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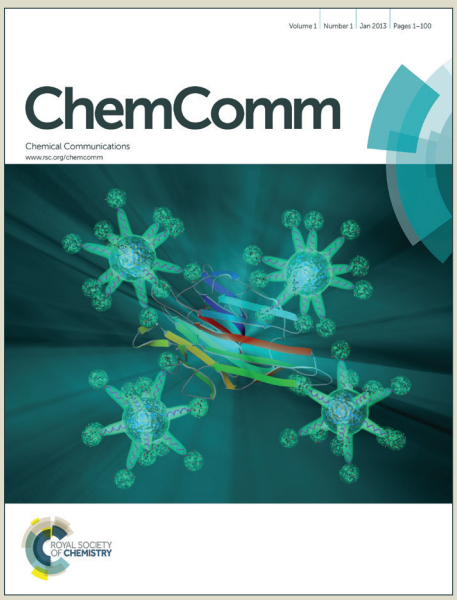

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Iron−Catalyzed Aerobic C−H Functionalization of Pyrrolones

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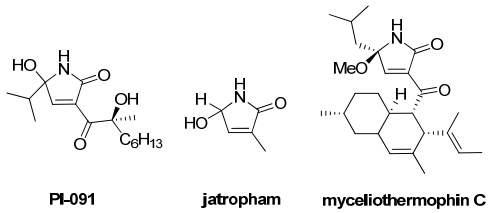
The aerobic oxidation of pyrrolones catalyzed by $Fe(OTf)_3$ to form reactive *N*-acyliminium ion intermediates that undergoes nucleophilic additions with alcohols to give the corresponding products in moderate to good yields is described.

The functionalization of C-H bonds by oxidative Mannich reaction methods is powerful for the synthesis of nitrogen-containing natural products and active pharmaceutical ingredients.[1] An iminium ion, generated through oxidation of the α C-H bond adjacent to the nitrogen atom of an amine, which can be quenched with various nucleophilic reagents to form the new C-X bonds.[2] Generally, these reactions are accomplished by a variety of conditions using transition metal catalysts including Cu,[3] Fe,[4] Pd,[5] Ru,[6] Rh,[7] Mo,[8] Zr,[9] and VO[10] complexes. Recent advances in the oxidative C-H functionalization of amines or amides rely on strong oxidants, such as TBHP,[11] DTBP,[12] DDQ,[13] PIDA[14] or $(NH_4)_2S_2O_8$.[15] Although these methods are efficient for C-H functionalization, a practical and efficient method for such a transformation is still a challenge in synthetic chemistry.

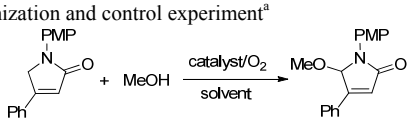


Scheme 1 Examples of Pyrrolone-containing Natural Products

Pyrrolone systems[16] exhibit a wide range of interesting pharmacological properties and can easily be transformed into highly reactive *N*-acyliminium ions (Scheme 1). These ions have historically been generated in *situ* by Lewis acid or Brønsted acid promoted elimination.[17] They are also suitable precursors for the preparation of alkaloid natural products.[18] With our continious interest in developing novel methodology for the functionalization of pyrrolones,[19] we focused on exploring a mild, selective, and efficient oxidative Mannich reaction that utilized inexpensive catalysts and more atom economical oxidants, such as O_2.

We commenced our investigations with the Fe-catalyzed reactions of *N*-(*p*-methoxyphenyl)-4-phenylpyrrolone (**1b**) using O_2 as oxidant (Table 1). We screened several readily available iron catalysts (10.0 mol %) such as $FeSO_4{\cdot}7H_2O$, $FeCl_3$, $Fe_2(SO_4)_3$, $Fe(NO_3)_3{\cdot}9H_2O$, $Fe(OTf)_2$, $Fe(acac)_3$ and $Fe(OTf)_3$ (Table 1, entries 1-7). We were pleased to observe formation of 5-methoxy-*N*-(*p*-methoxyphenyl)-4-phenylpyrrolone **3a** with all catalysts except $Fe(acac)_3$, and the $Fe(OTf)_3/O_2$ combination afforded the desired product **3a** in 89% yield (Table 1, entry 7). When $FeSO_4{\cdot}7H_2O$ and $Fe(OTf)_2$ were used in place of Fe (III) under the same conditions, the oxidative coupling product **3a** were formed in low yields (Table 1, entries 1 and 5). When the reaction was performed in the absence of catalyst, the reaction didn't occur (Table 1, entry 8). Subsequently, our solvent study showed that CH_3CN was superior to the other solvents including EtOAc, CH_2Cl_2, MeOH, THF and DMF (Table 1, entries 9-14). Also the use of air as the oxidant furnished **3a** in only 53% yield compared to 89% yield with oxygen (Table 1, entry 15).

Table 1 Optimization and control experiment[a]

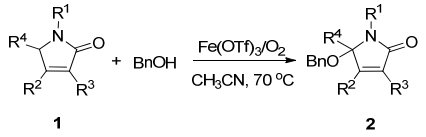


Entry	Catalyst	Solvent	T (°C)	Time(h)	Yield[b] (%)
1	$FeSO_4{\cdot}7H_2O$	CH_3CN	70	24	15
2	$FeCl_3$	CH_3CN	70	24	73
3	$Fe_2(SO_4)_3$	CH_3CN	70	24	73
4	$Fe(NO_3)_3{\cdot}9H_2O$	CH_3CN	70	24	62
5	$Fe(OTf)_2$	CH_3CN	70	24	46
6	$Fe(acac)_3$	CH_3CN	70	12	NR
7	$Fe(OTf)_3$	CH_3CN	70	8	89
8	-	CH_3CN	70	12	NR
9	$Fe(OTf)_3$	CH_3CN	25	48	62
10	$Fe(OTf)_3$	EtOAc	25	48	56
11	$Fe(OTf)_3$	CH_2Cl_2	25	48	33
12	$Fe(OTf)_3$	MeOH	25	48	27
13	$Fe(OTf)_3$	THF	25	48	18
14	$Fe(OTf)_3$	DMF	25	48	NR
15[c]	$Fe(OTf)_3$	CH_3CN	70	24	53

[a] Reaction conditions: Catalyst (10.0 mol %), MeOH (10.0 equiv) and substrate **1b** (0.2 mmol) in solvent (1.0 mL) under an atmosphere of oxygen. [b] Isolated yield. [c]The reaction was performed under an atmosphere of air. NR: no reaction.

With the optimal reaction conditions in hands, the scope and generality of this new one-pot protocol was investigated, the results of which are summarized in Table 2. By reacting pyrrolone **1** with benzyl alcohol, the desired products **2a-l** were conveniently generated in satisfactory to excellent yields (Table 2, entries 1-12) in each case. It was found that the reaction was tolerant to a variety of R substituents including electron-rich and electron-withdrawing groups. For instance, substrates containing electron-rich substituent such as methyl- and methoxy- groups on the benzene ring could be converted to the corresponding products in acceptable to good yields (Table 2, entries 1-3, 5-6). As for substrates with an electron-withdrawing group (R = Cl) on the benzene ring, the oxidation reaction also occurred smoothly in moderate yields (Table 2, entries 4 and 7). When there was a H or a methyl substituent at the *N* atom, the desired product was obtained in a low yield (Table 2, entries 8 and 9). Substrates with aromatic rings gave better yields probably due to resonance stabilization on the proposed *N*-acyliminium intermediate (Scheme 4). Further studies revealed that the aromatic ring could also be replaced with aliphatic groups or H at the C=C (Table 2, entries 10-13). 5-Phenyl pyrrolone was also a suitable substrate for the reaction, and the corresponding product was obtained in good yield (Table 2, entry 14). In summary, electron-donating group substituents on the *N*-aryl ring of **1** give the better results than electron-donating group substituents on the *N*-aryl ring and *N*-methyl, or H substituted pyrrolones.

Table 2 Oxidative coupling of various amides with benzyl alcohol[a]

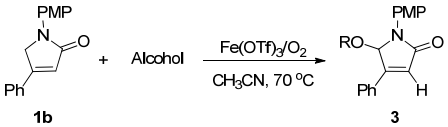


1 **2**

Entry	R^1	R^2	R^3	R^4	Yield[b]
1	Ph	Ph	H	H (**2a**)	58
2	*p*-$MeOC_6H_4$	Ph	H	H (**2b**)	83
3	*p*-MeC_6H_4	Ph	H	H (**2c**)	62
4	*p*-ClC_6H_4	Ph	H	H (**2d**)	77
5	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	H	H (**2e**)	77
6	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	H	H (**2f**)	81
7	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	H	H (**2g**)	74
8	H	Ph	H	H (**2h**)	26
9	Me	Ph	H	H (**2i**)	34
10	*p*-$MeOC_6H_4$	Me	H	H (**2j**)	65
11	*p*-$MeOC_6H_4$	H	H	H(**2k**)	35
12	*p*-$MeOC_6H_4$	H	Me	H(**2l**)	53
13	*p*-$MeOC_6H_4$	Ph	Me	H(**2m**)	81
14	*p*-$MeOC_6H_4$	Ph	H	Ph(**2n**)	82

[a]The reaction was carried out under an oxygen atmosphere using pyrrolone **1** (1.0 equiv), benzyl alcohol (5.0 equiv), $Fe(OTf)_3$ (0.1 equiv) in CH_3CN (1.0 mL). [b] Isolated yield.

Table 3 Oxidative coupling of various alcohols with **1b**[a]



1b **3**

Entry	Alcohol	Time (h)	Yield (%)[b]
1	MeOH(**3a**)	2	89
2	^{i}PrOH(**3b**)	2	55
3	^{t}BuOH(**3c**)	7	decomposed
4	BnOH (**2b**)	2	83
5	CH_2CHCH_2OH(**3d**)	5	82
6	CF_3CH_2OH(**3e**)	12	15

[a]The reaction was carried out under an oxygen atmosphere using pyrrolone **1b** (1.0 equiv), alcohol (10.0 equiv), $Fe(OTf)_3$ (0.1 equiv) in CH_3CN (1.0 mL). [b] Isolated yield.

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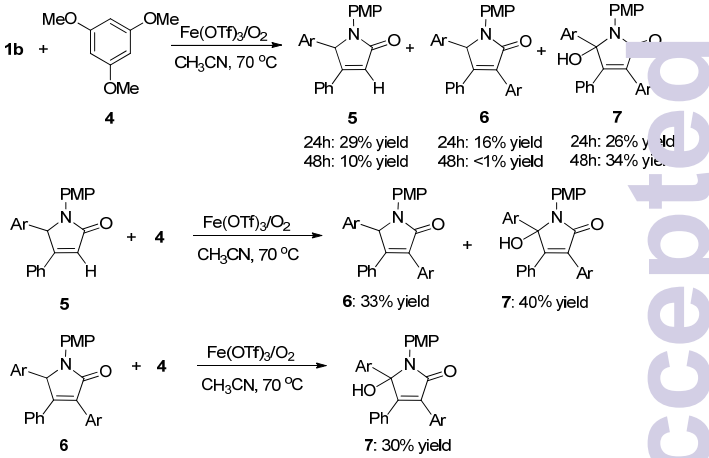
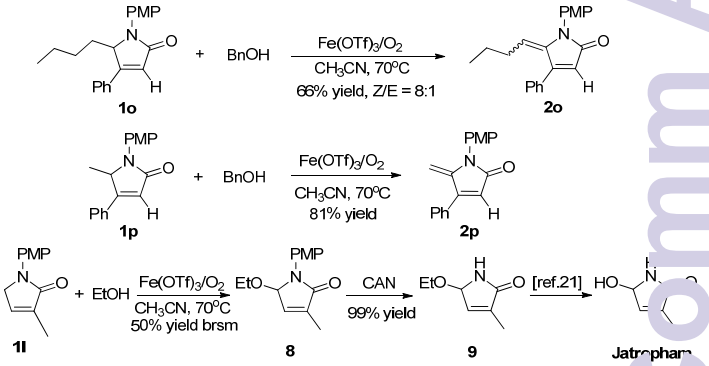
This transformation is amenable to a number of variations, both in the structure of the starting amides and in the nature of the nucleophile, as indicated by the examples compiled in Table 3. Primary and allylic alcohols were good nucleofiles for this reaction (Table 3, entries 1, 4, 5). Isopropanol and trifluoroethanol afforded the products in relatively lower yields (Table 3, entries 2 and 6), no product being isolated when ^{t}BuOH was used as nucleophile (Table 3, entry 3).

The Friedel−Crafts alkylation is one of the most versatile methods used for introduction of C (sp^3) substituents onto aromatic rings.[20] For this reason, we explored the use of electron-rich aromatics as nucleophiles to form C-C bonds *via* the Friedel−Crafts reaction. At the onset, 1,3,5-trimethoxybenzene was chosen as the nucleophilic reagent. After 24 hours at 70 °C, we obtained three products: monosubstituted **5**, and disubstituted **6** and **7** (Scheme 2). The yields of **5** and **6** decreased and the yield of **7** increased when the reaction time was prolonged. Also, pure **5** could be transformed into **6** and **7**, and pure **6** could be converted to **7** under the same conditions leading insight into the mechanism of the transformation.



Scheme 2 Oxidative coupling of **1b** and its derivatives with 1,3,5-trimethoxybenzene



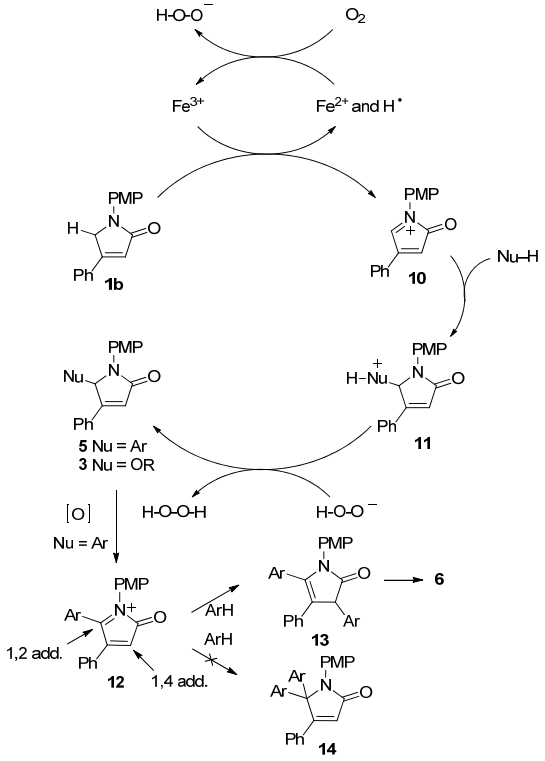
Scheme 3 Oxidative coupling of **1o-p** with benzyl alcohol and synthesis the precursor of **Jatropham**

With **1o** and **1p** as starting materials, eliminated products were obtained instead of the desired substituted products through the formation of *N*-acyliminium intermediate. To further demonstrate the potential applications of this novel method, we directed our efforts toward the synthesis of the naturally occurring **Jatropham** (Scheme 3). The required substrate **1l** reacted with ethanol under the

general procedure to give **8**, then clevage of 4-methoxyphenyl group afforded **9** quantitatively, and **9** could easily be transformed to **Jatropham** under the conditions given in the literature[21].

A plausible reaction mechanism is proposed based on previously reported results[4d,12c] as well as those form this study, shown in Scheme 4. The initiation step is proposed to be electron transfer between iron (III) and the amide to produce cation **10**，iron (II) and hydrogen radical. Next, nucleophilic addition generates the cation **11**. Iron (II) and hydrogen radical are oxidized by oxygen to give the peroxo species and regenerate iron (III). Hydrogen atom abstraction from the cation **11** produces the desired monosubstituted coupling product **3** or **5** and hydrogen peroxide**.** In the case of using 1,3,5-trimethoxybenzene as the nucleophile, a second oxidation occurs to give **12**, which may be trapped to afford β, γ-unsaturated amide **13** through 1,4-addition, which is believed to undergo isomerization to release the 3-phenyl substituted amide **6**. Disubstituted coupling product **14** was not formed probably because of stereoscopic configuration. The mechanisms of many oxidation processes are still unclear. Further research towards the design of a more powerful catalytic cycle should be based on mechanistic studies.

In summary, we have developed an efficient and practical method for the functionalization of pyrrolones by simple oxidative protocol.



Scheme 4 A plausible reaction mechanism

The reaction was carried out under mild conditions using green and atom-efficient O_2 as the oxidant and $Fe(OTf)_3$ as the catalyst. We believe that the simplicity offered by the present methods to accomplish pyrrolones makes the methodology more useful and attractive. Application of this methodology for the synthesis of natural products and mechanistic study are presently pursued in our laboratories.

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Notes and references

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Electronic Supplementary Information (ESI) available: copies of ^1H and ^{13}C NMR spectra for all products. See DOI: 10.1039/c000000x/

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