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Efficient Nitroalkene Synthesis

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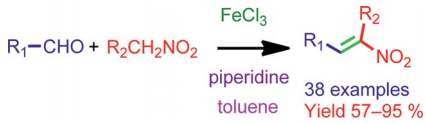

Keywords: Synthetic methods / Domino reactions / Nitrogen heterocycles / Cooperative catalysis / Alkenes

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Synthesis of Nitroalkenes Involving a Cooperative Catalytic Action of Iron(III) and Piperidine: A One-Pot Synthetic Strategy to 3-Alkylindoles, 2*H*-Chromenes and *N*-Arylpyrrole

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Keywords: Synthetic methods / Domino reactions / Nitrogen heterocycles / Cooperative catalysis / Alkenes

An efficient and simple strategy has been developed to synthesize various substituted nitroalkenes involving a cooperative catalytic system of $FeCl_3$ and piperidine. This dual catalytic protocol simultaneously activates both electrophile and nucleophile and works under mild reaction conditions so that many sensitive functional groups were tolerated. Moreover, this cooperative catalytic reaction is also suitable for various one-pot reactions involving nitroalkenes such as, 2*H*-chromenes, *N*-arylpyrrole and Michael reaction with indole. Notably, this method is low-cost, efficient and environmentally friendly.

Introduction

Nitroalkenes are important building blocks in organic synthesis[1] and are commonly used as substrates in a wide variety of transformations including Michael,[2] Friedel–Crafts alkylation,[3] Diels–Alder[4] and 1,3-dipolar cycloaddition[5] reactions. They are also very important substrates for the synthesis of natural products,[6] heterocyclic compounds[7] and useful in the area of asymmetric synthesis.[8] Furthermore, the nitro group can easily be converted into other valuable functional groups such as amines and carbonyl groups, and hence nitroalkenes are important substrates in organic synthesis.[9] In addition, nitroalkenes are well known for their biological activity such as insecticides,[10] fungicides[11] and in various pharmacologically active[12] substrates. Very recently β-nitrostyrene motifs have also been reported as pro-apoptotic anticancer[13] and antibacterial agents.[14] Accordingly, a number of synthetic methods have been developed for the preparation of conjugated nitroolefins.

The most common method for the preparation of nitroalkenes involves a Henry condensation reaction of a carbonyl compound with a nitroalkane that provides a β-nitro alcohol, which upon dehydration affords a nitroalkene.[15] The Henry reaction is generally performed under mildly basic conditions with a variety of bases, but the dehydration step requires harsh reaction conditions. Only a few one-pot preparations of nitroalkenes have been described, which include the use of microwave and ultrasound techniques in ammonium acetate,[16] amphiphilic ionic liquids,[17] ethylenediamine[18] and direct nitration of alkenes by using $NaNO_2$ in the presence of various oxidizing agents.[19] In addition, a few heterogeneous catalysis have also been employed for the direct synthesis of nitroalkenes from aromatic aldehydes and nitroalkanes.[20] Very recently, a one-pot synthesis of aliphatic nitroalkenes by using a secondary amine in combination with molecular sieves has been reported.[21] Although some of these methods are efficient, many suffer from one or more drawbacks: for example, the need a large excess of nitroalkane and expensive and toxic reagents, low product yields, complicated reaction assembly, harsh reaction conditions, laborious isolation procedure, and large amounts of acid to neutralize the bases. Therefore, the development of an efficient, general and environmentally friendly process, which enables rapid and easy access to nitroalkene derivatives, is of great importance, particularly for the synthesis of complex molecules.

Our aim was to develop a protocol that overcomes the problems associated with the traditional methods of nitroalkene preparation and to extend it to develop new tandem reactions involving nitroalkenes in one pot. In doing so, we believe that the concept of dual catalysis, i.e. the combination of metal catalysis and organocatalysis[22] in one process, will be effective for nitroalkene formation. Suitable Lewis base/Lewis acid will help to form the carbon–carbon bond, and the Lewis acid would help the elimination step and subsequent reactions with other suitable substrates. As part of our continuous interest in the area of iron catalysis towards the development of environmentally friendly and sustainable reactions,[23] herein we wish to report a new

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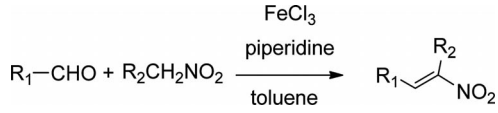
method for the synthesis of nitroalkenes by the reaction between aldehydes and nitroalkanes by using a combination of iron and secondary amines in one process under mild conditions (Scheme 1). This reaction offers an efficient, environmentally friendly and straightforward strategy to achieve nitroalkenes. Moreover, we have demonstrated that the cooperative catalytic conditions are also suitable for carrying out the one-pot synthesis of *2H*-chromenes, multisubstituted *N*-arylpyrroles and 3-substituted indoles involving nitroalkenes.



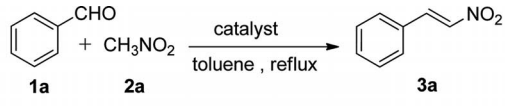
Scheme 1. One-pot preparation of nitroalkenes.

Results and Discussion

The present idea stems from our recently developed iron(III)-salt catalyzed four-component synthesis of pyrrole. We demonstrated that this reaction proceeded through in situ generation of nitroalkenes,[23a] however, we could not isolate it during the course of the reaction because it was very reactive and immediately underwent subsequent steps. In connection with those studies, we decided to apply a cooperative catalytic reaction by using Lewis acids and organocatalysts to prepare nitroalkenes.

To optimize the reaction conditions, first we studied the reaction between benzaldehyde and nitromethane in the presence of different Lewis acids and bases. After screening a large number of catalysts under similar conditions (Table 1), we observed that the reaction in the presence of only $FeCl_3$ (10 mol-%) did not afford any nitroalkene **3a**. Desired nitroalkene **3a** is obtained in 15% yield upon heating to reflux for 24 h in the presence of piperidine (10 mol-%) in toluene solvent. But, when the reaction was carried out in the presence of a combination of anhydrous $FeCl_3$ (10 mol-%) and piperidine (10 mol-%), target nitrostyrene **3a** formed in an excellent 95% yield (Table 1, Entry 2). Further studies indicated that reducing the amount of either of the catalysts to 5 mol-% reduced the yield of the product (Table 1, Entry 3). Then a series of other iron catalysts such as $FeCl_3{\cdot}6H_2O$, $FeBr_3$, $Fe(OTf)_3$ and $Fe(acac)_3$ were also tested, however, they did not improve the results. Among the various organic bases tested in combination with $FeCl_3$, piperidine was found to be the best organocatalyst for this transformation. Bases, such as primary amine, tertiary amine and K_2CO_3, were less effective under similar reaction conditions. This reaction was also studied without toluene as solvent but lower yields resulted of desired product (Table 1, Entry 7). Without toluene, formation of a dinitro derivative through Michael reaction of nitrostyrene and nitromethane was observed. Finally, relative to other commonly available metal catalysts such as $Yb(OTf)_3$, $AlCl_3$, $ZnCl_2$ and $InCl_3$(Table 1, Entries 14–17), anhydrous $FeCl_3$ proved to be the best Lewis acid. These results show the superiority of $FeCl_3$ in combination with piperidine under the same reaction conditions. All the products were characterized spectroscopically. With regard to stereochemistry, the reaction gave exclusively the *E*-isomers.

Table 1. Catalysts screening studies.[a]



Entry	Lewis acid	Base	Time (h)	Yield (%)[b]
1	$FeCl_3$ (10 mol-%)	Aniline (10 mol-%)	16	13
2	$FeCl_3$ (10 mol-%)	Piperidine (10 mol-%)	4	95
3	$FeCl_3$ (5 mol-%)	Piperidine (10 mol-%)	8	69
4	$FeCl_3$ (10 mol-%)	–	24	0
5	–	Piperidine (10 mol-%)	24	15
6	$FeCl_3$ (10mol-%)	Pyrrolidine	8	70
7	$FeCl_3$ (10 mol-%)	Piperidine (10 mol-%)	6	79[c]
8	$FeCl_3$ (10 mol-%)	Et_3N (10 mol-%)	16	8
9	$FeCl_3$ (10 mol-%)	DBU (10 mol-%)	16	30
10	$FeCl_3$ (10 mol-%)	K_2CO_3 (10 mol-%)	16	22
11	$Fe(OTf)_3$ (10 mol-%)	Piperidine (10 mol-%)	16	35
12	$FeCl_3{,}6H_2O$ (10 mol-%)	Piperidine (10 mol-%)	16	75
13	$Fe(acac)_3$ (10 mol-%)	Piperidine (10 mol-%)	16	31
14	$Yb(OTf)_3$ (10 mol-%)	Piperidine (10 mol %)	16	60
15	$InCl_3$ (10 mol-%)	Piperidine (10 mol %)	16	61
16	$AlCl_3$ (10 mol-%)	Piperidine (10 mol-%)	16	57
17	$ZnCl_2$ (10 mol-%)	Piperidine(10 mol-%)	16	40

[a] Reaction conditions: Benzaldehyde (1 mmol), nitromethane (6 mmol), piperidine (0.10 mmol), $FeCl_3$ (0.10 mmol), toluene (1 mL), gentle reflux, 4 h. [b] Pure, isolated yield. [c] Without toluene.

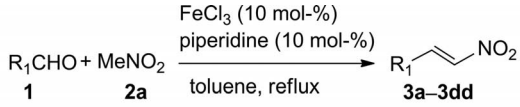
The experimental procedure for this reaction was very simple and straightforward. A mixture of aldehyde (1 mmol), nitroalkane (6 mmol), piperidine (0.1 mmol) and $FeCl_3$ (0.1 mmol) in toluene (1 mL) was gently heated to reflux for a set period of time. After completion of the reaction (TLC) and removal of the solvent, the crude product was directly purified by silica gel column chromatography to afford the desired product with high purity.

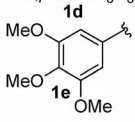
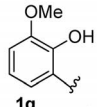
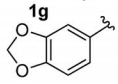
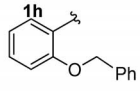
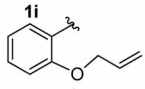
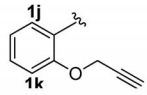
Following the optimized reaction conditions, we then explored the substrate scope of this reaction. The results are summarized in Table 2. Different aldehydes were successfully reacted with nitromethane to afford the respective nitrostyrenes in very good yields. Aromatic, heteroaromatic and aliphatic aldehydes condensed efficiently with nitromethane leading exclusively to the desired nitroalkenes in high yield. Aromatic aldehydes containing electron-donating groups such as methyl and varieties of ethers substituents at *ortho*-, *meta*- or *para*- gave the desired products in high yields. Free –OH bearing substrates such as **1f** and **1g** also reacted smoothly with nitromethane under optimized

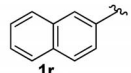
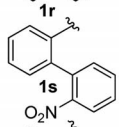
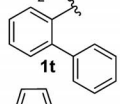
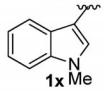
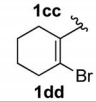
reaction conditions in good yields (Table 2, Entries 6 and 7). Notably, Lewis-acid-sensitive functional groups such as, 1,3-dioxolane, benzyl ether, allyl ether and propargyl ethers were also tolerated and gave excellent yields, 75, 80, 85 and 96%, respectively (Table 2, Entries 8–11). Moreover, the combination of $FeCl_3$ (10 mol-%) and piperidine (10 mol-%) also worked efficiently in the case of aromatic aldehydes containing weakly electron-withdrawing substituents such as, *p*-Cl, *o*-Br, *o*-F and *p*-F (Table 2, Entries 12–15), and strong electron-withdrawing groups such as *p*-CN and *m*-NO_2 (Table 2, Entries 16 and 17), and gave exclusively desired products **3l**, **3m** and **3n**–**3q** in high yields. However, in contrast to *m*-nitrobenzaldehyde, *para*-nitrobenzaldehyde produced mixtures of products including trace amounts of desired product. The strong electron-withdrawing effect of the *p*-NO_2 group may make the substrate and the product more reactive so that many unwanted side reactions take place. Naphthyl-2-carbaldehyde **1r**, and *ortho*-biphenylcarbaldehydes **1s** and **1t** were also smoothly converted into the desired products in good yields (Table 2, Entries 18–20).

Next, we investigated various heterocyclic carbaldehydes such as furan-2-carbaldehyde **1u** and thiophene-2-carbaldehyde **1v** (Table 2, Entries 21 and 22). They were smoothly converted into corresponding nitroolefins **3u** and **3v** in 85 and 95% yield, respectively. Although, indole-3-carbaldehyde **1w** completely converted into the desired nitroalkene, the concomitant Michael addition product, 2,2-bi-(indolyl)nitroethane, was also observed with the reaction of

Table 2. Reaction of various aldehydes and nitromethane in the presence of a combination of $FeCl_3$ and piperidine.[a]



Entry	R	Time (h)	Products	Yield (%)
1	Ph **1a**	4	**3a**	95
2	*p*-MeC_6H_4 **1b**	4	**3b**	94
3	*p*-$MeOC_6H_4$ **1c**	5	**3c**	94
4	*m*,*p*-$MeOC_6H_3$ **1d**	6	3d	88
5	 **1e**	5	**3e**	82
6	*o*-OHC_6H_4 **1f**	4	**3f**	70
7	 **1g**	4	**3g**	71
8	 **1h**	2	**3h**	75
9	 **1i**	6	**3i**	80
10	 **1j**	6	**3j**	85
11	 **1k**	6	**3k**	96
12	**p**-ClC_6H_4 **1l**	6	**3l**	92
13	*o*-BrC_6H_4 **1m**	4	3m	88
14	*o*-FC_6H_4 **1n**	5	**3n**	85

Entry	R	Time (h)	Products	Yield (%)
15	*p*-FC_6H_3 **1o**	4	3o	75
16	*p*-CNC_6H_4 **1p**	5	**3p**	75
17	*m*-$NO_2C_6H_4$ **1q**	5	**3q**	77
18	 **1r**	6	**3r**	68
19	 **1s**	5	**3s**	75
20	 **1t**	8	**3t**	76
21	 **1u**	2	**3u**	85
22	 **1v**	2	**3v**	95
23	 **1w**	5	**3w**	93[c]
24	 **1x**	7	**3x**	84
25	*n*-C_7H_{15} **1aa**	2	**3aa**	70
26	*n*-C_5H_{11} **1bb**	2	**3bb**	65
27	 **1cc**	2	**3cc**	85
28	 **1dd**	8	**3dd**	65

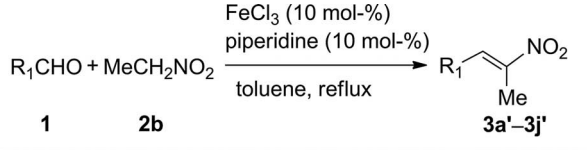
[a] Reaction conditions: Aldehyde (1 mmol), nitromethane. (6 mmol), piperidine (0.10 mmol), $FeCl_3$ (0.10 mmol), toluene (1 mL), gentle reflux, 4 h. [b] Pure, isolated yield. [c] A mixture of **3w** and 2,2-bis(indolyl)nitroethane (82:18) were isolated.

nitromethane (Table 2, Entry 23). Interestingly, no Michael addition product was observed in the case of *N*-methylindole-3-carbaldehyde, which gave the desired nitroalkene as a single product in 84% yield (Table 2, Entry 24).

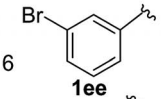
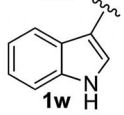
Encouraged by the above results, we further studied a few aliphatic aldehydes to show the versatility of this method (Table 2, Entries 25–28). As shown, these reactions proceeded successfully to afford the corresponding aliphatic nitroalkenes in moderate to good yields. It is noteworthy that 2-bromocyclohexene-1-carbaldehyde (**1dd**) also reacted with nitromethane and gave desired product **3dd** in 65% yield (Table 2, Entry 28). The tolerance of a halide substituent (Table 2, Entries 12, 13 and 28) might provide an additional benefit for further synthetic transformations through cross coupling reactions.

Finally, the reaction of nitroethane instead of nitromethane with varieties of aromatic aldehydes was also explored to show the generality of this reaction for the preparation of α-substituted nitroalkenes. We were delighted to find that the optimized reaction conditions were also suitable for the preparation of α-substituted nitroalkenes (Table 3, Entries 1–10). Interestingly, strong electron-withdrawing groups, such as *p*-F, *p*-CN and *p*-NO_2 containing aldehydes (Table 3, Entries 8–10), worked more efficiently with nitroethane relative to nitromethane and gave higher yields of the desired nitroalkenes. Pleasingly, only (*E*)-isomers were obtained in all the examples given in Table 3.

Table 3. Reaction of various aldehydes and nitroethane in the presence of a combination of $FeCl_3$ and piperidine.[a]



1 **2b** **3a'–3j'**

Entry	Aldehydes	Time (h)	Product(s)	Yield(%)[b]
1	**1a**	4	**3a'**	84
2	**1b**	5	**3b'**	86
3	**1c**	6	**3c'**	94
4	**1l**	5	**3d'**	85
5	**1t**	5	**3e'**	75
6	 **1ee**	4	**3f'**	85
7	 **1w**	4	**3g'**	90
8	*p*-FC_6H_3 **1o**	6	**3h'**	95
9	*p*-CNC_6H_4 **1p**	5	**3i'**	84
10	*p*-$NO_2C_6H_4$ **1ff**	8	**3j'**	64

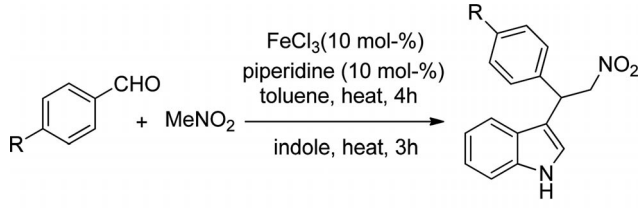
[a] Reaction conditions: Aldehyde (1 mmol), nitroethane (6 mmol), piperidine (0.10 mmol), $FeCl_3$ (0.10 mmol), toluene (1 mL), gentle reflux. [b] Pure, isolated yield.

Thus we have developed a simple and efficient method for the preparation of structurally varied nitroalkenes in the presence of a combination of metal catalysis and organocatalysis through a cooperative action. The present reaction did not work with ketones. Although, all the above studies were performed by using 1 mmol of aldehyde, we also checked the applicability of the method for large-scale synthesis with aldehydes **1a** (18.87 mmol), **1f** (10 mmol) and **1v** (10 mmol). Pleasingly, the present protocol worked for large-scale syntheses and gave corresponding nitroalkenes **3a**, **3f** and **3v** in 75, 58 and 61% yields, respectively (see Supporting Information).

Finally, to make this cooperative catalysis more attractive, we investigated a few one-pot syntheses of complex molecules such as 3-substituted indoles, 3-nitrochromenes and substituted pyrroles in the same catalytic conditions.

One-Pot Synthesis of 3-Alkylindoles

Indole and its derivatives are widely distributed in nature and possess a diverse range of biological and pharmacological activity. Therefore, the synthesis of 3-substituted indoles has received much attention in modern organic synthesis.[24] A Michael addition reaction between indole and nitroalkenes in the presence of various Lewis acids is an important tool for the synthesis of 3-substituted indole derivatives. We thought our reaction conditions would allow a one-pot synthesis of nitroalkenes and a subsequent Michael addition reaction because the Lewis acid was in the reaction medium. To our delight, this one-pot reaction worked efficiently and gave desired products **4a** and **4b** in good yields (Scheme 2).

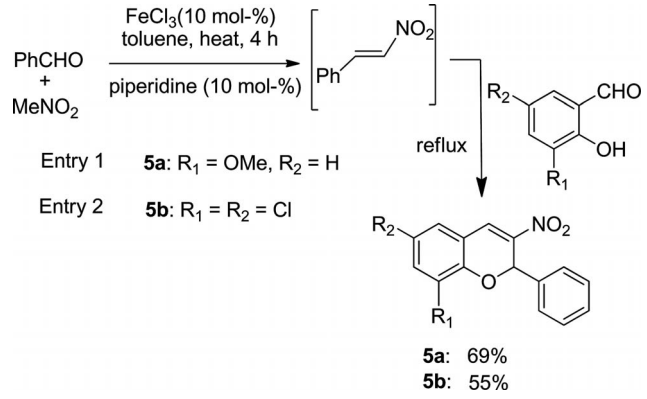


Scheme 2. Tandem nitroalkenes formation/Michael addition reaction with indole.

One-Pot Synthesis of 3-Nitrochromenes

3-Nitrochromenes are another important class of heterocyclic compounds owing to their biological activity and their importance as precursors of flavonols, amines, and other important targets. Normally it is prepared from salicylaldehydes and pre-formed nitroalkenes in the presence

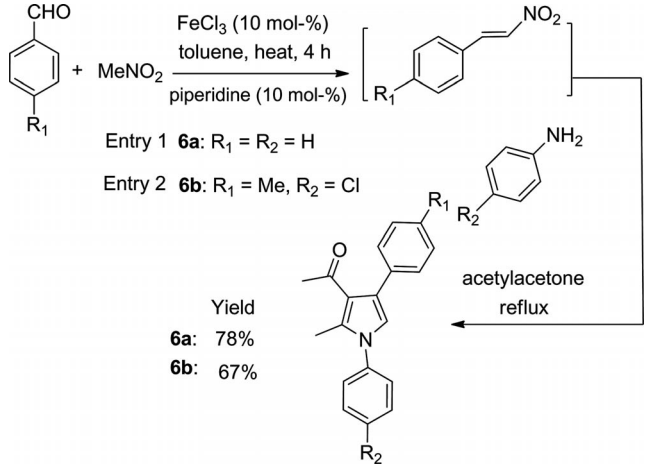
of various organocatalysts and alumina.[25] We demonstrated that this cooperative catalysis reaction condition was well suited for the preparation of 3-nitrochromenes in one pot through the sequential formation of nitroalkene/Michael addition/aldol condensation reactions, and afforded good yields of 3-nitrochromenes **5a** and **5b** (Scheme 3).



Scheme 3. Tandem nitroalkenes formation/Michael-aldol reaction for 3-nitrochromenes.

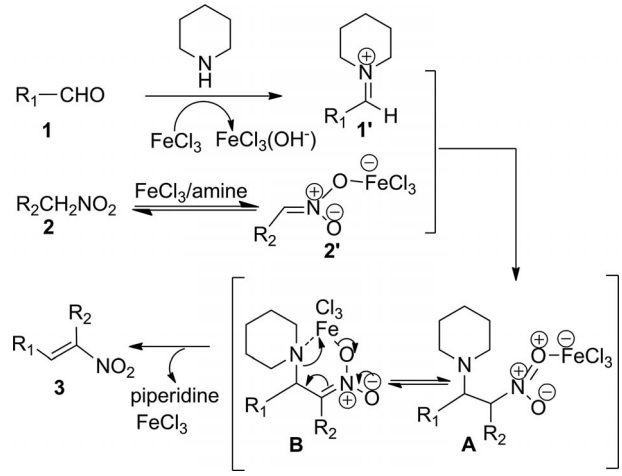
One-Pot Synthesis of *N*-Arylpyrrole

N-Arylpyrrole containing compounds exhibit a wide array of biological activities and it is also an important building block for the synthesis of many complex molecules.[26] With this in mind, we next turned our attention to develop an efficient method for the synthesis of *N*-arylpyrroles by using the present catalytic conditions. The one-pot generation of nitroalkenes, followed by addition of aromatic amine and 1,3-diketone gave the corresponding substituted *N*-arylpyrroles in good yield (Scheme 4). This present protocol is an improved method for the preparation of *N*-arylpyrrole relative to our previous report.[23a]



Scheme 4. One pot nitroalkenes/*N*-arylpyrroles synthesis.

Based on the experimental observations and other studies by using cooperative catalysis of secondary amines and Lewis acids, we proposed a tentative mechanistic pathway to account for the formation of nitro olefins. Aldehyde **1** reacts with piperidine, catalyzed by $FeCl_3$ to give iminium ion intermediate **1′**.[27] Lewis acid may also activate nitroalkane **2** in combination with the organobase to generate reactive metalo *aci*-nitronate intermediate **2′**.[28] The activated electrophilic species **1′**, and nucleophilic species **2′** are then efficiently coupled to form a β-amino nitro derivative **A**. Intermediate **B** is then converted into desired nitroolefin **3** by the elimination of piperidine through an EIcB-type mechanism regenerating the catalysts (Scheme 5).



Scheme 5. A plausible mechanism.

Conclusions

In conclusion, we have developed a simple and practical method for the one-pot synthesis of nitroalkenes catalyzed by a cooperative catalysis system involving piperidine and iron(III) chloride. To the best of our knowledge this is the first report of nitroalkenes preparation involving cooperative catalysis. This method has several advantages: (a) use of inexpensive and environmentally friendly catalysts; (b) simple work up and isolation of procedure; (c) tolerance of many sensitive functional groups and molecules; (d) applicable to aromatic, heteroaromatic and aliphatic aldehydes; (e) applicable for large-scale synthesis; (f) useful to design many tandem reactions. The above advantages and experimental simplicity make this cooperative catalytic system very attractive for the efficient preparation of nitroalkenes and their application towards the synthesis of complex molecules in one pot.

Experimental Section

Representative Experimental Procedure for the Synthesis of (*E*)-(2-Nitrovinyl)benzene (3a): Aldehyde **1a** (106 mg, 1 mmol), nitroalkane **2a** (366 mg, 6 mmol) and piperidine (8.5 mg, 0.1 mmol) were added sequentially to a round-bottomed flask containing toluene (1 mL). To this mixture anhydrous $FeCl_3$ (16.2 mg, 0.1 mmol) was added, and the mixture was heated to reflux slowly for 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. The excess solvent

was removed under reduced pressure and the residue was purified by silica gel (60–120 mesh) column chromatography (5% ethyl acetate in petroleum ether) to afford **3a** as a yellow solid (141.55 mg, 0.95 mmol, 95%), m.p. 56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.43–7.49 (m, 2 H), 7.53–7.54 (m, 1 H), 7.57 (s, 2 H), 7.61 (s, 1 H), 8.01 (d, J = 13.7 Hz, 1 H) ppm.

Supporting Information (see footnote on the first page of this article): Full experimental details for all compounds and ^{1}H and ^{13}C NMR spectra are provided.

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