Enantioselective Intramolecular Nicholas Reaction Catalyzed by Chiral Phosphoric Acid: Enantioconvergent Synthesis of Seven-Membered Cyclic Ethers from Racemic Diols

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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

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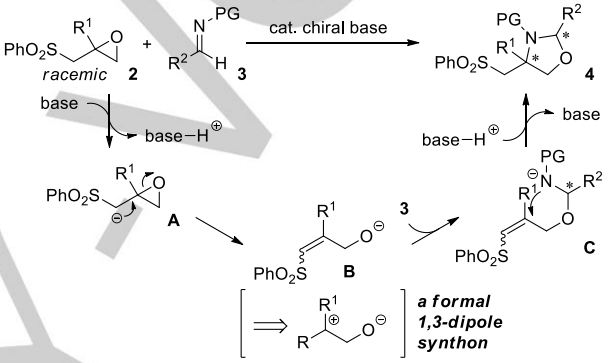
Abstract: The formal [3+2] cycloaddition of epoxides with unsaturated compounds is a powerful methodology for the synthesis of densely functionalized five-membered heterocyclic compounds containing oxygen. We have developed a novel enantioselective formal [3+2] cycloaddition of epoxides under Brønsted base catalysis. The bis(guanidino)iminophosphorane as a chiral organosuperbase catalyst enabled the enantioselective reaction of *β,γ*-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.[1] 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,[2] Lewis acids[3] or the combination of Lewis acids with halides.[4] 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.[5] 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 *β,γ*-epoxyesters with imines providing 2,4,5-trisubstituted 1,3-oxazolidines in a highly diastereoselective manner.[6] 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 *β,γ*-epoxysulfones **2** having a substituent on the *β*-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 *β,γ*-epoxysulfone **2** with a chiral Brønsted base would result in deprotonation at the position *α* 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.[7] 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,[8] and ligands in transition metal catalysis.[9] They are also an important structural motif found in many biologically active compounds.[10] Therefore, the intended reaction would provide new efficient access to enantioenriched 1,3-oxazolidines that are difficult to synthesize by other methods.[11] Based on this idea, we describe herein an enantioselective formal [3+2] cycloaddition of *β,γ*-epoxysulfones with imines under Brønsted base catalysis. A chiral bis(guanidino)iminophosphorane (*M*)-**1** (Figure 1),[12] 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.

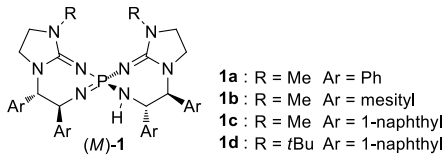
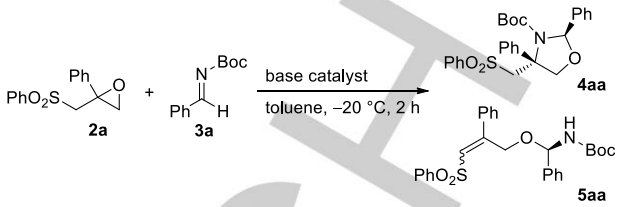


Figure 1. Chiral Bis(guanidino)iminophosphoranes (*M*)-**1**.

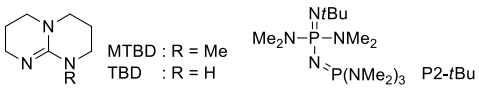
We began our investigation by evaluating the viability of our designed reaction by using achiral organobases having different basicities (Table 1, entries 1-4). *β,γ*-Epoxysulfone **2a** having a phenyl group at the *β* position was chosen as the primary substrate and treated with *N*-Boc imine **3a** in the presence of 10 mol% organobase in toluene at -20 °C. As a result, the use of DBU (pK_{BH^+} = 24.3 in CH_3CN),[13] MTBD (pK_{BH^+} = 25.4), and TBD (pK_{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}H NMR spectra (entries 1-3).[14] In contrast, P2-*t*Bu having much stronger basicity (pK_{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 *β,β*-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,[12] possessing comparably high basicity to P2-*t*Bu.[15] The initial experiment was conducted with the catalyst generated in situ by treating 11 mol% (*M*)-**1a**·HBr with 10 mol% $KN(SiMe_3)_2$ 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 $NaN(SiMe_3)_2$ and NaO*t*Bu, for generation of the catalyst provided results similar to that with $KN(SiMe_3)_2$ (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 $KN(SiMe_3)_2$ 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-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

Table 1. Initial Screening of Reaction Conditions[a]



entry	base catalyst	yield [%][b] **4aa** (dr)	yield [%][b] **5aa** (*Z*/*E*)	ee [%][c] **4aa**	ee [%][c] **5aa**
1	DBU	<5 (-)	95 (98/2)	-	-
2	MTBD	2 (-)	98 (99/1)	-	-
3	TBD	1 (-)	99 (98/2)	-	-
4	P2-*t*Bu	85 (87/13)	3 (<1/99)	-	-
5	(*M*)-**1a**·HBr/ $KN(SiMe_3)_2$	<1 (-)	>99 (96/4)	-	82[i]
6	(*M*)-**1a**·HBr/ $NaN(SiMe_3)_2$	1 (-)	98 (98/2)	-	77
7	(*M*)-**1a**·HBr/ NaO*t*Bu	<1 (-)	95 (97/3)	-	82
8[d]	(*M*)-**1a**·HBr/ $KN(SiMe_3)_2$	84 (>99/1)	12 (86/14)	75	-
9[d,e]	(*M*)-**1a**·HBr/ $KN(SiMe_3)_2$	98 (>99/1)	<1 (-)	75	-
10[d,e]	(*M*)-**1b**·HCl/ $KN(SiMe_3)_2$	97 (>99/1)	<3 (-)	-3	-
11[d,e]	(*M*)-**1c**·HCl/ $KN(SiMe_3)_2$	40 (>99/1)	60 (93/7)	91	97
12[d,e]	(*M*)-**1d**·HCl/ $KN(SiMe_3)_2$	95[f] (>99/1)	3 (<1/99)	93	-
13[d,e,g]	(*M*)-**1d**·HCl/ $KN(SiMe_3)_2$	97[h] (>99/1)	3 (<1/99)	93	-

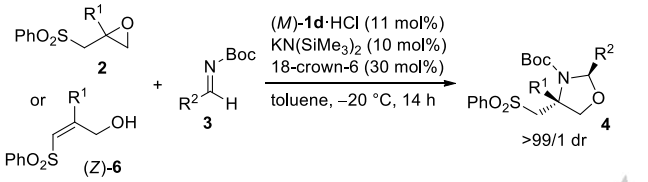
[a] Reaction conditions: **2a** (0.10 mmol), **3a** (0.12 mmol), organobase (0.010 mmol) or (*M*)-**1**·HX (0.011 mmol) with inorganic base (0.010 mmol), toluene (4.0 mL), -20 °C. [b] NMR yields unless otherwise noted. Diastereomeric ratio of **4aa** and *Z*/*E* ratio of **5aa** were determined by ^{1}H 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%.



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).[16]

With the optimum reaction conditions in hand, the scope of substrates was investigated (Table 2). First, the substituent at the *β*-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[a]



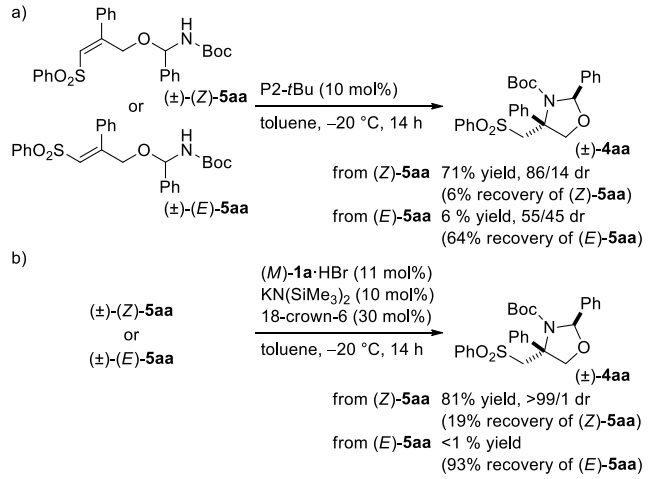
entry	**2** or **6**	R^1	R^2	**4**	yield [%][b]	ee [%][c]
1	**2b**	4-F-C_6H_4	Ph	**4ba**	89	92
2	**2c**	4-Cl-C_6H_4	Ph	**4ca**	90	88
3	**2d**	4-Br-C_6H_4	Ph	**4da**	92	87
4	**2e**	4-CF_3-C_6H_4	Ph	**4ea**	87	72
5	**6f**	4-Me-C_6H_4	Ph	**4fa**	99	87
6	**6g**	3-Me-C_6H_4	Ph	**4ga**	90	84
7	**6h**	3-MeO-C_6H_4	Ph	**4ha**	90	88
8	**6i**	2-naphthyl	Ph	**4ia**	99	92
9	**2a**	Ph	4-Cl-C_6H_4	**4ab**	88	93
10	**2a**	Ph	4-MeO-C_6H_4	**4ac**	86	93
11	**2a**	Ph	2-Me-C_6H_4	**4ad**	92	41
12	**2a**	Ph	2-naphthyl	**4ae**	92	89
13	**2a**	Ph	2-thienyl	**4af**	99	90
14	**2a**	Ph	2-furyl	**4ag**	97	76

[a] Reaction conditions: **2** or **6** (0.10 mmol), **3** (0.12 mmol), (*M*)-**1d**·HCl (0.011 mmol), $KN(SiMe_3)_2$ (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 *β,γ*-epoxysulfones were difficult to prepare in pure form. In these cases, the *β,γ*-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**.[17] 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.[18] 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.

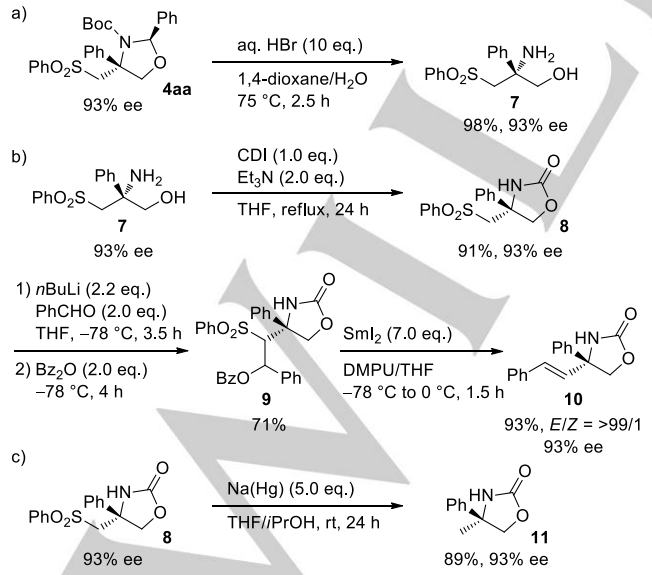
It is worth noting that all of the reactions conducted with (*M*)-**1** provided 1,3-oxazolidines **4** as a single diastereomer. In order to gain some insight into the origin of the diastereoselectivity, some control experiments were carried out (Scheme 2). Specifically, both *Z* and *E* isomers of racemic *N*,*O*-acetal (±)-**5aa** were treated with P2-*t*Bu or (*M*)-**1a**·HBr/$KN(SiMe_3)_2$/18-crown-6. In the case of P2-*t*Bu as a catalyst, (±)-(*Z*)-**5aa** provided (±)-**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 (±)-(*E*)-**5aa** provided (±)-**4aa** in only low yield in a 55/45 ratio (Scheme 2a). In contrast, (*M*)-**1a** provided (±)-**4aa** in 81% yield as a single diastereomer from (±)-(*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 (±)-(*E*)-**5aa** was far less reactive than (±)-(*Z*)-**5aa**. In the case of (*M*)-**1a** as a catalyst, the cyclization of (±)-(*E*)-**5aa** did not proceed, and 93% of starting (±)-(*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.[19] Therefore, the selective formation of the (*Z*) configuration of the alkoxide intermediate through the ring opening of *β,γ*-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 SmI_2 as a reductant.[20] The direct desulfonylation 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 *β,γ*-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 µL, 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), $KN(SiMe_3)_2$ (0.50 M in toluene, 20 µL, 0.010 mmol), and 18-crown-6 (1.0 M in toluene, 30 µL, 0.030 mmol) dropwise in 15 seconds at -20 °C. After stirred for 14 h at that temperature, the reaction was quenched with sat. aq. NH_4Cl. The product was extracted with AcOEt for three times. The combined organic layer was washed with brine, dried over Na_2SO_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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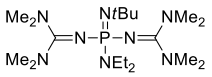

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[16] CCDC No.1822255 for racemic **4aa** and CCDC No.1822257 for (*R*)-**7**. See the Supporting Information for details.

[17] See the Supporting Information for details.

[18] The reaction of β,γ-epoxysulfone having an ethoxycarbonyl group at the R^1 position was also examined under the optimized reaction conditions. However, the conversion of the substrate was very low (ca. 30%), and the corresponding oxazolidine was not obtained. The introduction of such electron-withdrawing groups seems to have a detrimental effect on the reaction system.

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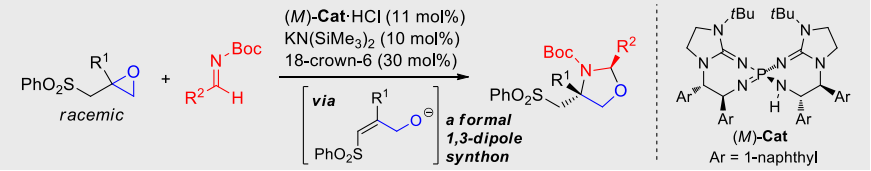

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Enantioselective Formal [3+2] Cycloaddition of Epoxides with Imines under Brønsted Base Catalysis: Synthesis of 1,3-Oxazolidines with Quaternary Stereogenic Center

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 *β,γ*-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.