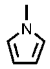
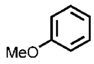
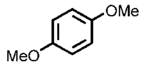
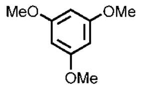
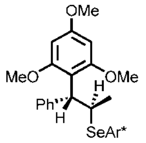
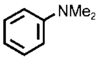
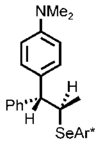
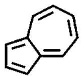
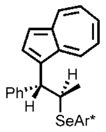
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200500573

(Table 1, entry 5). A high diastereoselectivity was only attained by the use of **1a**. When other C_2-symmetric areneselenenyl triflates bearing two ethoxy groups (**1b**)[15] and two benzyloxy groups (**1c**) were used instead of **1a**, a lower diastereoselectivity of the product and no formation of the product were observed, respectively. Although extremely high diastereoselectivities were reported in the selenenylation of **3a** with heteroatom-centered nucleophiles such as alcohols by using a variety of active areneselenenyl triflates (Scheme 2, **1d**–**1f**),[11,12h] these areneselenenyl triflates did not work effectively in this carboselenenylation reaction. Detailed results are given in the Supporting Information.

Table 2: Asymmetric carboselenenylation reaction of (*E*)-β-methylstyrene (**3a**) with aromatic compound (**4**) by using **1a**.[a]

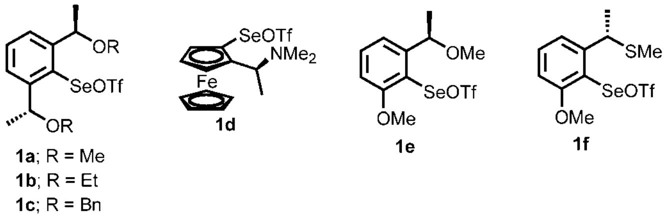


Entry	ArH (4)		Product (5)		Yield[%][b]	d.r.[c]
1		**4b**	 X = O; R^1 = H; R^2 = H	**5b**	36	91:9
2		**4c**	X = O; R^1 = Et; R^2 = H	**5c**	67	91:9
3		**4d**	X = O; R^1 = Me; R^2 = Me	**5d**	63	92:8
4		**4e**	X = S; R^1 = Me; R^2 = H	**5e**	52	91:9
5		**4f**	X = NMe; R^1 = H; R^2 = H	**5f**	48	89:11
6		**4g**			0	–
7		**4h**			0	–
8		**4i**		**5i**	77	95:5
9		**4j**		**5j**	51	90:10
10		**4k**		**5k**	34	91:9

[a] All the reactions of **3a** (2.00 mmol) with **4** (1.00 mmol) in the presence of **1a** (0.20 mmol) were carried out at −78 °C for 2 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR.

The asymmetric carboselenenylation reactions of **3a** with other furans **4b**–**4d** by using **1a** as an optically active electrophilic selenium reagent under similar reaction conditions gave the corresponding alkylated furans **5b**–**5d** in good yields with high diastereoselectivity (Table 2). In the reaction with furan (**4b**), the product **5b** was obtained in slightly lower yield (Table 2, entry 1). Other heterocyclic aromatic compounds such as 2-methylthiophene (**4e**) and *N*-methylpyrrole (**4f**) can be alkylated at the α position of the heterocyclic rings. In both cases, high diastereoselectivities (91:9 and 89:11 d.r., respectively) were attained (Table 2, entries 4 and 5). Unfortunately, no reaction occurred when *N*-methylindole was used as a heterocyclic aromatic compound. Not only heterocyclic aromatic compounds but also electron-rich benzene derivatives can be used in this asymmetric carboselenenylation reaction. The best diastereoselectivity was found in the reaction of **3a** with 1,3,5-trimethoxybenzene (**4i**), and the corresponding alkyl substituted derivative was formed with 95:5 d.r. (Table 2, entry 8). Recrystallization of the mixture from methanol gave only the major diastereoisomer in pure form. The molecular structure of the major diastereoisomer of **5i** was unambiguously determined by X-ray crystallographic analysis (see Supporting Information).[16] In contrast to the good reactivity of *N*,*N*-dimethylaniline (**4j**) and azulene (**4k**) (Table 2, entries 9 and 10), no reaction proceeded when anisole (**4g**) and 1,4-dimethoxybenzene (**4h**) were used as benzene derivatives (Table 2, entries 6 and 7).

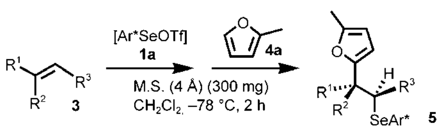
The asymmetric carboselenenylation reaction of other alkenes (**3**) was investigated next (Table 3). The introduction of a *p*-fluoro or *p*-phenyl substituent in the aromatic ring of β-methylstyrene slightly increased the diastereoselectivity (Table 3, entries 1 and 2). On the other hand, a slightly lower diastereoselectivity was attained in the reaction of *p*-methyl-(*E*)-β-methylstyrene (**3d**) (Table 3, entry 3). The introduction of a chloro substituent in the aromatic ring decreased the reactivity (Table 3, entries 4 and 5). Furthermore, the reaction of 2-((*E*)-1-propenyl)naphthalene (**3g**) proceeded smoothly to give the corresponding alkylated furan (**5q**) in good yield with 87:13 d.r. (Table 3, entry 6). Although the reason is not known, the presence of 4-Å molecular sieves decreased both the reactivity and the

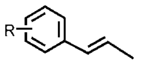
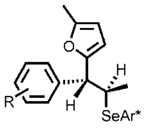
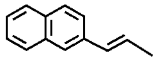
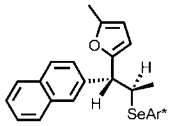
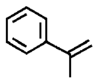
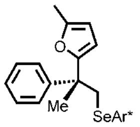
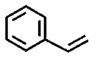
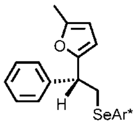
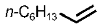
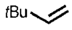


1a; R = Me
1b; R = Et
1c; R = Bn
1d
1e
1f

Scheme 2. Optically active electrophilic selenium reagents.

Table 3: Asymmetric carboselenenylation reaction of alkenes (**3**) with with 2-methylfuran (**4a**) by using **1a**.[a]



Entry	Alkene (3)		Product (5)		Yield[b]	d.r.[c]
						
1	R = *p*-F	**3b**		**5l**	55	93:7
2	R = *p*-Ph	**3c**		**5m**	55	94:6
3	R = *p*-Me	**3d**		**5n**	67	89:11
4	R = *p*-Cl	**3e**		**5o**	39	90:10
5	R = *m*-Cl	**3f**		**5p**	39	94:6
6		**3g**		**5q**	70	87:13
7[d]		**3h**		**5r**	40	90:10
8		**3i**		**5s**	45	78:22
9		**3j**		**5t**	0	–
10		**3k**		**5u**	0	–

[a] All the reactions of **3** (2.00 mmol) with **4a** (1.00 mmol) in the presence of **1a** (0.20 mmol) were carried out at −78 °C for 2 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] In the absence of 4-Å molecular sieves.

diastereoselectivity of the reaction of α-methylstyrene (**3h**) (Table 3, entry 7). A lower diastereoselectivity was observed when styrene (**3i**) was used as an alkene (Table 3, entry 8). A similar trend of lower diastereoselectivity in the cases of **3h** and **3i** has been observed in the asymmetric oxyselenenylation with methanol by using **1b**.[15] Unfortunately, no reaction occurred in the reactions of aliphatic alkenes such as 1-octene (**3j**) and 3,3-dimethylbutene (**3k**).

The stereochemistry of the major diastereoisomer of **5i** (*R* configuration at the benzylic position) indicates that **3a** undergoes *Si*-face attack by the chiral areneselenium moiety (Figure 1). This stereoselective approach is supported by previous theoretical studies with density-functional calculations on the transition states by using **1a**.[17] Separately, we confirmed that the reductive cleavage of a chiral arylselenium moiety of **5j** (90:10 d.r.) with Bu$_3$SnH in the presence of a catalytic amount of AIBN in toluene at reflux for 6 h afforded optically active 1-(*N*,*N*-dimethylaminophenyl)-1-phenylpropane (**7**) in quantitative yield with 90:10 d.r. (HPLC) (Scheme 3). This result indicates that the removal of the arylselenium moiety in **5** proceeded without loss of optical purity at the benzylic position.

In summary, we have developed an asymmetric carboselenenylation reaction of simple alkenes with aromatic compounds by using a C_2-symmetric areneselenenyl triflate. The carbon–carbon bond-forming reaction proceeds with high diastereoselectivity. This reaction is a convenient procedure for the preparation of chiral hydrocarbons that bear an aryl moiety at the stereogenic carbon atom and can be considered as a new type of asymmetric Friedel–Crafts alkylation reaction of aromatic compounds with alkenes. Further work is aimed at the elucidation of the reaction mechanism in detail and broadening the scope of the asymmetric reaction.

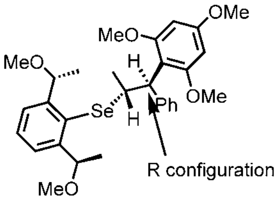
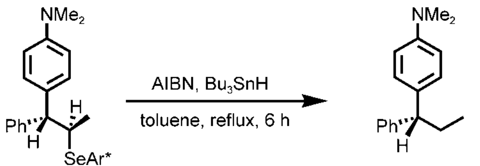


Figure 1. Stereochemistry of the major diastereoisomer of **5i**.



5j (90:10 d.r.)

7 (quant., 80% *ee*)

Scheme 3. Reductive cleavage of a chiral arylselenium moiety of **5j**. AIBN = azobisisobutyronitrile.

Experimental Section

5a: Molecular sieves (4 Å) (300 mg) and a solution of bromine (0.12 mmol) in CCl$_4$ (0.12 mL) were added to a solution of diselenide **2a** (54.4 mg, 0.10 mmol, > 99 % *ee*) in CH$_2$Cl$_2$ (4.0 mL) at −78 °C. After 30 min, silver triflate (61.7 mg, 0.24 mmol) was added. The resulting heterogeneous mixture was stirred at −78 °C for 30 min. *(E)*-β-Methylstyrene (**3a**) (236.4 mg, 2.00 mmol) was then added to the mixture at −78 °C followed by 2-methylfuran (**4a**) (81.2 mg, 1.00 mmol). The mixture was stirred for 2 h, quenched with saturated aqueous NaHCO$_3$ at −78 °C, and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated. The residue was purified by silica-gel chromatography to give **5a** as a colorless oil (68.4 mg, 0.145 mmol, 73 % yield, 91:9 d.r.). The diastereoisomers could not be separated by flash chromatography. The diastereoselectivity does not change during the purification. The ratio of two diastereoisomers was determined by ^{1}H NMR and ^{77}Se NMR; ^{1}H NMR (CDCl$_3$, 400 MHz): major diastereoisomer: δ = 1.24 (d, J = 6.8 Hz, 3 H), 1.39 (d, J = 6.4 Hz, 6 H), 2.26 (s, 3 H), 3.12 (s, 6 H), 3.74 (dq, J = 10 and 6.8 Hz, 1 H), 4.06 (d, J = 10 Hz, 1 H), 5.13 (q,

$J = 6.4$ Hz, 2H), 5.86 (d, $J = 3.2$ Hz, 1H), 6.03 (d, $J = 3.2$ Hz, 1H), 7.27–7.46 ppm (m, 8H); minor diastereoisomer: $\delta = 3.83$ (dq, $J = 8.8$ and 6.4 Hz, 1H), 4.11 ppm (d, $J = 8.8$ Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): major diastereoisomer: $\delta = 13.7$, 20.6, 24.2, 44.3, 52.4, 56.3, 78.4, 105.9, 107.5, 125.2, 127.2, 128.1, 128.3, 128.5, 129.7, 140.6, 148.3, 151.2, 153.0 ppm; ^{77}Se{^{1}H} NMR ($CDCl_3$, 76 MHz): major diastereoisomer: $\delta = 236.9$ ppm (s); minor diastereoisomer: $\delta = 236.3$ ppm (s). Elemental analysis: calcd for $C_{26}H_{32}O_3Se$: C 66.23, H 6.84; found: C 66.31, H 6.92.

Received: February 16, 2005
Published online: May 4, 2005

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

Keywords: alkenes · asymmetric synthesis · diastereoselectivity · selenium · synthetic methods

---

[1] For a review, see: T. Katsuki, *Coord. Chem. Rev.* **1995**, *140*, 189, and references therein.

[2] For a review, see: H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483, and references therein.

[3] a) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 449; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451; b) G. Li, H. H. Angert, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 2995; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813.

[4] a) T. Hayashi, Y. Matsumoto, Y. Ito, *J. Am. Chem. Soc.* **1989**, *111*, 3426; b) K. Burgess, M. J. Ohlmeyer, *Chem. Rev.* **1991**, *91*, 1179, and references therein.

[5] a) Y. Uozumi, T. Hayashi, *J. Am. Chem. Soc.* **1991**, *113*, 9887; b) T. Hayashi, *Acc. Chem. Res.* **2000**, *33*, 354, and references therein.

[6] For a recent review, see: H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977, and references therein.

[7] For a review, see: F. Agbossou, J.-F. Carpentier, A. Mortreux, *Chem. Rev.* **1995**, *95*, 2485, and references therein.

[8] a) O. Kitagawa, T. Hanano, K. Tanabe, M. Shiro, T. Taguchi, *J. Chem. Soc. Chem. Commun.* **1992**, 1005; b) S. H. Kang, S. B. Lee, C. M. Park, *J. Am. Chem. Soc.* **2003**, *125*, 15748.

[9] a) S. H. Kang, M. Kim, *J. Am. Chem. Soc.* **2003**, *125*, 4684; b) S. H. Kang, M. Kim, S. Y. Kang, *Angew. Chem.* **2004**, *116*, 6303; *Angew. Chem. Int. Ed.* **2004**, *43*, 6177.

[10] For recent reviews, see: a) *Organoselenium Chemistry* (Ed.: T. G. Back), Oxford University Press, Oxford, **1999**; b) T. Wirth (Ed.), *Top. Curr. Chem.* **2000**, *208*; c) T. Wirth, *Angew. Chem.* **2000**, *112*, 3890; *Angew. Chem. Int. Ed.* **2000**, *39*, 3741.

[11] a) S. Fukuzawa, Y. Kasugahara, S. Uemura, *Tetrahedron Lett.* **1994**, *35*, 9403; b) Y. Nishibayashi, S. K. Srivastava, H. Takada, S. Fukuzawa, S. Uemura, *J. Chem. Soc. Chem. Commun.* **1995**, 2321; c) H. Takada, Y. Nishibayashi, S. Uemura, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1511.

[12] a) S. Tomoda, M. Iwaoka, *Chem. Lett.* **1988**, 1895; b) T. Wirth, *Angew. Chem.* **1995**, *107*, 1872; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1726; c) S. Fukuzawa, K. Takahashi, H. Kato, H. Yamazaki, *J. Org. Chem.* **1997**, *62*, 7711; d) M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Eur. J. Org. Chem.* **2000**, 3451; e) M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, C. Santi, L. Bagnoli, A. Temperini, *Tetrahedron: Asymmetry* **2001**, *12*, 3053; f) M. Tiecco, L. Testaferri, L. Bagnoli, V. Purgatorio, A. Temperini, F. Marini, C. Santi, *Tetrahedron: Asymmetry* **2001**, *12*, 3297; g) T. G. Back, Z. Moussa, M. Parvez, *J. Org. Chem.* **2002**, *67*, 499; h) M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Chem. Eur. J.* **2002**, *8*, 1118; i) L. Uehlin, G. Fragale, T. Wirth, *Chem. Eur. J.* **2002**, *8*, 1125; j) M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Angew. Chem.* **2003**, *115*, 3239; *Angew. Chem. Int. Ed.* **2003**, *42*, 3131.

[13] a) A. Toshimitsu, K. Nakano, T. Mukai, K. Tamao, *J. Am. Chem. Soc.* **1996**, *118*, 2756; b) K. Okamoto, Y. Nishibayashi, S. Uemura, A. Toshimitsu, *Tetrahedron Lett.* **2004**, *45*, 6137.

[14] An asymmetric intramolecular cyclization of alkenes with aromatic compounds by using an optically active electrophilic selenium reagent was reported, but the reaction is not a direct carboselenenylation; the stepwise reaction first involves an oxyselenenylation and then a stereoselective intramolecular cyclization of an episelenonium ion with benzene derivatives to give the corresponding cyclic products with high diastereoselectivity: R. Déziel, E. Malenfant, C. Thibault, *Tetrahedron Lett.* **1998**, *39*, 5493.

[15] R. Déziel, S. Goulet, L. Grenier, J. Bordeleau, J. Bernier, *J. Org. Chem.* **1993**, *58*, 3619.

[16] The molecular structure of a major diastereoisomer of **5i** was unambiguously clarified by X-ray crystallographic analysis. CCDC-261554 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.

[17] a) T. Wirth, G. Fragale, M. Spichty, *J. Am. Chem. Soc.* **1998**, *120*, 3376; b) X. Wang, K. N. Houk, M. Spichty, T. Wirth, *J. Am. Chem. Soc.* **1999**, *121*, 8567; c) M. Spichty, G. Fragale, T. Wirth, *J. Am. Chem. Soc.* **2000**, *122*, 10914.