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Iron(III)-Catalyzed Selective N–O Bond Cleavage to Prepare Tetrasubstituted Pyridines and 3,5-Disubstituted Isoxazolines from N-Vinyl-α,β-Unsaturated Ketonitrones

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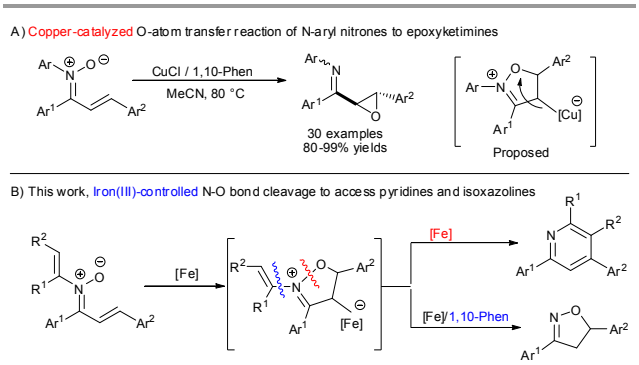
An iron(III)-catalyst controlled cyclization and selective N–O bond cleavage of N-vinyl-α,β-unsaturated nitrones has been achieved under mild conditions to access tetrasubstituted pyridines and 3,5-disustituted isoxazolines in moderate to good yields. The tetrasubstituted pyridines were afforded under $FeCl_3$ as catalyst while using $FeCl_3$•$6H_2O$ combined with 1,10-phenanthroline delivered isoxazolines. The regioselectivity for cyclization of styrenyl groups in N-vinyl-α,β-unsaturated nitrones was completely different during the formation of pyridines and isoxazolines. A rational mechanism for the formation of pyridines and isoxazolines was proposed based on the further control experimental studies. The isoxazolines can be converted to a novel bidentate N-ligand over four steps and an epoxypyridine scaffold was obtained from N-vinyl nitrone when copper(II) acetate combanied with the prepared bidentate N-ligand was used.

Introduction

Diversity-oriented synthesis (DOS) is an efficient strategy that not only is crucial to the generation of spatially diverse chemical libraries for biological screening from a single material, but also improves the synthetic efficiency and simplifies the operations.[1] Controlling reaction selectivity is an important and challenging topic that rapidly builds molecular complexity and has been employed for the synthesis of complicated molecules in both target- and diversity-oriented syntheses.[2] Examples of substrate-, reagent-, solvent-, and catalyst-controlled divergent cascade process that lead to either skeletally or stereochemically distinct products are known, however, the use of catalyst to control the reaction selectivity is one of the most appealing strategies.[3-7] Therefore, to explore a new and efficient catalyst-oriented method toward important chemical libraries for biological screening from simple molecules is desirable.

Nitrone, one of the most important 1,3-dipoles in cycloaddition reactions, has been extensively used in diverse organic synthesis and total synthesis.[8] In particular, α,β-unsaturated nitrones have attracted much attention in recent years due to the rich chemistry of the double bonds.[9] In 2013, Anderson and coworker firstly reported that N-aryl-α,β-unsaturated nitrones could go through a O-atom transfer reaction to afford α,β-epoxyketimines under copper(I) chloride combined with 1,10-phenanthroline (1,10-Phen) (Scheme 1-A).[10] An isoxazoline intermediate and a sequence of N–O bond cleavage were proposed, but the intermediate has not yet been isolated and completely characterized. We envisioned that according to the proposed isoxazoline intermediate, different types of catalysts and the substituted groups on N-atom of nitrones might control the sequential N–O bond cleavage.



Scheme 1. Strategies to control the selectivity of N–O bond cleavage

Recently, N-vinyl nitrone has become a new type of nitrone in organic synthesis due to its new reactivity and conversions.[11] During our studies of N-vinyl nitrones,[12] we surmised that N-vinyl-α,β-unsaturated nitrones might also undergo an intramolecular attack to form isoxazoline intermediate, which then afforded pyridine or isoxazoline scaffolds by further conversion of the double bond on N-atom after N–O bond cleavage (Scheme 1-B). The pyridine and

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isoxazoline units are two important N-heterocycles that are present in a number of natural and pharmacological compounds and display a wide range of biological activity (Figure 1).[13] Both two scaffolds have not only been used as powerful building blocks in organic synthesis but also played extensively as versatile N-ligands in catalysis.[14] Therefore, to develop efficient methods, especially for the general, practical and environmentally benign synthetic methods to prepare pyridine and isoxazoline units remain desirable. Many elegant and efficient strategies to prepare pyridine and isoxazoline scaffolds were developed in the past decades.[15,16] However, most of these methods suffered from harsh reaction conditions, expensive metals, and various starting materials. There are no examples reported to prepare both pyridine and isoxazoline units from a single starting material, which limited the synthetic efficiency and diversity of products. Although Anderson group has reported a metal-free synthesis of polysubstituted pyridines from N-vinyl-α,β-unsaturated nitrones, high temperature (at 140 °C) was required and the scope and diversity of products were limited because there were no catalyst to control.[17] As the most abundant transition metal on earth, using iron catalysts in synthetic chemistry has clear advantages because of the inexpensive, nontoxic, and environmentally benign properties of iron species.[18] However, there was few report that iron-catalyst can be used to control the selectivity of N–O bond cleavage. Herein, we reported an iron(III)-controlled N–O bond cleavage and oriented synthesis of tetrasubstituted pyridines and isoxazolines from N-vinyl-α,β-unsaturated nitrones.

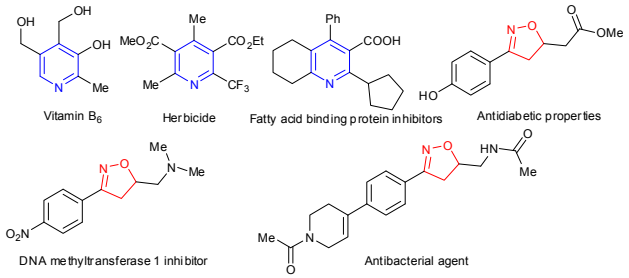
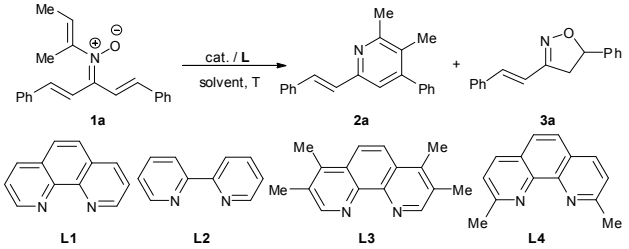


Figure 1. Bioactive compounds containing pyridine and isoxazoline units

Results and Discussion

Initially, N-vinyl-α,β-unsaturated nitrone **1a** was chosen as the model substrate to evaluate the cyclization and N–O bond cleavage process. When nitrone **1a** was heated in THF at 80 °C for 24 h without adding catalyst, product **2a** or **3a** was observed less than 5% yield and nitrone **1a** was almost recovered (Table 1, entry 1). Addition of 20 mol% of $FeCl_3$ and $FeCl_3$•$6H_2O$ afforded pyridine **2a** as a major product in 39% and 33% yields, respectively (Table 1, entries 2-3). The solvent screening revealed that using alcohols as solvents, such as MeOH, *t*-BuOH or *i*-PrOH, gave higher yields of product **2a** compared to THF, MeCN, toluene, DCE, and DMSO (Table 1, entries 8-10 *vs* entries 2-7). The reaction delivered pyridine **2a** in 56% yield in *i*-PrOH (Table 1, entry 10). Addition of 3Å MS improved the yield of product **2a** to 65% (Table 1, entry 11). The yield of product **2a** was dropped either at lower or higher reaction temperature (Table 1, entries 12-13). To our surprise, a mixture of pyridine **2a** and isoxazoline **3a** was afforded in 10% and 31% yields by using $FeCl_3$ with 1,10-Phen (**L1**) and isoxazoline **3a** was obtained as the major product (Table 1, entry 14). Almost the same result was obtained when *i*-PrOH was replaced by MeCN (Table 1, entry 15). Moreover, using $FeCl_3$•$6H_2O$ and ligand **L1** could further increase the total yield of products **2a** and **3a** (Table 1, entry 16). These results demonstrated that the iron-catalysts might control the N-O bond cleavage. Inspired by these results, the effect of solvents was next examined by using $FeCl_3$•$6H_2O$ and 1,10-Phen (**L1**). The solvent screening revealed that isoxazoline **3a** was furnished in moderate to good yields as the major product in most solvents, such as toluene, DMF, and THF except that DCE delivered lower yield (Table 1, entries 17-20). It was shown that THF was the best solvent resulting product **3a** in 79% yield (Table 1, entry 20). Other bidentate N-ligands **L2-L4** were also tested (Table 1, entries 21-23). Ligand **L2** afforded lower yield of product **3a** while ligands **L3** and **L4** furnished product **3a** smoothly in 73% and 71% yields, respectively. When the reaction temperature was lowered to 60 °C, product **3a** was also obtained in 75% yield (Table 1, entry 24). Further lowering temperature decreased the yield of **3a** obviously and no reaction occurred at room temperature (Table 1, entry 25). Other iron, copper or palladium catalysts were also evaluated. Iron(III) combined with OTf anion furnished product **3a** in lower yield while iron(II) catalyst combined with either Cl or OTf anions did not promote the reaction (Table 1, entries 26-28). Product **3a** was not observed while pyridine **2a** was obtained in 10% and 6% yields by using copper(II) acetate or copper(I) chloride combined with 1,10-Phen (**L1**) as catalysts (Table 1, entries 29-30). 23% yield of product **3a** was afforded without product **2a** when the copper was replaced by $Pd(OAc)_2$ (Table 1, entry 31). Therefore, the optimal reaction conditions for preparing pyridine **2a** were using 20 mol% of $FeCl_3$ with 3Å MS as additive in *i*-PrOH at 80 °C (Table 1, entry 11). The optimal conditions for preparing isoxazoline **3a** was using 20 mol% of $FeCl_3$•$6H_2O$ and 40 mol% of 1,10-Phen (**L1**) in THF at 80 °C (Table 1, entry 20).[19]

Table 1. Optimization of the Reaction Conditions.[a]



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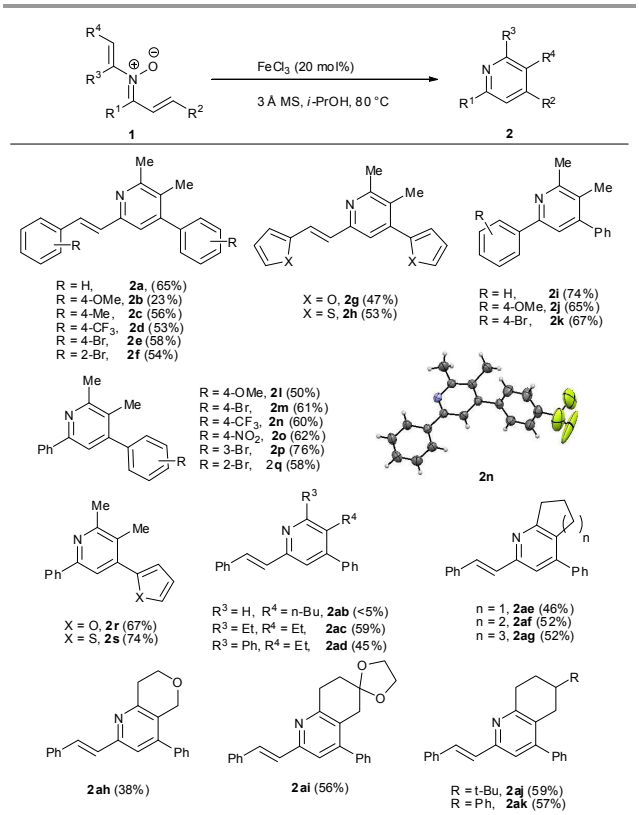
entry	cat. / **L**	solvent	T (°C)	**2a**%[b]	**3a**%[b]
1	-	THF	80	<5	<5
2	$FeCl_3$	THF	80	39	<5
3	$FeCl_3•6H_2O$	THF	80	33	<5
4	$FeCl_3$	MeCN	80	30	<5
5	$FeCl_3$	toluene	80	38	<5
6	$FeCl_3$	DCE	80	24	<5
7	$FeCl_3$	DMSO	80	27	<5
8	$FeCl_3$	MeOH	80	46	<5
9	$FeCl_3$	*t*-BuOH	80	51	<5
10	$FeCl_3$	*i*-PrOH	80	56	<5
11[c]	$FeCl_3$	*i*-PrOH	80	65	<5
12[c]	$FeCl_3$	*i*-PrOH	70	58	<5
13[c]	$FeCl_3$	*i*-PrOH	100	64	<5
14	$FeCl_3$ / **L1**	*i*-PrOH	80	10	31
15	$FeCl_3$ / **L1**	MeCN	80	14	38
16	$FeCl_3•6H_2O$ / **L1**	MeCN	80	18	43
17	$FeCl_3•6H_2O$ / **L1**	DCE	80	15	26
18	$FeCl_3•6H_2O$ / **L1**	toluene	80	<5	60
19	$FeCl_3•6H_2O$ / **L1**	DMF	80	<5	63
20	$FeCl_3•6H_2O$ / **L1**	THF	80	<5	79
21	$FeCl_3•6H_2O$ / **L2**	THF	80	<5	32
22	$FeCl_3•6H_2O$ / **L3**	THF	80	<5	73
23	$FeCl_3•6H_2O$ / **L4**	THF	80	<5	71
24	$FeCl_3•6H_2O$ / **L1**	THF	60	<5	75
25	$FeCl_3•6H_2O$ / **L1**	THF	25	<5	<5
26	$Fe(OTf)_3$ / **L1**	THF	80	<5	24
27	$FeCl_2$ / **L1**	THF	80	<5	<5
28	$Fe(OTf)_2$ / **L1**	THF	80	<5	<5
29	$Cu(OAc)_2$ /**L1**	THF	80	10	<5
30	CuCl / **L1**	THF	80	6	<5
31	$Pd(OAc)_2$ / **L1**	THF	80	<5	23

[a] Reaction conditions: **1a** (0.2 mmol), cat. (20 mol%), **L** (40 mol%), solvent (2 mL), 80 °C, 7–24 h; [b] Isolated yield; [c] 3Å MS (200 mg) was added.

With the optimized reaction conditions in hand (Table 1, entry 11), a variety of N-vinyl nitrones **1** were investigated for the scope of preparing tetrasubstituted pyridines **2**. As shown in Table 2, various 2,4,5,6-tetrasubstituted pyridines with electron-donating and electron-withdrawing groups were obtained in moderate yields when symmetric dibenzylideneacetone-derived N-vinyl nitrones were used, but nitrone **1b** with a methoxy group gave pyridine **2b** only in 23% yield (Table 2, **2a**-**f**). The reaction also tolerated heteroaryl groups such as 2-furanyl and 2-thienyl giving pyridines **2g** and **2h** in 47% and 53% yields, respectively. The vinyl groups at 2-position of pyridines would allow these compounds more potential transformations in organic synthesis. The scope of N-vinyl chalcone nitrones was also evaluated. Both aryl groups of chalcone nitrones were compatible with electron-donating and electron-withdrawing groups at *ortho*, *meta*, and *para* positions (Table 2, **2i-q**). The structure of pyridine **2** was further confirmed by the X-ray diffraction analysis of compound **2n**.[20] The *E/Z* ratio for chalcone nitrone **1i-q** have little effect on the yields of **2i-q** because the *E/Z* isomer of vinyl nitrones were interconvertible under thermal conditions.[21] The vinyl moieties on N-atom of nitrones were also tested. Disubstituted linear and cyclic N-vinyl nitrones proceeded smoothly to afford 2,4,5,6-tetrasubstituted pyridines in good yields (Table 2, **2ac-ak**). However, monosubstituted linear N-vinyl nitrone **1ab** failed to furnish pyridine **2ab** and decomposed to dibenzylideneacetone. For cyclic vinyl group on N-atom of nitrone, the ring size did not affect the yield of pyridines much (Table 2, **2ae-ag**). Interestingly, compounds **2ai-ak** were obtained in good yields even through there were substituents presented on the six-membered ring, such as acetal, *t*-Bu or phenyl groups. The introduction of an acetal group onto the six-membered ring was particularly appealing (Table 2, **2ai**), because this group could be removed by deprotection to provide a synthetic handle for further manipulation.

Table 2. The scope of preparing tetrasubstituted pyridines **2** for N-vinyl nitrones **1**.[a,b]



[a] Reaction conditions: **1** (0.2 mmol), $FeCl_3$ (20 mol%), 3Å MS (200 mg), *i*-PrOH (2 mL), 80 °C, 12–15 h; [b] Isolated yield.

We subsequently investigated the substrate scope for preparing isoxazolines using the optimal conditions (Table 1, entry 20). As shown in Table 3, a wide range of N-vinyl nitrones proceeded smoothly to provide various isoxazolines in good yields. N-vinyl nitrones **1a-f** with both electron-rich and electron-deficient styrenyl functional groups having *ortho*, *meta*, and *para* substitution patterns were tolerated under the optimized conditions and afforded the desired isoxazolines in moderate to good yields (Table 3, **3a-f**). To our delight, the reaction was compatible with 2-furanyl and 2-thienyl groups on the nitrones, and the corresponding isoxazolines **3g** and **3h** were obtained in 76% and 78% yields, respectively. When asymmetric N-vinyl chalcone nitrones were tested, the aryl

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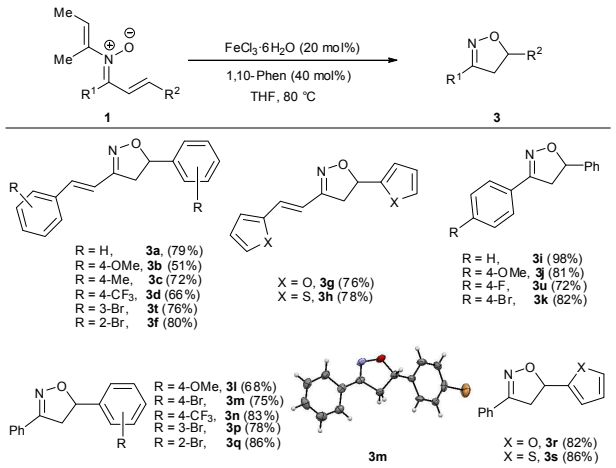
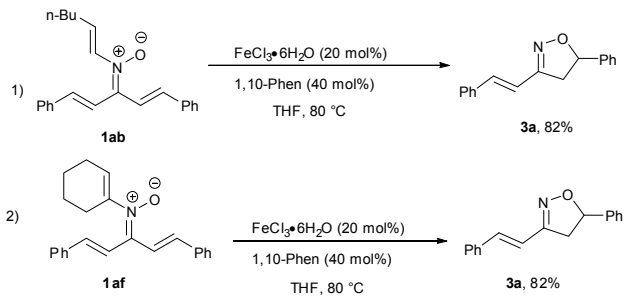
bearing electron-donating and electron-withdrawing groups delivered the corresponding isoxazolines in good to excellent yields (Table 3, entries **3i-q**). Interestingly, N-vinyl chalcone nitrones **1i-q**, always used with an *E/Z* ratio of the C=N bond from 3:1 to 15:1, did not affect the formation of isoxazolines much and both of *E/Z* isomers could be converted to isoxazolines.[21] The structure of isoxazoline **3** was further confirmed by X-ray diffraction analysis of compound **3m**.[20] N-Vinyl nitrones containing 2-furanyl and 2-thienyl groups afforded the desired isoxazolines **3r** and **3s** in 82% and 86% yields, respectively, which provided an alternative method to access double heterocyclic compounds.

Table 3. The scope of preparing isoxazolines **3** for N-vinyl nitrone **1**.[a,b]



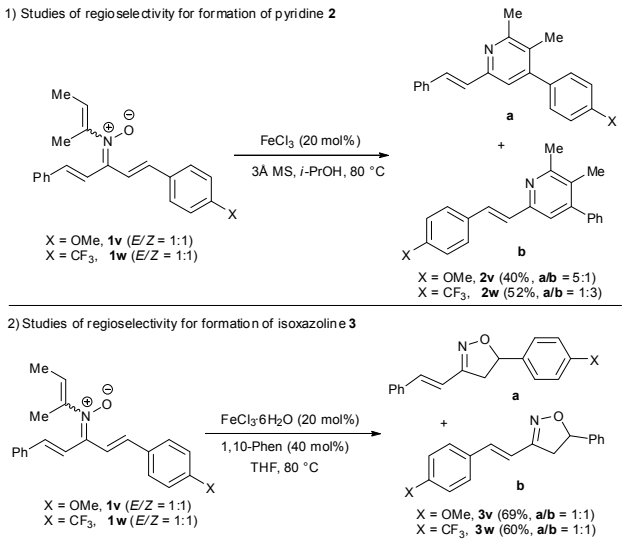
[a] Reaction conditions: **1** (0.2 mmol), $FeCl_3$•$6H_2O$ (20 mol%), 1,10-Phen (40 mol%), THF (2 mL), 80 °C, 7–15 h; [b] Isolated yield.

Obviously, the vinyl substituent on N-atom of nitrone was dropped during the formation of isoxazolines. Therefore, substituents on N-atom were evaluated. As shown in Scheme 2, both monosubstituted linear N-vinyl nitrone **1ab** and cyclic *N*-vinyl nitrone **1af** proceed smoothly to afford isoxazoline **3a** in 82% yield. These results revealed that the vinyl substituents on N-atom did not have a great effect on the formation of isoxazolines.



Scheme 2. The reactivity of substituents on N-atom of nitrones

Next, the regioselectivity of cyclization for the formation of pyridines and isoxazolines were studied (Scheme 3). For the formation of pyridines, when 1:1 *E/Z* ratio of nitrone **1v** with a methoxy group was subjected to 20 mol% of $FeCl_3$ in *i*-PrOH at 80 °C, product **2v** was afforded in 40% yield and the regioselectivity of cyclization was observed with a 5:1 ratio (Scheme 3-1). However, 1:1 *E/Z* ratio of nitrone **1w** with trifluoromethyl group delivered product **2w** in 52% yield and the regioselectivity of cyclization was observed with a 1:3 ratio. The major isomers of **2v** and **2w** were determined by their NOESY spectra. This regioselectivity of cyclization under iron(III) catalyst was completely different from metal-free thermal conditions.[17] In this case, cyclization for the formation of pyridines was favorable for styrenyl group with an electron-donating group in nitrone. For the formation of isoxazolines, when nitrone **1v** with a methoxy group and **1w** with trifluoromethyl group at 4-position of styrenyl group were subjected to 20 mol% of $FeCl_3$•$6H_2O$ with 1,10-Phen in THF at 80 °C, products **3v** and **3w** were obtained in 69% and 60% yields, respectively (Scheme 3-2). The regioselectivity of cyclization for the styrenyl group is 1:1 ratio, which suggested that the electron-donating or electron-withdrawing groups did not affect the regioselectivity of cyclization for isoxazoline formation.



Scheme 3. Exploration of regioselectivity for forming pyridines and isoxazolines

Some control experiments were conducted to gain some information on the reaction mechanism (Scheme 4). When nitrone **1a** was conducted under $FeCl_3$ in *i*-PrOH with radical trapping reagent TEMPO, 36% yield of pyridine **2a** was obtained (Scheme 4-1). However, an isoxazole product **4** was afforded in 61% yield when **1a** reacted with TEMPO under $FeCl_3$•$6H_2O$ with 1,10-Phen (Scheme 4-2). The isoxazoline **3a** was converted to isoxazole **4** in 29% yield in the presence of $FeCl_3$•$6H_2O$ with 1,10-Phen and TEMPO (Scheme 4-3), which suggested that isoxazole **4** might be generated from isoxazoline **3a**. These results revealed that the formation of both pyridines and isoxazolines did not involve a radical process. When N-vinyl nitrone **1al** was conducted under $FeCl_3$• $6H_2O$ with 1,10-Phen, product **3a** was obtained in 49% yield accompanied by 79% yield of acetophenone which might be

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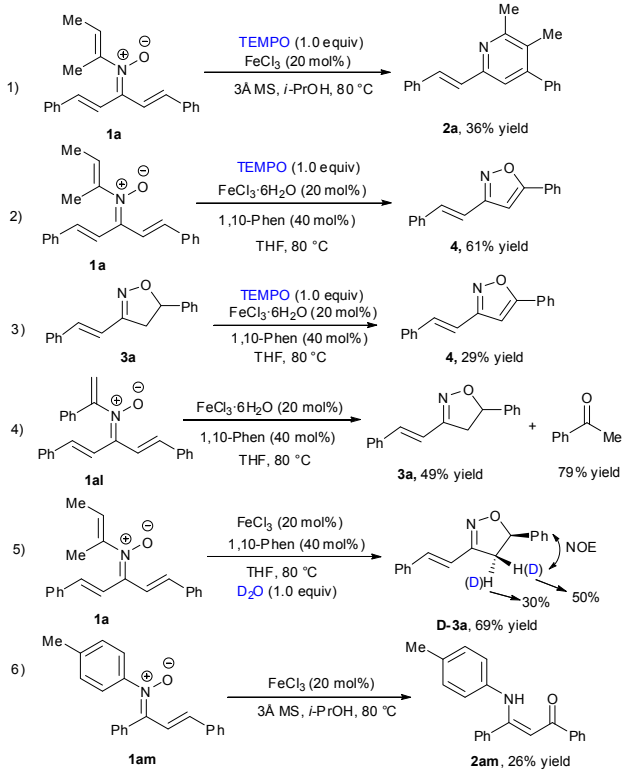
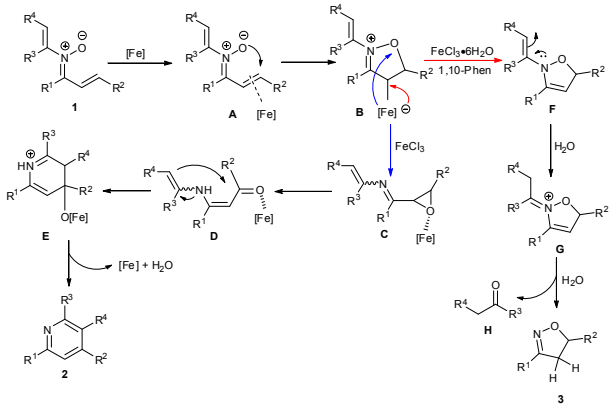
produced by hydrolysis from the vinyl group on N-atom of nitrone (Scheme 4-4). When nitrone **1a** ran under $FeCl_3$ with 1,10-Phen in THF with addition of 1.0 equiv of D_2O, the yield of **3a** was obtained in 69% and the deuterated ratio of methylene group in **3a** was 50% and 30%. The NOESY spectra of compound **D-3a** showed that D (50%) was *cis* relationship with phenyl group (Scheme 4-5). These results suggested that the protonolysis step was an intermolecular scratching. When N-aryl nitrone **1am** was subjected to the pyridine formation conditions, enaminoketone **2am** was obtained in 26% yield (Scheme 4-6). This result indicated that enaminoketone might be the key intermediate for the formation of pyridines.



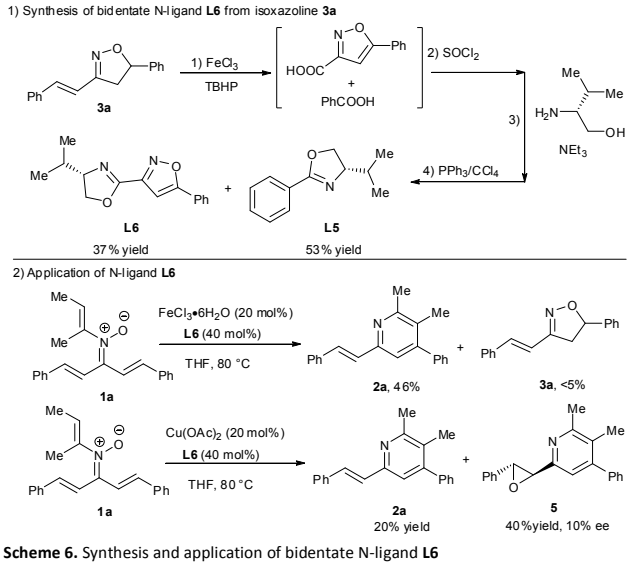
Scheme 4. Mechanistic studies

Based on the experimental results and literatures on N–O bond cleavage,[22] a plausible mechanism for the formation of pyridines and isoxazolines from N-vinyl nitrones under iron(III)-catalyst was proposed. As shown in Scheme 5, intermediate **A** was formed by nitrone **1** coordinated to iron(III), which occurred an intramolecular attack to give **B**. Intermediate **B** might undergo a subsequent N–O bond cleavage to result epoxyketimine **C**, Then, a ring-opening under iron(III)-catalyst gave enaminoketone **D**.[23] The **D** proceeded an intramolecular nucleophilic addition of enamine to ketone to afford **E**, which finally underwent an elimination to provide pyridine **2** and release iron(III) catalyst and water. Alternatively, isomerisation of **B** converted to **F** under iron(III) with 1,10-Phen, and then underwent hydrolysis to form isoxazoline **3** releasing by-product ketones, which were supported by the result of Scheme 4-4. Iron(III) catalyst might play as a Lewis acid to promote these cyclization reactions.



Scheme 5. Proposed mechanism

Oxazoline and isoxazole are two important types of N-ligand and have been extensively applied in transition-metal catalysis. Hence, a new bidentate N-ligand containing oxazoline and isoxazole was investigated (Scheme 6-1). Treatment of isoxazoline **3a** under $FeCl_3$ and TBHP, followed with $SOCl_2$, condensation with L-valinol and cyclization with PPh_3 and CCl_4 conditions provided ligand **L5** and **L6** in 53% and 37% yields in four steps, respectively. The N-ligand **L6** was the first time synthesized. When nitrone **1a** was subjected to isoxazoline formation conditions, pyridine **2a** was obtained in 46% yield as a major product while an epoxypyridine **5** was afforded in 40% yield and 10% ee accompanied by pyridine **2a** in 20% yield (Scheme 6-2). These results demonstrated that ligand **L6** definitely possessed asymmetric induction. Compared to the optimization by using copper and ligand **L1** in Table 1, ligand **L6** showed its special catalytic reactivity for N-vinyl nitrone.



Scheme 6. Synthesis and application of bidentate N-ligand **L6**

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Conclusions

We have developed an iron(III) catalyst-controlled cyclization and selective N–O bond cleavage of N-vinyl-α,β-unsaturated nitrones to access tetrasubstituted pyridines and 3,5-disubstituted isoxazolines in moderate to good yields. The reaction tolerated various N-vinyl-α,β-unsaturated nitrones with functional groups. A new bidentate N-ligand was easily prepared in 37% yield from isoxazoline over four steps and an epoxypyridine scaffold was obtained by using copper acetate combined with the prepared N-ligand. The current strategy features simple and mild reaction conditions, broad substrate scope, cheap catalyst-controlled N–O bond cleavage, diversity of N-heterocycles, and facile to access a chiral bidentate N-ligand.

Experimental

General procedure for preparing of pyridines 2: A Teflon-sealed flask was charged with N-vinyl nitrone **1** (0.2 mmol), $FeCl_3$ (7 mg, 20 mol%), 3Å MS (200 mg) under N_2 atmosphere. *i*-PrOH (2 mL) was then added via syringe and the reaction vessel was once again sealed with a Teflon cap. The reaction mixture was stirred at 25 °C for 5 min and then heated at 80 °C for 12–15 h until nitrones **1** were consumed completely (monitored by TLC). At this time, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (the crude residue was dry loaded on silica gel, 1/50 to 1/20, ethyl acetate/petroleum ether) to afford tetrasubstituted pyridines **2**.

General procedure for preparing isoxazolines 3: A Teflon-sealed flask was charged with N-vinyl nitrones **1** (0.2 mmol), $FeCl_3$•$6H_2O$ (11 mg, 20 mol%), 1,10-Phen (15 mg, 40 mol%) under N_2 atmosphere. THF (2 mL) was then added via syringe and the reaction vessel was once again sealed with a Teflon cap. The reaction mixture was stirred at 25 °C for 5 min and then heated at 80 °C for 7–15 h until nitrones **1** were consumed completely (monitored by TLC). At this time, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (the crude residue was dry loaded on silica gel, 1/50 to 1/20, ethyl acetate/petroleum ether) to afford isoxazolines **3**.

Conflicts of interest

There are no conflicts of interest to declare

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19 See more optimized reaction conditions for the formation of pyridine **2a** and isoxazoline **3a** in Supporting Information.

20 CCDC: 1819201 (compound **2n**) and CCDC: 1819200 (compound **3m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

21 The *E/Z* ratio for N-vinyl nitrones **1i-q** used as follows: **1i** (15:1), **1j** (10:1), **1k** (8:1), **1l** (10:1), **1m** (8:1), **1n** (3.5:1), **1o** (10:1), **1p** (8:1), **1q** (8:1). The *E/Z* isomerisation of N-vinyl chalcone nitrone **1i** was tested. The results showed that *E/Z* = 15/1 of nitrone **1i** turned to *E/Z* = 5.8/1 for heating 5.5 h. And *E/Z* = 1/1.4 of nitrone **1i** turned to *E/Z* = 7.2/1 for heating 1.5 h. Please see the spectra in Supporting Information.

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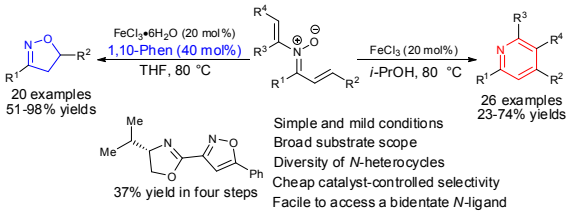
Graphic Abstract



An iron(III)-controlled selective N−O bond cleavage was developed for the synthesis of tetrasubstituted pyridines and isoxazolines from N-vinyl-α,β-unsaturated ketonitrones.