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A remarkably simple α-oximation of aldehydes *via* organo-SOMO catalysis†

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A novel α-oximation reaction of unactivated aldehydes has been achieved in excellent yields by reaction with $NaNO_2$–$FeCl_3$ couple and in the presence of pyrrolidine as organocatalyst.

As a result of major developments in the field of organocatalysis in recent years, a new activation methodology termed SOMO (singly occupied molecular orbital)-enamine activation was developed by MacMillan *et al.* in 2007.[1] In the same year, Sibi *et al.* reported that using a MacMillan organocatalyst and $FeCl_3$ as a single electron-transfer (SET) catalyst, aldehydes reacted with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) *via* an electron-deficient enamine radical intermediate, giving α-oxyamination products of aldehydes in satisfactory yields with high enantioselectivities.[2] In the last four years, MacMillan's research group has developed highly stereoselective α-allylation[1a] and intramolecular allylation,[3a] α-enolation,[3b] α-alkylation,[3c] α-vinylation,[3d] α-trifluoromethylation,[3e] α-nitroalkylation,[3f] α-arylation[3g] and α-chlorination[3h] of aldehydes, and carbon-oxidation of styrene[3i] *via* SOMO enamine of aldehydes. In 2009, Nicolaou *et al.* demonstrated that in the presence of a MacMillan-type catalyst and cerium ammonium nitrate, aldehydes bearing electron-donating groups on aromatic rings underwent an intramolecular Friedel–Crafts-type arylation with excellent enantioselectivities.[4]

Continuing our studies on aminoxyl radicals ($R_2NO^{\bullet}$),[5] we decided to extend the α-oxyamination reaction of aldehydes to this class of reactive intermediates other than TEMPO.[2] Instead of the expected α-oxyaminated products, we surprisingly obtained α-oximinoaldehydes, which are important synthetic building blocks for many biologically significant compounds and pharmaceutically useful heterocyclic compounds.[6]

The direct α-oximation of ketones, esters and aldehydes by NOCl is well established.[7a] Generally, it is carried out in aqueous acid solutions using as nitrosating agent organic nitrites (*iso*amyl, *iso*butyl or *tert*-butyl nitrite) or inorganic salts such as $NaNO_2$. In a very interesting article, Rüedi and colleagues presented a convenient α-oximation method that allows for the selective preparation of 1,2-dione monoximes using simple acyclic or cyclic ketones as starting materials in the presence of an excess of concentrated HCl and an equimolar amount of sodium nitrite in tetrahydrofuran as solvent at 0 °C.[7b] Alternatively, treating chlorotrimethylsilane with *iso*amyl nitrite is an effective method for the *in situ* generation of NOCl in aprotic solvent media as well as under solvent-free conditions.[7c] Rasmussen and Hassner showed that addition of an excess of NOCl to trimethylsilyl enol ethers of ketones and esters in dichloromethane at −10 °C to −15 °C gives good yields of 2-hydroxyimino carbonyl derivatives. Unfortunately, in the case of aldehydes, the initial 2-hydroxyimino carbonyl products are unstable, but might be trapped by hydroxylamine as glyoxime derivatives.[7d] Finally, Sugamoto and colleagues attempted the reduction–nitrosation of conjugated olefins; α,β-unsaturated ketones, aldehydes and esters were directly converted to the corresponding α-oximino carbonyl compounds in good or moderate yields by reduction–nitrosation with *tert*-butyl nitrite and triethylsilane in the presence of 5,10,15,20-tetraphenylporphinatocobalt(II) as catalyst in *i*-PrOH–CH_2Cl_2 at room temperature.[7e]

We present here a new and highly efficient α-oximation reaction with $NaNO_2$ and $FeCl_3$ in dimethylformamide (DMF) as solvent, using pyrrolidine as organocatalyst. First, the reaction conditions for the α-functionalisation of aldehydes were identified (Table 1). Treatment of 3-phenylpropanal **1a** for 4.5 h at room temperature with a stoichiometric amount of $NaNO_2$ and $FeCl_3$ in the presence of 20 mol% of pyrrolidine and *p*-toluenesulfonic acid (*p*-TsOH) in DMF resulted in a good yield of 2-hydroxyimino-3-phenylpropanal **2a** (Table 1, entry 1). An excess of $NaNO_2$ and $FeCl_3$ did not increase product yield (Table 1, entry 2). The reaction carried out in the presence of 30 mol% of iron(III) chloride gave product **2a** (yield 68%) together with 15% of (*E*)-2-benzyl-5-phenyl-2-pentenal **3** (Table 1, entry 3). Accomplishing the reaction in the absence of $FeCl_3$ only **3** was obtained (yield 60%) and **1a** was partially recovered (Table 1, entry 4). In the absence of pyrrolidine, the starting aldehyde was completely recovered (Table 1, entry 5). The reaction under anaerobic conditions gave **2a** in quantitative yield (Table 1, entry 6).

Carrying out the reaction in the presence of $NaNO_2$–*p*-TsOH couple, known as a nitrosating system able to produce the ion NO^+,[8] the product **2a** was obtained in low to moderate yields even in the presence of an excess of protic acid (Table 1, entries 7 and 8). When DMSO was employed instead of DMF, the

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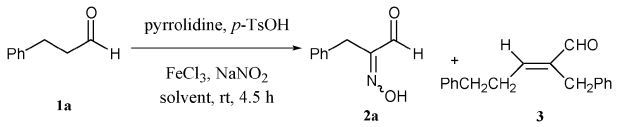
† Electronic supplementary information (ESI) available: Experimental details and characterization data for the compounds **2a–g**, **4** and **8**. See DOI: 10.1039/c2cc31566a

Table 1 Screening of reaction conditions for α-oximation of 3-phenylpropanal **1a**[a]



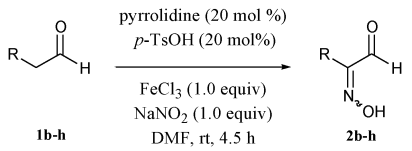
Entry	Solvent	Yields[b] (%) 2a	3	Recovered, 1a[b] (%)
1	DMF	89	3	4
2[c]	DMF	77	—	—
3[d]	DMF	68	15	17
4[e]	DMF	—	60	22
5[f]	DMF	—	—	96
6[g]	DMF	98	Traces	2
7[e,h]	DMF	31	—	67
8[e,i]	DMF	69	—	31
9	DMSO	58	12	7
10	CH_3CN	2	Traces	82
11	EtOAc	5	7	60
12	THF	8	—	84
13	CH_2Cl_2	66[j]	—	Traces

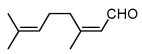
[a] The reaction of **1a** (1.0 mmol), pyrrolidine (0.2 mmol), *p*-TsOH (0.2 mmol), H_2O (2.0 mmol), $NaNO_2$ (1.0 mmol) and $FeCl_3$ (1.0 mmol) in 1.5 mL of anhydrous solvent was performed for 4.5 h at room temperature. [b] Determined by GC with an internal standard method *versus* initial moles of **1a**. [c] 1.5 mmol $NaNO_2$ and 1.5 mmol $FeCl_3$ were employed. [d] 0.3 mmol $FeCl_3$ was used. [e] There is not $FeCl_3$. [f] There is not pyrrolidine. [g] Under an argon atmosphere. [h] 2.2 mmol *p*-TsOH was used. [i] 3.7 mmol *p*-TsOH was used. [j] As $PhCH_2CH_2CO_2H$ and isolated yield.

product **2a** was obtained but in moderate yield (Table 1, entry 9). In other solvents (CH_3CN, EtOAc and THF), the reaction barely occurred (Table 1, entries 10–12).

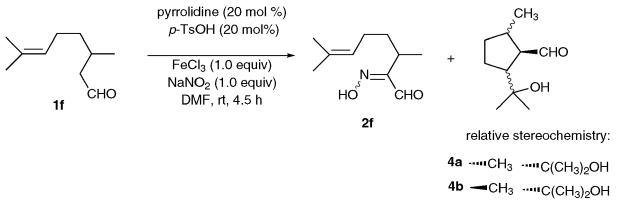
In CH_2Cl_2, the isolated product was 3-phenylpropionic acid instead of **2a** (Table 1, entry 13), probably formed by oxidation of aldehyde **1a** by nitrogen oxides (their formation was indicated

Table 2 α-Oximation of aldehydes by the $NaNO_2$–$FeCl_3$ system[a]



Entry	Aldehyde, R		Yield[b] (%), 2-hydroxyimino-aldehyde	Recovered, aldehyde[b] (%)
1	C_6H_5–	**1b**	**2b** 95	5
2	C_8H_{17}–	**1c**	**2c** 84	7
3	$(CH_3)_3CCH_2CH(CH_3)$–	**1d**	**2d** 96	4
4	C_6H_{11}–	**1e**	**2e** 93	7
5	$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)$–	**1f**	**2f** 77 **4** 19	— —
6	$(CH_3)_3C$–	**1g**	**2g** 98	Trace
7		**1h**	— —	99

[a] The reaction of aldehyde **1b–h** (1.0 mmol), pyrrolidine (0.2 mmol), *p*-TsOH (0.20 mmol), H_2O (2.0 mmol), $NaNO_2$ (1.0 mmol) and $FeCl_3$ (1.0 mmol) in 1.5 mL of anhydrous DMF was performed for 3–4.5 h at room temperature. [b] Determined by GC with an internal standard method *versus* initial moles of aldehyde.



Scheme 1 α-Oximation reaction of citronellal **1f**.

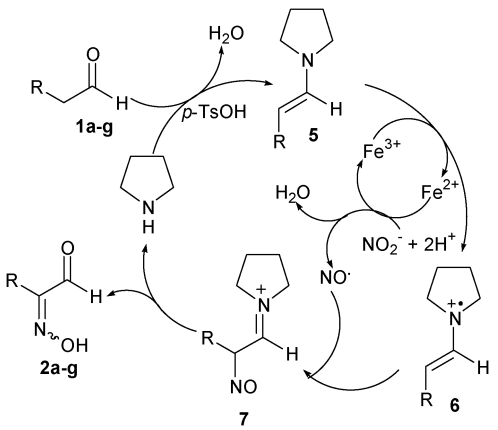
by the development of red-brown vapours after the introduction of $FeCl_3$ in the reaction vessel).[9]

Having identified an appropriate set of conditions, we then performed reactions with a variety of aldehydes (Table 2). The experimental results showed that a variety of aliphatic aldehydes underwent the reaction smoothly, to give the desired α-oximino product **2b–2g** with high yields, regardless of the steric hindrance of the substituent on Cα (Table 2). When the reaction was carried out with neral **1h**, unfortunately the starting α,β-unsaturated aldehyde was totally recovered and no trace of γ- or α-oximino aldehyde was present (Table 2, entry 7). Moreover, the reaction of citronellal **1f** with $NaNO_2$–$FeCl_3$ couple gave α-oximino aldehyde **2f** (yield 77%) and 19% of 2-methyl-5-(1-hydroxy-1-methylethyl)cyclopentanecarbaldehyde **4** as a mixture of the two diastereomers **4a** and **4b** in the ratio 2 : 1 (Table 2, entry 5 and Scheme 1).

This latter result provides circumstantial evidence for the generation and participation of a radical-cation species given the propensity of these radicals to undergo cyclization with unactivated olefins,[1a,3a,10] thus suggesting the plausible mechanism depicted in Scheme 2 for the direct α-oximation of aldehydes.

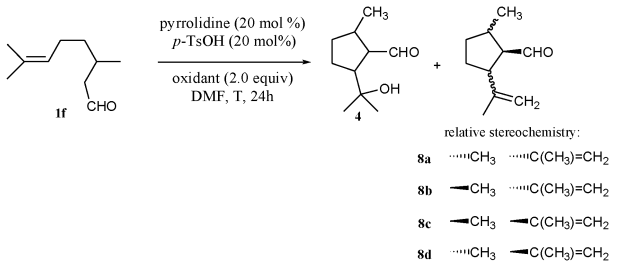
In the presence of *p*-TsOH, pyrrolidine as an organocatalyst initially reacts with aldehyde **1a–1g** to form the corresponding enamine **5**, followed by oxidation with SET reagent Fe^{3+} to generate the three-π-electron SOMO-activated intermediate **6** and Fe^{2+}.[2] This transient aminyl radical-cation **6** according to the persistent radical effect (PRE)[11] undergoes highly selective cross-coupling with the persistent NO· radical (probably formed by reaction of Fe^{2+} with nitrite in the presence of H^+)[12] to give the cationic imine **7**. The nitroso-imine cation **7** tautomerises and hydrolyses to ultimately form 2-hydroxyimino-aldehyde **2a–2g**.

We undertook studies to investigate more precisely the participation of the putative radical-cation intermediate **6** in



Scheme 2 Plausible mechanism for the direct α-oximation of aldehydes.

Table 3 Oxidation of citronellal **1f** with metallic oxidants[a]



Entry	Oxidant	T/°C	Yield[b] (%) **4** (dr)[c]	**8** (dr)[c,d]	Recovered, **1f**[b] (%)
1	$Cu(OAc)_2$	80	—	38[e]	—
2	$Cu(OAc)_2$	25	8 (4)	3 (2)	73
3	$Mn(OAc)_3$	25	7 (4)	6 (4)	33
4	$NaNO_2$–$FeCl_3$[f]	25	13 (0.4)	3 (2)	73[g]

[a] The reaction of **1f** (0.33 mmol), pyrrolidine (0.065 mmol), *p*-TsOH (0065 mmol) and oxidant (0.65 mmol) in 0.5 mL of anhydrous DMF was performed for 24 h. [b] Determined by GC with an internal standard method *versus* initial moles of **1f**. [c] Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis. [d] Diastereomeric ratio **8a** : **8c** (only **8a** and **8c** were formed). [e] Diastereomeric ratio **8a** : **8b** : **8c** : **8d** = 29 : 5 : 1 : 1. [f] $NaNO_2$ 0.065 mmol and $FeCl_3$ 0.065 mmol; reaction time 4.5 h. [g] Product **2f** was present (yield 3%).

this catalytic process. Specifically, aldehyde activation–addition experiments were performed with $Cu(OAc)_2$ and $Mn(OAc)_3$, established metallic oxidants used in oxidative free-radical cyclizations.[10]

For instance, oxidation of citronellal **1f** with 2 equivalents of $Cu(OAc)_2$ in the presence of 20 mol% of pyrrolidine and *p*-TsOH in DMF at 80 °C for 24 h (Table 3, entry 1) afforded a yield of 38% containing a 29 : 5 : 1 : 1 mixture of the 2-methyl-5-(prop-1-en-2-yl)cyclopentanecarbaldehydes **8a**, photocitral A (**8b**), **8c** and epiphotocitral A (**8d**).[3a,13] The same reaction carried out at room temperature gave 8% of **4** and 3% of **8** (Table 3, entry 2). Similar results were obtained when the oxidation was performed with $Mn(OAc)_3$ (Table 3, entry 3). Finally, the reaction of citronellal **1f** under the experimental conditions for α-oximation, but in the presence of only 20 mol% of both $NaNO_2$ and $FeCl_3$ (Table 3, entry 4), gave principally products **4** and **8** (13% and 3%, respectively), and only 3% of 2-hydroxyimino-aldehyde **2f**. These experimental results showed that cyclization of **1f** could be accomplished using $Cu(OAc)_2$ and $Mn(OAc)_3$ as oxidants for *bona fide* free-radical cyclizations (Table 3, entries 1–3). Moreover, in the presence of a low concentration of $NaNO_2$–$FeCl_3$ couple, unsaturated aldehyde **1f** gave principally the cyclization products **4** and **8** (Table 3, entry 4), thus confirming that the radical-cation **6** is the key intermediate of the α-oximation mechanism (Scheme 2).

In conclusion, we have developed an efficient radical α-oximation reaction of aldehydes using $NaNO_2$–$FeCl_3$ couple and pyrrolidine as organocatalyst. The reactions proceed with good to excellent yields. The introduction of a nitrogen atom at the α-position of a carbonyl compound provides a valuable route for the synthesis of a large variety of natural products and drugs. In particular, the nitroso function is recognised as a unique source to prepare nitrogen- and oxygen-containing molecules. Hence, the methodology reported here adds to the repertoire of organocatalytic direct α-heteroatom functionalisation of aldehydes and ketones.[14]

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