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Iron-Catalyzed Radical Cycloaddition of 2*H*-Azirines and Enamides for the Synthesis of Pyrroles

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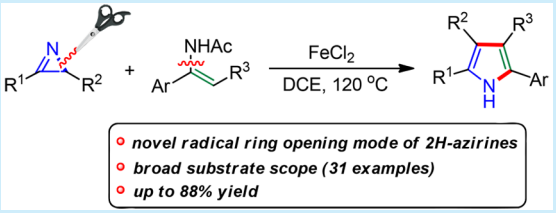
Supporting Information

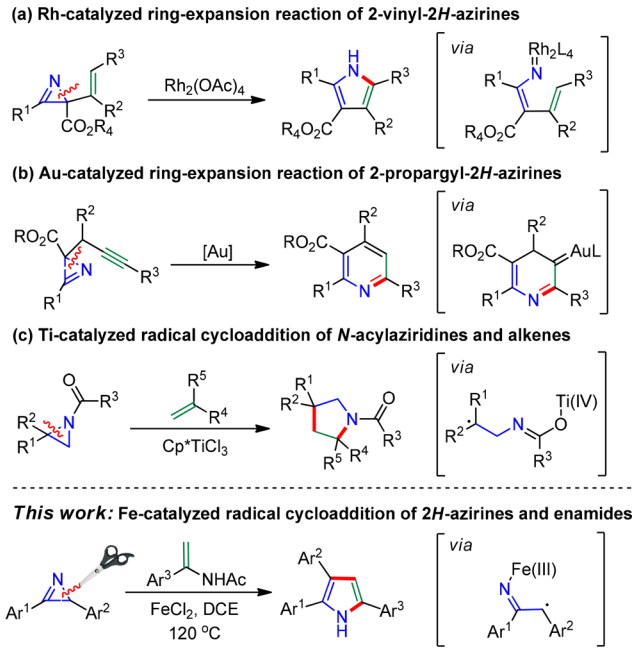
ABSTRACT: A novel and efficient Fe-catalyzed radical cycloaddition of 2*H*-azirines and enamides for the synthesis of substituted pyrroles has been developed. The radical cycloaddition reaction proceeded through a conceptually new Fe(II)-catalyzed homolytic cleavage of C−N bond of 2*H*-azirines sequential radical cyclization with enamides. The reaction used readily available starting materials, tolerated various functional groups, and afforded valuable triaryl-substituted pyrroles in good to high yields under mild reaction conditions.



2*H*-Azirines, the smallest nitrogen-containing three-membered ring, represent a highly important class of compounds found in natural products and biological active compounds.[1] Due to their high ring strain and easy ring opening, 2*H*-azirines are also powerful building blocks in organic synthesis.[2,3] In particular, the ring-opening reactions of 2*H*-azirines for the synthesis of various azaheterocycles, such as indoles,[4] pyrroles,[5] pyridines,[6] and pyrazines,[7] have attracted extensive attention in the past decade. For example, Rh-catalyzed ring-expansion of 2-vinyl-2*H*-azirines for the synthesis of pyrroles has been developed by Park and co-workers (Scheme 1a).[8] The Au-catalyzed ring-expansion of 2-propargyl-2*H*-azirines for the synthesis of pyridines has been developed by the group of Gagosz (Scheme 1b).[6a] However, the ring-opening of 2*H*-azirines was still generally involved in the heterolytic C−N single-bond-cleavage mode, thus restricting the broader utility of 2*H*-azirines. Therefore, the development of a novel ring-opening mode to exploit the new reactions of 2*H*-azirines is an urgent but challenging task.

Very recently, elegant Ti(III)-catalyzed homolytic cleavage of the C−N single bond of *N*-acylaziridines sequential with radical coupling with alkenes has been developed independently by the groups of Lin[9] and Gansäuer[10] (Scheme 1c). In these reactions, the polar C−N single bond was homolytically cleaved in the presence of a redox-active Ti(III) catalyst,[11] thus initiating the radical-coupling reaction. We hypothesized that a radical ring opening of 2*H*-azirines might occur in the presence of redox-active transition-metal catalysis,[12] thus providing a new ring-opening mode of 2*H*-azirines for versatile reactions. In this paper, we describe a conceptually new Fe(II)-catalyzed radical ring opening of 2*H*-azirines sequential cycloaddition with enamides for the synthesis of substituted pyrroles (Scheme 1). The Fe-catalyzed ring-opening reaction opens a novel mode for radical cycloaddition reactions of 2*H*-azirines.

Scheme 1. Transition-Metal-Catalyzed Cycloaddition of 2*H*-Azirines/Aziridines



We began our study with the transition-metal-catalyzed radical cycloaddition of 2*H*-azirines and enamides because the easily accessible and versatile enamides would make the coupling reaction highly flexible and broadly useful.[13,14] Therefore, the cycloaddition reaction of 2,3-diphenyl-2*H*-

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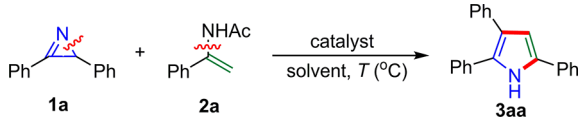
azirine **1a** and enamide **2a** was conducted in the presence of various transition-metal catalysts (Table 1, entries 1–6).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	T (°C)	yield (%)
1[b]	Cp*$TiCl_3$	toluene	25	0
2[b]	Cp*$TiCl_3$	CH_3CN	25	0
3[b]	Cp*$TiCl_3$	CH_3CN	100	7
4	$CuBr_2$	CH_3CN	100	<5
5	$Cu(TFA)_2$	CH_3CN	100	<5
6[c]	[M]	CH_3CN	100	0
7	$FeCl_2$	CH_3CN	100	12
8	$FeCl_2$	THF	100	8
9	$FeCl_2$	toluene	100	26
10	$FeCl_2$	DCE	100	74
11	$FeCl_3$	DCE	100	62
12	$Fe(OTf)_2$	DCE	100	70
13	$Fe(OTf)_3$	DCE	100	61
14	$FeBr_3$	DCE	100	65
15		DCE	100	0
16	$FeCl_2$	DCE	80	0
17	**$FeCl_2$**	**DCE**	**120**	**85**

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (10 mol %), solvent (2 mL); isolated yield. [b]Zn dust (20 mol %) was added. [c][Rh(cod)Cl_2]$_2$, $Rh_2(OAc)_4$, Ru(cod)Cl_2, $NiCl_2$, or $Ni(OAc)_2$ was used as the catalyst.

However, after several attempts, only 7% yield of the desired pyrrole **3aa** was observed in the presence of Ti(III) catalyst in CH_3CN at 100 °C (Table 1, entries 1–3). Copper catalysts gave only a trace amount of the product **3aa** (Table 1, entries 4 and 5), whereas no reaction occurred when Rh, Ru, or Ni catalyst was employed in the reaction (Table 1, entry 6).

Gratifyingly, a 12% yield of cycloaddition product 2,3,5-triphenyl-1*H*-pyrrole **3aa** was obtained when $FeCl_2$ was used as the catalyst (Table 1, entry 7). This primary result prompted us to focus on the Fe-catalyzed cycloaddition of 2*H*-azirines and enamides. Then, different solvents such as THF, toluene, and DCE were screened to optimize the reaction conditions (Table 1, entries 8–10). DCE was found to be the most suitable solvent for the reaction, providing **3aa** in 74% yield (Table 1, entry 10). Further experiments showed that other Fe catalysts, such as $FeCl_3$, $Fe(OTf)_2$, $Fe(OTf)_3$, and $FeBr_3$, were inferior to $FeCl_2$ (Table 1, entries 11–14). Notably, Fe catalyst plays a vital role in the reaction. No reaction occurred in the absence of the iron catalyst (Table 1, entry 15). Finally, the reaction temperature was also varied, and 120 °C gave the best result, improving the yield of **3aa** to 85% (Table 1, entries 16 and 17).

Having optimized the reaction conditions, a series of enamides were investigated for extending the substrate scope (Figure 1). Enamides with electron-neutral or electron-donating groups on aryl rings, such as alkyl, methoxyl, phenyl, and amido, all gave the corresponding trisubstituted pyrroles **3ab–ah** in high yields. Enamides with an electron-withdrawing group such as fluoro, chloro, bromo, and trifluoromethyl were well tolerated in the reaction, generating the corresponding pyrroles **3ai–am** in 50–88% yields. The structure of **3aj** was unambiguously confirmed by X-ray diffraction analysis. *o*-

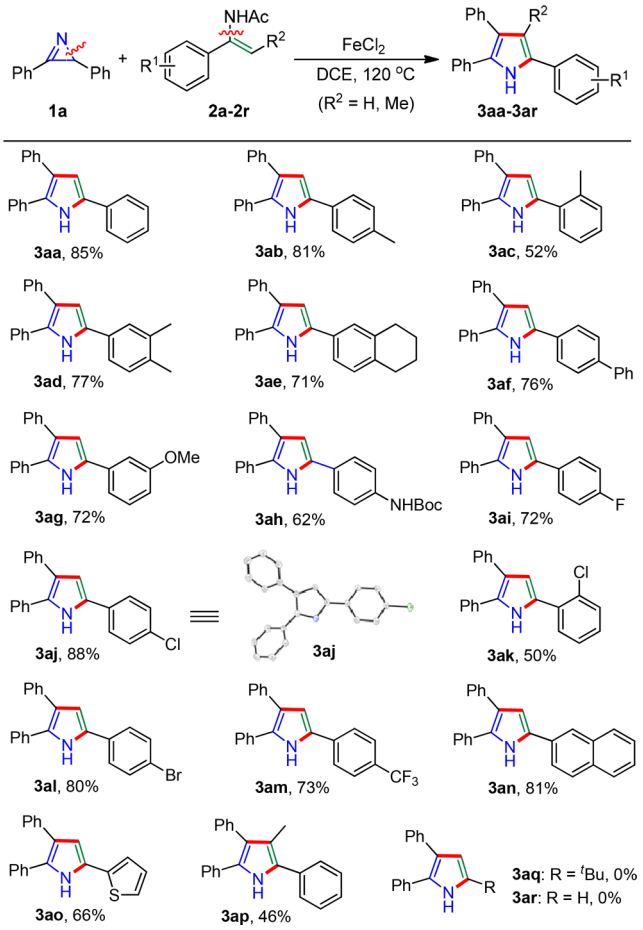


Figure 1. Fe-catalyzed cycloaddition of 2*H*-azirine **1a** and various enamides. Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $FeCl_2$ (10 mol %), DCE (2 mL); isolated yield.

Methyl- and chloro-substituted enamides gave the desired pyrroles **3ac** and **3ak** in 50% and 52% yields, probably due to steric hindrance of the substrates. Furthermore, 2-naphthyl enamide **2n** and thienyl enamide **2o** proceeded smoothly as well to give the desired pyrroles **3an–ao** in 81% and 66% yields, respectively. In addition, the desired tetrasubstituted pyrrole **3ap** was obtained in 46% yield when *β*-methyl-substituted enamide **2p** was used as the substrate. However, no reaction occurred when an aliphatic enamide such as *N*-(3,3-dimethylbut-1-en-2-yl)acetamide **2q** or *N*-vinylacetamide **2r** was used as the substrate.

Subsequently, the scope of 2*H*-azirines was investigated, and the results are summarized in Figure 2. Variations of the R^3 group on the C=N double bond moiety of 2*H*-azirines were first examined. Both electron-donating (**1b–f**) and electron-withdrawing (**1g,h**) groups on the aryl ring were successfully introduced, thus providing the corresponding pyrroles **3ba–ha** in 64–87% yields. 2*H*-Azirine with an *o*-methyl group on the phenyl ring afforded the pyrrole **3ca** in 87% yield, implying that the transformation was insensitive to steric hindrance of the 2*H*-azirines. The 2-naphthyl group was also compatible to provide the desired pyrrole **3ia** in 60% yield. However, 3-methyl-2-phenyl-2*H*-azirine **1j** was inactive under the reaction conditions. Notably, the electronic nature of the R^4 substituent had little effect on this reaction. Various aromatic substituents on R^4 were tolerated to give the corresponding trisubstituted pyrroles **3ka–na** in 69–72% yields. In addition, the 3-phenyl-

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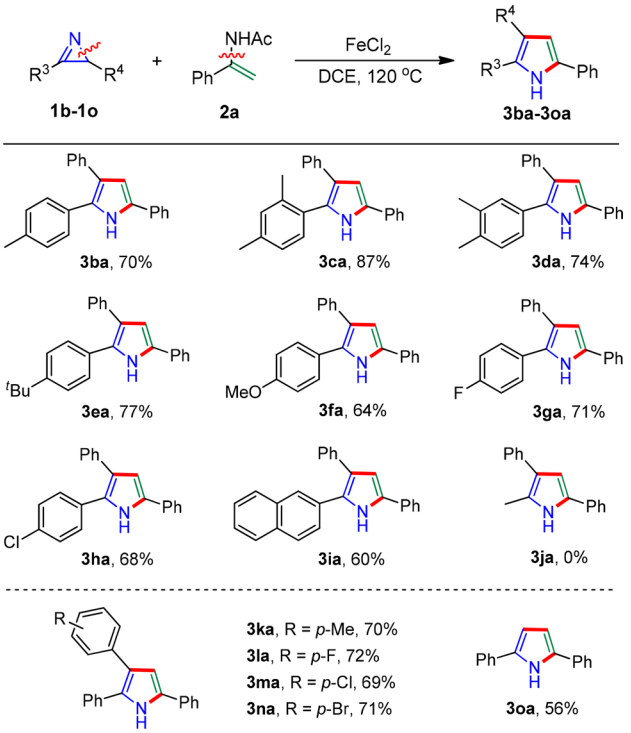
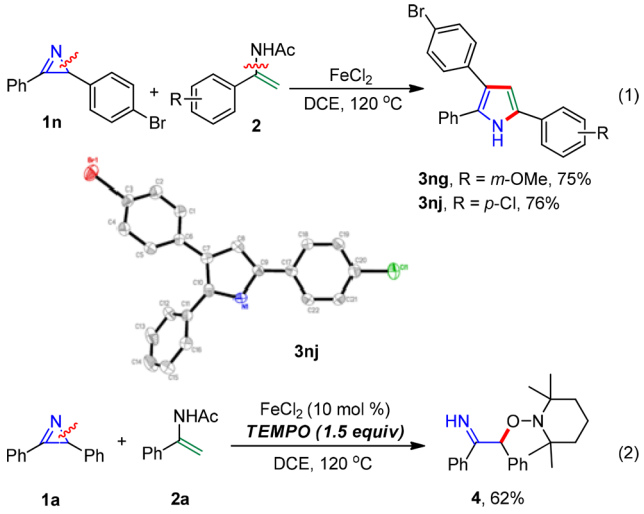


Figure 2. Fe-catalyzed cycloaddition of various 2*H*-azirines and enamide **2a**. Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $FeCl_2$ (10 mol %), DCE (2 mL); isolated yield.

2*H*-azirine **1o** also successfully performed the cycloaddition reaction to give the 2,5-diphenyl-1*H*-pyrrole **3oa** in 56% yield.

Furthermore, the trisubstituted pyrroles with different aryl groups **3ng** and **3nj** were synthesized in 75% and 76% yields, respectively, by the cycloaddition reaction (Scheme 2, eq 1).

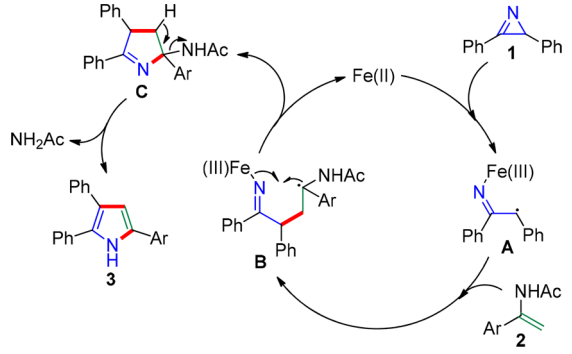
Scheme 2. Preliminary Mechanistic Studies



These trisubstituted pyrrole products **3ng**–**nj** not only clearly confirmed that the C–N single bond cleavage of 2*H*-azirines was involved in the reaction but also suggested the regioselectivity of the reaction. To gain insight into the ring-opening mechanism, the radical-trapping experiment has been conducted as well (Scheme 2, eq 2). The TEMPO-trapped product **4** was obtained in 62% yield, indicating that the homolytic radical ring opening of 2*H*-azirine should be involved in the transformation.

On the basis of the above results, a tentative mechanism for the Fe-catalyzed cycloaddition reaction is proposed in Scheme 3.[9−12,15] First, the reductive radial ring opening of 2*H*-azirine **1**

Scheme 3. Proposed Mechanism for Fe-Catalyzed Cycloaddition of 2*H*-Azirines and Enamides



occurred in the presence of Fe(II) to give a secondary radical intermediate **A**. Next, radical coupling of intermediate **A** and enamide **2** afforded the tertiary radical intermediate **B**. Then oxidative radical ring closure of intermediate **B** gave the intermediate **C**. Simultaneously, the active Fe(II) catalyst was released to facilitate the next catalytic cycle. Finally, elimination of a molecular of amide (NH_2Ac) sequential with tautomerization produced the pyrrole **3**.

In summary, we have developed an unprecedented Fe(II)-catalyzed ring opening of 2*H*-azirines and cycloaddition with enamides for the synthesis of pyrroles. The homolytic C–N bond cleavage and radical coupling with enamides proceeded under mild overall redox-neutral conditions. This novel Fe(II)-catalyzed radical ring opening mode of 2*H*-azirines allowed the rapid synthesis of valuable triaryl-substituted pyrroles in high yields. The method shows broad substrate scope and good functional group tolerance. Further studies on the Fe-catalyzed transformations of 2*H*-azirines are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b04007.

Detailed experimental procedures, characterization data, and NMR spectra for all products (PDF)

Accession Codes

CCDC 1590238–1590239 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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