Synthetic Methods

DOI: 10.1002/anie.200500923

Highly Diastereoselective Alkylation of Aziridine-2-carboxylate Esters: Enantioselective Synthesis of LFA-1 Antagonist BIRT-377**

*Aniruddha P. Patwardhan, V. Reddy Pulgam, Yu Zhang, and William D. Wulff**

Aziridines are important synthons in organic chemistry as they provide convenient entry to optically pure amines, α-amino acids, amino alcohols, diamines, and a variety of other amino compounds that are useful both in industrial and academic endeavors. In the past, most optically pure aziridines were derived from acyclic members of the chiral pool, however, methods are emerging for the direct synthesis of optically pure aziridines through catalytic asymmetric reactions.[1] We have developed a process for the catalytic asymmetric synthesis of aziridines from the reaction of benzhydryl imines with diazo compounds mediated by a chiral boron Lewis acid prepared from the VAPOL and VANOL ligands.[2–4] This asymmetric aziridination (AZ) proved general for a range imines including those prepared from a variety of aryl aldehydes and also from primary, secondary, and tertiary aliphatic aldehydes (90–99% *ee*). Much lower enantioselectivities were observed with *N*-benzyl imines.[2d]

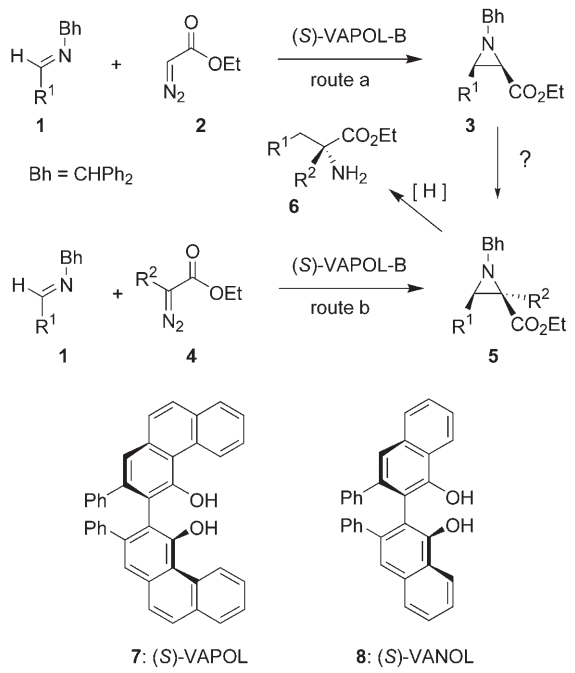
α-Amino acids which are tetrasubstituted at the α-carbon are very popular tools that are used to control conformation in peptides, and hence their biological and pharmaceutical properties. A large number of methods have been developed for the synthesis of tetrasubstituted α-amino acids, and this subject has been reviewed.[5] Interestingly, aziridines have rarely been used for the synthesis of tetrasubstituted α-amino acids and this may be partly due to the fact that the alkylation of aziridine-2-carboxylates is virtually an unknown reaction. Typically, attempts to alkylate aziridine-2-carboxylate esters leads to either ring opening or to self-condensation.[6,7] The only known examples involve the use of either thioesters of aziridine-2-carboxylates[6] or the use of a nitrogen substituent on the aziridine that can chelate a metal enolate.[7]

A direct application of the AZ reaction to the synthesis of tetrasubstituted α-amino acids could be envisioned through the asymmetric aziridination of imine **1** with diazo compound

[*] Dr. A. P. Patwardhan, Dr. V. R. Pulgam, Y. Zhang, Prof. W. D. Wulff
Department of Chemistry
Michigan State University
East Lansing, MI 48824 (USA)
Fax: (+1) 517-353-1793
E-mail: wulff@cem.msu.edu

[**] This work was supported by a grant from the NIH (NIGMS 63019). We thank Dr. Rui Hang for his help with the X-ray analysis.

Supporting information for this article, including preparative procedures and spectral data for all new compounds and X-ray diffraction data for **5a** and **10**, is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Application of the AZ reaction to the synthesis of tetrasubstituted α-amino acids.

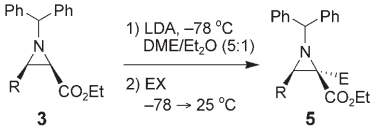
4 followed by the reductive opening of the aziridine ring (route a, Scheme 1). However, we found that substituted diazoesters of the type **4** ($R^2 \neq H$) are sluggish substrates in the AZ reaction. Thus route B, which involves the less readily available and sterically hindered diazo compound **4**, is not viable. Herein, we report the development of an alternative method (route A, Scheme 1) that utilizes commercially available ethyl diazoacetate and a subsequent stereoselective alkylation of an aziridine-2-carboxylate. This strategy has led to the first examples of alkylations of aziridine-2-carboxylate esters with nonchelating N substituents. The synthetic utility of the sequential AZ reaction and aziridine alkylation is illustrated in the asymmetric catalytic synthesis of the leukointegrin LFA-1 antagonist BIRT-377.[8]

Aside from thioesters,[6] the only known examples of aziridine-2-carboxylate alkylations employ a 2-methoxy-1-phenylethyl substituent on nitrogen to stabilize the metal enolate intermediate.[7] Thus it was not clear if the desired alkylation of **3** to **5** would be feasible. Indeed, initial attempts to alkylate the aziridine **3a** with methyl iodide met with failure. Both the lithium and potassium amides of hexamethyldisilazane failed to deprotonate aziridine **3a**. Methylation was successful with lithium diisopropylamide (LDA). The optimal conditions involved the treatment of **3a** with 2.0 equivalents of LDA at −78 °C followed by addition of 3 equivalents of methyl iodide, and then allowing the reaction mixture to warm to room temperature to give **5a** in 82% yield (1.1 equiv of LDA gave a 48% yield of **5a**). We screened the reactions in Table 1 with a mixture of DME (1,2-dimethoxyethane) and diethyl ether (5:1) as solvent,[7] but have subsequently found that comparable yields of **5a** can be achieved with either DME (79%) or THF (85%). Interestingly, the use of diethyl ether led to a complicated reaction mixture with the formation of only a trace amount of the product. The aziridine **5a** was formed as a single diastereomer, as determined by ^{1}H NMR spectroscopy (>99% d.r.). The assignment of the stereochemistry of **5a** was made on the basis of NOE experiments and by an X-ray diffraction analysis of a single crystal of **5a**.

The scope of the alkylation reaction was investigated with a number of different aziridines and electrophiles (Table 1). In all cases a single C2 epimer was observed and, on the basis of the structure of **5a**, was assigned as that formed from retention at the 2-position. Attempts to epimerize the enolate of **3a** failed. Deprotonation of **3a** at −78 °C and then warming to 0 °C for 2 h before quenching with water at −78 °C led to 98% recovery of **3a** with complete retention of stereochemistry. Primary alkyl iodides gave moderate yields, while aldehydes gave high yields but with no selectivity at the alcohol sterogenic center. The only electrophile that gave a mixture of isomers at the aziridine was tributyltin chloride, and in this case the minor product was assigned as the *O*-alkylated product.

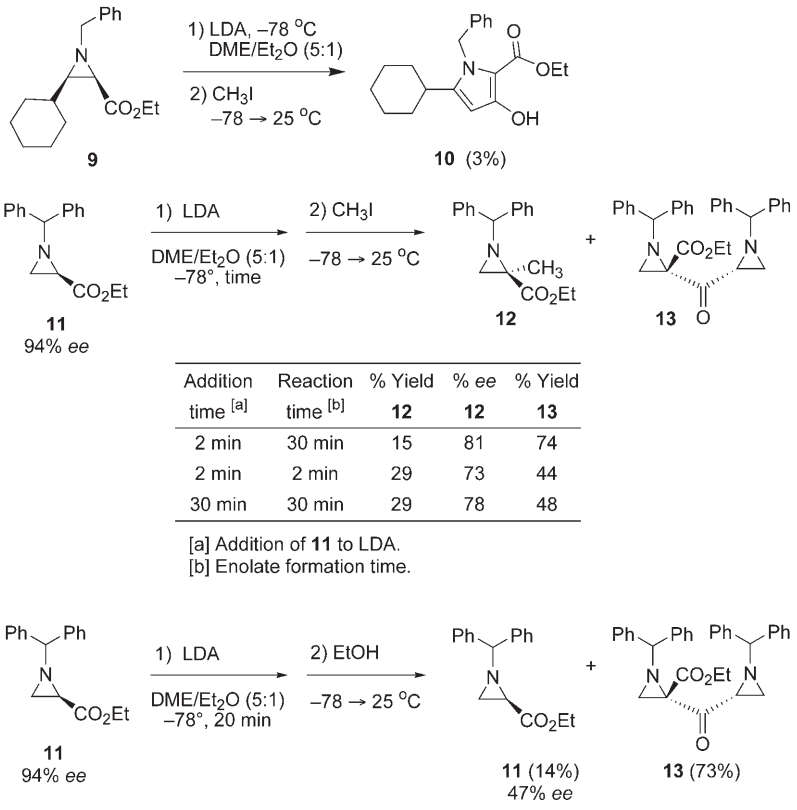
The alkylations of aziridine-2-carboxylates with a benzhydryl group on the nitrogen have never been reported, nor have the alkylations of aziridine-2-carboxylates with a

Table 1: Alkylation of **3**.[a]



Entry	R	Substrate	EX	Product	Yield [%]
1	Ph	**3a**	H_2O	**3a**	98
2	Ph	**3a**	H_2O	**3a**	98[b]
3	Ph	**3a**	CH_3I	**5a**	82
4	Ph	**3a**	*n*-$C_8H_{17}I$	**5b**	50
5	Ph	**3a**	CH_2=$CHCH_2Br$	**5c**	61
6	Ph	**3a**	$PhCH_2Br$	**5d**	33
7	Ph	**3a**	MOMCl	**5e**	63
8	Ph	**3a**	PhCHO	**5f**	95[c]
9	Ph	**3a**	*n*-C_3H_7CHO	**5g**	89[c]
10	Ph	**3a**	Bu_3SnCl	**5h**	73[d]
11	2-naphthyl	**3b**	CH_3I	**5i**	70
12	*p*-PhC_6H_4	**3c**	CH_3I	**5j**	64
13	*p*-BrC_6H_4	**3d**	CH_3I	**5k**	86
14	*c*-C_6H_{11}	**3e**	CH_3I	**5l**	70
15	*t*Bu	**3f**	MOMCl	**5m**	66

[a] Unless otherwise specified, the reaction was performed with 2 equivalents of LDA in a solution of **3** (0.06 M) in DME/Et_2O (5:1). Only one isomer of **5** was observed except for entries 8–10. [b] Reaction mixture warmed to 0 °C for 2 h and then quenched at −78 °C. [c] A 1:1 mixture of diastereomers at the carbinol carbon. [d] Includes an 18% yield of a product tentatively assigned as an *O*-alkylated isomer. MOM = methoxymethyl.



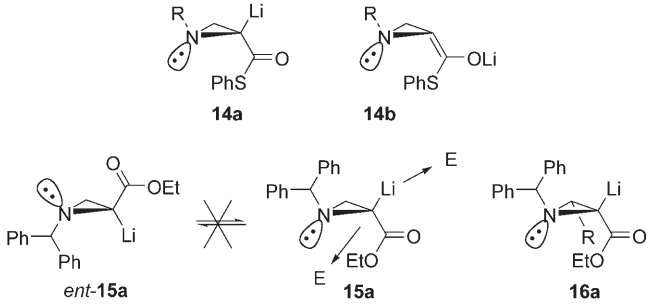
Addition time [a]	Reaction time [b]	% Yield **12**	% *ee* **12**	% Yield **13**
2 min	30 min	15	81	74
2 min	2 min	29	73	44
30 min	30 min	29	78	48

[a] Addition of **11** to LDA.
[b] Enolate formation time.

Scheme 2. Influence of substituents on aziridine-2-carboxylates in alkylation reactions.

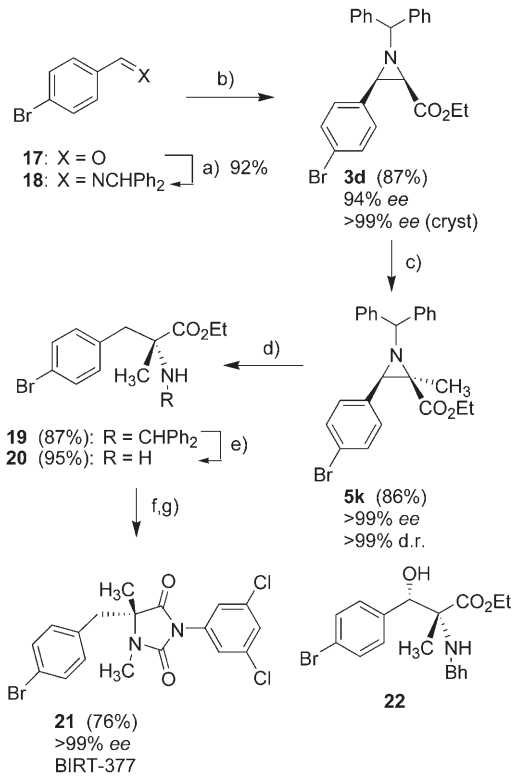
substituent in the 3-position. Thus, we decided to investigate the alkylations of aziridines **9** and **11** in an effort to see which has the greater influence (Scheme 2). The results indicate that the benzhydryl group has the most significant impact. Whereas the cyclohexyl-substituted aziridine **3e** is methylated cleanly in 70% yield with methyl iodide (Table 1, entry 14), the benzyl analogue **9** gives a complicated reaction mixture under the same conditions and none of the expected alkylated aziridines could be detected or isolated from the crude reaction mixture (all starting material was consumed). The only product that was isolated and identified from this reaction mixture was the pyrrole **10**, whose origin is unclear but whose structure was confirmed by X-ray diffraction analysis. It is also clear that the presence of a substituent at the 3-position of the aziridine is important. Aziridine **11** which has no substituent in the 3-position gives only a 15% yield of the alkylated aziridine **12** while all of the aziridines in Table 1 can be alkylated with methyl iodide in 64–82% yield under the same conditions. The major product in the methylation of **11** is the Claisen condensation product **13**, which is the only product that has been seen from the attempted alkylation of ethyl esters of aziridine-2-carboxylates.[7]

Interestingly, the optical purity of the methylated aziridine **12** (81% *ee*) is less than the starting aziridine **11** (94% *ee*). The loss of optical activity (47% *ee*) is greater for the protonation of the enolate of **11** which occurs with retention of configuration. This result suggests that the loss of optical activity is dependent on the electrophile. The enolate of **11** was allowed to age for only 2 minutes before methyl iodide was added, and the optical purity of **12** was found to be 73% *ee*. Thus, there does not seem to be a time dependence on the loss of optical activity. The normal aging time of the enolate is 30 minutes, and in this case its optical purity is not lower but in fact slightly higher (81% *ee*). Increasing the time of addition of **11** to LDA leads to only a slight increase in the proportion of the alkylated product **12** to the Claisen product **13**. Seebach and co-workers previously observed that the enolates of aziridine thioesters can also be alkylated with retention and that the enolate must either exist as the *C*-metalloenolate **14a** or the *O*-metalloenolate **14b**, which is substantially pyramidal at the enolate carbon (Scheme 3).[6b] We interpret the above results as involving a configurationally stable enolate (drawn as the *C*-enolate **15a** but could also be the pyramidal *O*-enolate **15b**) that does not epimerize with time but rather reacts with either retention or inversion, the proportion of which is electrophile dependent. This would be consistent with the observation that all of the *cis*-3-substituted aziridines shown in Table 1 give exclusively alkylated products with retention of configuration. The R group in enolate **16a** would be expected to disfavor alkylation with inversion by approach of the electrophile from the rear side.



Scheme 3. Alkylation of aziridine thioesters. E = electrophile.

The utility of the alkylation of aziridine-2-carboxylates in the synthesis of tetrasubstituted α-amino acids is demonstrated in the synthesis of BIRT-377 (Scheme 4). BIRT-377 has been developed as an agent for the treatment of inflammatory and immune disorders.[8] The asymmetric synthesis was achieved through the aziridine **3d**, which was prepared by the AZ reaction with 1 mol% catalyst in 87% yield and with 94% *ee* with greater than 50:1 selectivity for the *cis* isomer. A single recrystallization gave material with over 99% *ee* (72% recovery, first crop). The methylation of **3d** followed from the above procedure to give **5k** in 86% yield as a single diastereomer. Reductive ring opening was performed with borane–trimethylamine complex in the presence of trifluoroacetic acid (TFA) to give the amino ester **19** in 87% yield ($BH_3{\cdot}Me_3N$ with TFA gave a 6:1 mixture of **19** and **22**).[9] Ring opening by hydrogenolysis under a variety of conditions including Pd-C/HCO_2H occurred with simultaneous bromide reduction. Surprisingly, the



Scheme 4. Reagents and conditions: a) Ph_2CHNH_2 (1.0 equiv), CH_2Cl_2, $MgSO_4$, room temperature, 24 h; b) ethyl diazoacetate (1.1 equiv), (*S*)-VAPOL-B catalyst (1 mol%; see footnote 3), CCl_4, room temperature, 20 h; c) LDA (2 equiv), DME/Et_2O (5:1), −78 °C, 0.5 h; MeI (3 equiv), −78 to RT; d) $BH_3{\cdot}Me_3N$ (12 equiv), TFA (9 equiv), CH_2Cl_2, 0° to RT, 36 h; e) Et_3SiH (3 equiv), TFA, reflux, 5 h; f) 3,5-dichloro-phenyl isocyanate (1.1 equiv), DMSO, Na_2CO_3, 120 °C, 1.5 h; g) NaHMDS (1.2 equiv), DMF, room temperature; MeI (1.2 equiv), 2 h. DMSO = dimethyl sulfoxide; HMDS = hexamethyldisilazide; DMF = *N*,*N*-dimethylformamide.

reductive ring opening of **5k** with triethylsilane and TFA gave mainly the amino alcohol **22**, which results from ring opening with trifluoroacetate. Cleavage of the benzhydryl group in **19** with triethylsilane in the presence of trifluoroacetic acid gave the amine **20** in 95% yield. The conversion of amine **20** into BIRT-377 (**21**) follows methods employed in previous syntheses.[8d]

The fact that benzhydryl-protected aziridine-2-carboxylates can be readily alkylated at the 2-position greatly enhances the synthetic utility of the asymmetric aziridination (AZ) reaction, as illustrated by the synthesis of BIRT-377. Additional studies with other electrophiles and applications in other syntheses will be reported in due course.

Received: March 11, 2005
Published online: August 24, 2005

Keywords: asymmetric catalysis · aziridines · BIRT-377 · enols · synthetic methods

[1] P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905 – 2920.
[2] a) J. C. Antilla, W. D. Wulff, *J. Am. Chem. Soc.* **1999**, *121*, 5099 – 5100; b) J. C. Antilla, W. D. Wulff, *Angew. Chem.* **2000**, *112*, 4692 – 4695; *Angew. Chem. Int. Ed.* **2000**, *39*, 4518 – 4521; c) C. Loncaric, W. D. Wulff, *Org. Lett.* **2001**, *3*, 3675 – 3678; d) J. Antilla, W. D. Wulff, Y. Zhang, unpublished results.
[3] The catalyst is prepared by heating a solution of (*S*)-VAPOL and triphenylborate (3 equiv) in CCl_4 at 85 °C for 1 h and then by removing the volatiles under a high vacuum at 85 °C for 30 minutes.
[4] For other examples of aziridines from the reactions of imines with diazo compounds, see references [2a], [2b], and references therein, and the following: a) S. H. Lee, I. W. Song, *Bull. Korean Chem. Soc.* **2005**, *26*, 223 – 224; b) M. Redlich, M. M. Hossain, *Tetrahedron Lett.* **2004**, *45*, 8987 – 8990; c) B. Vanderhoydonck, C. V. Stevens, *Synthesis* **2004**, 722 – 734; d) A. L. Williams, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 1612 – 1613; e) Y. Li, P. W. H. Chan, N.-Y. Zhu, C.-M. Che, H.-L. Kwong, *Organometallics* **2004**, *23*, 54 – 66; f) J. R. Krumper, M. Gerisch, J. M. Suh, R. G. Bergman, T. D. Tilley, *J. Org. Chem.* **2003**, *68*, 9705 – 9710; g) J. S. Yadav, B. V. S. Reddy, P. N. Reddy, M. S. Rao, *Synthesis* **2003**, 1387 – 1390; h) T. Akiyama, S. Ogi, K. Fuchibe, *Tetrahedron Lett.* **2003**, *44*, 4011 – 4013; i) J. S. Yadav, B. V. S. Reddy, M. S. Rao, P. N. Reddy, *Tetrahedron Lett.* **2003**, *44*, 5275 – 5278; j) W. Sun, C.-G. Zia, H.-W. Wang, *Tetrahedron Lett.* **2003**, *44*, 2409 – 2411; k) E. Hevia, J. Perez, V. Riera, D. Miguel, S. Kassel, A. Rheingold, *Inorg. Chem.* **2002**, *41*, 4673 – 4679; l) M. F. Mayer, M. M. Hossain, *J. Organomet. Chem.* **2002**, *654*, 202 – 209; m) V. K. Aggarwal, E. Alonso, M. Ferrara, S. E. Spey, *J. Org. Chem.* **2002**, *67*, 2335 – 2344; n) D. Morales, J. Perez, L. Riera, V. Riera, R. Corzo-Suarez, S. Garcia-Granda, D. Miguel, *Organometallics* **2002**, *21*, 1540 – 1545; o) M. P. Spanedda, B. Crousse, S. Narizuka, D. Bonnet-Delphon, J.-P. Begue, *Collect. Czech. Chem. Commun.* **2002**, *67*, 1359 – 1365; p) K.-D. Lee, J.-M Suh, J.-H. Park, H.-J. Ha, H. G. Choi, C. S. Park, J. W. Chang, W. K. Lee, Y. Dong, H. Yun, *Tetrahedron* **2001**, *57*, 8267 – 8276; q) V. K. Aggarwal, M. Ferrara, C. J. O'Brien, A. Thompson, R. V. H. Jones, R. Fieldhouse, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1635 – 1643; r) B. Crousse, S. Narizuka, D. Bonnet-Delpon, J.-P. Begue, *Synlett* **2001**, *5*, 679 – 681; s) M. P. Doyle, W. Hu, D. J. Timmons, *Org. Lett.* **2001**, *3*, 933 – 935; t) M. F. Mayer, Q. Wang, M. M. Hossain, *J. Organomet. Chem.* **2001**, *630*, 78 – 83; u) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem.* **2001**, *113*, 1482 – 1485; *Angew. Chem. Int. Ed.* **2001**, *40*, 1433 – 1436; v) S. H. Lee, T. D. Han, K. Yu, K. H. Ahn, *Bull. Korean Chem. Soc.* **2001**, *22*, 449 – 450; w) V. K. Aggarwal, M. Ferrara, *Org. Lett.* **2000**, *2*, 4107 – 4110; x) R. Hori, T. Aoyama, T. Shioiri, *Tetrahedron Lett.* **2000**, *41*, 9455 – 9458; y) S. Sengupta, S. Mondal, *Tetrahedron Lett.* **2000**, *41*, 6245; z) T. Kubo, S. Sakaguchi, Y. Ishii, *Chem. Commun.* **2000**, 625 – 626; aa) W. Xie, J. Fang, J. Li, P. G. Wang, *Tetrahedron* **1999**, *55*, 12929 – 12938; ab) D. L. Wright, M. C. McMills, *Org. Lett.* **1999**, *1*, 667 – 670; ac) K. Juhl, R. G. Hazell, K. A. Jorgensen, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2293 – 2297.
[5] a) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517 – 3599; b) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry.* **2000**, *11*, 645 – 732.
[6] a) D. Seebach, R. Häner, *Chem. Lett.* **1987**, 49 – 52; b) R. Häner, B. Olano, D. Seebach, *Helv. Chim. Acta* **1987**, *70*, 1676 – 1691.
[7] a) V. Alezra, M. Bonin, L. Micouin, H.-P. Husson, *Tetrahedron Lett.* **2000**, *41*, 651 – 654; b) V. Alezra, M. Bonin, L. Micouin, C. Policar, H.-P. Husson, *Eur. J. Org. Chem.* **2001**, 2589 – 2594.
[8] a) N. K. Yee, *Org. Lett.* **2000**, *2*, 2781 – 2784; b) E. Napolitano, V. Farina, *Tetrahedron Lett.* **2001**, *42*, 3231 – 3234; c) R. P. Frutos, S. Stehle, L. Nummy, N. Yee, *Tetrahedron: Asymmetry* **2001**, *12*, 101 – 104; d) S. R. Kapadia, D. M. Spero, M. Eriksson, *J. Org. Chem.* **2001**, *66*, 1903 – 1905; e) N. S. Chowdari, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 867 – 870.
[9] a) E. Vedejs, A. Klapars, D. L. Warner, A. H. Weiss, *J. Org. Chem.* **2001**, *66*, 7542 – 7546; b) B. Carboni, L. Monnier, *Tetrahedron* **1999**, *55*, 1197 – 1248.

