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Iron Chloride-Catalyzed Three-Component Domino Sequences: Syntheses of Functionalized α-Oxy-*N*-acylhemiaminals and α-Oxyimides

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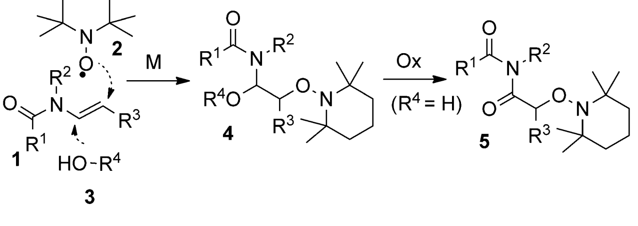
Abstract: The iron(III) chloride-multicatalyzed dioxygenation of enamides with TEMPO in the presence of alcohols has been developed. This multicomponent domino process affords efficient new strategies for the synthesis of α-oxy-*N*-acylhemiaminals or α-oxyimides in good to excellent yields under mild conditions.

Keywords: domino reactions; enamides; multicomponent reaction; radicals; SOMO activation

Transition metal-catalyzed reactions are versatile tools for carbon-oxygen bond formation. In particular, recent advances in the transition metal-catalyzed oxygenation of enamines have provided a rapid access to α-oxyaldehydes.[1–3] For example, Sibi et al.[1,2] reported the first $FeCl_3$-catalyzed enantioselective α-oxyamination of enamines, utilizing 2,2,6,6-tetramethylpiperidin-1-oxyl radical (TEMPO)[4] as a source of oxygen. Later, MacMillan et al.[3] studied the mechanism of this oxyamination and proved that the reaction proceeds *via* an enamine addition pathway.[5] Inspired by these works[1–3] and in connection with our recent interest in oxidative domino processes,[6] we envisaged a one-pot procedure for the synthesis of α-oxy-*N*-acylhemiaminals (ethers) **4** from readily available enamides.

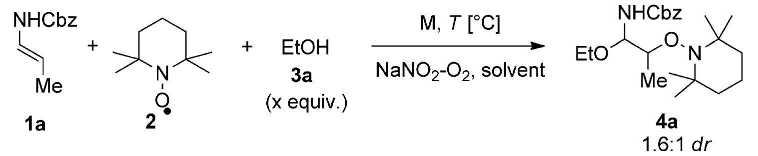
The α-oxy-*N*-acylhemiaminal (or α-oxy-*N*-acylhemiaminal ether) moiety is of great importance since it is found as a substructure in a multitude of naturally occurring and medicinally relevant substances.[7] In addition, this subunit might serve as a convenient and chemically stable precursor for the synthesis of the α-oxyimide moiety which is a privileged function in many bioactive natural products[8] and chelating ligands.[9] To the best of our knowledge, there are few methods for the synthesis of oxy-*N*-acylhemiaminal motif[10] and no method for the preparation of the α-oxyimide unit.[7,11,12] We therefore wanted to develop a straightforward synthesis of these oxygenated motifs based on a sequence involving the metal-catalyzed α-oxyamination[1–3] of enamides with TEMPO **2** and subsequent trapping of the *N*-acyliminium intermediate with an adequate oxygenated nucleophile such as an alcohol or water (Scheme 1).[13,14] In addition, α-oxyimides **5** could also be accessed by subsequent oxidation of hemiaminal intermediates **4** with a suitable oxidant.

The main difficulties associated with the development of such a domino MCR/oxidation sequence lie in the complexity of the reaction mechanism as well as the presence of multiple components and intermediates sensitive to oxidation.[11b] Consequently, the choice of the catalyst was expected to be crucial in order to guarantee the success of these complex domino processes. In this paper, we report the achievement of an Fe(III)-catalyzed, three-component synthesis of functionalized α-oxy-*N*-acylhemiaminals **4** and α-oxyimides **5**.



Scheme 1. Rational design for an oxidative three-component reaction of enamides, TEMPO and alcohols.

Table 1. Survey of reaction conditions for the iron-catalyzed three-component process.[a]



Entry	M	Temperature [°C]	**x** (equiv.)	Solvent	Time [h]	Yield [%][b]
1	$FeCl_3$	20	7	toluene	15	70
2	$Fe(OTf)_3$	20	7	toluene	15	33
3	$CuCl_2$	20	7	toluene	15	20
4	$Cu(OTf)_2$	20	7	toluene	15	46
5	$FeCl_2$	20	7	toluene	15	39
6	$FeCl_3$	20	7	toluene	7	82[c,d]
7	$FeCl_3$	20	3	toluene	7	54[c]
8	$FeCl_3$	75	3	toluene	3	86[c]
9	$FeCl_3$	75	3	MeCN	3	67[c]
10	$FeCl_3$	75	3	THF	3	75[c]
11	$FeCl_3$	75	3	DMF	3	60[c]
12	$FeCl_3$	75	3	1,2-DCE	3	80[c]
13	$FeCl_3$	75	3	toluene	3	86[c,e]
14	$FeCl_3$	75	3	toluene	3	88[c,f]
15	$FeCl_3$	60	3	toluene	3	91[c,f]

[a] *Reaction conditions:* (*E*)-enecarbamate (**1a**) (0.2 mmol), TEMPO (**2**) (0.4 mmol), **3a**, metal salt (0.06 mmol), $NaNO_2$ (0.06 mmol) and O_2 balloon, $c = 0.7$ M.

[b] Isolated yield after column chromatography.

[c] With anhydrous Na_2SO_4 as a drying agent.

[d] A 68% yield of **4a** was isolated with 4 Å MS. [e] $c = 0.4$ M or $c = 0.2$ M.

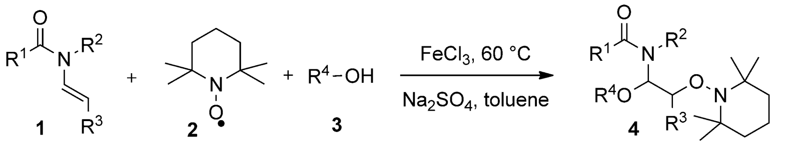
[f] Without $NaNO_2$-O_2 as co-oxidant.

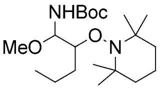
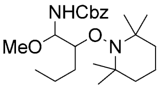
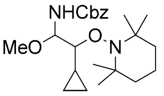
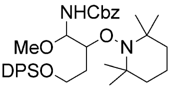
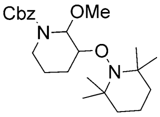
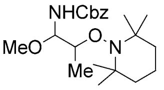
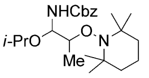
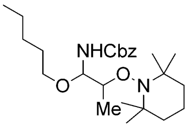
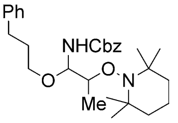
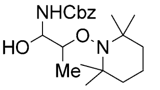
Benzyl (*E*)-prop-1-enylcarbamate (**1a**), TEMPO (**2**) and ethanol (**3a**) were chosen as model substrates. Gratefully, in the presence of $FeCl_3$ (0.3 equiv.) and $NaNO_2$ (0.3 equiv.) under an O_2 atmosphere in toluene,[1,3] the three-component reaction provided the desired α-oxyaminated *N*-acylhemiaminal ether **4a** in 70% yield as a diastereomeric mixture (ratio 1.6:1, Table 1, entry 1). Other metal salts such as $Fe(OTf)_3$, $FeCl_2$, $CuCl_2$ and $Cu(OTf)_2$ were also able to catalyze the reaction at room temperature, albeit affording the desired product with lower yields (entries 2–5). However, likely due to the presence of water, yields were not reproducible. Therefore, the addition of a drying agent to the reaction mixture permitted reproducible results. Although no enhancement of the conversion was obtained in the presence of pulverized 4 Å molecular sieves, the addition of Na_2SO_4 afforded **4a** in 82% yield (entry 6). On the other hand, decreasing the amount of ethanol to 3 equivalents resulted in a diminished yield because of competitive oxidation of the alcohol (entry 7).[11b,15] Fortunately, when the reaction was carried out at 75 °C with 3 equivalents of **3a**, the reaction was more chemoselective and proceeded faster to give an 86% yield of **4a** (entry 8). Subsequent solvent screening did not offer any further improvement and toluene remained the best reaction medium (entries 9–12).

Varying the concentration of the reaction mixture over a given range (0.7–0.2 M of **1a**) had no notable effect on the reaction yield (entry 13). Interestingly, the same result was obtained when only $FeCl_3$ was used as catalyst under an argon atmosphere, which indicated that the presence of neither $NaNO_2$ nor O_2 was essential for the three-component reaction to take place (entry 14).[16] Finally, as similar results were obtained at 60 °C, these conditions were retained as the optimum ones for further studies (entry 15).

To evaluate the scope of the present iron-catalyzed, three-component domino process, we examined the reaction of several enecarbamates with methanol (Table 2, entries 1–6). This transformation provided good to excellent yields of α-oxyaminated *N*-acylhemiaminal ethers **4** over a range of acyclic enecarbamates in short reaction times (3 h). Uniformly high chemical yields were achieved with enecarbamates bearing either a linear or branched alkyl group (entries 1–4). Interestingly, the enecarbamate geometry had only a slight influence on this transformation since both (*E*)- and (*Z*)-**1a** furnished the product in good yields (entry 6). In addition, a cyclic *N*-acyl(enecarbamate) also reacted efficiently to afford the corresponding α-oxyaminated *N*-acylhemiaminal ether **4f** in good yield as a 6:1 mixture of diastereomers (entry 5). A variety of protecting and functional

Table 2. Iron-catalyzed α-oxyamination of enamide derivatives.[a]



Entry	Product 4		Yield [%][a,b]	*dr*[c]
1		**4b**	87	3:1
2		**4c**	80	5.5:1[d]
3		**4d**	83	4:1[d]
4		**4e**	73	8:1
5		**4f**	82	6:1[d]
6		**4g**	98/78[e]	2:1[d]/1:1.3[d,e]
7		**4h**	76	2:1
8		**4i**	76	1.6:1[d]
9		**4j**	85	1.5:1
10		**4k**	74[f]	1:2.5[d]

[a] *Reaction conditions:* (*E*)-enecarbamate (**1**) (0.2 mmol), TEMPO (**2**) (0.4 mmol), **3a** (0.6 mmol), $FeCl_3$ (0.03 mmol), $c=0.4$ M at 60 °C in toluene for 3–6 h.

[b] Isolated yield after column chromatography.

[c] The *dr* was determined by ^{1}H NMR analysis of crude reaction mixtures.

[d] Diastereomers were separated by column chromatography.

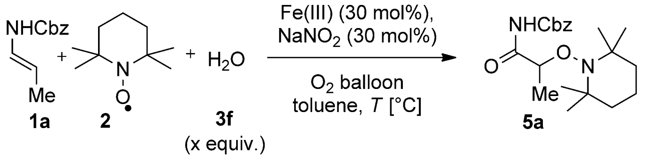
[e] With (*Z*)-enecarbamate.

[f] With $FeCl_3 \cdot 6H_2O$ as a metal salt and without Na_2SO_4.

groups, including Boc, Cbz and TBS, was compatible with the mild reaction conditions. The expected *N*-carbamoylhemiaminal ethers were obtained in excellent yields when several primary and secondary alcohols were used. Gratefully, water can also be used as a nucleophile, cleanly affording the formation of the desired hemiaminal products (entry 10).

Having established the feasibility of the three-component synthesis of hemiaminal **4k**, we turned our attention to investigating its oxidation in a one-pot domino process. Oxidative amidation of aldehydes with amines has received much attention in recent years.[17] Among various routes that have been developed so far, iron-catalyzed aerobic oxidative amidation could be adapted to a one-pot, three-component synthesis of α-oxyimides **5**.[17h] In our first attempts, the applicability of the previously reported conditions ($FeCl_3$-TEMPO-$NaNO_2$) was investigated for the

Table 3. Survey of reaction conditions for the iron-catalyzed three-component oxyamination/water trapping/oxidation domino reaction.[a]



Entry	Fe(III) source	Temp. [°C]	x [equiv.]	Yield [%][b]
1	$FeCl_3$	75	3	20
2	$FeCl_3$	75	1.5	37
3	$FeCl_3·6H_2O$	75	0	51
4	$FeCl_3·6H_2O$	55	0	72
5	$FeCl_3·6H_2O$	60	0	73
6	$FeCl_3·6H_2O$	65	0	60
7	$FeCl_3·6H_2O$	70	0	54
8	$FeCl_3·6H_2O$	60	0	80[c]
9	$FeCl_3·6H_2O$	60	0	63[c,d]

[a] *Reaction conditions:* (*E*)-enecarbamate (**1a**) (0.2 mmol), TEMPO (**2**) (0.4 mmol), **3a**, metal salt (0.06 mmol), $NaNO_2$ (0.06 mmol) and O_2 balloon, $c = 0.7$ M.

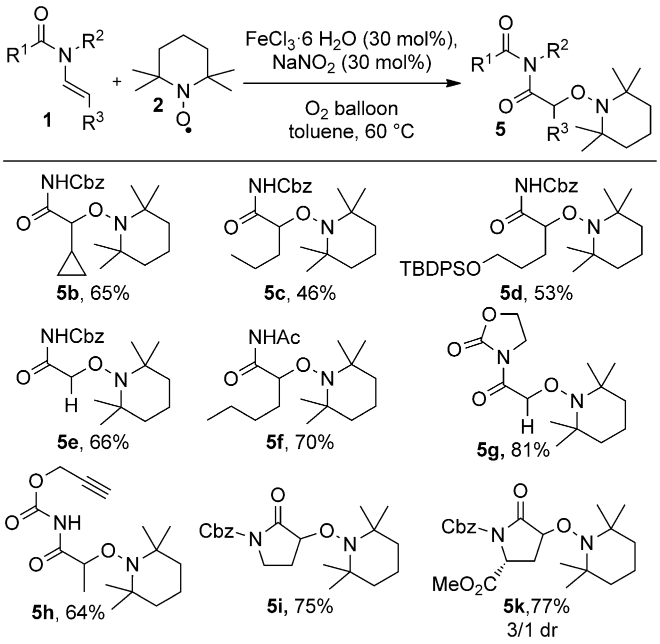
[b] Isolated yield after column chromatography.

[c] With anhydrous Na_2SO_4 as a drying agent.

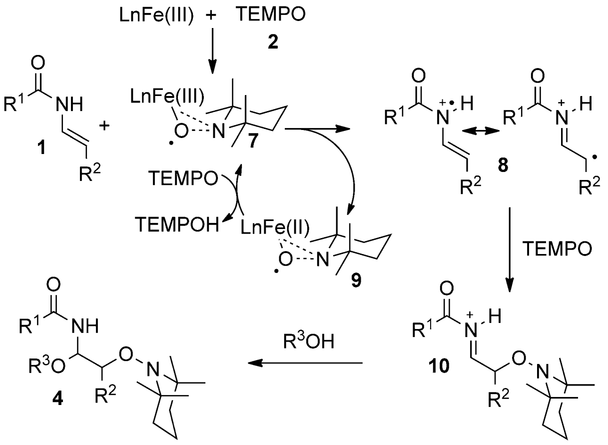
[d] A 68% yield of **4a** was isolated with 4 Å MS.

[e] $c = 0.4$ M or $c = 0.2$ M.

[f] Without $NaNO_2$-O_2 as co-oxidant.



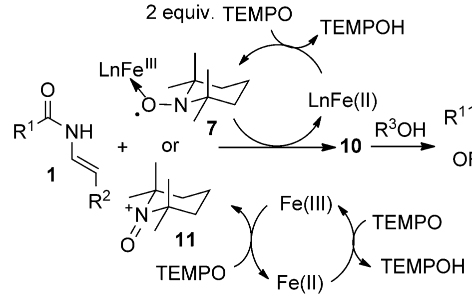
Scheme 2. Scope of enamide substrates for the oxidative three-component reaction.



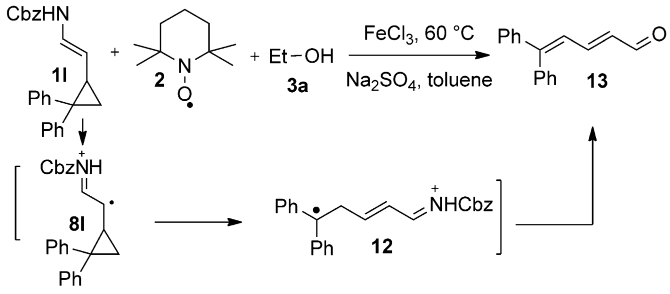
Scheme 3. Proposed radical mechanism.

three-step reaction sequence (oxyamination, water trapping, oxidation).[11b,15] Unfortunately, incomplete conversion to α-oxyimides **5a** was observed due to partial hydrolysis of enecarbamate **1a** (Table 3). Indeed, by carefully controlling the amount of water (with the use of $FeCl_3·6H_2O$) and temperature, the yield of **5a** increased to 73% (entry 5, Table 3). This demonstrated that the addition of an exact amount of water, along with a precise temperature of 60 °C is crucial for this three-component dioxygenation domino process. The reaction of (*E*)-**1a** with 3 equivalents of TEMPO afforded α-oxyimide **5a** in an excellent yield, whereas a lower yield was observed with (*Z*)-**1a** (entry 9 *vs.* 8). Satisfied with these results, we carried out this domino oxidation/three-component reaction sequence with a variety of enamide derivatives **1** (Scheme 2). The reaction proceeded well with linear as well as α-substituted enecarbamates. Moreover, unsubstituted enamide derivatives worked well to give the corresponding α-oxyimides **5e** and **5g** in good yields. Functional groups such as ester (**5k**), silyl ether (**5d**) and triple bond (**5h**) were well tolerated. The reaction could be applied to various carbamates and amides (Scheme 2) and no oxidation of unsaturated bonds present on enecarbamates was observed. Finally, cyclic enecarbamates such as **5i** and **5k** were successfully engaged into this oxidative three-component reaction to afford the corresponding adducts in good yields.

A possible reaction sequence for this aerobic dioxygenation of enamides is shown in Scheme 3 and Scheme 4. The α-oxyamination of enamides could proceed by three different mechanisms.[1–3] One possibility can be the formation of radical cation **8** *via* single electron oxidation of enamide followed by trapping with the oxygen radical TEMPO (Scheme 3).[1,2,18] The other possibilities would involve enamide addition to Fe(III)-bound TEMPO species **7** or to an oxoammonium salt **11** generated *in situ* by oxidation of TEMPO with Fe(III) (Scheme 4).[3,19–21] Although the absence of ring opening side product in the case of the above-mentioned reaction of 2-cyclo-

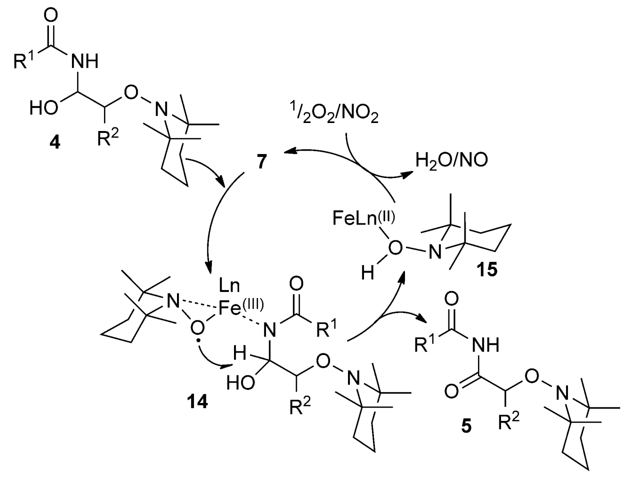


Scheme 4. Proposed ionic mechanism.



Scheme 5. Ring opening of 2,2-diphenylcyclopropyl radical cation.

propylvinylcarbamate **1d** with TEMPO leading to **4d** suggested a non-radical pathway, it would be possible that the ring-opened radical intermediate underwent a rapid ring closure.[22] We therefore decided to study the mechanism with the enecarbamate **1l**, substituted with a 2,2-diphenylcyclopropyl as a mechanistic probe.[23] In this case a stable ring-opened radical intermediate **12**, less amenable to ring closing, would be formed. Indeed, when (*E*)-benzyl [2-(2,2-diphenylcyclopropyl)vinyl]carbamate **1l** was exposed to $FeCl_3$, the cyclopropyl ring opening product **13** was isolated in 41% yield (Scheme 5). When we ran an additional control experiment, in which oxoammonium tetrafluoroborate salt was used instead of TEMPO, no α-aminoxylated product was formed. Although at the present stage we cannot exclude the occurrence of competitive radical and non-radical pathways, we propose that the mechanism involves the one-electron oxidation of **1** to generate radical cation **8** and Fe(II)-TEMPO **9**. Then, iminium intermediate **10** reacts with TEMPO and undergoes a subsequent trapping by alcohol **3**. Fe(III)-TEMPO **7** can be regenerated by the excess of TEMPO.[24] In addition, when water was used as a nucleophile in the presence of $NaNO_2$ and O_2, the α-oxy-*N*-acylhemiaminal (**4** with $R^3 = H$) would enter a second catalytic cycle resulting in oxidative amidation *via* intramolecular hydrogen abstraction of the Fe(III)-TEMPO-hemiaminal complex **14** (Scheme 6). Meanwhile, Fe(II)-TEMPOH **15** would be reoxidized by $NaNO_2$ and O_2.[21,25] However, again, another mechanism based on an oxoammonium intermediate cannot be excluded.[21,25]



Scheme 6. Proposed oxidation mechanism.

In summary, we have developed an iron-catalyzed, three-component domino sequence for the synthesis of a variety of α-oxy-*N*-acylhemiaminal ethers. The reaction is applicable to a wide range of enamides leading to dioxygenated products in excellent yields. In addition, an efficient one-pot method for aerobic oxidative amidation was also developed providing, to the best of our knowledge, the shortest route to α-oxyimides. A highlight of this study is that two catalytic cycles, both initiated by $FeCl_3$ as the sole catalyst, proceed successfully. This new type of multicatalytic system features high atom economy, use of easily available starting materials, operational simplicity and good tolerance for diverse functional groups. Further research on the development of related multicatalytic concepts is ongoing in our laboratories.

Experimental Section

General Protocol for α-Oxy-*N*-acylhemiaminals 4

The reaction was carried out under an argon atmosphere in dried glassware, with magnetic stirring. Enamide **1** (0.2 mmol, 1.0 equiv.) was dissolved in toluene (0.5 mL) in a flask containing dried Na_2SO_4. TEMPO **2** (0.4 mmol, 2.0 equiv.), $FeCl_3$ (0.06 mmol, 30 mol%) and alcohol **3** (0.6 mmol, 3 equiv.) were added successively and the reaction mixture was heated at 60 °C for 3–6 h (monitored by TLC). The reaction mixture was diluted with CH_2Cl_2, filtered through a short pad of silica gel and eluted with EtOAc (50 mL). Solvents were removed under vacuum and purification by flash column chromatography (SiO_2, 10–30% EtOAc in heptane) afforded the corresponding products **4**.

General Protocol for α-Oxymides 5

Enamide **1** (0.2 mmol, 1.0 equiv.) was dissolved in toluene (0.3 mL). TEMPO (0.6 mmol, 3.0 equiv.), $NaNO_2$ (0.06 mmol, 30 mol%) and $FeCl_3 \cdot 6H_2O$ (0.06 mmol, 30 mol%) were successively added and the reaction mixture was immediately put under an O_2 atmosphere (O_2 balloon) and heated at 60 °C for 15 h (monitored by TLC). The reaction mixture was then diluted with CH_2Cl_2, filtered through a pad of silica and eluted with EtOAc (50 mL). Solvents were removed under vacuum and purification by flash column chromatography (SiO_2, 30% EtOAc in heptane) afforded the pure product **5**.

Acknowledgements

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