

## Graphical Abstract

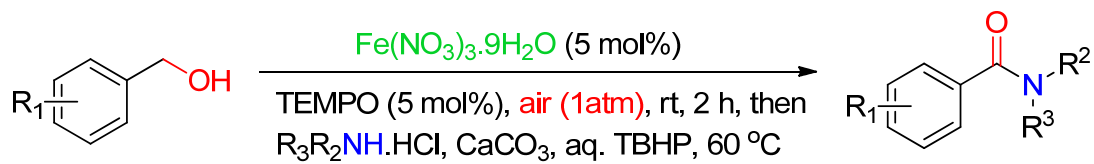
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### Tandem Oxidative Amidation of Benzyl

### Alcohols with Amine Hydrochloride Salts Catalysed by Iron Nitrate

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## Tandem Oxidative Amidation of Benzyl Alcohols with Amine Hydrochloride Salts Catalysed by Iron Nitrate

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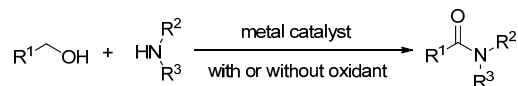
### ABSTRACT

A tandem process for the oxidative amidation of benzyl alcohols with amine hydrochloride salts has been developed using inexpensive  $\text{Fe}(\text{NO}_3)_3$  as the catalyst, air and aqueous *t*-butyl hydroperoxide as oxidants. A wide range of benzamides have been synthesized under mild conditions. This greener amide formation method provides an economical and practical access to benzamides from readily available and inexpensive starting materials.

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The amide bond is a ubiquitous functionality found in peptides, natural products, polymers, fine chemicals and pharmaceuticals.<sup>1</sup> Consequently, amide bond formation has been one of the most important transformations in organic synthesis and a plethora of methods have been reported.<sup>2</sup> Amongst these, direct amidation of alcohols with amines catalysed by transition metals is highly attractive owing to its high atom-efficiency and environmental friendliness.<sup>3</sup> This type of amide formation can be achieved by either dehydrogenative or oxidative amidation, depending on whether an oxidant is required (Scheme 1).

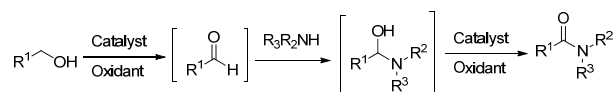
In dehydrogenative amidation, alcohols and amines are directly coupled to form amides without the presence of an oxidant and molecular hydrogen is formed as the by-product. Several catalyst systems based on homogenous ruthenium,<sup>4</sup> rhodium,<sup>5</sup> iridium<sup>6</sup> complexes and supported silver or gold nanoparticles<sup>7</sup> have been developed. Oxidative amidation, on the other hand, requires an oxidant to affect the coupling of alcohols and amines to form amides. Heterogeneous catalysts such as gold or its bimetallic nanoparticles,<sup>8</sup> manganese oxide octahedral molecular sieves (OMS-2)<sup>9</sup> have been shown to promote this type of amide formation.



**Scheme 1.** Metal-catalysed dehydrogenative and oxidative amidation.

These novel methods represent important advances toward environmentally benign and atom-efficient amide formation that could circumvent the poor efficiency and hazardous problems associated with the existing acid halide or coupling reagent based methods. However, the high cost of noble metal catalysts and their potential toxicity in pharmaceutical products<sup>10</sup> continue to promote exploration of more economical and safer catalysts for amide formation. For example, very recently  $\text{CuO}^{11a}$  and  $\text{FeCl}_3^{11b}$  have also been reported for the formation of benzamides from benzyl alcohols. In continuation of our efforts in developing atom-efficient and environmentally benign amide formation methodologies,<sup>12</sup> we report herein our extended work on iron-catalysed tandem oxidative amidation of benzyl alcohols with amine HCl salts.

A tandem oxidative amidation process of alcohol requires the catalyst to affect the oxidation of both the alcohol to aldehyde and the hemiaminal intermediate<sup>12,13</sup> formed between aldehyde and amine to the amide (Scheme 2). Iron compounds are particularly attractive catalysts for such a transformation because they are inexpensive and low toxic (permitted daily exposure limit >13 mg).<sup>10</sup> In addition, they have been shown to catalyse the oxidation of alcohols to aldehydes<sup>14</sup> and aldehydes to amides as demonstrated in our previous work.<sup>12a</sup>



**Scheme 2.** Tandem oxidative amidation of alcohols with amines.

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Our investigation of tandem amidation began with the screening of a number of inexpensive and readily available iron catalysts based on the reaction of benzyl alcohol and glycine methyl ester hydrochloride as a test reaction (Table 1). The reaction was carried in a tandem fashion by firstly oxidizing the alcohol to benzaldehyde using an iron catalyst in conjunction with TEMPO as a co-catalyst and molecular oxygen as an oxidant (step A), followed by oxidative amidation of the aldehyde by the addition of the amine salt, calcium carbonate (as the base) and a second oxidant T-hydro (70% aqueous TBHP).<sup>12a</sup> The initial results from two reported catalytic systems, i.e. FeCl<sub>3</sub>-TEMPO-NaNO<sub>2</sub><sup>14a</sup> and Fe(NO<sub>3</sub>)<sub>3</sub>-TEMPO-NaCl<sup>14b</sup> for alcohol oxidation showed only low to moderate activity for the amidation reaction in dichloroethane (DCE) (Table 1, entries 1, 2).

**Table 1.** Screening of iron catalysts and optimization of reaction conditions<sup>a</sup>

Entry	Catalyst	Oxidant	Additive	Solvent	Time <sup>b</sup> (h)	Yield (%) <sup>c</sup>
1	FeCl <sub>3</sub> .6H <sub>2</sub> O	O <sub>2</sub>	NaNO <sub>2</sub>	DCE	6	15
2	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	O <sub>2</sub>	NaCl	DCE	6	45
3	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	O <sub>2</sub>	NaCl	CH <sub>3</sub> CN	6	79
4	Fe(III)oxalate.6H <sub>2</sub> O	O <sub>2</sub>	NaCl	CH <sub>3</sub> CN	6	33
5	Fe(II)oxalate.2H <sub>2</sub> O	O <sub>2</sub>	NaCl	CH <sub>3</sub> CN	6	27
6	FeF <sub>3</sub> .6H <sub>2</sub> O	O <sub>2</sub>	NaCl	CH <sub>3</sub> CN	6	22
7	Fe(acac) <sub>3</sub>	O <sub>2</sub>	NaCl	CH <sub>3</sub> CN	6	30
8	FeSO <sub>4</sub> .7H <sub>2</sub> O	O <sub>2</sub>	NaCl	CH <sub>3</sub> CN	6	47
9	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	NaCl	CH <sub>3</sub> CN	6	76
10	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	6	77
11	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	6	57 <sup>d</sup>
12	-	air	-	CH <sub>3</sub> CN	6	12
13	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	6	85 <sup>e</sup>
14	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	4	85 <sup>e</sup>
15	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	2	86 <sup>e</sup>
16	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	0	38 <sup>e</sup>
17	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	2	68 <sup>e, f</sup>
18	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	2	74 <sup>e, g</sup>
19	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	2	48 <sup>e, h</sup>
20	Fe(NO <sub>3</sub> ) <sub>3</sub> .9H <sub>2</sub> O	air	-	CH <sub>3</sub> CN	2	69 <sup>e, i</sup>

<sup>a</sup> The reaction in step A was carried out with benzyl alcohol (1.0 mmol), TEMPO (5 mol%), additive (10 mol%), Fe catalyst (5 mol%), solvent (1 mL) at room temperature for the indicated time. Subsequently, glycine methyl ester HCl salt (1.2 mmol unless otherwise mentioned), TBHP (70% aq. solution, 1.1 mmol), CaCO<sub>3</sub> (1.1 mmol) were added and the reaction was heated at 60 °C for a further 16 h.

<sup>b</sup> Time for step A.

<sup>c</sup> Yields were determined by quantitative GC analysis using dodecane as an internal standard.

<sup>d</sup> In the absence of TEMPO.

<sup>e</sup> 1.5 mmol amine salt was used.

<sup>f</sup> 4-Hydroxy-TEMPO was used.

<sup>g</sup> 4-Acetamido-TEMPO was used.

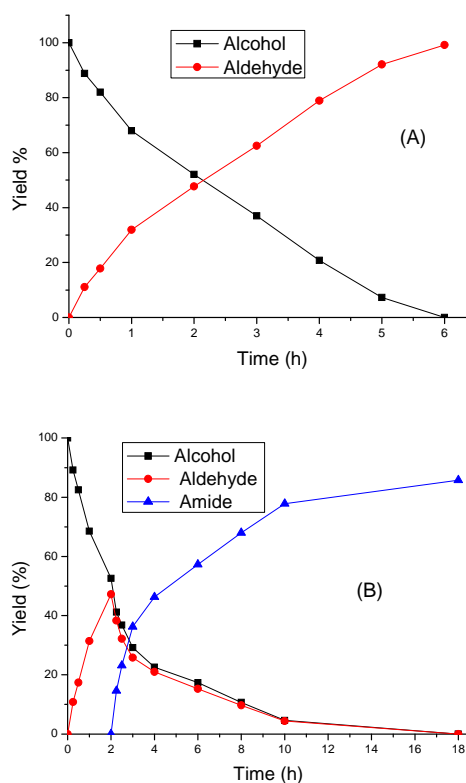
<sup>h</sup> 1-mol% Fe-catalyst was used.

<sup>i</sup> 3-mol% Fe-catalyst was used.

We reasoned that the lower yields could be due to poor solubility of the amine salt in the low polarity solvent DCE. Indeed, switching the solvent to more polar acetonitrile gave a much improved yield of 79% (entry 3). Further screening of a wide range of other iron salts concluded that Fe(NO<sub>3</sub>)<sub>3</sub>.9H<sub>2</sub>O was superior over others (entries 4-8). Since the use of pure oxygen could pose safety issues,<sup>15</sup> we examined the feasibility of using air (atmospheric oxygen) as a more practical and safer oxidant for our tandem oxidative amidation. This indeed proved feasible with the desired amide being formed in essentially the same yield (entry 9). Control experiments revealed that sodium chloride was

not necessary (entry 10) whereas in the absence of TEMPO, the yield of amide decreased to 57% (entry 11), and without iron nitrate, only 12% of the amide product was formed (entry 12), indicating the crucial role of the iron catalyst in the reaction. Increasing the amount of amine salt to 1.5 equivalents further improved the yield to 85% (entry 13). Furthermore, shortening the reaction time of step A to ca 2 h did not affect the reaction (entries 14-15). However, addition of all the reagents at the beginning resulted in significant decrease in yields (entry 16). This could be due to the known competitive oxidation of the amine under the reaction conditions<sup>16</sup> which could lead to ineffective oxidation of the alcohol as well as premature consumption of the amine. The performance of other TEMPO co-catalysts such as 4-hydroxy and 4-acetamido TEMPO (entries 16-17) was not as good as TEMPO itself.

In order to better understand the reaction profile, the conversion of benzyl alcohol alone (step A) was monitored (Figure 1 A). At ca 2 h, almost 50% of the alcohol was converted to the aldehyde and the oxidation was completed at 6 h. The reaction course after addition of glycine methyl ester HCl salt (step B) was also followed (Figure 1 B). The amidation reaction in the first 2 hours was faster (46% of amide formed) due to significant amount of aldehyde already present in the reaction. Subsequently, the reaction progressed more slowly and essentially leveled off at ~11 h with 80% yield of amide formed.



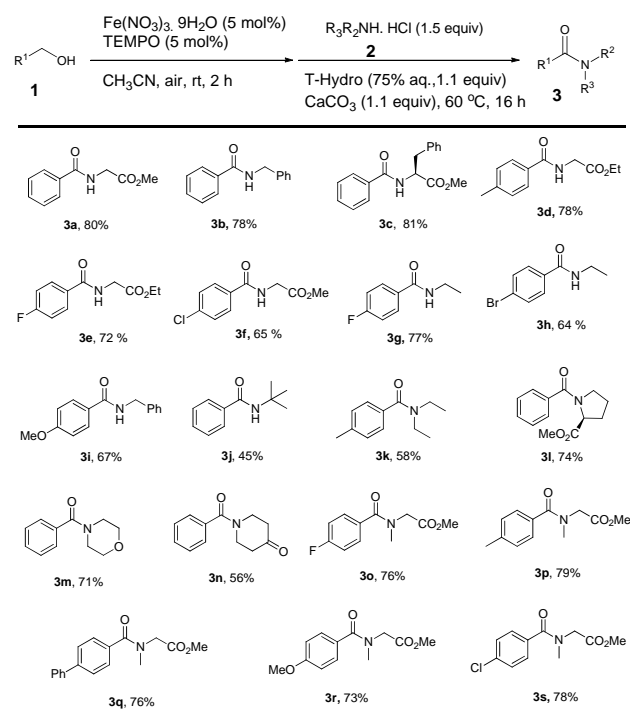
**Figure 1.** Reaction progress monitored by GC: A) Oxidation of benzyl alcohol to benzaldehyde; B) Oxidative amidation of benzyl alcohol and glycine methyl ester hydrochloride to methyl-2-benzamidoacetate. Amine salt was added after 2 h of alcohol oxidation.

With the optimized conditions in hand, the scope of this tandem amidation reaction was investigated with various benzyl alcohols and amine hydrochloride salts. In general, amides were obtained

in good yields (Table 2). Electronic effects were not significant as both electron-donating (**3d**, **3i**, **3p** and **3r**) and electron-withdrawing groups (**3f-h**, **3o** and **3r**) on benzyl alcohols gave similar yields of amide products. Several functional groups such as ester, halides, ketone and ether were compatible with the reaction conditions. This method worked well with both primary and secondary amines to form the corresponding secondary and tertiary amides. Chiral amine salts derived from amino acids such as *L*-phenylalanine and *L*-proline underwent smooth amidation providing the corresponding amides without detectable racemisation (**3c** and **3l**). Nevertheless, the reaction appeared to be sensitive to steric hindrance of the amine as bulky *t*-butyl amine HCl salt gave reduced yield (**3j**).

Other alcohols, including heterocyclic, allylic and aliphatic ones, were also examined for this oxidative amidation. However, most of these alcohols either gave low yields of the respective amide products or failed to provide the desired products. For example, amidation of furfuryl alcohol and cinnamyl alcohol with primary amines hydrochlorides provided <40% of the desired amides whereas the reaction of aliphatic alcohols gave inseparable mixtures. These limitations in substrate scope are likely due to undesired reactions under the reaction conditions, such as ring-opening of furan under acidic conditions,<sup>[17]</sup> aza-Michael reaction of amines with  $\alpha,\beta$ -unsaturated aldehydes<sup>[18]</sup> formed and aldol condensation of enolisable aldehydes produced in the first step. The limitation of aliphatic alcohols<sup>[11]</sup> and aldehydes<sup>[12,13, 19]</sup> in oxidative amidation has been observed previously. Hence, the development of catalyst systems that could be applied to the oxidative amidation of these more difficult substrates remains a challenge.

**Table 2.** Amide formation from benzyl alcohols and amine salts<sup>a</sup>  
b.



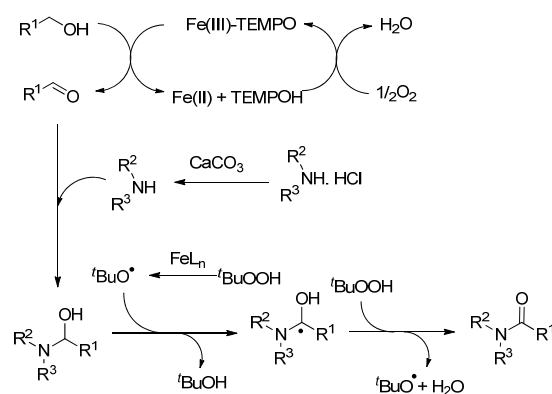
<sup>a</sup> Reaction conditions: A vial containing a solution of benzyl alcohol (1.0 mmol), TEMPO (0.05 mmol) and  $Fe(NO_3)_3 \cdot 9H_2O$  (0.05 mmol) in acetonitrile (1 mL) was stirred under open air at room temperature for 2 h. Subsequently, amine hydrochloride salt (1.5 mmol), calcium carbonate (1.1 mmol) and T-

hydro (70% TBHP in water, 1.1 mmol) were added and the reaction mixture was capped and stirred for additional 16 h at 60 °C.

<sup>b</sup> Yields in the table refer to isolated yields.

Based on a reported iron-TEMPO mediated alcohol oxidation, a general mechanism was proposed for this tandem oxidative amidation as shown in Figure 2. Initially, Fe(III)-TEMPO mediated oxidation of alcohol<sup>14</sup> takes place to generate the aldehyde. This then reacts with amine generated in situ to form a hemiaminal intermediate<sup>12,13,19</sup> which is further oxidized to the amide by Fe(III)-TBHP catalytic system via a free radical mechanism.<sup>12,20</sup> The free radical nature of this reaction was confirmed, as demonstrated previously,<sup>12,13</sup> by the addition of a free radical inhibitor 2,6-di-*t*-butyl-4-methylphenol (BHT, 1 equiv) which resulted in complete inhibition of amide formation.

In conclusion, we have developed a tandem oxidative amidation of benzyl alcohols with amine hydrochloride salts using inexpensive  $Fe(NO_3)_3 \cdot 9H_2O$ -TEMPO as the catalyst, air and aqueous TBHP as the oxidants. Both secondary and tertiary benzamides can be prepared under mild conditions and without using any noxious reagents.



**Figure 2.** A proposed mechanism for (Fe-TEMPO)-catalyzed tandem oxidative amidation of alcohols with amine hydrochloride salts.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://>

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