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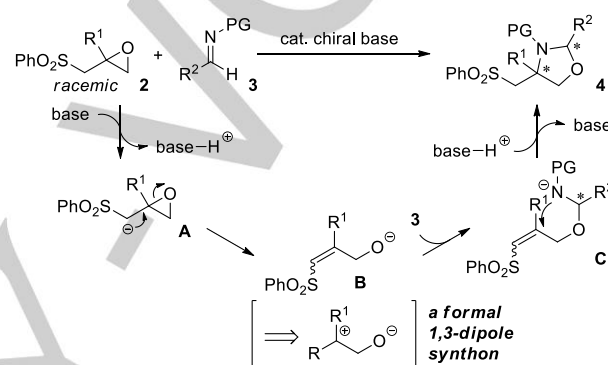
# Enantioselective Formal [3+2] Cycloaddition of Epoxides with Imines under Brønsted Base Catalysis: Synthesis of 1,3-Oxazolidines with Quaternary Stereogenic Center

Azusa Kondoh,<sup>[b]</sup> Shiori Akahira,<sup>[a]</sup> Masafumi Oishi,<sup>[a]</sup> and Masahiro Terada<sup>\*,[a]</sup>

**Abstract:** The formal [3+2] cycloaddition of epoxides with unsaturated compounds is a powerful methodology for the synthesis of densely functionalized five-membered heterocyclic compounds containing oxygen. We have developed a novel enantioselective formal [3+2] cycloaddition of epoxides under Brønsted base catalysis. The bis(guanidino)iminophosphorane as a chiral organosuperbase catalyst enabled the enantioselective reaction of  $\beta,\gamma$ -epoxysulfones with imines, owing to its strong basicity and high stereocontrolling ability, to provide enantioenriched 1,3-oxazolidines having two stereogenic centers including a quaternary one in a highly diastereo- and enantioselective manner.

The ring expansion of strained cyclic compounds has attracted considerable attention as a useful strategy for constructing polysubstituted cyclic frameworks.<sup>[1]</sup> Among a variety of reactions based on this strategy, the formal [3+2] cycloaddition of epoxides with unsaturated compounds is a particularly powerful methodology for the synthesis of densely functionalized five-membered heterocyclic compounds containing oxygen. These reactions are generally catalyzed by transition metal complexes,<sup>[2]</sup> Lewis acids<sup>[3]</sup> or the combination of Lewis acids with halides.<sup>[4]</sup> Epoxides formally serve as the synthetic equivalent of a 1,3-dipole under the influence of these catalysts, which is the key to the reaction proceeding with a variety of unsaturated compounds. Recently, development of asymmetric variants has also been advanced by utilizing transition metal catalysts or Lewis acid catalysts with chiral ligands.<sup>[5]</sup> However, catalytic systems that can construct multiple stereogenic centers in a highly stereoselective manner are still rather limited. Therefore, the expansion of the repertoire for this methodology through the establishment of new catalytic systems is highly anticipated. We recently established a conceptually different catalytic system for the formal [3+2] cycloaddition of epoxides under Brønsted base catalysis, which is complementary to the conventional catalytic systems. We have developed a formal [3+2] cycloaddition of  $\beta,\gamma$ -epoxyesters with imines providing 2,4,5-trisubstituted 1,3-oxazolidines in a highly diastereoselective manner.<sup>[6]</sup> As the next stage of our research, we envisioned the development of an asymmetric variant of this catalytic system by utilizing a chiral Brønsted base catalyst.

Specifically, we designed an enantioselective formal [3+2] cycloaddition of  $\beta,\gamma$ -epoxysulfones **2** having a substituent on the  $\beta$ -carbon with imines **3**, which involves the construction of two stereogenic centers, including a quaternary one, through an enantioconvergent process to provide enantioenriched 1,3-oxazolidines **4** (Scheme 1).



**Scheme 1.** Designed Reaction System.

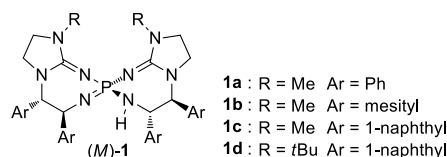
Treatment of racemic  $\beta,\gamma$ -epoxysulfone **2** with a chiral Brønsted base would result in deprotonation at the position  $\alpha$  to the sulfonyl group, followed by epoxide opening to provide alkoxide **B** possessing an alkenyl sulfone moiety. The driving force for this would be the release of ring strain. At this stage, the chiral information of starting **2** has disappeared. This intermediate would then formally serve as the synthetic equivalent of a 1,3-dipole, and the cycloaddition with imine **3** would proceed in a stepwise fashion, i.e., addition of alkoxide **B** to imine **3** followed by intramolecular aza-Michael addition of intermediate **C**, to afford 1,3-oxazolidine **4**. The main challenge of the intended reaction is the stereocontrol of the two stereogenic centers. To this end, we expected that a suitable choice of chiral Brønsted base would enable the enantioselective addition of alkoxide **B** to imine **3** although such precedents are rather limited.<sup>[7]</sup> In addition, the diastereocontrol of the subsequent aza-Michael addition of **C** would be achieved by substrate control and/or catalyst control, thus providing stereocontrolled 1,3-oxazolidines **4**. Enantioenriched 1,3-oxazolidines can be utilized as synthetically versatile intermediates, chiral auxiliaries,<sup>[8]</sup> and ligands in transition metal catalysis.<sup>[9]</sup> They are also an important structural motif found in many biologically active compounds.<sup>[10]</sup> Therefore, the intended reaction would provide new efficient access to enantioenriched 1,3-oxazolidines that are difficult to synthesize by other methods.<sup>[11]</sup> Based on this idea, we describe herein an enantioselective formal [3+2] cycloaddition of  $\beta,\gamma$ -epoxysulfones with imines under Brønsted base catalysis. A chiral bis(guanidino)iminophosphorane (*M*)-**1** (Figure 1),<sup>[12]</sup> as a chiral organosuperbase catalyst, enabled the efficient synthesis of

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enantioenriched 1,3-oxazolidines having two stereogenic centers including a quaternary one in a highly diastereo- and enantioselective manner.



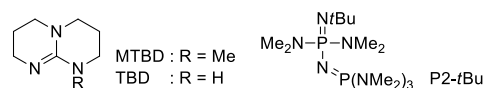
**Figure 1.** Chiral Bis(guanidino)iminophosphoranes (*M*)-1.

We began our investigation by evaluating the viability of our designed reaction by using achiral organobases having different basicities (Table 1, entries 1-4).  $\beta,\gamma$ -Epoxy sulfone **2a** having a phenyl group at the  $\beta$  position was chosen as the primary substrate and treated with *N*-Boc imine **3a** in the presence of 10 mol% organobase in toluene at  $-20^\circ\text{C}$ . As a result, the use of DBU ( $pK_{\text{BH}^+} = 24.3$  in  $\text{CH}_3\text{CN}$ ),<sup>[13]</sup> MTBD ( $pK_{\text{BH}^+} = 25.4$ ), and TBD ( $pK_{\text{BH}^+} = 26.0$ ) resulted in the formation of *N,O*-acetal **5aa** in almost quantitative yield with a high *Z/E* ratio, and only a trace amount of the desired 1,3-oxazolidine **4aa** was observed in the crude  $^1\text{H}$  NMR spectra (entries 1-3).<sup>[14]</sup> In contrast, P2-*t*Bu having much stronger basicity ( $pK_{\text{BH}^+} = 33.5$ ) provided **4aa** in good yield with good diastereoselectivity (entry 4). These results clearly suggest that the use of a catalyst having strong basicity, which facilitates the intramolecular aza-Michael addition of the anion of *N,O*-acetal **5aa**, is essential for completing the tandem catalytic process due to the low electrophilicity of the  $\beta,\beta$ -disubstituted sulfone moiety of the intermediate. These preliminary results prompted us to start the investigation of the enantioselective reaction of **2a** with **3a** by using chiral bis(guanidino)iminophosphoranes (*M*)-1, which were developed by our group,<sup>[12]</sup> possessing comparably high basicity to P2-*t*Bu.<sup>[15]</sup> The initial experiment was conducted with the catalyst generated in situ by treating 11 mol% (*M*)-1a·HBr with 10 mol%  $\text{KN}(\text{SiMe}_3)_2$  prior to use. However, **4aa** was not formed, and instead, *N,O*-acetal **5aa** was obtained quantitatively with 82% ee for the major *Z* isomer (entry 5). The use of other inorganic bases, such as  $\text{NaN}(\text{SiMe}_3)_2$  and  $\text{NaOtBu}$ , for generation of the catalyst provided results similar to that with  $\text{KN}(\text{SiMe}_3)_2$  (entries 6 and 7). We assumed that the failure of the aza-Michael addition was attributed to the detrimental effect of alkali metal cations, such as potassium cation and sodium cation, which would reduce the requisite nucleophilicity of the anion of the *N,O*-acetal **5aa**. Based on this hypothesis, we next attempted the reaction by using  $\text{KN}(\text{SiMe}_3)_2$  with 30 mol% 18-crown-6 as an additive. As a result, the formal [3+2] cycloaddition proceeded to afford **4aa** in good yield as a single diastereomer with 75% ee (entry 8), which is a similar level of enantioselectivity to that of *N,O*-acetal **5aa** without 18-crown-6 (entries 5 vs. 8). The extension of the reaction time further improved the yield of **4aa** (entry 9). In order to increase the enantioselectivity, other precatalysts (*M*)-1·HX having different substituents were examined (entries 10-12). The reaction with precatalyst (*M*)-1b·HCl possessing mesityl groups on the 7,7-

**Table 1.** Initial Screening of Reaction Conditions<sup>[a]</sup>

entry	base catalyst	yield [%] <sup>[b]</sup>		ee [%] <sup>[c]</sup>	
		<b>4aa</b> (dr)	<b>5aa</b> ( <i>Z/E</i> )	<b>4aa</b>	<b>5aa</b>
1	DBU	<5 (-)	95 (98/2)	-	-
2	MTBD	2 (-)	98 (99/1)	-	-
3	TBD	1 (-)	99 (98/2)	-	-
4	P2- <i>t</i> Bu	85 (87/13)	3 (<1/99)	-	-
5	( <i>M</i> )-1a·HBr/ $\text{KN}(\text{SiMe}_3)_2$	<1 (-)	>99 (96/4)	-	82 <sup>[i]</sup>
6	( <i>M</i> )-1a·HBr/ $\text{NaN}(\text{SiMe}_3)_2$	1 (-)	98 (98/2)	-	77
7	( <i>M</i> )-1a·HBr/ $\text{NaOtBu}$	<1 (-)	95 (97/3)	-	82
8 <sup>[d]</sup>	( <i>M</i> )-1a·HBr/ $\text{KN}(\text{SiMe}_3)_2$	84 (>99/1)	12 (86/14)	75	-
9 <sup>[d,e]</sup>	( <i>M</i> )-1a·HBr/ $\text{KN}(\text{SiMe}_3)_2$	98 (>99/1)	<1 (-)	75	-
10 <sup>[d,e]</sup>	( <i>M</i> )-1b·HCl/ $\text{KN}(\text{SiMe}_3)_2$	97 (>99/1)	<3 (-)	-3	-
11 <sup>[d,e]</sup>	( <i>M</i> )-1c·HCl/ $\text{KN}(\text{SiMe}_3)_2$	40 (>99/1)	60 (93/7)	91	97
12 <sup>[d,e]</sup>	( <i>M</i> )-1d·HCl/ $\text{KN}(\text{SiMe}_3)_2$	95 <sup>[f]</sup> (>99/1)	3 (<1/99)	93	-
13 <sup>[d,e,g]</sup>	( <i>M</i> )-1d·HCl/ $\text{KN}(\text{SiMe}_3)_2$	97 <sup>[h]</sup> (>99/1)	3 (<1/99)	93	-

[a] Reaction conditions: **2a** (0.10 mmol), **3a** (0.12 mmol), organobase (0.010 mmol) or (*M*)-1·HX (0.011 mmol) with inorganic base (0.010 mmol), toluene (4.0 mL),  $-20^\circ\text{C}$ . [b] NMR yields unless otherwise noted. Diastereomeric ratio of **4aa** and *Z/E* ratio of **5aa** were determined by  $^1\text{H}$  NMR analysis. [c] Enantiomeric excess of the major isomer of **4aa** or (*Z*)-**5aa** was determined by chiral stationary phase HPLC analysis. [d] 0.030 mmol of 18-crown-6 (30 mol%) was used. [e] The reaction was conducted for 14 h. [f] 88% isolated yield. [g] The reaction was performed in 0.50 mmol scale. [h] Isolated yield. [i] Enantiomeric excess of (*E*)-**5aa** was 46%.

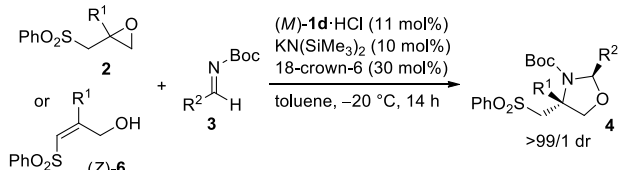


membered spirocyclic rings proceeded smoothly, however, nearly racemic **4aa** was obtained (entry 10). In contrast, (*M*)-1c·HCl with 1-naphthyl groups substantially increased the

enantioselectivity albeit with moderate yield (entry 11). Finally, (*M*)-**1d**·HCl, which had 1-naphthyl groups on the spirocyclic rings and *t*Bu groups on the nitrogen of the guanidine moieties, was found to be the best precatalyst to provide **4aa** in 88% isolated yield with 93% ee (entry 12). The reaction in larger scale proceeded without any problem (entry 13). The absolute configuration of **4aa** was unambiguously determined to be (2*R*,4*R*) by single-crystal X-ray diffraction analysis of racemic **4aa** and enantioenriched amino alcohol **7** derived from enantioenriched **4aa** (vide infra).<sup>[16]</sup>

With the optimum reaction conditions in hand, the scope of substrates was investigated (Table 2). First, the substituent at the  $\beta$ -position of the epoxysulfones **2** was screened (entries 1-8). The reaction of substrates **2b-2d** having a halogen moiety at the *para* position of the phenyl ring provided the corresponding products **4ba-4ea** in high yields with high enantioselectivities

**Table 2.** Substrate Scope<sup>[a]</sup>



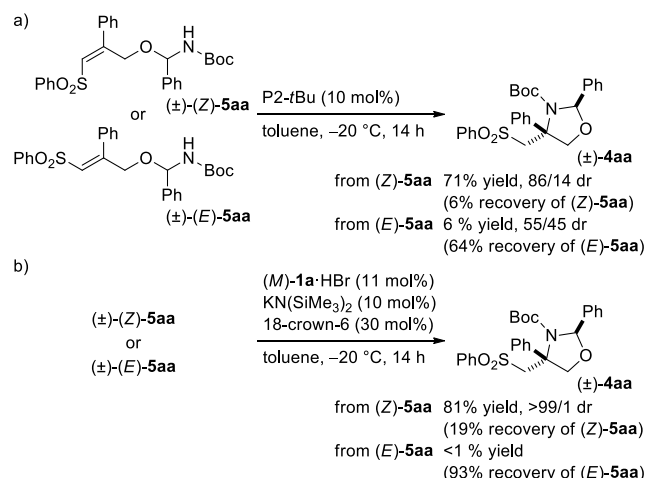
entry	<b>2</b> or <b>6</b>	R <sup>1</sup>	R <sup>2</sup>	<b>4</b>	yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	<b>2b</b>	4-F-C <sub>6</sub> H <sub>4</sub>	Ph	<b>4ba</b>	89	92
2	<b>2c</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	Ph	<b>4ca</b>	90	88
3	<b>2d</b>	4-Br-C <sub>6</sub> H <sub>4</sub>	Ph	<b>4da</b>	92	87
4	<b>2e</b>	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	Ph	<b>4ea</b>	87	72
5	<b>6f</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	Ph	<b>4fa</b>	99	87
6	<b>6g</b>	3-Me-C <sub>6</sub> H <sub>4</sub>	Ph	<b>4ga</b>	90	84
7	<b>6h</b>	3-MeO-C <sub>6</sub> H <sub>4</sub>	Ph	<b>4ha</b>	90	88
8	<b>6i</b>	2-naphthyl	Ph	<b>4ia</b>	99	92
9	<b>2a</b>	Ph	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>4ab</b>	88	93
10	<b>2a</b>	Ph	4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>4ac</b>	86	93
11	<b>2a</b>	Ph	2-Me-C <sub>6</sub> H <sub>4</sub>	<b>4ad</b>	92	41
12	<b>2a</b>	Ph	2-naphthyl	<b>4ae</b>	92	89
13	<b>2a</b>	Ph	2-thienyl	<b>4af</b>	99	90
14	<b>2a</b>	Ph	2-furyl	<b>4ag</b>	97	76

[a] Reaction conditions: **2** or **6** (0.10 mmol), **3** (0.12 mmol), (*M*)-**1d**·HCl (0.011 mmol), KN(SiMe<sub>3</sub>)<sub>2</sub> (0.010 mmol), 18-crown-6 (0.030 mmol), toluene (4.0 mL), -20 °C. [b] Isolated yields. [c] Enantiomeric excess was determined by chiral stationary phase HPLC analysis.

(entries 1-3). 4-Trifluoromethylphenyl-substituted **2e** also underwent the reaction smoothly albeit with moderate ee (entry 4). Some  $\beta,\gamma$ -epoxysulfones were difficult to prepare in pure form. In these cases, the  $\beta,\gamma$ -epoxysulfones **2** were converted to the corresponding allylic alcohols **6** by treatment with a catalytic amount of TBD in THF, and the pure isolated (*Z*)-**6**, which were formed as the major isomer (*Z/E* > 95/5 in each case), were used as substrates in the reaction with imine **3a**.<sup>[17]</sup> With this alternative protocol, each substrate possessing *para*-tolyl, *meta*-tolyl, 3-methoxyphenyl, or 2-naphthyl groups, afforded the corresponding oxazolidines in high yields with high enantioselectivities (entries 5-8). An alkyl substituent, such as a methyl group, was also examined. However, the corresponding 1,3-oxazolidine was not formed and an unidentified mixture of products was obtained.<sup>[18]</sup> Next, the scope of *N*-Boc imines was examined by using **2a** as a substrate (entries 9-14). Both aryl imines having an electron-withdrawing chloro group and an electron-donating methoxy group at the *para* position provided **4ab** and **4ac**, respectively, in high yields with high enantioselectivities (entries 9-10). In contrast, the reaction with **3d** having an *ortho*-tolyl group provided **4ad** in good yield with only modest ee value (entry 11). 2-Naphthyl-substituted **3e** and heteroaryl imines, such as 2-thienyl- and 2-furyl-substituted imines, underwent the reaction without any problem, and the corresponding products **4ae-4ag** were obtained in high yields with good to high enantioselectivities.

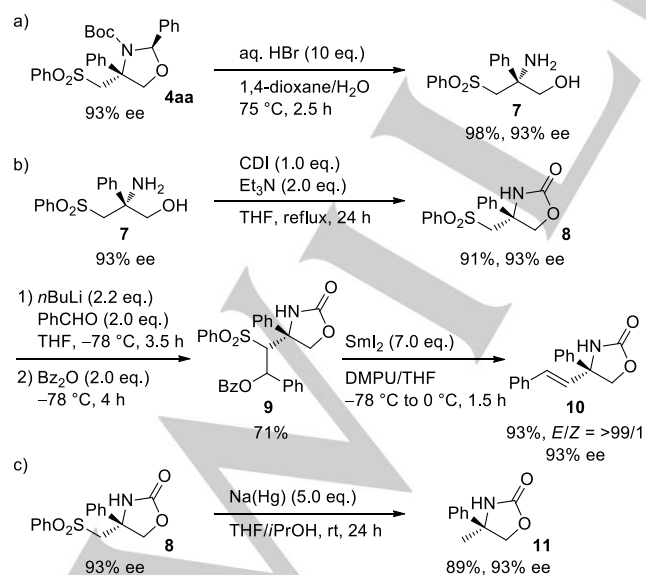
It is worth noting that all of the reactions conducted with (*M*)-**1** provided 1,3-oxazolidines **4** as a single diastereomer. In order to gain some insight into the origin of the diastereoselectivity, some control experiments were carried out (Scheme 2). Specifically, both *Z* and *E* isomers of racemic *N*,*O*-acetal ( $\pm$ )-**5aa** were treated with P2-*t*Bu or (*M*)-**1a**·HBr/KN(SiMe<sub>3</sub>)<sub>2</sub>/18-crown-6. In the case of P2-*t*Bu as a catalyst, ( $\pm$ )-(*Z*)-**5aa** provided ( $\pm$ )-**4aa** as a mixture of diastereomers in a 86/14 ratio, which was almost identical to that obtained in the reaction of **2a** with **3a** (Table 1, entry 4), while ( $\pm$ )-(*E*)-**5aa** provided ( $\pm$ )-**4aa** in only low yield in a 55/45 ratio (Scheme 2a). In contrast, (*M*)-**1a** provided ( $\pm$ )-**4aa** in 81% yield as a single diastereomer from ( $\pm$ )-(*Z*)-**5aa** (Scheme 2b). These results suggest that the Brønsted base catalysts are partially responsible for the diastereocontrol in the intramolecular aza-Michael addition of **5aa** although substrate control is mainly operative. Therefore, in this tandem catalytic process, the key roles of (*M*)-**1** are as follows: 1) facilitating the reaction with its strong basicity, 2) controlling the enantioselectivity in the addition of the alkoxide to the imine, and 3) assisting the diastereocontrol of the aza-Michael addition. Furthermore, the control experiment revealed that ( $\pm$ )-(*E*)-**5aa** was far less reactive than ( $\pm$ )-(*Z*)-**5aa**. In the case of (*M*)-**1a** as a catalyst, the cyclization of ( $\pm$ )-(*E*)-**5aa** did not proceed, and 93% of starting ( $\pm$ )-(*E*)-**5aa** was recovered (Scheme 2b). In addition, the preliminary experiment revealed that the enantioselectivity in the addition of *Z* isomer of the alkoxide is much higher than that in the addition of *E* isomer (Table 1, entry 5), suggesting that (*M*)-**1** can effectively control the enantioselectivity with *Z* isomer compared with *E* isomer.<sup>[19]</sup> Therefore, the selective formation of the (*Z*) configuration of the alkoxide intermediate through the ring opening of  $\beta,\gamma$ -epoxysulfone **2**, which would be independent

of the choice of Brønsted base catalyst, was critical for achieving both high yield and high stereoselectivity of **4**.



**Scheme 2.** Control Experiments.

Finally, derivatization of 1,3-oxazolidine **4aa** was conducted (Scheme 3). **4aa** was easily convertible to the corresponding amino alcohol **7** in almost quantitative yield by treatment with aqueous HBr (Scheme 3a). Further transformation of **7** was attempted to utilize the sulfone moiety as a handle for manipulation (Scheme 3b). Thus, treatment of **7** with 1,1'-carbonyldiimidazole (CDI) provided cyclic carbamate **8** in good yield. The Julia-Lithgoe olefination was then conducted, and the desired **10** was obtained in good overall yield with perfect *E* selectivity by using  $\text{Sml}_2$  as a reductant.<sup>[20]</sup> The direct desulfonation of **8** was also operable by using Na(Hg) to provide **11** in good yield (Scheme 3c).



**Scheme 3.** Derivatization of **4aa**.

In conclusion, we have developed a novel enantioselective formal [3+2] cycloaddition of epoxides under Brønsted base catalysis. A bis(guanidino)iminophosphorane as a chiral organosuperbase efficiently catalyzed the enantioselective reaction of  $\beta,\gamma$ -epoxysulfones with imines to provide enantioenriched 1,3-oxazolidines having two stereogenic centers including a quaternary one in a highly diastereo- and enantioselective manner. This reaction involves: 1) the generation of the key alkoxide intermediate through epoxide opening, which is a formal synthetic equivalent of a 1,3-dipole, 2) the enantioselective addition of the intermediate to the imine, and 3) a diastereoselective intramolecular aza-Michael addition. Both strong basicity and high stereocontrolling ability were the required properties of the catalysts for achieving this tandem catalytic process, which emphasized the usability of a bis(guanidino)iminophosphorane as a chiral organosuperbase catalyst. Further studies, including a mechanistic study on the stereocontrol of the reaction, are in progress.

## Experimental Section

The reaction of **2a** with **3a** is representative (Table 1, entry 12). To a solution of **2a** (27 mg, 0.10 mmol) and **3a** (24  $\mu\text{L}$ , 0.12 mmol) in toluene (2.0 mL) was added a toluene solution (2.0 mL) containing (*M*)-**1d**·HCl (12 mg, 0.011 mmol),  $\text{KN}(\text{SiMe}_3)_2$  (0.50 M in toluene, 20  $\mu\text{L}$ , 0.010 mmol), and 18-crown-6 (1.0 M in toluene, 30  $\mu\text{L}$ , 0.030 mmol) dropwise in 15 seconds at  $-20^\circ\text{C}$ . After stirred for 14 h at that temperature, the reaction was quenched with sat. aq.  $\text{NH}_4\text{Cl}$ . The product was extracted with AcOEt for three times. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and evaporated. The crude mixture was purified by silica-gel column chromatography (hexane/AcOEt = 3/1) to afford **4aa** (46 mg, 0.095 mmol, 95%, >99/1 dr, 93% ee) as a white solid.

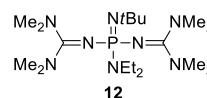
## Acknowledgements

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**Keywords:** Brønsted base • cycloaddition • organocatalyst • asymmetric catalysis • quaternary stereogenic center

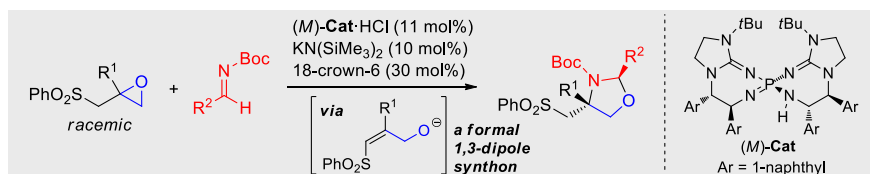
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## COMMUNICATION



A novel enantioselective formal [3+2] cycloaddition of epoxides was developed under Brønsted base catalysis. The bis(guanidino)iminophosphorane as a chiral organosuperbase catalyst enabled the enantioselective reaction of  $\beta,\gamma$ -epoxysulfones with imines, owing to its strong basicity and high stereocontrolling ability, to provide enantioenriched 1,3-oxazolidines having two stereogenic centers including a quaternary one in a highly diastereo- and enantioselective manner.

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**Enantioselective Formal [3+2]  
Cycloaddition of Epoxides with  
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Catalysis: Synthesis of 1,3-  
Oxazolidines with Quaternary  
Stereogenic Center**