Asymmetric Catalysis

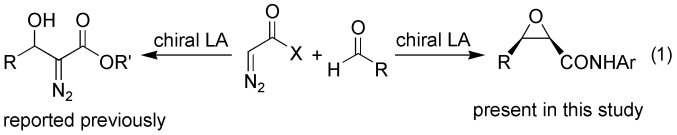
DOI: 10.1002/anie.200903061

An Asymmetric Catalytic Darzens Reaction between Diazoacetamides and Aldehydes Generates *cis*-Glycidic Amides with High Enantiomeric Purity**

*Wei-Jun Liu, Bing-Da Lv, and Liu-Zhu Gong**

Optically pure epoxides are one of the most important classes of chiral molecules because they have broad application in organic synthesis, and thus occupy a privileged position.[1] The presence of ester and amide functionality in glycidic esters and amides provides more flexibility in the modulation of these molecules and thus allows better access to the synthesis of structurally diverse targets in comparison with simple expoxides. Indeed, by starting with enantiomerically pure glycidic esters or amides, the bulky synthesis of some key chiral intermediates for building up medicinally relevant molecules has been realized, as exemplified by the preparation of the side chain of taxol.[2] Recently, the glycidic amide was found to be a key structural motif present in natural products such as SB-204900 and prebalamide.[3] The well-established methods to access optically active glycidic esters and amides include asymmetric catalytic epoxidation of α,β-unsaturated carbonyl compounds using either chiral organo- or metal-based catalysts.[2] Despite these elegant advances, relatively few protocols are available for accessing both *cis*-glycidic esters or amides. Although asymmetric epoxidation affords optically active *cis*-glycidic esters, the diastereochemistry depends essentially on the geometry of the carbon–carbon double bond and thus (*Z*)-acrylates are necessary.[4]

The Darzens reaction represents a robust alternative to expoxidation for producing α,β-epoxy carbonyl and related compounds.[5] An asymmetric Darzens reaction with chiral phase transfer catalysts resulted in moderate enantioselectivity.[6,7] Recently, North and co-workers reported an asymmetric Darzens reaction using a chiral cobalt complex as the catalyst, giving epoxy esters with moderate diastereoselectivity and enantioselectivity.[8] The catalytic asymmetric synthesis of *trans*-glycidic amides through chiral sulfur ylides, which are generated in situ from diazoacetamides and chiral binaphthylsulfide using a copper complex, provided a low yield and moderate enantioselectivity.[9a] Camphor-derived sulfonium amide could participate in a Darzens reaction with aldehydes to yield *trans*-glycidic amides with high enantioselectivity, although stoichiometric amounts of chiral sulfide was required.[9b,c] To date, no reports describe a highly *cis*-selective Darzens reaction with excellent enantioselectivity. Herein, we report an asymmetric Darzens reaction between diazoacetamides and aldehydes catalyzed by a readily accessible binol/titanium(IV) complex to yield *cis*-glycidic amides with excellent enantioselectivity [Eq. (1); LA = Lewis acid].



Diazo carbonyl compounds are an important type of reactant used in many transformations.[10] Diazoacetates generally participate in an aldol reaction in the presence of Lewis acid catalysts.[11] Very recently, Maruoka and co-workers found that diazoacetamides of type **3** (see Table 1) underwent an aziridination reaction,[12] whereas diazoacetates preferred Mannich reactions under similar reaction conditions.[13] The aziridine product was preferentially formed, probably because the lower acidity of the α proton of the diazoacetamide group compared with that of the diazoacetate group resists hydrogen abstraction. This outcome inspired us to consider whether it is possible to initiate an asymmetric Darzens reaction between diazoacetamides (**3**) and aldehydes using an appropriate chiral Lewis acid [Eq. (1)].

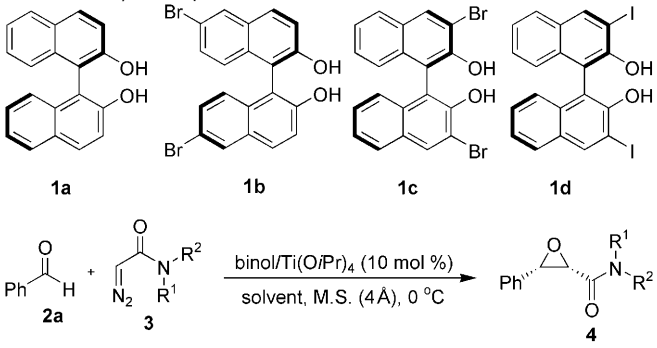
To validate our hypothesis, we examined a reaction of diazo-*N*,*N*-dimethylacetamide (**3a**) with benzaldehyde in CH_2Cl_2 at 0°C using a chiral titanium complex, formed in situ from (*R*)-binol and $Ti(OiPr)_4$,[14] as the catalyst. Unfortunately, no reaction occurred (Table 1, entry 1). *N*-benzyl-2-diazoacetamide (**3b**) also showed no reactivity and decomposed under the reaction conditions (Table 1, entry 2). Gratifyingly, *N*-(*p*-methoxylphenyl)-diazoacetamide (**3c**) reacted smoothly with benzaldehyde and furnished *cis*-glycidic amide **4c** in a high yield with excellent enantioselectivity (95% *ee*; Table 1, entry 3). Notably, *N*-phenyl-diazoacetamide (**3d**) participated in a similar reaction and generated *cis*-glycidic amide **4d** with 99% *ee* (Table 1, entry 4). Significantly, this reaction exhibited excellent diastereoselectivity and no *trans*-diastereomer was detected by ^1H NMR analysis of the crude product. Lowering the catalyst loading resulted in a slow reaction with diminished enantioselectivity (Table 1, entry 5). An evaluation of titanium (IV)

[*] Dr. W.-J. Liu, B.-D. Lv, Prof. L.-Z. Gong
Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry
University of Science and Technology of China
Hefei, 230026 (China)
Fax: (+86) 551-3600-622
E-mail: gonglz@ustc.edu.cn

[**] We are grateful for financial support from CAS, the 973 program (grant no. 2009CB825300), and the Ministry of Education (China).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903061.

Table 1: Darzens reaction of benzaldehyde with diazoacetamide using various binol/Ti complexes.[a]



Entry	4	R^1, R^2	1	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	Me, Me	**1a**	CH_2Cl_2	1	n.r.	–
2[d]	**4b**	Bn, H	**1a**	CH_2Cl_2	1	–	–
3	**4c**	PMP, H	**1a**	CH_2Cl_2	1	87	95
4	**4d**	Ph, H	**1a**	CH_2Cl_2	1	88	99
5[e]	**4d**	Ph, H	**1a**	CH_2Cl_2	7	81	88
6	**4d**	Ph, H	**1b**	CH_2Cl_2	18	77	89
7	**4d**	Ph, H	**1c**	CH_2Cl_2	30	67	20[f]
8	**4d**	Ph, H	**1d**	CH_2Cl_2	18	69	26[f]
9	**4d**	Ph, H	**1a**	$CHCl_3$	1	84	97
10	**4d**	Ph, H	**1a**	DCE	1	84	99
11	**4d**	Ph, H	**1a**	$(Et)_2O$	1	92	98
12	**4d**	Ph, H	**1a**	THF	1	92	92
13	**4d**	Ph, H	**1a**	toluene	18	65	97

[a] The reaction was carried out on a 0.2 mmol scale in solvent (2 mL) with M.S. (4 Å, 120 mg) in an argon atmosphere, and the ratio of **2**/**3** was 1.2:1. [b] Yield of isolated product was based on **3**. [c] Determined by HPLC on a chiral stationary phase. [d] **3b** decomposed under these reaction condition. [e] 2.5 mol% of the catalyst was used. [f] The opposite enantiomer was obtained. Bn = benzyl, M.S. = molecular sieves, PMP = *para*-methoxyphenyl, THF = tetrahydrofuran.

complexes of different binaphthol derivatives **1a–d** revealed that the 3,3′ substituents have considerable effect on the enantioselectivity (compare Table 1, entry 4 with entries 6–8). Among them, the (*R*)-binol/titanium complex turned out to be the most efficient catalyst and offered the highest stereoselectivity. An investigation of solvents found that halogenated and ether solvents were suitable reaction media (Table 1, entries 9–13). Among which, dichloromethane and 1,2-dichloroethane (DCE) were the solvents of choice in terms of the stereoselective outcome (Table 1, entries 4 and 10). Nonpolar solvent provided a much slower reaction, although the enantioselectivity remained high (Table 1, entry 13).

Under the optimized reaction conditions, we first explored the generality of the use of aromatic and unsaturated aldehydes in the current Darzens reaction (Table 2). Benzaldehyde derivatives bearing electron-withdrawing substituents at either *para*, *ortho*, or *meta* positions provided *cis*-epoxides in high yields and with excellent enantioselectivity (96–99% *ee*; Table 2, entries 1–9). Electron-rich and neutral aromatic aldehydes also participated in clean Darzens reactions with excellent enantioselectivity (Table 2, entries 10–13). Interestingly, heteroaromatic aldehydes could be tolerated and gave high stereoselectivity, as exemplified by picolinaldehyde and 2-quinolinyl carbaldehyde (Table 2, entries 14 and 15). More importantly, unsaturated aldehydes afforded vinyl epoxides in good yields and with excellent enantiomeric purity (Table 2, entries 16 and 17). Significantly, ynals were also good reactants for the Darzens reaction, as exemplified by oct-2-ynal (Table 2, entry 18). The relative and absolute configurations of the products were determined by X-ray crystal structure analysis of **4h** (see the Supporting Information).

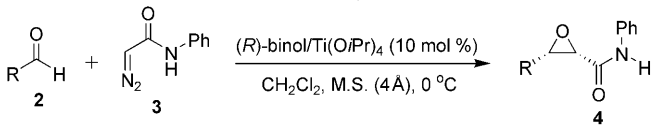
Further exploration of the scope of the current Darzens reaction for aliphatic aldehydes is shown in Table 3. Either linear or branched aliphatic aldehydes underwent a highly stereoselective Darzens reaction, and gave epoxides with *ee* values ranging from 97 to more than 99% (Table 3, entries 1–6). The Darzens reactions of cyclohexanecarbaldehyde and ethyl 2-oxoacetate were conducted at room temperature, and yielded *cis*-glycidic amides with comparably lower enantiomeric excess (87% and 89% *ee*, respectively; Table 3, entries 7 and 10). Linear aliphatic aldehydes bearing a remote vinyl or an adjacent benzoxy group also afforded high yields and excellent enantioselectivity (Table 3, entries 8 and 9). These additional functionalities definitely increase the flexibility for the transformation of glycidic amides into other structurally diverse chiral building blocks.

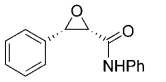
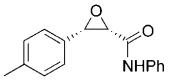
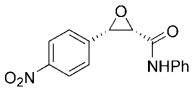
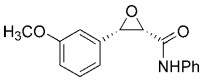
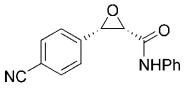
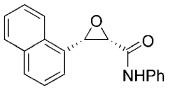
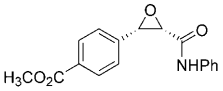
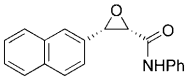
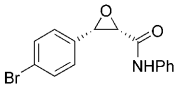
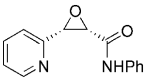
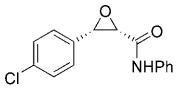
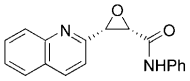
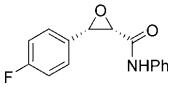
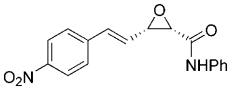
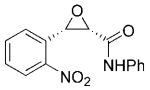
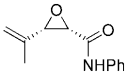
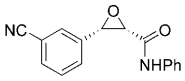
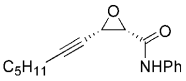
On the basis of previous reports,[15] a reaction mechanism consistent with the results observed is proposed (Scheme 1). Activation of aldehydes by coordination with the titanium complex of (*R*)-binol and subsequent *re*-face selective nucleophilic addition of diazoacetamides leads to the favorable formation of intermediate **II** owing to steric considerations. Bond rotation results in the formation of intermediate **III**, which subsequently undergoes a backside displacement to give *cis*-epoxides of type **4** and releases the Lewis acid catalyst.

The potential of the current Darzens reactions in the synthesis of important chiral intermediates or building blocks is demonstrated in Scheme 2. The treatment of glycidic amides (2*R*,3*R*)-**4d** and (2*S*,3*S*)-**4aa** with $(Boc)_2O$ and DMAP, and subsequent alcoholysis with sodium ethoxide afforded glycidic esters **5** and **6**, respectively, in good yields and with the high level of stereoselectivity maintained. By using readily available synthetic procedures, (2*R*,3*R*)-ethyl-3-phenyloxiranyl carboxylate (**5**) could be converted into enantiomerically pure (2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoic acid (**7**),[16] which is the side chain of taxol. Meanwhile, (2*S*,3*S*)-ethyl-3-benzyloxirane-2-carboxylate (**6**) served as a key synthetic intermediate for (−)-bestatin (**8**), which could be prepared according to an established procedure.[17]

In conclusion, we have disclosed a highly diastereo- and enantioselective Darzens reaction of aldehydes with diazoacetamides catalyzed by a chiral titanium complex formed in situ from commercially available $Ti(OiPr)_4$ and (*R*)-binol, thus giving *cis*-glycidic amides with excellent enantiomeric purity. The protocol tolerated a broad range of structurally diverse aldehydes, including aromatic, unsaturated, and aliphatic aldehydes. This new method has high potential in the enantioselective synthesis of biologically active substan-

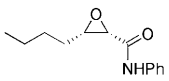
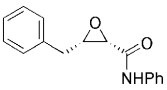
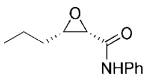
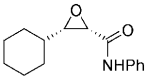
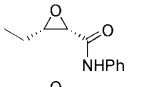
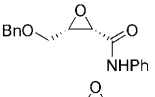
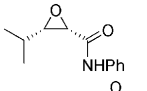
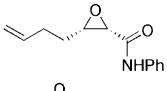
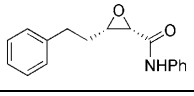
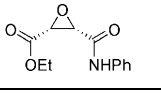
Table 2: Scope of the Darzens reaction with aromatic and unsaturated aldehydes.[a]



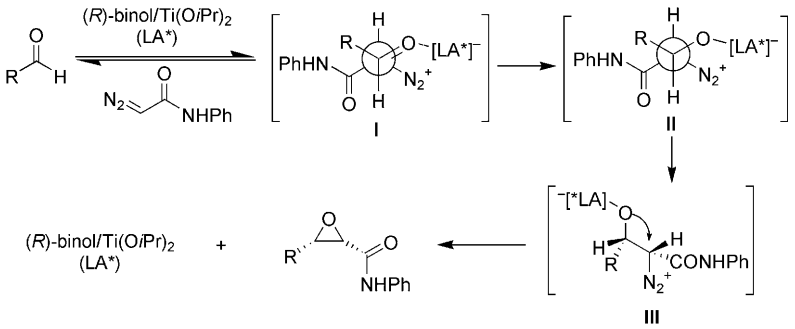
Entry	Product	Yield [%][b]	*ee* [%][c]	Entry	Product	Yield [%][b]	*ee* [%][c]
1	**4d** 	88	99	10	**4m** 	81	96
2	**4e** 	91	99	11	**4n** 	87	97
3	**4f** 	89	99	12	**4o** 	93	97
4	**4g** 	80	99	13	**4p** 	83	98
5	**4h** 	83	99	14	**4q** 	81	97
6	**4i** 	86	>99	15	**4r** 	88	98
7	**4j** 	82	98	16	**4s** 	52	95
8	**4k** 	84	96	17	**4t** 	62	98
9	**4l** 	95	99	18	**4u** 	66	88

[a] The reaction was carried out on a 0.2 mmol scale in CH_2Cl_2 (2 mL) with M.S. (4 Å, 120 mg) in an argon atmosphere at 0 °C, and the ratio of **2**/**3** was 1.2:1. [b] Yield of isolated product was based on **3**. [c] Determined by HPLC methods using a chiral stationary phase.

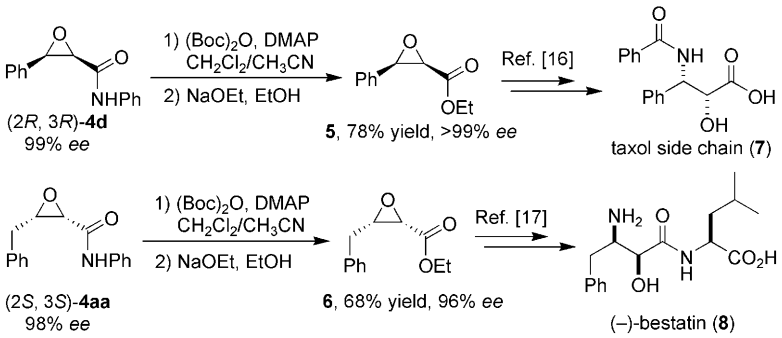
Table 3: Scope of the Darzens reaction with aliphatic aldehydes.[a]

Entry	Product	Yield [%][b]	*ee* [%][c]	Entry	Product	Yield [%][b]	*ee* [%][c]
1	**4v** 	75	98	6	**4aa** 	88	92 (98)[d]
2	**4w** 	76	>99	7[e]	**4ab** 	67	87
3	**4x** 	86	>99	8[f]	**4ac** 	93	94
4	**4y** 	80	98	9	**4ad** 	64	99
5	**4z** 	88	97	10[e]	**4ae** 	87	89

[a] The reaction was carried out on a 0.2 mmol scale in CH_2Cl_2 (2 mL) with M.S. (4 Å, 120 mg) in an argon atmosphere at 0 °C, and the ratio of **2**/**3** was 1.2:1. [b] Yield of isolated product was based on **3**. [c] Determined by HPLC methods using a chiral stationary phase. [d] The result in parentheses was obtained after single recrystallization. [e] The reaction temperature was 25 °C. [f] The ratio of **2**/**3** was 3:1.



Scheme 1. Proposed reaction mechanism.



Scheme 2. Synthetic application of *cis*-glycidic amides. $(Boc)_2O$ = di-*tert*-butyl dicarbonate, DMAP = 4-dimethylaminopyridine.

ces as demonstrated by the preparation of chiral building block for the side chain of taxol and (−)-bestatin.

Received: June 7, 2009
Published online: July 27, 2009

Keywords: asymmetric catalysis · binol · glycidic amides · Darzens reaction · epoxidation · titanium

[1] For reviews, see: a) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603 – 1662; b) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches, V. K. Aggarwal, *Chem. Rev.* **2007**, *107*, 5841 – 5883; c) O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958 – 3987.

[2] For a review, see: a) D. Diez, M. G. Nunez, A. B. Anton, P. Garcia, R. F. Moro, N. M. Garrido, I. S. Marcos, P. Basabe, J. G. Urones, *Curr. Org. Synth.* **2008**, *5*, 186 – 216; b) J. P. Michael, S. John, *Chem. Commun.* **2000**, 1215 – 1225.

[3] a) P. H. Milner, N. J. Gilpin, S. R. Speat, D. S. Eggleston, *J. Nat. Prod.* **1996**, *59*, 400 – 402; b) B. Riemer, O. Hofer, H. Greger, *Phytochemistry* **1997**, *45*, 337 – 341.

[4] a) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.* **1991**, *113*, 7063 – 7064; b) L. Deng, E. N. Jacobsen, *J. Org. Chem.* **1992**, *57*, 4320 – 4323; c) E. N. Jacobsen, L. Deng, Y. Furukawa, L. E. Martínez, *Tetrahedron* **1994**, *50*, 4323 – 4334; d) S. Watanabe, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *J. Org. Chem.* **1998**, *63*, 8090 – 8091; e) K. M. S. Tony, L. To, M. Lee, M. L. Chi, *Tetrahedron* **2006**, *62*, 6621 – 6629.

[5] For a review, see: T. Rosen in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 409 – 439.

[6] a) S. Arai, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 2145 – 2148; b) S. Arai, Y. Shirai, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 8299 – 8302; c) S. Arai, Y. Shirai, T. Ishida, T. Shioiri, *Chem. Commun.* **1999**, 49 – 50; d) S. Arai, Y. Shirai, T. Ishida, T. Shioiri, *Tetrahedron* **1999**, *55*, 6375 – 6386; e) S. Arai, T. Shioiri, *Tetrahedron* **2002**, *58*, 1407 – 1413; f) S. Arai, K. Tokumaru, T. Aoyama, *Tetrahedron Lett.* **2004**, *45*, 1845 – 1848.

[7] a) P. Bakó, A. Szöllõsy, P. Bombicz, L. Tõke, *Synlett* **1997**, 291 – 292; b) P. Bakó, K. Vizárdi, Z. Bajorm, L. Tõke, *Chem. Commun.* **1998**, 1193 – 1195; c) P. Bakó, K. Vizárdi, S. Toppet, E. Van der Eycken, G. J. Hoornaert, L. Tõke, *Tetrahedron* **1998**, *54*, 14975 – 14988; d) P. Bakó, E. Czinege, T. Bakó, M. Czugler, L. Tõke, *Tetrahedron: Asymmetry* **1999**, *10*, 4539 – 4551; e) P. Bakó, A. Makó, G. Keglevich, M. Kubinyi, K. Pál, *Tetrahedron: Asymmetry* **2005**, *16*, 1861 – 1871.

[8] T. J. R. Achard, Y. N. Belokon, M. Ilyin, M. Moskalenko, M. North, F. Pizzato, *Tetrahedron Lett.* **2007**, *48*, 2965 – 2969.

[9] a) R. Imashiro, T. Yamanaka, M. Seki, *Tetrahedron: Asymmetry* **1999**, *10*, 2845 – 2851; b) V. K. Aggarwal, G. Hynd, W. Picoul, J.-L. Vasse, *J. Am. Chem. Soc.* **2002**, *124*, 9964 – 9965; c) V. K. Aggarwal, J. P. H. Charmant, D. Fuentes, J. N. Harvey, G. Hynd, D. Ohara, W. Picoul, C. Smith, J.-L. Vasse, C. L. Winn, *J. Am. Chem. Soc.* **2006**, *128*, 2105 – 2114.

[10] For reviews, see: a) M. P. Doyle, M. A. Mckervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223 – 270; c) T. Ye, M. A. Mckervey, *Chem. Rev.* **1994**, *94*, 1091 – 1160.

[11] a) W.-G. Yao, J.-B. Wang, *Org. Lett.* **2003**, *5*, 1527 – 1530; b) B. M. Trost, S. Malhotra, B. A. Fried, *J. Am. Chem. Soc.* **2009**, *131*, 1674 – 1675.

[12] T. Hashimoto, N. Uchiyama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 14380 – 14381.

[13] T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054 – 10055.

[14] For reviews, see: a) D. J. Ramon, M. Yus, *Chem. Rev.* **2006**, *106*, 2126 – 2208; b) K. Mikami, Y. Matsumoto, T. Shiono in *Science of Synthesis*, *Vol.* 2 (Ed.: T. Imamoto), Thieme, Stuttgart, **2003**, pp. 457 – 679; c) E. Bermudez, J. B. Mangum, B. Asghariam, B. A. Wong, E. E. Reverdy, D. B. Janszen, P. M. Hext, D. B. Warheit, J. I. Everitt, *Toxicol. Sci.* **2002**, *70*, 86 – 97; d) K. Mikami, M. Mashiro in *Lewis Acids in Organic Synthesis*, *Vol. 2* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**, pp. 799 – 847.

[15] a) Y. Zhang, A. Desai, Z. Lu, G. Hu, Z. Ding, W. D. Wuff, *Chem. Eur. J.* **2008**, *14*, 3785 – 3803; b) L. Casarrubios, J. A. Perez, M. Brookhart, J. L. Templeton, *J. Org. Chem.* **1996**, *61*, 8358 – 8359.

[16] L. Deng, E. N. Jacobsen, *J. Org. Chem.* **1992**, *57*, 4320 – 4323.

[17] B. D. Feske, J. D. Stewart, *Tetrahedron: Asymmetry* **2005**, *16*, 3124 – 3127.

