



## 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 assess to benzamides from readily available and inexpensive starting materials.

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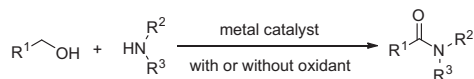
The amide bond is a ubiquitous functionality found in peptides, natural products, polymers, fine chemicals and pharmaceuticals.<sup>1</sup> Consequently, amide bond formation has been one of the most important transformations in organic synthesis and a plethora of methods have been reported.<sup>2</sup> 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

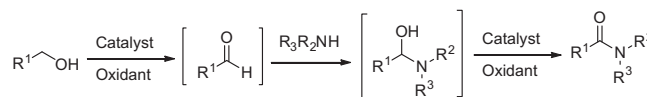
nanoparticles,<sup>8</sup> manganese oxide octahedral molecular sieves (OMS-2)<sup>9</sup> have been shown to promote this type of amide formation.

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



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



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

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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>

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 out 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, that is, 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 and 2).

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 equiv 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 and 15). However, addition of all the reagents at the beginning resulted in a 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 and 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 (Fig. 1A). At ca. 2 h, almost 50% of the alcohol was converted into the aldehyde and the oxidation was completed at 6 h. The reaction course after the addition of glycine methyl ester HCl salt (step B) was also followed (Fig. 1B). The amidation reaction in the first 2 h was faster

**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 %) and 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) and 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.

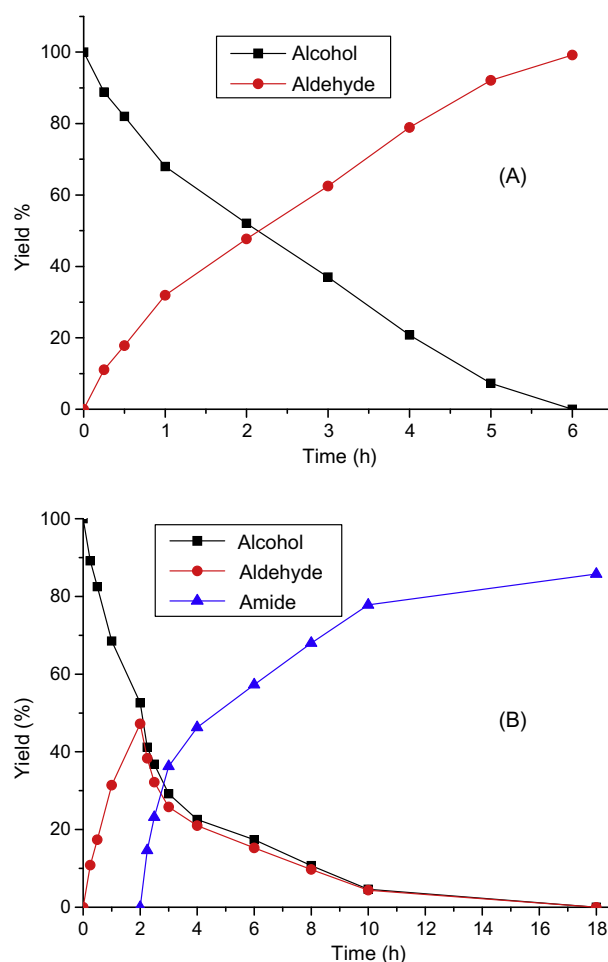
<sup>e</sup> 1.5 mmol amine salt was used.

<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.



**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.

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