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Catalytic Asymmetric Darzens-Type Epoxidation of Diazoesters: Highly Enantioselective Synthesis of Trisubstituted Epoxides

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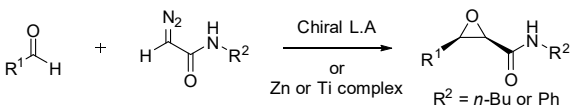
Abstract: Highly enantioselective Darzens-type epoxidation of diazoesters with glyoxal derivatives was accomplished using a chiral boron-Lewis acid catalyst, which facilitated asymmetric synthesis of trisubstituted *α,β*-epoxy esters. In the presence of a chiral oxazaborolidinium ion catalyst, the reaction proceeded in high yield (up to 99%) with excellent enantio- and diastereoselectivity (up to >99% ee and >20:1 dr, respectively). The synthetic potential of this method was illustrated by conversion of the products to various compounds such as epoxy *γ*-butyrolactone, tertiary *β*-hydroxy ketone and epoxy diester.

Optically active *α,β*-epoxy carbonyl compounds are versatile building blocks for the synthesis of biologically active molecules and powerful key intermediates in a broad array of applications for asymmetric synthesis.[1-3] Accordingly, numerous efforts have been dedicated to efficient preparation of these compounds.[4,5] Among the various synthetic methods, asymmetric Darzens condensation[6,7] and Corey-Chaykovsky reaction[8,9] using a sulfur ylide are a particularly powerful approaches in terms of direct asymmetric conversion of carbonyl compounds into epoxides.[2a-b] However, except for a few examples of catalytic methods, synthetic application of these reactions depends on chiral auxiliary methods or chiral reagent-mediated approaches.[6-9]

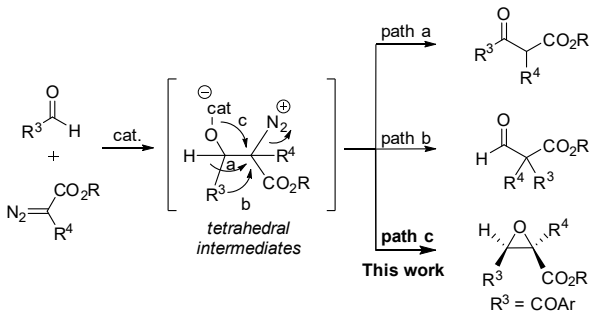
A carbonyl addition-initiated ring-closure of carbonyl compounds using diazo compounds is complementary to these variants.[1b] Since Gong reported pioneering studies on catalytic enantioselective versions with diazoacetamide to afford *α,β-Z*-epoxy amide compounds, there have been a few reports using diazoacetamide as the ylide to give disubstituted *α,β*-epoxy amides (Scheme 1A).[10] However, no study has been successful in synthesizing trisubstituted epoxides, which remain the most challenging class of oxirane despite having been documented in a Darzens-type aziridination.[6c],[11]

Recently, our group reported highly enantioselective catalytic tandem reactions of diazo compounds with the chiral oxazaborolidinium ion (COBI)[12,13] as a Lewis acid catalyst. After forming tetrahedral intermediate through nucleophilic addition of diazo compounds into aldehyde, H-migration[12a-12d] (Roskamp reaction, path a) and C-migration (path b)[12e] led to the construction of optically active *β*-keto ester and the all-carbon quaternary aldehyde, respectively (Scheme 1B). However, epoxide products were observed as side products in the case of *o*-fluorobenzaldehyde.[12a] Based on our observations and reports in the literature,[1a] we envisioned that the reaction of electron-withdrawing group-substituted aldehyde such as glyoxal with diazo compound would generate the epoxide through direct ring-closure of oxygen atom (path c). Efficient enantioselective reactions of glyoxal derivatives with *α*-substituted diazo compounds could provide a valuable method for asymmetric synthesis of optically active trisubstituted *α,β*-epoxy carbonyl compounds (Scheme 1B). Herein, we describe the first highly asymmetric catalytic method for synthesis of trisubstituted *α,β*-epoxy carbonyl compounds in Darzens-type reaction.

A. Enantioselective Darzens epoxidation with diazoacetamide



B. This work : Enantioselective epoxidation for producing trisubstituted epoxide



- Highly functionalized trisubstituted epoxide
- Excellent stereoselectivity (>20:1 dr, up to 99% ee)

Scheme 1. Enantioselective synthesis of epoxide with diazo compounds.

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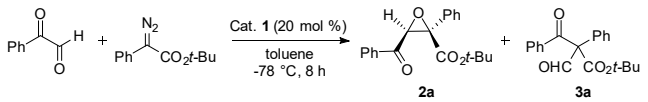
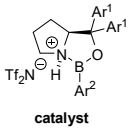
Table 1. Optimization of conditions for enantioselective synthesis of trisubstituted *α*,*β*-epoxy ester.[a,b]





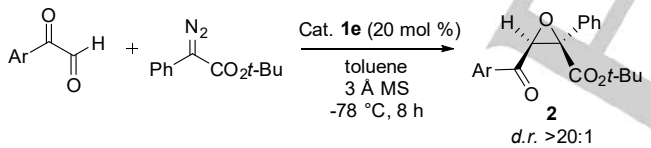
1a, Ar^1 = Phenyl, Ar^2 = Phenyl
1b, Ar^1 = 3,5-Dimethylphenyl, Ar^2 = Phenyl
1c, Ar^1 = 3,5-Dimethylphenyl, Ar^2 = 4-Methoxyphenyl
1d, Ar^1 = 3,5-Dimethylphenyl, Ar^2 = 4-(trifluoromethyl)phenyl
1e, Ar^1 = 2,3-Dimethylphenyl, Ar^2 = 4-(trifluoromethyl)phenyl

catalyst

Entry	Cat. 1	*Z*/*E*	Yield (%)[c]	ee (%)[d]
1	**1a**	10:1	29	90
2	**1b**	>20:1	56	99
3	**1c**	>20:1	63	76
4	**1d**	>20:1	59	99
5	**1e**	>20:1	80	99
6[e]	**1e**	>20:1	85	99
7[e,f]	**1e**	>20:1	54	95

[a] The reaction of phenyl glyoxal (0.6 mmol) with *α*-phenyldiazoester (0.2 mmol) was performed in the presence of catalyst **1** (20 mol %) in 2.0 ml of toluene at –78 °C for 8 hours. [b] The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of **2a**. [d] The ee of **2a** was determined by chiral HPLC. [e] The reaction was carried out with powdered 3 Å molecular sieves (100 mg) and phenyl glyoxal (0.3 mmol). [f] The catalyst was activated by triflic acid instead of triflimide.

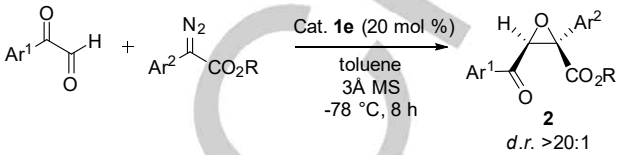
Table 2. Enantioselective formation of trisubstituted *α*,*β*-epoxy ester with various aromatic glyoxal.[a]



Entry	2	Ar	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**	Ph	8	85	99
2[d]	**2a**	Ph	9	83	99
3[e]	**2a**	Ph	14	80	99
4	**2b**	4-MeC_6H_4	24	74	98
5	**2c**	4-$MeOC_6H_4$	24	90	98
6	**2d**	4-BrC_6H_4	8	86	>99
7	**2e**	2-BrC_6H_4	8	50[f]	96
8	**2f**	3-ClC_6H_4	8	73	98
9	**2g**	4-CNC_6H_4	6	85	98
10	**2h**	4-$NO_2C_6H_4$	5	58[f]	93
11	**2i**	2-Naph	8	68	99
12	**2j**	2-Thienyl	8	99	94
13	**2k**	2-Furyl	8	99	99

[a] The reaction of *α*-phenyldiazoester (0.2 mmol) with aromatic glyoxal (0.3 mmol) was performed in the presence of **1e** (20 mol %) and powdered 3 Å molecular sieves (100 mg) in 1.8 ml of toluene at –78 °C. [b] Isolated yield of **2**. [c] ee was determined by chiral HPLC. [d] Performed on a 1.0 mmol scale. [e] 10 mol % of catalyst **1e** was used. [f] **3e** and **3h** were produced in 41% and 32% yield, respectively.

Table 3. Enantioselective formation of trisubstituted *α*,*β*-epoxy ester with various aromatic diazoesters.[a]



Entry	2	Ar^1	Ar^2	R	Yield (%)[b]	ee (%)[c]
1	**2l**	Ph	4-FC_6H_4	*t*-Bu	76	>99
2	**2m**	Ph	4-ClC_6H_4	*t*-Bu	83	>99
3	**2n**	Ph	4-BrC_6H_4	*t*-Bu	81	99
4	**2o**	Ph	4-IC_6H_4	*t*-Bu	70	>99
5	**2p**	Ph	4-$CF_3C_6H_4$	*t*-Bu	75	>99
6	**2q**	Ph	4-MeC_6H_4	*t*-Bu	41[d],[e]	99
7	**2r**	Ph	3-BrC_6H_4	*t*-Bu	80	>99
8	**2s**	Ph	2-BrC_6H_4	*t*-Bu	99	>99
9	**2t**	Ph	2-FC_6H_4	*t*-Bu	98	99
10	**2u**	Ph	2-MeC_6H_4	*t*-Bu	69	>99
11	**2v**	4-BrC_6H_4	4-BrC_6H_4	*t*-Bu	78	99
12	**2w**	4-$MeOC_6H_4$	4-BrC_6H_4	*t*-Bu	98	99
13	**2x**	Ph	Ph	Me	66	>99
14	**2y**	Ph	Ph	Et	72	>99
15	**2z**	Ph	Ph	*i*-Pr	60	>99
16	**2aa**	Ph	Ph	Bn	86	>99

[a] The reaction of *α*-aromatic diazoester (0.2 mmol) with aromatic glyoxal (0.3 mmol) was performed in the presence of **1e** (20 mol %) and powdered 3 Å molecular sieves (100 mg) in 5.0 ml of toluene at –78 °C for 8 h. [b] Isolated yield of **2**. [c] ee was determined by chiral HPLC. [d] Isolated by deactivated silica gel column chromatography at -78 ℃. [e] *β*-keto aldehyde **3q** was produced in 58%.

Initially, enantioselective formation of trisubstituted *α*,*β*-epoxy ester from reaction of phenyl glyoxal and *t*-butyl *α*-phenyl diazoester was examined in the presence of 20 mol % COBI catalyst activated by bis(trifluoromethane)sulfonimide (Table 1). When the reaction was carried out at –78 °C in toluene with catalyst **1a**, *α*,*β*-epoxy *γ*-keto ester **2a** was formed in 29% yield with 90% ee and high *Z* selectivity (Table 1, entry 1). At the same time, a 60% yield of *β*-keto aldehyde **3a** was isolated via Lewis acid-mediated rearrangement.[2a],[14] Since partial rearrangement of the epoxide was observed during purification on a silica gel

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column, product **2a** was purified by deactivated silica gel column chromatography.[15] Changing the catalyst diaryl substituent (Ar^1) to sterically bulky 3,5-dimethylphenyl group led to dramatically improved yield and enantioselectivity (Table 1, entry 2). After screening various catalyst structures, we found that the electron-deficient catalyst **1e**, which has a 4-(trifluoromethyl) phenyl Ar^2 substituent and 2,3-dimethylphenyl Ar^1 substituent, activated by triflimide, gave the best result of 80% yield and 99% ee (Table 1, entries 2-5). Significantly, this reaction exhibited excellent diastereoselectivity and no *E*-diastereomer was detected by ^{1}H NMR analysis of the crude mixture. Interestingly, adding 3 Å molecular sieves led to an improved yield of 85%, and the amount of aryl glyoxal was decreased to 1.5 equivalents (Table 1, entry 6). When the COBI catalyst activated by triflic acid was used, product **2a** was obtained with reduced yield and enantioselectivity (Table 1, entry 7). To the best of our knowledge, catalytic enantioselective formation of a trisubstituted *α,β*-epoxy *γ*-keto ester is without precedent.

Having optimized the reaction conditions, we examined the scope of this reaction with a range of substituted aromatic glyoxals (Table 2).[16] 10 mol % of catalyst loading was successfully applied giving epoxide in 80% yield with 99% ee (Table 2, entry 3). Regardless of the electronic properties of substituents on the phenyl glyoxal, highly enantioenriched trisubstituted *α,β*-epoxy esters **2** were obtained (Table 2, entries 4-10). Phenyl glyoxals with electron-donating groups such as 4-methyl or 4-methoxy group showed lower reactivities, but high yields with excellent enantioselectivities (Table 2, entries 4, 5). Notably the strongly electron-withdrawing 4-nitrophenyl-glyoxal and 2-bromophenyl-glyoxal gave the products in reduced yields due to formation of *β*-keto aldehydes **3** (Table 2, entries 7, 10). The condensed-ring glyoxal (2-naphthylglyoxal) reacted with *α*-phenyl diazoester, giving the desired product with 99% ee (entry 11). This catalytic system was successfully applied to reactions of various heteroaromatic glyoxals such as thienyl, and furyl (Table 2, entries 12, 13). In particular, furyl-substituted glyoxal gave the desired epoxide **2k** in excellent yield with excellent enantioselectivity (99% yield, 99% ee; entry 13).

Encouraged by the good results exhibited in Table 2, we applied this catalytic methodology to Darzens-type epoxidation of various substituted aromatic diazoester (Table 3).[17] Various aromatic diazoesters with halogen and electron-withdrawing groups successfully reacted to give the corresponding epoxides in high to excellent yields with excellent diastereo- and enantioselectivities (Table 3, entries 1-5, 7-9). Use of *p*-tolyl diazoester diminished the yield due to the undesired formation of *β*-keto aldehyde **3q** as side product, but high diastereo- and enantiocontrol were achieved for major epoxide **2q** (99% ee, dr >20:1; Table 3, entry 6). The reaction of substituted phenyl glyoxal (4-methoxy-, 4-bromo-) with 4-bromophenyl diazoester were successful, resulting high to excellent yield with excellent enantioselectivities (Table 3, entries 11-12). Asymmetric formation of *α,β*-epoxy esters with various ester groups of the diazoester proceeded with complete control of enantio- and diastereoselectivities (Table 3, entries 13-16). The absolute configurations of trisubstituted *α,β*-epoxy ester **2a** was unambiguously established by X-ray crystallographic analysis (Figure 1), and the configurations for all other products **2b**-**2aa** are based on this assignment by analogy.[18]

The observed stereochemistry for enantioselective formation of trisubstituted *α,β-Z*-epoxy ester with COBI catalyst **1e** can be rationalized on the basis of the transition-state model shown in Figure 2. The coordination mode of the phenyl glyoxal to catalyst **1e** and the enantioselective carbonyl addition of phenyl diazoester are the same as have been observed for the asymmetric Roskamp reaction.[12b-12e] In the pre-transition-state assembly **4**, shown in Figure 2. the glyoxal is activated through coordination to the boron in a monodentate fashion[19] and placed above the 2,3 dimethylphenylgroup of COBI catalyst **1e**. This group effectively block the *re* face (back) from attack by the phenyl diazoester. Because of the dipole-dipole interaction between the aldehyde of glyoxal and ester of phenyl diazoester, the diazoester approaches for nucleophilic addition with its ester group situated away from the aldehyde group of glyoxal. Meanwhile, *π-π* interaction hold together the benzoyl group of glyoxal and phenyl group of diazoester.[20],[12d] Thus, nucleophilic addition of the phenyl diazoester from the *si* face (front) of the aryl diazoester leads to intermediate **5**, which then cyclizes with loss of nitrogen to form trisubstituted *α,β-Z*-(2*R*,3*S*)-epoxy ester **2a** as the major enantiomer.

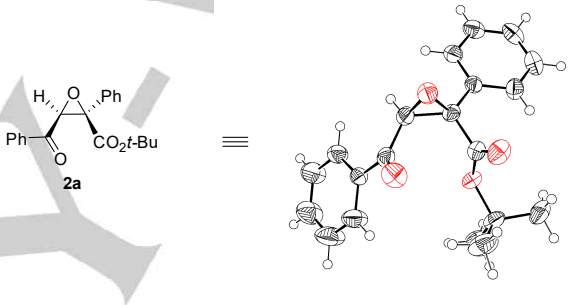

Figure 1. X-ray structure of **2a**.

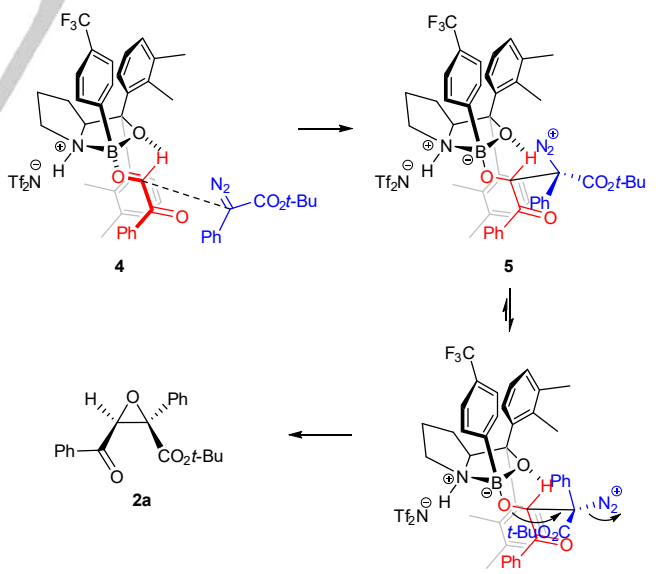

Figure 2. Transition-state model for enantioselective formation of trisubstituted *α,β-Z*-epoxy ester **2a** catalyzed by COBI **1e**.

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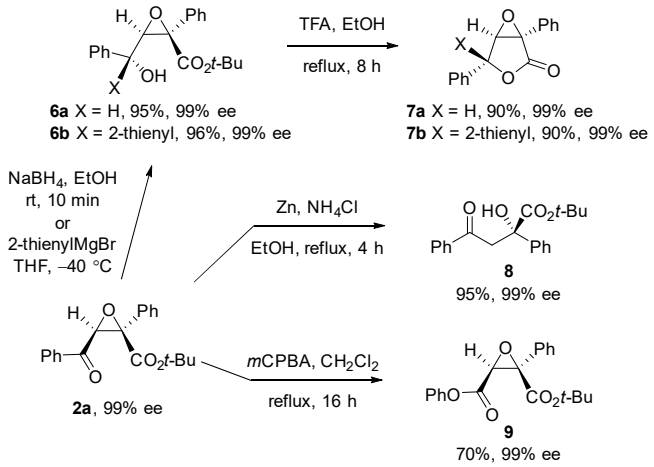

Scheme 2. Derivatizations of trisubstituted *α*,*β*-epoxy esters.

To demonstrate the synthetic utility of these products, further chemical transformations of the resulting optically active *α*,*β*-epoxy ester **2a** were conducted and illustrated in Scheme 2. Chelation-controlled reduction with $NaBH_4$ proceeded effectively to afford a single diastereomeric epoxy alcohol **6a** in 95% yield without loss of enantiopurity.[21] Subsequent cyclization of alcohol **6a** with trifluoroacetic acid gave optically active *α*,*β*-epoxy-*γ*-butyrolactone **7a**.[22],[23] Grignard addition with 2-thienyl magnesium bromide also successfully produced a single diastereomeric epoxy *tert*-alcohol **6b** in 96% yield and acid mediated cyclization gave 4-disubstituted epoxy-*γ*-butyrolactone **7b** in 90% yield with 99% ee. This intriguing structure is found in numerous naturally occurring biologically active compounds, such as Clavilactones,[24] Coralloidolides,[25] and Briaranolides.[26] Additionally, reduction of the epoxide with Zn and, NH_4Cl led to the highly enantioenriched tertiary *β*-hydroxy ketone **8** in 95% yield. [27] Baeyer-Viliger oxidation of the epoxide successfully provided epoxide **9** bearing two different ester groups.

In summary, the first case of highly enantiocontrolled catalytic Darzens-type epoxidation with a diazoester was successfully developed. This highly enantio- and diastereocontrolled synthetic method provides optically active trisubstituted *α*,*β*-epoxy esters in high yields. The resulting densely functionalized esters can be easily converted to optically active *α*,*β*-epoxy-*γ*-butyrolactone and tertiary *β*-hydroxy ketone without loss of optical purity. The absolute configuration of the product was predicted by the transition state model in Figure 2. We believe that the resulting trisubstituted *α*,*β*-*Z*-epoxy esters could be highly valuable and versatile intermediates for further transformations.

Acknowledgements

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Keywords: enantioselectivity • trisubstituted epoxide • Lewis acid • diazoester • Darzens reaction

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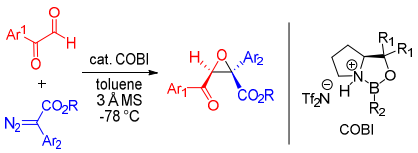

•Highly functionalized trisubstituted epoxide
• Excellent stereoselectivity (>20:1 dr, up to >99% ee)

Chiral trisubstituted epoxides were synthesized by boron-Lewis acid catalyzed Darzens-type epoxidation of diazoesters in high yields with excellent enantio- and diastereoselectivity. The developed reaction provides an efficient synthetic route to various chiral compounds such as epoxy γ-butyrolactone, tertiary β-hydroxy ketone, and epoxy diester.