Asymmetric Synthesis

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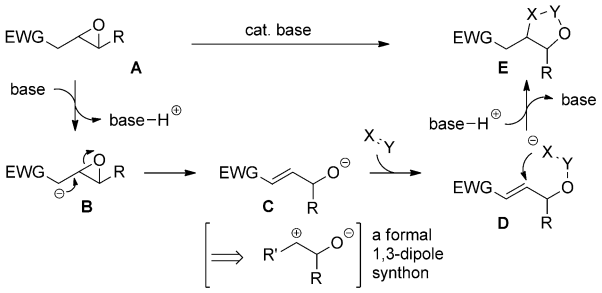
Ring Expansion of Epoxides under Brønsted Base Catalysis: Formal [3+2] Cycloaddition of β,γ-Epoxy Esters with Imines Providing 2,4,5-Trisubstituted 1,3-Oxazolidines

*Azusa Kondoh, Kenta Odaira, and Masahiro Terada**

Abstract: *A novel ring-expansion reaction of epoxides under Brønsted base catalysis was developed. The formal [3+2] cycloaddition reaction of β,γ-epoxy esters with imines proceeds in the presence of triazabicyclodecene (TBD) as a superior Brønsted base catalyst to afford 2,4,5-trisubstituted 1,3-oxazolidines in a highly diastereoselective manner. This reaction involves the ring opening of the epoxides with the aid of the Brønsted base catalyst to generate α,β-unsaturated esters having an alkoxide at the allylic position, which would formally serve as a synthetic equivalent of the 1,3-dipole, followed by a cycloaddition reaction with imines in a stepwise fashion. This methodology enables the facile synthesis of enantioenriched 1,3-oxazolidines from easily accessible enantioenriched epoxides.*

The ring expansion of strained ring compounds has attracted a great deal of attention as a useful method for the construction of polysubstituted cyclic frameworks.[1] In particular, the formal [3+2] cycloaddition reaction of epoxides with unsaturated compounds has been intensively investigated as a powerful tool for the synthesis of five-membered heterocyclic compounds containing oxygen. Generally, in catalytic reactions, transition metals[2] as well as Lewis acids[3] are utilized as the catalyst. In addition, the combination of Lewis acidic metals and halides is employed in some cases.[4] In each case, epoxides formally serve as the synthetic equivalent of the 1,3-dipole under the influence of those catalysts, and thus the [3+2] cycloaddition successfully proceeds with various types of unsaturated compounds to provide a variety of heterocyclic compounds. However, there still remains the issue of the limitation of the substituents on the epoxides and therefore the development of novel methodologies is highly anticipated. In this context, we envisioned employing a conceptually different approach, that is, Brønsted base catalysis, which has rarely been utilized in the ring expansion of strained-ring compounds. We considered that the generation of the synthetic equivalent of the 1,3-dipole from epoxides with the aid of a Brønsted base catalyst is the key to the development of the stereoselective cycloaddition reactions. To this end, we envisioned epoxides **A** possessing an EWG (electron-withdrawing group)-substituted methyl group as the possible precursor of the synthetic equivalent of the 1,3-dipole. Our reaction design is shown in Scheme 1.



Scheme 1. Reaction design.

Treatment of **A** with a Brønsted base would result in deprotonation at the position α to the EWG group followed by epoxide opening, for which the release of ring strain would serve as a driving force for the generation of electron-deficient alkenes **C** having an alkoxide at the allylic position. This intermediate would then formally serve as the synthetic equivalent of the 1,3-dipole, and the cycloaddition reaction with unsaturated compounds (X = Y) would proceed in a stepwise fashion, that is, the addition of the alkoxide moiety to the unsaturated compounds followed by cyclization of the resulting anion to the electron-deficient alkene moiety, to provide five-membered ring compound **E**.[5,6] In our investigation, imines were chosen as a potential partner of the formal 1,3-dipole in light of the synthetic value of the adduct, 2,4,5-trisubstituted 1,3-oxazolidines. 1,3-Oxazolidines can be utilized as versatile intermediates in organic synthesis, as chiral auxiliaries in asymmetric synthesis,[7] and as ligands in transition metal catalysis.[8] They are also found in many natural products as well as bioactive compounds.[9] Whereas several catalytic [3+2] cycloaddition reactions of epoxides with imines have been developed,[10] the synthesis of 2,4,5-trisubstituted 1,3-oxazolidines is rather limited because of the difficulty of using 2,3-disubstituted epoxides in most cases. Furthermore, diastereocontrol in multisubstituted 1,3-oxazolidine formation, particularly the formation of trisubstituted 1,3-oxazolidines, represents a great challenge. We envisaged that in our reaction system, the diastereocontrol would be

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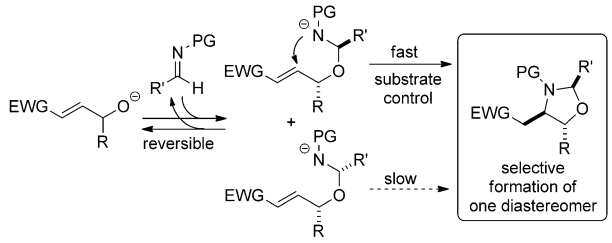
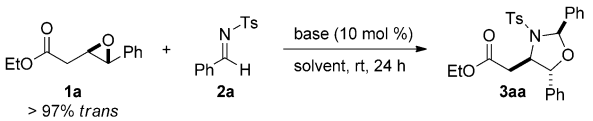


Scheme 2. Diastereocontrol in 2,4,5-trisubstituted 1,3-oxazolidine formation under Brønsted base catalysis.

achieved by substrate control in cooperation with the reversibility of the hemiaminal ether formation through addition of the alkoxide to the imine (Scheme 2). If one of the diastereomers of the hemiaminal ether undergoes substrate-controlled cyclization whereas the other reverses to the alkoxide in preference to the cyclization, one of the four diastereomers would be formed selectively. To establish the proposed stereo-controlling system, a conceptually novel approach, i.e., the use of a Brønsted base catalyst, is crucial because of adopting the equilibrium process prior to the cyclization. Herein we report a formal [3+2] cycloaddition reaction of β,γ-epoxy esters with imines under Brønsted base catalysis, which provides 2,4,5-trisubstituted 1,3-oxazolidines in a highly diastereoselective manner. By adopting this methodology, we achieved the facile synthesis of enantioenriched 2,4,5-trisubstituted 1,3-oxazolidines from easily accessible enantioenriched epoxides.

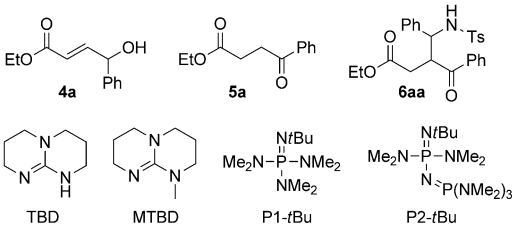
To ascertain the viability of the designed reaction, β,γ-epoxy ester **1a** was chosen as the initial substrate and treated with tosyl imine **2a** in the presence of a catalytic amount of DBU in THF for 24 h. As a result, **1a** was completely consumed and the desired oxazolidine **3aa** was formed in a highly diastereoselective manner albeit in low yield (Table 1, entry 1). Various by-products, such as alcohol **4a**, γ-ketoester **5a**, and the diastereomers of **6aa** were detected. **5a** would be formed by isomerization of the carbon–carbon double bond of **4a**, and **6aa** is the adduct of **5a** and **2a**. A screening of Brønsted bases showed that the choice of base was critical for the formation of the desired product **3aa** (entries 1–7). Among the bases tested, guanidines were superior and **3aa** was obtained in moderate yield (entries 2 and 3). In particular, TBD gave the best result (entry 2). The difference between the results obtained when TBD was used as the base and those obtained when MTBD was used indicates that the two hydrogen donor sites of the conjugated acid of TBD may play a key role in accelerating the [3+2] cycloaddition. Weak bases, such as tertiary amines, resulted in no reaction (not shown) whereas strong bases, including phosphazene bases, provided **3aa** only in low yield along with a significant amount of by-products (entries 4 and 5). Inorganic bases, such as *t*BuOK and Cs_2CO_3, were less effective, and unreacted **1a** (39% and 25%, respectively) as well as alcohol **4a** was intact even after 24 h (entries 6 and 7). With regard to the diastereoselectivity, the choice of the base had minimal influence, and **3aa** was obtained with a high diastereoselectivity in all cases, indicating that substrate control is operative, as expected. Next, solvents were

Table 1: Initial screening for reaction conditions.[a]



Entry	Base	Solvent	Yield [%][b] 3aa[c]	d.r. of 3aa[d]	4a	5a	6aa
1	DBU	THF	13	94:6	<1	35	51
2	TBD	THF	67	97:3	<1	12	10
3	MTBD	THF	49	95:5	2	29	16
4	P1-*t*Bu	THF	8	97:3	30	10	16
5	P2-*t*Bu	THF	3	99:1	1	22	51
6	*t*BuOK	THF	24	94:6	22	1	2
7	Cs_2CO_3	THF	36	95:5	26	1	3
8	TBD	Et_2O	73	95:5	2	6	4
9	TBD	toluene	84	95:5	4	2	1
10	TBD	CH_3CN	81	97:3	8	4	2
11	TBD	DMF	51	98:2	2	12	27
12[e]	TBD	CH_3CN	91 (84)	97:3	1	<1	1

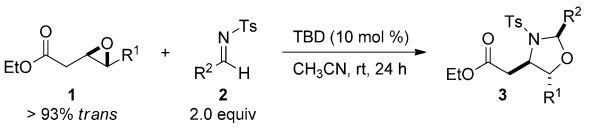
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), base (0.025 mmol), solvent (2.0 mL), rt, 24 h. [b] Yields were determined by ^{1}H NMR measurement. $CHBr_3$ was used as the internal standard. The yield of isolated product is shown in parenthesis. [c] Yields of the major diastereomer of **3aa**. [d] The ratio of the major diastereomer to the sum of the other three diastereomers as determined by ^{1}H NMR analysis of the crude mixture. [e] 2.0 equivalents of **2a** was used.



screened with TBD as the Brønsted base catalyst (entries 8–11). Among the solvents tested, acetonitrile was the solvent of choice from the point of view of both yield and diastereoselectivity. Employment of a higher amount of tosyl imine **2a** suppressed the formation of by-products, and the major diastereomer of **3aa** was obtained in 91% yield (entry 12). The relative configuration of the major diastereomer was determined by single-crystal X-ray diffraction analysis.[11] The control experiments suggested the involvement of the alkoxide of **4a** in the reaction.[12] The reaction of **4a** with **2a** provided an almost identical result as the reaction of **1a** with **2a**. In addition, treatment of **1a** or **4a** in the absence of **2** generated **5a** smoothly. These results indicate that the presence of imines is essential for the formation of the desired product during the course of generating the alkoxides from epoxy esters.

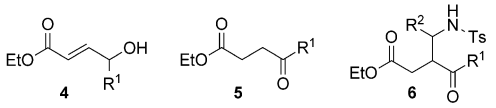
With the optimum conditions in hand, the scope of imines and substituents on the epoxide was investigated (Table 2). At first, the effect of the substituents on imines was examined (entries 1–3). Both electron-donating and the electron-withdrawing groups on the benzene ring affected the reaction. The reaction with electron-rich imine **2b** proceeded smoothly to provide the product in good yield, but substantial amounts of by-products **5a** and **6ab** were formed (entry 1). In contrast,

Table 2: Scope of β,γ-epoxy esters and imines.[a]



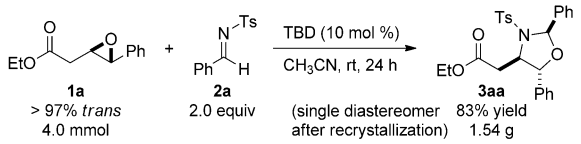
Entry	R^1	R^2	3	Yield [%][b] 3[c]	d.r. of 3[d]	4	5	6
1	Ph	4-MeO-C_6H_4	**3ab**	68	96:4	3	6	7
2	Ph	4-Cl-C_6H_4	**3ac**	78	97:3	2	<1	2
3	Ph	2-Me-C_6H_4	**3ad**	67	96:4	7	10	5
4	4-MeO-C_6H_4	Ph	**3ba**	93	97:3	<1	<1	<1
5[e]	4-Cl-C_6H_4	Ph	**3ca**	79	97:3	1	2	7
6	2-Me-C_6H_4	Ph	**3da**	79	91:9	2	<1	<1
7	2-naphthyl	Ph	**3ea**	81	96:4	<1	<1	5
8	Bn	Ph	**3fa**	80	90:10	2	<1	<1
9	*i*Pr	Ph	**3ga**	72	98:2	4	<1	<1

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), TBD (0.025 mmol), CH_3CN (2.0 mL), rt, 24 h. [b] Determined by ^1H NMR measurement after column chromatography. See the Supporting Information for details. [c] Yields of the major diastereomer of **3**. [d] Ratio of the major diastereomer to the sum of the other three diastereomers as determined by ^1H NMR analysis of the crude mixture. [e] The reaction was performed for 48 h.

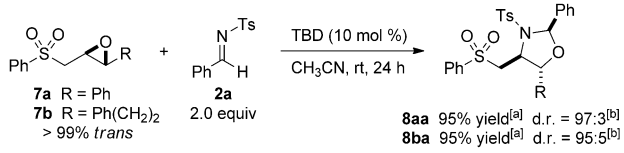


the reaction with electron-poor imine **2c** was slow compared to the reactions with **2a** and **2b**, and 9% of **1a** remained even after 24 h (entry 2). The reaction with sterically congested aryl imine **2d** provided the product in good yield but starting material **1a** (4%) and considerable amounts of by-products **4a**, **5a**, and **6ad** were detected (entry 3). In all cases, the diastereoselectivity was as good as that with **2a**.[13] The tosyl group on the nitrogen was essential for this reaction. Imines with other substituents, such as Boc and the diphenylphosphoryl group, provided a complex mixture of products. Next, the scope of substituents on the epoxide was examined (entries 4–9). The substrate with a *para*-methoxyphenyl group provided the product in high yield (entry 4). The reaction with the *para*-chlorophenyl-substituted substrate required a long time (entry 5). The *ortho*-tolyl-substituted substrate furnished the product in good yield, but the diastereoselectivity was slightly lower (entry 6). 2-Naphthyl-substituted epoxide **1d** underwent the reaction without any problem (entry 7). In this reaction, aliphatic substituents were also applicable. Primary and secondary alkyl-substituted substrates **1f** and **1g** afforded the corresponding products in good yields (entries 8 and 9).

This reaction was sufficiently reliable to permit the synthesis of **3** in gram scale, and 1.54 g of the single diastereomer of **3aa** was isolated after recrystallization (Scheme 3). This methodology was further extended to the reaction of β,γ-epoxy sulfones **7** (Scheme 4). Both aryl- and alkyl-substituted substrates underwent the reaction to provide the corresponding 1,3-oxazolidines **8** possessing a sulfonylmethyl group, which can potentially function as a handle



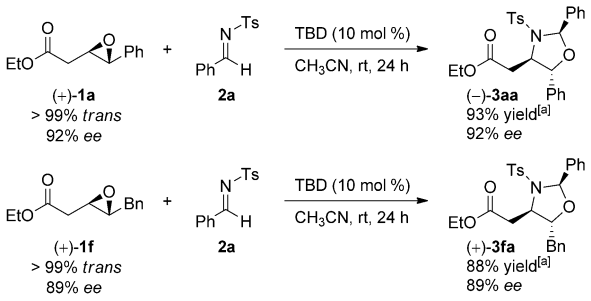
Scheme 3. Gram-scale synthesis of **3aa**.



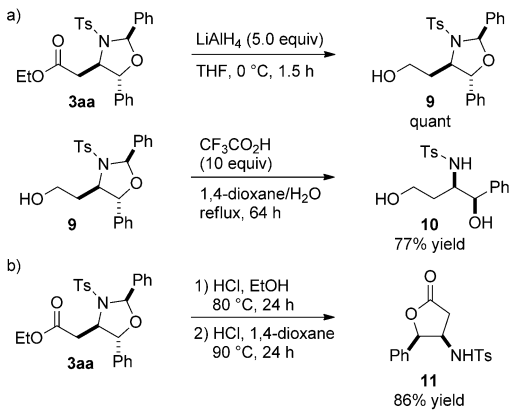
Scheme 4. Reaction of β,γ-epoxy sulfones. [a] Yield of the major diastereomer as determined by ^1H NMR spectroscopy after column chromatography. [b] The ratio of the major diastereomer to the sum of the other three diastereomers.

for further manipulation, in high yields with high diastereoselectivities. It is worth noting that no by-products were detected in the reaction of the epoxy sulfones in contrast to the reactions with epoxy esters.

In this reaction, cleavage of the carbon–oxygen bond of the unsymmetrical 2,3-disubstituted epoxides proceeds regioselectively, and thus the stereochemistry of one of the carbon centers of the epoxide is retained throughout the reaction, enabling the synthesis of enantioenriched 2,4,5-trisubstituted 1,3-oxazolidine derivatives from enantioenriched epoxides. Indeed, the reaction of enantioenriched epoxides was attempted (Scheme 5). Enantioenriched epoxides **1a** and **1f**, which have an aryl and an alkyl substituent, respectively, were easily synthesized by Shi's protocol.[14] The thus synthesized enantioenriched epoxides were subjected to the reaction conditions, and the corresponding enantioenriched 2,4,5-trisubstituted 1,3-oxazolidines were formed without erosion of the enantiomeric purity. Whereas in principle, from a mechanistic point of view, the reaction of enantioenriched alcohols **4** with imines **2** would also allow the synthesis of the same compounds, this methodology has an advantage due to the high accessibility of enantioenriched epoxides **1** as substrates compared to the corresponding enantioenriched alcohols **4**.[15]



Scheme 5. Reactions of enantioenriched β,γ-epoxy esters. [a] NMR yields of the major diastereomer.



Scheme 6. Transformation of **3aa**.

Finally, the transformation of 1,3-oxazolidine **3aa** was performed (Scheme 6). The reduction of the ester moiety of **3aa** with $LiAlH_4$ followed by treatment with trifluoroacetic acid in a mixed solvent of 1,4-dioxane and H_2O provided the 2-aminobutane-1,4-diol derivative in good yield (Scheme 6a). The removal of the hemiaminal ether moiety followed by lactonization afforded lactone **11** in good yield (Scheme 6b).

In conclusion, a novel ring expansion reaction of epoxides under Brønsted base catalysis was developed. The formal [3+2] cycloaddition reaction of β,γ-epoxy esters with imines proceeded in the presence of TBD as a superior Brønsted base catalyst to afford 2,4,5-trisubstitued 1,3-oxazolidines in a highly diastereoselective manner. This reaction involves the regioselective cleavage of the carbon–oxygen bond of unsymmetrical 2,3-disubstituted epoxides to generate a formal synthetic equivalent of the 1,3-dipole, followed by the cycloaddition reaction with imines in a stepwise fashion. The operationally simple reaction enables the facile synthesis of enantioenriched 2,4,5-trisubstitued 1,3-oxazolidines from easily accessible enantioenriched epoxides. Further investigations to expand the scope of this methodology are in progress.

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Keywords: asymmetric synthesis · brønsted base · cycloaddition · organocatalyst · ring expansion

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[11] CCDC 1062825. See the Supporting Information for details.

[12] See the Supporting Information for details.

[13] An aliphatic imine, such as cyclohexyl-substituted imine, and a heteroaromatic imine, such as 2-furyl-substituted imine, were

also tested. However, the reaction with those imines provided the corresponding 1,3-oxazolidines only in moderate yields and a significant amount of the starting material **1** was recovered. In both cases, the diastereoselectivity was as high as those in the reaction with other imines (> 95:5).

[14] a) Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806 – 9807; b) Z.-X. Wang, Y. Tu, M. Frohn, Y. Shi, *J. Org. Chem.* **1997**, *62*, 2328 – 2329; c) T. B. Bisol, A. J. Bortoluzzi, M. M. Sá, *J. Org. Chem.* **2011**, *76*, 948 – 962.

[15] Generally, the synthesis of enantioenriched γ-hydroxy-α,β-unsaturated esters requires many steps, see: a) J. Marcus, P. J. van Meurs, A. M. C. H. van den Nieuwendijk, M. Porchet, J. Brussee, A. vab der Gen, *Tetrahedron* **2000**, *56*, 2491 – 2495; b) C. Harcken, R. Brückner, *Synlett* **2001**, 718 – 721.

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