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Diastereoselective Synthesis of 1,3-Oxazolidines via Cationic Iron Porphyrin-catalyzed Cycloaddition of Aziridines with Aldehydes

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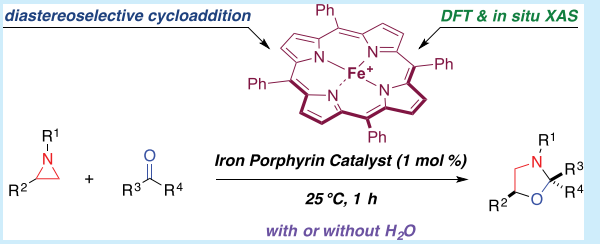
Supporting Information

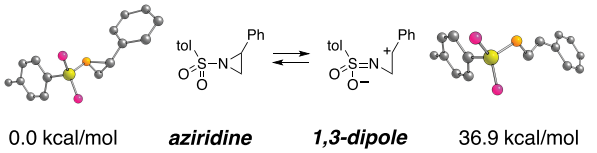
ABSTRACT: An efficient iron porphyrin Lewis acid-catalyzed cycloaddition of aziridines with aldehydes has been developed to provide oxazolidines with high regio- and diastereoselectivity. The cycloaddition proceeds in toluene with 1 mol % of the iron catalyst at 25 °C. A theoretical study and synchrotron-based X-ray absorption fine structure measurements provided fundamental insights into the aziridine−iron porphyrin complex, which is the key intermediate for the generation of the 1,3-dipole synthon.



Metalloporphyrins perform important biochemical functions in nature. Therefore, the related chemistry has been a topic of great interest.[1] Recently, we reported that metalloporphyrins could perform as Lewis acid and catalyze various reactions such as formal hetero-Diels−Alder reaction and cycloisomerization.[2] Herein, we report that iron porphyrin can catalyze [3 + 2] cycloaddition of aziridines via formation of 1,3-dipole synthon with carbonyl compounds to give 1,3-oxazolidines diastereoselectively.

Aziridine is a valuable synthetic building block for various nitrogen-containing cyclic compounds, as it readily reacts as a 1,3-dipole synthon with various dipolarophiles,[3] and the high reactivity of aziridine is attributed to its facile formation of 1,3-dipolar intermediate mediated by a Lewis acid. From the point of Gibbs free energy change, the use of Lewis acid is mandatory for activation of aziridine and stabilization of the resulting 1,3-dipole since in the absence of Lewis acid this step is highly endergonic as shown in Scheme 1. Thus, the use of

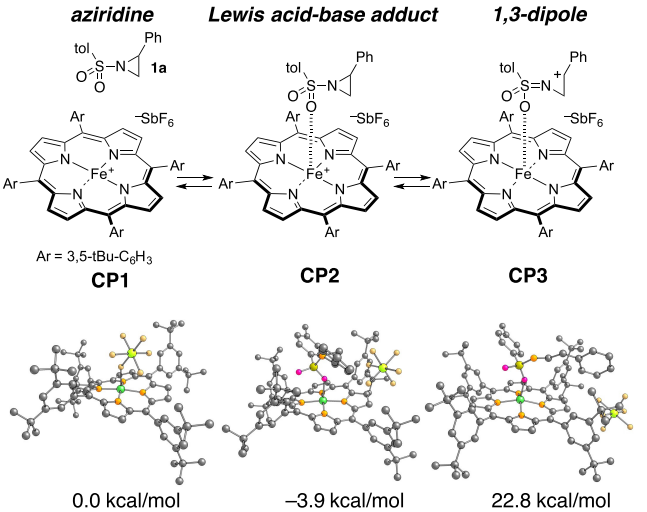
Scheme 1. Gibbs Free Energy Change of 1,3-Dipole Synthon Formation without Stabilization by Lewis Acid



appropriate Lewis acid to activate aziridine and stabilize the resulting 1,3-dipole synthon is key for the reaction. We hypothesized that with its high Lewis acidity, the cationic iron porphyrin complex would catalytically facilitate the activation of aziridine to generate 1,3-dipole synthon, thereby promoting the reaction with dipolarophiles to afford nitrogen-containing cyclic compounds. Moreover, the steric hindrance of the porphyrin ligand would promote the dissociation of the product to achieve high turnover frequency.

To prove our hypothesis, we initially examined the Gibbs free energy change for the complexion of cationic iron(III) porphyrin catalyst Fe[(TArP)]SbF_6 (Ar = 1,3-*t*Bu-C_6H_3) **CP1** with aziridine **1a** by means of density functional theory calculation (Scheme 2). It was found that the coordination of

Scheme 2. Gibbs Free Energy Change of 1,3-Dipole Synthon Formation via Activation of Aziridine with Iron Porphyrin Lewis Acid



aziridine **1a** to **CP1** formed **CP2** in an exergonic step. The interaction between **CP1** and **1a** is further confirmed by using noncovalent interaction plot (NCIPlot) and second-order perturbation theory analysis of the Fock matrix in NBO (see Supporting Information). The activated aziridine, i.e., 1,3-dipole synthon, is also thermodynamically stabilized by

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coordination to the cationic iron porphyrin to form **CP3**, with a Gibbs energy change of 22.8 kcal/mol that is a reasonable value for the reaction intermediate and rather small compared to the case without the iron complex (36.9 kcal/mol in Scheme 1). To gain further insight into the structure of **CP2** in solution phase, Fe *K*-edge X-ray absorption spectroscopy (XAS) analysis was performed using a synchrotron radiation beamline, where the ultrahigh brightness made solution-phase XAS accessible for *in situ* structural investigation. Analysis of the extended X-ray absorption fine structure (EXAFS) spectrum of the solution of **CP2** in toluene indicated good agreement with the theoretically calculated model for the Lewis acid−base adduct with R_f = 3.0% (Figure 1).

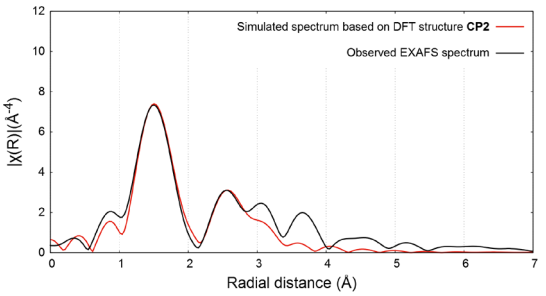
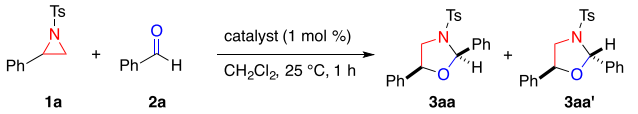


Figure 1. Solution-phase Fe *K*-edge EXAFS analysis (Fourier transform of k^3-weighted spectrum, Δk = 3.0−9.7 Å^{-1}, ΔR = 1.1−3.4 Å, spatial resolution δR = 0.162 Å, R_f = 3.0%): simulated spectrum based on DFT structure **CP2** (red line) and experimental spectrum (black line).

Based on the theoretical study and X-ray spectroscopic analysis of complexation between iron porphyrin and aziridine, we envisioned that iron porphyrin may promote the 1,3-dipole addition with dipolarophiles. Indeed, the reaction of aziridine **1a** with benzaldehyde (**2a**) in the presence of cationic iron(III) porphyrin catalyst **CP1** (1 mol %) in dichloromethane at 25 °C for 1 h afforded 1,3-oxazolidine **3aa** in 97% yield with a diastereomer ratio of 10/1 (Table 1, entry 1). Upon optimization of the iron porphyrin catalyst structure, [Fe(TPP)]SbF_6 showed improved diastereoselectivity (entry 2). Among various counteranions such as SbF_6, OTf, ClO_4, BF_4, and Cl, the cationic iron porphyrin complex having SbF_6 counteranion provided the cycloadduct in the highest yield (entries 2−5). The use of other cationic metalloporphyrin complexes, such as [Mn(TPP)]SbF_6, [Co(TPP)]SbF_6, and [Cr(TPP)]SbF_6 in place of [Fe(TPP)]SbF_6 also resulted in the formation of 1,3-oxazolidine **3aa** in trace amount or much lower yield. Furthermore, the reaction with conventional Lewis acid catalysts such as Fe(OTf)$_3$, $AgSbF_6$, BF_3·Et_2O, Zn(OTf)$_2$, Sc(OTf)$_2$, Cu(OTf)$_2$, and Brønsted acid TfOH also afforded the cycloadduct **3aa** in high yield but with far lower diastereoselectivity (entries 10−16). Iron salts catalyst, such as $FeCl_3$, $FeCl_2$, and Fe(OAc)$_2$ did not afford cycloadduct **3aa** (entries 17−19).

With the optimized reaction conditions in hand, we first evaluated the cationic iron(III) porphyrin-catalyzed [3 + 2] cycloaddition by using aziridine **1a** with various carbonyl compounds **2**, and the results are summarized in Chart 1. The reaction of anisaldehyde (**2b**) with **1a** provided **3ab** in 82% yield. Cycloaddition of arylaldehydes having an electron-donating substituent reacted with **1a** to afford the corresponding substituted oxazolidines in high yields with diastereoselectivity (**3ac** and **3ad**). Not only aryl aldehydes but also aliphatic aldehydes participated in the reaction to afford cycloadducts in high yields. For example, cylcohexylcarboxaldehyde (**2e**) reacted with **1a** in the presence of iron catalyst to give cycloadducts in 97% yield with a diastereomer ratio of 17/1. We next applied the iron porphyrin catalyst to the reaction with ketones. The cycloaddition of ketone **2j** with **1a** gave bicyclic compound **3aj** in 72% yield. The reaction also proceeded with cyclohexanone **2m** to provide **3am** in 80% yield. Of note, the asymmetrical ketone **2m** also reacted with **1a** to give **3am** diastereoselectively. It is also remarkable that the [Fe(TPP)]SbF_6-catalyzed [3 + 2] cycloaddition is feasible in the presence of water: an aqueous solution of formaldehyde **2n** could react with **1a** to obtain cycloadduct **3an** in 64% yield.

Table 1. Cycloaddition of Aziridine 1a with Aldehyde 2a[a]



1a 2a 3aa 3aa'

entry	catalyst	yield (%)[b]	3aa/3aa'[c]
1	[Fe(TArP)]SbF_6	97	10/1
2	[Fe(TPP)]SbF_6	87	50/1
3	[Fe(TPP)]OTf	30	20/1
4	[Fe(TPP)]ClO_4	18	20/1
5	[Fe(TPP)]BF_4	24	20/1
6	[Fe(TPP)]Cl	<1	
7	[Mn(TPP)]SbF_6	<1	
8	[Co(TPP)]SbF_6	52	7/1
9	[Cr(TPP)]SbF_6	59	20/1
10	Fe(OTf)$_3$	69	1/1
11	$AgSbF_6$	90	5/1
12	BF_3·Et_2O	79	1/1
13	Zn(OTf)$_2$	91	3/1
14	Sc(OTf)$_3$	73	1/1
15	Cu(OTf)$_2$	82	1/1
16	TfOH	99	1/1
17	$FeCl_3$	<1	
18	$FeCl_2$	<1	
19	Fe(OAc)$_2$	<1	

[a]Reaction conditions: catalyst (1 mol %), aziridine **1a** (0.1 mmol), and aldehyde **2a** (0.15 mmol, 1.5 equiv) in 1 mL of CH_2Cl_2 for 1 h. [b]NMR yields are given. [c]Ratio of diastereomers (**3aa**/**3aa'**).

In order to demonstrate the scope of this cycloaddition, we next examined the reaction of various aziridines **1** with benzaldehyde **2a** (Chart 2). Under the optimized reaction conditions, 2-arylaziridines possessing an electron-withdrawing substituent and an electron-donating one on phenyl moiety reacted with benzaldehyde **2a** to afford the corresponding substituted 1,3-oxazolidines in good yield diastereoselectively (**3ba** and **3ca**). Note that 2,2-dialkyl-substituted aziridine **1d** also participated in the reaction to give **3da** in 82% yield.

It is possible for the present reaction to proceed via either a concerted mechanism or a stepwise mechanism, as shown in Figure 2. In order to determine which one is the case, the chiral aziridine **1a** (99% ee) was reacted with **2a** in the presence of iron porphyrin catalyst under the standard reaction conditions (Scheme 3). The isolated cycloadduct from the experiment was found to be almost racemic (11% ee). Furthermore, it was found that chiral aziridine **1a** racemized in the presence of iron porphyrin catalyst under the standard reaction conditions. Based on these results, it is proposed that

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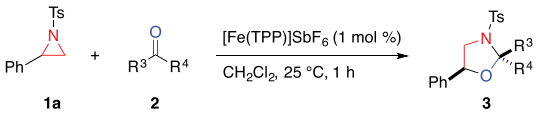
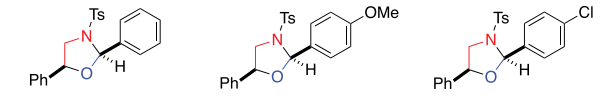
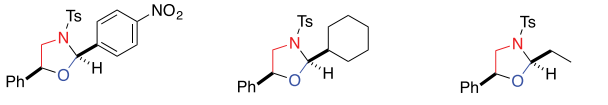
Chart 1. Diastereoselective Cycloaddition of Aziridine 1a with Aldehydes[a]



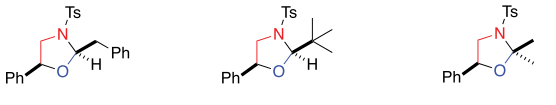
product[b]



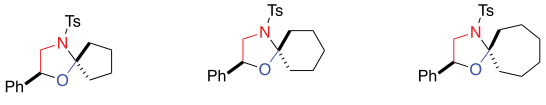
3aa 73% (50 / 1) **3ab** 82%[c] (5 / 1) **3ac** 77% (50 / 1)



3ad 90% (20 / 1) **3ae** 97% (14 / 1) **3af** 77% (13 / 1)



3ag 82% (10 / 1) **3ah** 46% (17 / 1) **3ai** 81%



3aj 72%[d] **3ak** 80%[e] **3al** 65%[f]

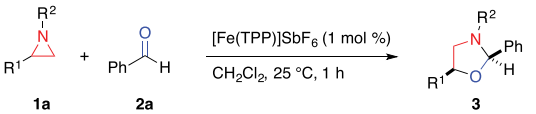
3am 70%[g] (50/1) **3an** 64%[h]

[a]Reaction conditions: iron porphyrin catalyst (1 mol %), aziridine **1a** (0.1 mmol), and aldehyde **2** (0.15 mmol, 1.5 equiv) in 1 mL of CH_2Cl_2 for 1 h. [b]Isolated yields are given. [c]Reaction time: 3 h. [d]Reaction time: 7 h. [e]Reaction time: 4 h. [f]Reaction time: 6 h. [g]Reaction temperature: 60 °C. Reaction time: 4 h. [h]Reaction temperature: 60 °C (CH_2Cl_2/water mixture in sealed tube). Reaction time: 2 h.

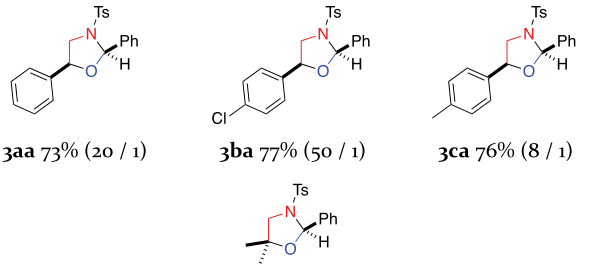
the reaction involves coordination of the aziridine to the iron porphyrin, leading to the cleavage of C−N bond to produce a discrete and stable 1,3-dipole synthon, which reacts with the carbonyl compound in a stepwise fashion to afford the cycloadduct. It should be noted that epimerization of 1,3-oxazolidines was not observed under the reaction conditions (Scheme 4), suggesting that the diastereoselectivity is mainly due to the kinetics rather than thermodynamics, and the cycloadduct **3aa** and its diastereomer **3aa′** are stable enough to tolerate the reaction conditions without opening the oxazolidine ring.

In summary, we found that the Lewis acid-catalyzed cycloaddition of aziridines with carbonyl compound provides oxazolidines with high regio- and diastereoselectivity. The use of cationic iron porphyrin complex as Lewis acid catalyst facilitates the reaction under mild condition within a short time. The cycloaddition proceeds in toluene with 1 mol % of the iron catalyst at 25 °C within 1 h. The reaction occurs in a stepwise mechanism involving ring opening of aziridine to form a discrete stable 1,3-dipole synthon, which reacts with various types of carbonyl compounds. The coordination of 1,3-

Chart 2. Diastereoselective Cycloaddition of Aziridines with Aldehyde 2a[a]



product[b]



3aa 73% (20 / 1) **3ba** 77% (50 / 1) **3ca** 76% (8 / 1)

3da 82%

[a]Reaction conditions: iron porphyrin catalyst (1 mol %), aziridine **1** (0.1 mmol), and aldehyde **2a** (0.15 mmol, 1.5 equiv) in 1 mL of CH_2Cl_2 for 1 h. [b]Isolated yields are given. [c]Reaction time: 3 h.

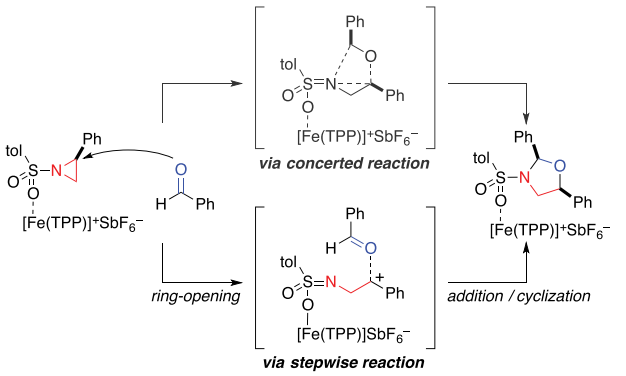
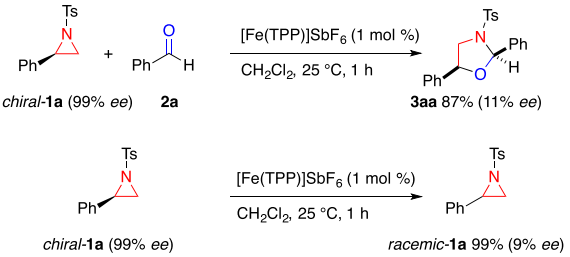
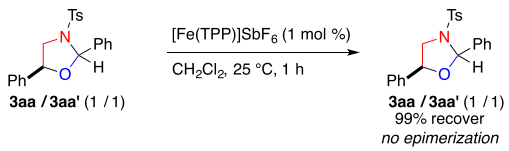


Figure 2. Possible reaction paths for the cycloaddition.

Scheme 3. Cationic Iron Porphyrin-catalyzed Cycloaddition of Chiral Aziridine 1a with Aldehyde 2a, and Racemization of 1a



Scheme 4. Stability of 1,3-Oxazolidines 3aa/3aa′ Under the Reaction Conditions



dipole synthon to the iron porphyrin catalyst was also elucidated with Fe *K*-edge XAS analysis and density functional

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theory calculation. Since the use of appropriate metalloporphyrin Lewis acid as a catalyst enables the [3 + 2] cycloaddition of aziridines with both high diastereoselectivity and high turnover frequency, further study on these metalloporphyrin Lewis acid catalysts may reveal intrinsic catalytic activity of first-row transition metals; these studies are currently under investigation in our laboratory.[4−7]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00560.

Experimental procedures including spectroscopic and analytical data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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