Communications

Synthetic Methods

DOI: 10.1002/anie.200500838

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

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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 palladiumcatalyzed 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 $S_N 2$ processes to afford a substitution product with double inversion of configuration in contrast with the normal $S_N 2$ epoxideopening reactions.^[7]

Initially, we chose ethyl *trans*-4,5-epoxy-(2E)-octenoate $(1)^{[5]}$ as a model substrate and examined its palladiumcatalyzed reaction with TMSN₃ to confirm whether such a reaction indeed takes place. Thus, first TMSN₃ (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.

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- [**] 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.

a palladium catalyst ([Pd(PPh₃)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-tertbutyl dicarbonate (Boc₂O)^[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.



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Scheme 2. Pd⁰-catalyzed azide substitution reaction of ethyl *trans*-4,5epoxy-(2*E*)-octenoate (1): a) TMSN₃ (2 equiv), [Pd(PPh₃)₄] (10 mol%), THF, RT, 20 min (90%); b) H₂, PtO₂, Boc₂O, EtOAc, RT, 5 h (84%); c) PPTS, ClCH₂CH₂Cl, 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-benzyloxytrans-4,5-epoxy-(2E)-hexenoate (4) proceeded cleanly to furnish the syn azido alcohol 5 as a single product in 97% 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 TMSN₃ (2 equiv), $Pd(OAc)_2$ (10 mol%), and PPh₃ (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 PPh₃ (Table 2, entry 3). In contrast to these ligands, P(2-

Table 1: Pd⁰-catalyzed azide substitution reactions of acyclic α,β -unsaturated γ,δ -epoxy esters with TMSN₃ in THF.^[a]

Entry	Substrate		t	Product			
						Yield [%] ^[b]	syn/anti
1	BnOCO2Et	4	20 min	BnO N ₃ OH CO ₂ Et	5	97	> 99:1
2	C ₃ H ₇ CO ₂ Et	6	1h	C ₃ H ₇ N ₃ OH CO ₂ Et	7	95	> 1:99
3	BnO CO2Et	8	2 h	BnO N ₃ OH CO ₂ Et	9	93	> 1:99
4	$C_3H_7 \xrightarrow{O} CO_2Et$	10	8 h	C ₃ H ₇ Me ^{OH} N ₃ CO ₂ Et	11	93	>99:1

[a] The reaction was carried out with TMSN₃ (2 equiv) and $[Pd(PPh_3)_4]$ (10 mol%) in THF at room temperature. [b] Yield of isolated product. Bn=benzyl.

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 TMSN₃ 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.

Next, we focused on the azide substitution reaction of cyclic unsaturated epoxy esters, since Tsuda, Saegusa, and coworkers reported that the Pd⁰-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-

furyl)₃ was found to improve this particular reaction dramatically. Thus, the reaction of 12 with TMSN₃ (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: Pd⁰-catalyzed azide substitution reactions of cyclic unsaturated γ,δ -epoxy ester 12 with TMSN₃ in THF.^[a]

0	.CO ₂ Me Pd(OAc) ₂ (10 phosphine (3 THF	uiv)) mol%) 0 mol%) →	N ₃ HO	+ 0	∕CO₂Me
12			13	14	
Entry	Phosphine	T [°C]	t	Yield [%]	
				13	14
1	PPh₃	RT	5 min	37	61
2	PnBu₃	$0 \rightarrow 50$	4 h	< 2	10
3	P(O <i>i</i> Pr)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 $P(2-furyl)_3$.

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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

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*)-

Table 3: Pd⁰-catalyzed azide substitution reactions of cyclic unsaturated epoxy esters with TMSN₃.^[a]



[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 TMSN₃ (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 TMSN₃ (2 equiv) and [Pd(PPh₃)₄] (10 mol%); [Pd(PPh₃)₄] (10 mol%) was added after 2.5 and 4.5 h, respectively. TBS = *tert*-butyldimethylsilyl, quant. = quantitative yield.

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 TMSN₃ 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 y-position with double inversion of configuration, thus producing azido alcohols in high yields regardless of the stereochemistry of the epoxide and unsaturated ester moieties.

lactate, with meta-chloroperoxybenzoic acid (mCPBA) in CH₂Cl₂ 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 NaN3 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 Boc₂O^[8] and 2) oxidative cleavage of the diol moiety with RuCl₃ and NaIO₄ in CCl₄/H₂O/CH₃CN.^[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 TMSN₃ 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), CH₂Cl₂, 0°C, 1 h (99%); b) TMSN₃ (2 equiv), [Pd(PPh₃)₄] (5 mol%), THF, RT, 1 h (93%); c) H₂, PtO₂, Boc₂O (4 equiv), AcOEt, RT, 4 h; d) RuCl₃ (cat.), NalO₄ (6 equiv), CCl₄, aq. CH₃CN, RT, 2 h; e) NaN₃ (4 equiv), [Ti(OEt)₄] (2 equiv), DMF, RT, 1 h.

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Angew. Chem. Int. Ed. 2005, 44, 5094-5097



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

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obtained by the removal of the TBS protecting group with HF in CH₃CN (90%) and subsequent treatment of the resulting 1,3diol with *para*-toluenesulfonic acid and 2,2-dimethoxypropane in CH₂Cl₂ (99%).

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