Synthetic Methods

DOI: 10.1002/ange.200500838

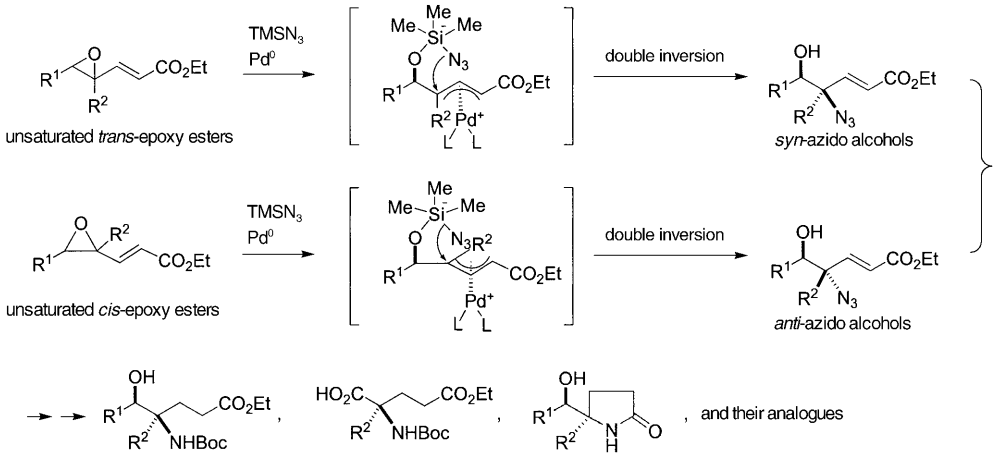
Pd-Catalyzed Stereospecific Azide Substitution of α,β-Unsaturated γ,δ-Epoxy Esters with Double Inversion of Configuration**

Masaaki Miyashita, Taiku Mizutani, Genta Tadano, Yasuhiro Iwata, Masahiro Miyazawa, and Keiji Tanino*

Over recent years, much interest has been focused on the development of not only a stereoselective but also a practical methodology for the synthesis of chiral β-amino alcohols,[1] α-amino acids,[2] and α,α-disubstituted amino acids[2–4] (including natural and unnatural congeners) in the context of medicinal chemistry. Although many synthetic approaches to these biologically important compounds have been reported,[1–4] there is still a need for a new type of methodology that allows the stereospecific synthesis of functionalized amino alcohols and amino acids that bear contiguous chiral centers. We report herein an approach that permits the highly stereoselective synthesis of a variety of amino alcohols, amino acids, and quaternary amino acids, including acyclic and cyclic congeners. This methodology involves the palladium-catalyzed stereospecific azide substitution reaction of α,β-unsaturated γ,δ-epoxy esters with a double inversion of configuration as the key step.

In connection with our recent studies on the palladium-catalyzed stereospecific hydroxy substitution reactions of unsaturated γ,δ-epoxy esters with phenylboronic acid[5] and boric acid[6] with a double inversion of configuration, we anticipated that the palladium-catalyzed azide substitution reaction of α,β-unsaturated γ,δ-epoxy esters with an appropriate azide reagent might occur by a similar π-allyl palladium species to afford an azide substitution product with double inversion of configuration, as shown in Scheme 1. Namely, this new method involves two consecutive S_N2 processes to afford a substitution product with double inversion of configuration in contrast with the normal S_N2 epoxide-opening reactions.[7]

Initially, we chose ethyl *trans*-4,5-epoxy-(2*E*)-octenoate (**1**)[5] as a model substrate and examined its palladium-catalyzed reaction with $TMSN_3$ to confirm whether such a reaction indeed takes place. Thus, first $TMSN_3$ (2 equiv) then



Scheme 1. Pd^0-catalyzed stereospecific azide substitution reaction of unsaturated γ,δ-epoxy esters with double inversion of configuration. TMS = trimethylsilyl, Boc = *tert*-butoxycarbonyl, L = ligand.

a palladium catalyst ($[Pd(PPh_3)_4]$ (10 mol %)) was added to a solution of **1** in THF and the mixture was stirred at room temperature for 20 minutes. The reaction was then quenched with a solution of citric acid in MeOH. The azide substitution reaction of **1** with double inversion of configuration did occur at the γ-position to afford a single *syn* azido alcohol **2** in 90 % yield of the isolated product after purification by chromatography on silica gel (Scheme 2). The configuration of the product was unambiguously determined by NOE interaction studies of its δ-lactone derivative **3**, which was readily derived from **2** by catalytic hydrogenation in the presence of di-*tert*-butyl dicarbonate (Boc_2O)[8] followed by lactonization with PPTS in dichloroethane (Scheme 2). It should be noted that the present palladium-catalyzed azide substitution reaction took place not only in high yield but also with complete stereoselectivity, thus giving rise to the single product with a double inversion of configuration.

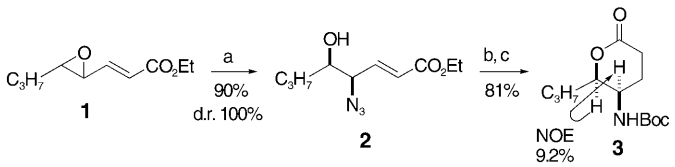
[*] Prof. Dr. M. Miyashita, T. Mizutani, G. Tadano, Dr. Y. Iwata, Dr. M. Miyazawa,[+] Dr. K. Tanino
Division of Chemistry
Graduate School of Science, Hokkaido University
060-0810 Sapporo (Japan)
Fax: (+81) 11-706-4920
E-mail: miyasita@sci.hokudai.ac.jp

[+] Present Address:
Department of Chemistry
Faculty of Science, Toyama University
930-8555 Toyama (Japan)

[**] Financial support from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (a Grant-in-Aid for Scientific Research (A) (No. 12304042), a Grant-in-Aid for Scientific Research (B) (No. 16350049), and a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multielement Cyclic Molecules" (No. 13029003)) is gratefully acknowledged.

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

InterScience
© 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

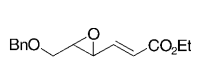
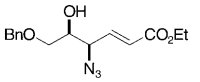
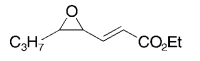
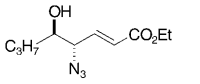
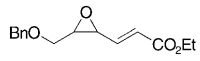
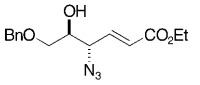
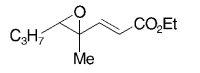
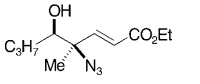


1 2 3

Scheme 2. Pd^0-catalyzed azide substitution reaction of ethyl *trans*-4,5-epoxy-(2*E*)-octenoate (**1**): a) $TMSN_3$ (2 equiv), $[Pd(PPh_3)_4]$ (10 mol%), THF, RT, 20 min (90%); b) H_2, PtO_2, Boc_2O, EtOAc, RT, 5 h (84%); c) PPTS, $ClCH_2CH_2Cl$, 90 °C, 3 h (96%). Ac = acetate, PPTS = pyridinium *para*-toluenesulfonate, Boc = *tert*-butoxycarbonyl.

These excellent preliminary results led us to examine the scope of the new synthetic methodology with various substrates (Table 1). Thus, the reaction of ethyl 6-benzyloxy-*trans*-4,5-epoxy-(2*E*)-hexenoate (**4**) proceeded cleanly to furnish the *syn* azido alcohol **5** as a single product in 97% yield (Table 1, entry 1). On the other hand, the reaction of a unsaturated *cis* epoxy ester **6** afforded an *anti* azido alcohol **7** in 95% yield (Table 1, entry 2), and a benzyloxy-substituted substrate **8** similarly produced the *anti* isomer **9** in 93% yield with complete stereoselectivity (Table 1, entry 3). Furthermore, a trisubstituted unsaturated epoxy ester **10** containing a methyl group at the γ-position reacted smoothly to produce a *syn tert*-azido alcohol **11** in 93% yield. It is critical to add $TMSN_3$ first to the substrate in solution then the palladium catalyst for a successful reaction. Thus, the palladium-catalyzed azide substitution reaction of acyclic unsaturated γ,δ-epoxy esters was shown to occur stereospecifically at the γ-position with complete stereoselectivity, namely, with double inversion of configuration, regardless of the configuration and substitution pattern of the epoxide substrates.

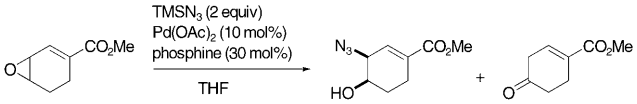
Table 1: Pd^0-catalyzed azide substitution reactions of acyclic α,β-unsaturated γ,δ-epoxy esters with $TMSN_3$ in THF.[a]

Entry	Substrate		*t*	Product		Yield [%][b]	*syn*/*anti*
1		**4**	20 min		**5**	97	>99:1
2		**6**	1 h		**7**	95	>1:99
3		**8**	2 h		**9**	93	>1:99
4		**10**	8 h		**11**	93	>99:1

[a] The reaction was carried out with $TMSN_3$ (2 equiv) and $[Pd(PPh_3)_4]$ (10 mol%) in THF at room temperature. [b] Yield of isolated product. Bn = benzyl.

Next, we focused on the azide substitution reaction of cyclic unsaturated epoxy esters, since Tsuda, Saegusa, and coworkers reported that the Pd^0-catalyzed reaction of an α,β-unsaturated γ,δ-epoxy ester containing a cyclohexane ring with nitrogen nucleophiles did not produce the corresponding substitution products at all.[9] To probe the behavior of cyclic substrates, we initially examined the reaction of methyl 3,4-epoxy-1-cylochexenecarboxylate (**12**).[10] Contrary to our expectations, however, the reaction of **12** under the same conditions as those for acyclic substrates was fruitless. Namely, the reaction of **12** with $TMSN_3$ (2 equiv), $Pd(OAc)_2$ (10 mol%), and PPh_3 (30 mol%) in THF afforded ketone **14** as the unexpected major product (61% yield), along with a smaller amount of the desired product **13** (37% yield; Table 2, entry 1). Therefore, we examined in detail the effect of a phosphine ligand on the reaction, and it was found that the azide substitution reaction of **12** was critically dependent on the nature of the phosphine ligand: The use of $PnBu_3$ was totally ineffective, and a large amount of the starting material was recovered (Table 2, entry 2). Similarly, the reaction with a bulky phosphine, such as $P(C_6H_{11})_3$, $P(tolyl)_3$, or $PtBu_3$, merely resulted in the recovery of the starting material. However, the use of $P(OiPr)_3$ gave a similar result to that of PPh_3 (Table 2, entry 3). In contrast to these ligands, P(2-furyl)$_3$ was found to improve this particular reaction dramatically. Thus, the reaction of **12** with $TMSN_3$ (2 equiv), $Pd(OAc)_2$ (10 mol%), and P(2-furyl)$_3$ (30 mol%) in THF produced the desired product **13** in 87% yield along with 13% yield of **14** (Table 2, entry 4). It is noteworthy that the reaction with P(2-furyl)$_3$ was very fast and was completed in 5 minutes at 0 °C, thus producing **13** in high yield. The configuration of **13** was determined unambiguously by X-ray crystallographic analysis of its *para*-bromobenzoate derivative. In turn, we examined the stoichiometry in which P(2-furyl)$_3$ was added and the effect of the solvent on the reaction, and it was found eventually that the use of 25 mol% of P(2-furyl)$_3$ in THF gave the best result. Under these conditions, the desired product **13** was obtained in 96% yield of isolated product and the formation of **14** was suppressed to less than 4% (Table 2, entry 5).[11]

Table 2: Pd^0-catalyzed azide substitution reactions of cyclic unsaturated γ,δ-epoxy ester **12** with $TMSN_3$ in THF.[a]



12 **13** **14**

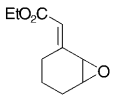
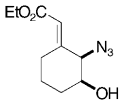
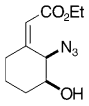
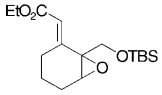
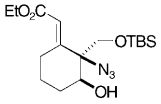
Entry	Phosphine	*T* [°C]	*t*	Yield [%] **13**	**14**
1	PPh_3	RT	5 min	37	61
2	$PnBu_3$	0→50	4 h	<2	10
3	$P(OiPr)_3$	0	5 min	39	57
4	P(2-furyl)$_3$	0	5 min	87	13
5[b]	P(2-furyl)$_3$	0	5 min	96	4

[a] The reaction was carried out by adding a premixed solution of $Pd(OAc)_2$ (5 mol%) and P(2-furyl)$_3$ (30 mol%) in THF. [b] The reaction was carried out with 25 mol% of P(2-furyl)$_3$.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

We then applied these optimized conditions to various cyclic substrates (Table 3). Both the *Z*-unsaturated ester **17**[12] and the cyclic *E*-unsaturated γ,δ-epoxy ester **15**[12] (as seen previously) were found to react smoothly under these conditions (Table 3, entries 2 and 1, respectively), thus furnishing the corresponding azide substitution products **18** and **16**, respectively. It should be noted that products **16** and **18** were obtained in remarkably high yields, whereas they had been inaccessible using the previously reported method.[9] Contrary to our expectations, a trisubstituted unsaturated epoxy ester **19**[13] did not react at all under similar conditions and the starting material was recovered (Table 3, entry 3). Fortunately, we found that the reaction of **19** with $TMSN_3$ and $[Pd(PPh_3)_4]$ in *N*,*N*-dimethylformamide (DMF) proceeded smoothly at 50 °C and gave rise to the desired product **20** in 92% yield (Table 3, entry 4).[14] These results demonstrate unambiguously that the palladium-catalyzed azide substitution reaction of unsaturated γ,δ-epoxy esters with acyclic and cyclic substrates occurs stereospecifically at the γ-position with double inversion of configuration, thus producing azido alcohols in high yields regardless of the stereochemistry of the epoxide and unsaturated ester moieties.

Table 3: Pd^0-catalyzed azide substitution reactions of cyclic unsaturated epoxy esters with $TMSN_3$.[a]

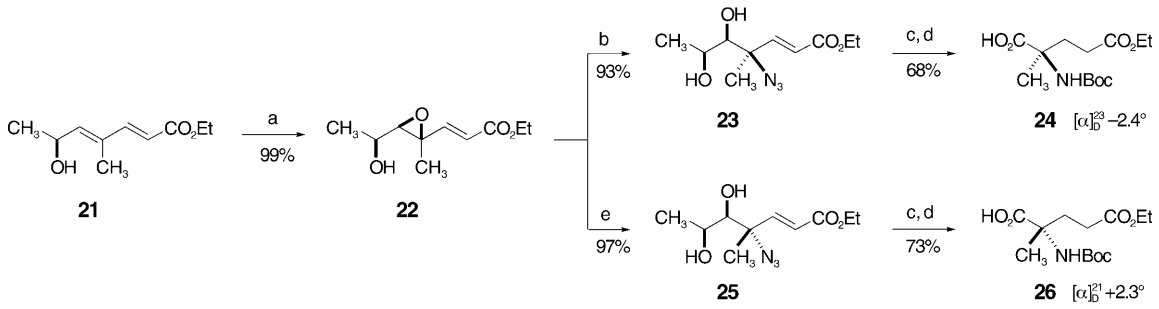
Entry	Substrate		Ligand	Solvent	*t* [h]	Product		Yield [%]
1[b]		**15**	$P(2\text{-furyl})_3$	THF	1		**16**	98
2		**17**	$P(2\text{-furyl})_3$	THF	1		**18**	quant.
3		**19**	$P(2\text{-furyl})_3$	THF	4		**20**	trace
4[c]		**19**	PPh_3	DMF	6		**20**	92

[a] The reaction was carried out by adding a mixture of $Pd(OAc)_2$ (5 mol%) and the phosphine (25 mol%) in THF to a solution of each substrate and $TMSN_3$ (2 equiv) in THF at room temperature. [b] After the reaction mixture had been stirred for 50 min at room temperature, $Pd(OAc)_2$ (5 mol%) and the phosphine (25 mol%) were added and then the mixture was stirred for an additional 10 min at room temperature. [c] The reaction was carried out in DMF at 50 °C using $TMSN_3$ (2 equiv) and $[Pd(PPh_3)_4]$ (10 mol%); $[Pd(PPh_3)_4]$ (10 mol%) was added after 2.5 and 4.5 h, respectively. TBS = *tert*-butyldimethylsilyl, quant. = quantitative yield.

To demonstrate the synthetic potential of the current method, we performed a stereospecific synthesis of both (*R*)- and (*S*)-*N*-*tert*-butoxycarbonyl-α-methylglutamic acid γ-ethyl ester (**24** and **26**, respectively; Scheme 3). Thus, treatment of the diene ester **21**, which is readily derived from ethyl (*S*)-lactate, with *meta*-chloroperoxybenzoic acid (*m*CPBA) in CH_2Cl_2 led to unsaturated β-epoxy ester **22** being obtained as a single product in quantitative yield. When the unsaturated epoxy ester **22** was subjected to the palladium-catalyzed azide substitution reaction under the conditions employed for acyclic substrates, azido alcohol **23** was produced exclusively in 93% yield with double inversion of configuration. In contrast, the reaction of **22** with NaN_3 and $[Ti(OEt)_4]$ in DMF under modified Sharpless conditions[15] proceeded through an S_N2 process to afford the single azido alcohol **25** in 97% yield. These products were efficiently transformed into **24** and **26** by the two-step reaction sequence of 1) concomitant hydrogenation of the double bond and the azido group over the Adams catalyst in EtOAc in the presence of Boc_2O[8] and 2) oxidative cleavage of the diol moiety with $RuCl_3$ and $NaIO_4$ in $CCl_4/H_2O/CH_3CN$.[16] The two enantiomers **24** and **26** were efficiently and highly stereoselectively prepared starting from the same compound **21** by applying two contrasting azide substitution reactions.

In summary, we have developed a palladium-catalyzed azide substitution reaction of α,β-unsaturated γ,δ-epoxy esters with $TMSN_3$ that occurs stereospecifically at the γ-position to produce azido alcohols in excellent yields with double inversion of configuration. This new method is widely applicable to various acyclic and cyclic substrates and provides a powerful tool in the synthesis of functionalized β-amino alcohols and α-amino acids, including α,α-disubstituted amino acids. Further investigations into the synthetic applications of this methodology are ongoing.

Received: March 7, 2005
Published online: July 15, 2005



Scheme 3. Stereospecific synthesis of both enantiomers of *N*-*tert*-butoxycarbonyl-α-methylglutamic acid γ-ethyl ester: a) *m*CPBA (1.5 equiv), CH_2Cl_2, 0 °C, 1 h (99%); b) $TMSN_3$ (2 equiv), $[Pd(PPh_3)_4]$ (5 mol%), THF, RT, 1 h (93%); c) H_2, PtO_2, Boc_2O (4 equiv), AcOEt, RT, 4 h; d) $RuCl_3$ (cat.), $NaIO_4$ (6 equiv), CCl_4, aq. CH_3CN, RT, 2 h; e) NaN_3 (4 equiv), $[Ti(OEt)_4]$ (2 equiv), DMF, RT, 1 h.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Keywords: amino acids · asymmetric synthesis · azides · epoxides · palladium

[1] a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835; b) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1998**, *120*, 11798; c) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827; d) B. Olofsson, P. Somfai, *J. Org. Chem.* **2002**, *67*, 8574; e) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338; f) N. J. Adderley, D. J. Buchanan, D. J. Dixon, D. I. Laine, *Angew. Chem.* **2003**, *115*, 4373; *Angew. Chem. Int. Ed.* **2003**, *42*, 4241.

[2] For representative reviews on the preparation of optically active α-amino acids, see: a) R. M. Williams, *Synthesis of Optically Active α-Amino Acids* (Ed.: J. E. Baldwin), Pergamon, Oxford, **1989**; b) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889; c) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539; d) D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem.* **1996**, *108*, 2880; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708; e) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetr.* **1998**, *9*, 3517; f) J.-A. Ma, *Angew. Chem.* **2003**, *115*, 4426; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290; g) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013; h) J. M. O'Donnel, *Acc. Chem. Res.* **2004**, *37*, 506.

[3] a) B. G. M. Burgaud, D. C. Horwell, A. Padova, M. C. Pritchard, *Tetrahedron* **1996**, *52*, 13050; b) T. Wirth, *Angew. Chem.* **1997**, *109*, 235; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225; c) S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugi, H. Irie, *J. Org. Chem.* **1997**, *62*, 2275; d) D. Obrecht, M. Altorfer, U. Bohdal, J. Daly, W. Huber, A. Labhardt, C. Lehmann, K. Müller, R. Ruffieux, P. Schönholzer, C. Spiegler, C. Zumbrunn, *Biopolymers* **1997**, *42*, 575; e) T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228; f) T. Ooi, E. Tayama, K. Maruoka, *Angew. Chem.* **2003**, *115*, 599; *Angew. Chem. Int. Ed.* **2003**, *42*, 579.

[4] For the synthesis of chiral α,α-disubstituted α-amino acids by enzymatic resolution, see: a) V. S. Parmar, A. Singh, K. S. Sisht, N. Kumar, Y. N. Belokon, K. A. Kocketkov, N. S. Ikonnikiv, S. A. Orlova, V. I. Taranov, T. F. Saveleva, *J. Org. Chem.* **1996**, *61*, 1223, and references therein; b) D. M. Spero, S. J. Kapadia, *J. Org. Chem.* **1996**, *61*, 7398; c) S. Sano, K. Hayashi, T. Miwa, T. Ishii, M. Fujii, H. Mima, Y. Nagao. Y. *Tetrahedron* **1998**, *39*, 5571.

[5] A. Hirai, X.-Qiang Yu, T. Tonooka, M. Miyashita, *Chem. Commun.* **2003**, 2482.

[6] X.-Qiang Yu, A. Hirai, M. Miyashita, *Chem. Lett.* **2004**, *33*, 764.

[7] For epoxide-opening reactions with azides, see: a) K. Maruoka, H. Sano, H. Yamamoto, *Chem. Lett.* **1985**, 599; b) C. H. Behrens, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 5696; c) M. Onaka, K. Sugita, Y. Izumi, *Chem. Lett.* **1986**, 1327; d) M. Caron, P. R. Carlier, K. B. Sharpless, *J. Org. Chem.* **1988**, *53*, 5185; e) S. Saito, S. Yamashita, T. Nishikawa, Y. Yokoyama, M. Inaba, T. Moriwake, *Tetrahedron Lett.* **1989**, *30*, 4153; f) K. I. Sutowardoyo, M. Emziane, P. Lhoste, D. Sinou, *Tetrahedron* **1991**, *47*, 1435; g) F. Benedetti, F. Berti, S. Norbedo, *Tetrahedron Lett.* **1998**, *39*, 7971; h) H. Hayakawa, N. Okada, M. Miyazawa, M. Miyashita, *Tetrahedron Lett.* **1999**, *40*, 4589; i) C. Schneider, *Synlett* **2000**, *12*, 1840; j) R. Martin, G. Islas, A. Moyano, M. A. Pericas, A. Riera, *Tetrahedron* **2001**, *57*, 6367; k) G. Sabitha, R. S. Babu, M. S. K. Reddy, J. S. Yadav, *Synthesis* **2002**, *15*, 2254; l) M. Sasaki, K. Tanino, A. Hirai, M. Miyashita, *Org. Lett.* **2003**, *5*, 1789.

[8] a) H. Kotsuki, A. Miyazaki, M. Ochi, *Tetrahedron Lett.* **1991**, *32*, 4503; b) M. Miyashita, T. Yamasaki, T. Shiratani, S. Hatakeyama, M. Miyazawa, H. Irie, *Chem. Commun.* **1997**, 1787.

[9] T. Tsuda, Y. Horii, Y. Nakagawa, T. Ishida, T. Saegusa, *J. Org. Chem.* **1989**, *54*, 977.

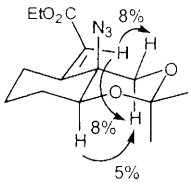
[10] E. Wolfgang, C. J. Claude, *Chem. Ber.* **1981**, *114*, 1027.

[11] The use of P(2-furyl)$_3$ in the reaction of acyclic substrates also gave excellent results with even better yields of isolated product than with the use of [Pd(PPh$_3$)$_4$].

[12] B. Norbert, H. Juergen, M. Helga, W. Peter, *Chem. Ber.* **1979**, *112*, 2256.

[13] The substrate **19** was prepared from 2-hydroxymethyl-2-cyclohexenone in five steps.

[14] The configuration of **20** was confirmed unambiguously by NOE interaction studies of its acetonide derivative, which was



obtained by the removal of the TBS protecting group with HF in CH_3CN (90%) and subsequent treatment of the resulting 1,3-diol with *para*-toluenesulfonic acid and 2,2-dimethoxypropane in CH_2Cl_2 (99%).

[15] M. Carron, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1557.

[16] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim