

Pd(OAc)₂ promoted *bis*-*N*-heterocyclic carbene-catalyzed oxidative transformation of aldehydes

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Abstract

The *bis*-*N*-heterocyclic carbene-catalyzed (*bis*-NHC-catalyzed) oxidative transformation of aldehydes was successfully studied in water under air. The reaction rate increased through the use of Pd(OAc)₂ as an additive. Notably, the catalytic system exhibited good tolerance toward aliphatic and aromatic aldehydes bearing halide and alkyl functional groups. In addition, gram-scale reaction was also tested in this study. The use of water and operational simplicity make this methodology environmentally benign and cost-effective.

KEYWORDS

bis-NHC-catalyzed, oxidative transformation, water

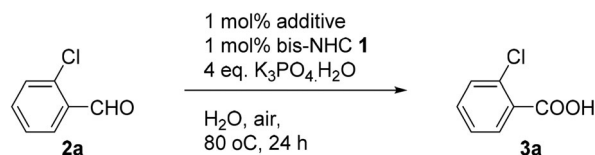
1 | INTRODUCTION

Carboxylic acids are important compounds that are used as industrial chemicals, pharmaceuticals, and agrochemicals.^[1] The aldehydes are also popular compounds that can be oxidized to carboxylic acids using various oxidants such as KMnO₄ and Cr(VI). However, these oxidants are dangerous for use in process operations and are hazardous for the environment. Therefore, the development of novel strategies for the oxidation of aldehydes to carboxylic acids and their derivatives is necessary.

Recently, *N*-heterocyclic carbenes (NHCs) and their metal complexes possessing a strong metal–carbene bond were developed, and these complexes present a new concept in organometallic catalysis. These are considered valuable catalytic systems in various reactions, including C–C cross-coupling reactions,^[2] C–N formation,^[3] olefin metathesis,^[4] and hydrogenative transformation.^[5] In particular, NHC-catalyzed oxidative transformation^[6] of aldehydes for preparing carboxylic acids and their derivatives are attracting significant attention. Recent findings have reported the reaction of NHC and imidazoles with CO₂, resulting in the NHC-CO₂ adduct, which has been proposed as a carrier of NHCs and CO₂^[7]; thereafter, the reaction of NHC-CO₂ adduct with aldehydes occurs to

form acids.^[8] Unfortunately, this transformation required a high catalyst loading (10–15 mol%) and carbon dioxide as the stoichiometric oxidant. Additional reports have described the oxidation of aldehydes via a nucleophilic acyl azolium ion.^[9] In this approach, first, the NHC catalyst is afforded by deprotonation of azolium salts. Second, an active species, known as Breslow intermediate, is formed in situ after the nucleophilic attack of the carbene on a carbonyl carbon atom. Finally, this acyl azolium ion undergoes esterification or hydrolysis to afford an ester or acid in the presence of a suitable oxidant. In 2013, Fu and coworkers reported a protocol for an uncharacteristic *bis*-NHC-mediated aerial oxidation of aryl aldehydes.^{9d} However, these approaches required a large catalyst loading (5 mol%) and longer reaction times of 2–3 days. The low solubility of most organic substrates in water implies that the use of a cosolvent, such as dimethylsulfoxide and *N,N*-dimethylformamide, is necessary in the NHC-catalyzed oxidative transformation of aldehydes. Furthermore, the oxidation of the aliphatic aldehydes is still a major challenge that needs to be overcome.

Green chemistry has emerged as one of the most attention-attracting issues worldwide. Using water as a reaction medium is an excellent way due to its non-toxicity, nonflammability, safety, and cost. In fact, the

TABLE 1 Oxidation reaction conditions catalyzed by *bis*-NHC **1**

Entry	Additive	Atmosphere	HCO ₂ H	3a yield (%) ^a
1	—	N ₂	—	8
2 ^b	—	CO ₂	—	17
3	Pd(OAc) ₂	CO ₂	—	47
4	Pd(OAc) ₂	Air	4 equiv	65

^aIsolated yields.^bDegassed solvent was used.

bis-NHC precursors have excellent solubility in water and possess two carbene moieties that can accelerate the NHC-catalyzed oxidative transformation of aldehydes. In this study, we report an efficient *bis*-NHC catalytic system for the oxidative transformation of aldehydes under air.

2 | RESULTS AND DISCUSSION

Our initial efforts were directed toward establishing an efficient preparative procedure for the *bis*-NHC-catalyzed oxidative transformation of aldehydes that could exhibit high reactivity. The results are summarized in Table 1. The oxidation of 2-chlorobenzaldehyde was carried out in water in the presence of 1 mol% *bis*-NHC **1** (Figure 1) at 80 °C for 24 hr under a nitrogen atmosphere. A trace of the corresponding acid **3a** was observed in 8% yield (entry 1). The yield was slightly increased to 17% by replacing N₂ with molecular CO₂ but in degassed water (entry 2). The significant enhancement of the yield (47%) was observed when the reaction was carried out in the water using 1 mol% Pd(OAc)₂ as an additive (entry 3). The experimental results (entries 1–3) show that only Pd(OAc)₂ cannot accelerate the reaction rate; an oxidant (oxygen dissolved in water) and CO₂ are also necessary. In 2011, Bode and coworkers postulated that exogenous oxygen was the actual oxidant in the open-air condition and that CO₂ played a role in reducing the generation of side products.^{9c} To improve the yield of the reaction, we briefly studied the application of the open-air oxidation conditions in the presence of CO₂. To achieve this, formic acid was determined to be the best choice as a source of CO₂ because the decarboxylation could occur in the presence of palladium. The best yield (65%) was afforded under air when 4 equiv. of HCO₂H was used as a source of CO₂ (entry 4).

Subsequently, the oxidative reaction conditions were applied to a wide variety of aldehydes to assess the scope and limitations of the present protocol (Table 2). Most aromatic aldehydes bearing electron-withdrawing groups selectively afforded their respective carboxylic acids in excellent yields, except **2a** and **2c** (entries 1–6). In contrast, the moderate yields of the desired carboxylic acid were observed in the case of aromatic aldehydes with electron-donating groups (entries 7–9). Aliphatic aldehydes such as **2k** and **2l** were also oxidized to the corresponding products in excellent yields without the formation of any aldol byproducts (entries 11 and 12). *trans*-Cinnamaldehyde could be oxidized by this catalytic system in moderate yield (entry 13). Notably, the catalytic system exhibited a good tolerance toward aliphatic and aromatic aldehydes bearing halide and alkyl functional groups.

To study the scalability of this oxidation reaction of aldehydes, the reaction was performed on a gram scale in water and afforded an 81% isolated yield (Figure 2). In addition, 4-trifluoromethylbenzaldehyde was oxidized to 4-trifluoromethylbenzoic acid with an 85% yield with 0.005 mol% catalytic system loading (Data S1). The advantage of this work is further highlighted through the successful transformation of aromatic and aliphatic aldehydes in water under air. Good yields were also obtained

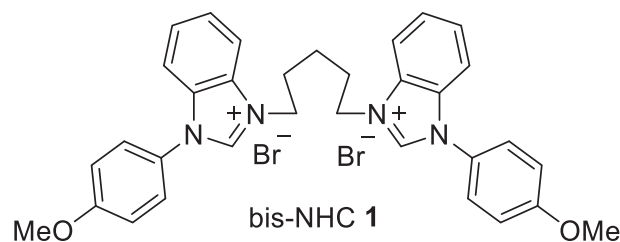
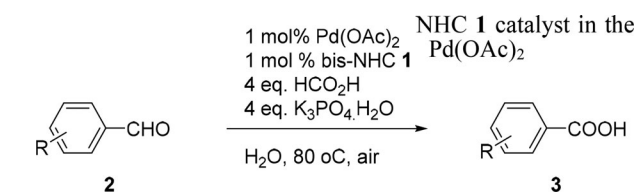
**FIGURE 1** Structure of *bis*-benzimidazolium salt **1**

TABLE 2 Oxidative transformation of aldehydes catalyzed using the *bis*-NHC **1** catalyst in the presence of Pd(OAc)₂

Entry ^a	Aldehyde 2	3 yield (%) ^b
1	2-ClC ₆ H ₄ CHO (2a)	3a (66)
2	3-ClC ₆ H ₄ CHO (2b)	3b (90)
3	4-ClC ₆ H ₄ CHO (2c)	3c (66)
4	2-FC ₆ H ₄ CHO (2d)	3d (96)
5	4-FC ₆ H ₄ CHO (2e)	3e (96)
6	4-CF ₃ C ₆ H ₄ CHO (2f)	3f (98)
7	2-MeC ₆ H ₄ CHO (2g)	3g (51)
8	3-MeC ₆ H ₄ CHO (2h)	3h (64)
9	4-MeC ₆ H ₄ CHO (2i)	3i (56)
10	C ₆ H ₅ CHO (2j)	3j (92)
11	C ₆ H ₁₁ CHO (2k)	3k (93)
12	3-phenylpropanal (2l)	3l (89)
13	<i>trans</i> -Cinnamaldehyde (2m)	3m (63)

^aReaction conditions: *bis*-NHC **1** (1 mol%), Pd(OAc)₂ (1 mol%), **2** (1 mmol), HCO₂H (4 mmol), K₃PO₄·H₂O (4 mmol), and H₂O (3 ml) were stirred for 24 hr at 80°C under air.

^bIsolated yields.

with a low catalyst loading (1 mol%) compared to prior reports (5–30 mol%).

3 | EXPERIMENTAL

3.1 | General aspects

All reactions were carried out in Shlenk flasks under an atmosphere of dry CO₂ or N₂ for gas effect studies; the reactions utilizing air as an oxidant were carried out in round flasks that were exposed to air directly. All liquid aldehydes were purified by distillation in vacuo. The synthesis of *bis*-NHC precursor **1** was obtained according to our previous report.^[1] Reactions were analyzed using precoated silica gel 60 (F-254) plates (0.2 mm layer thickness). Column chromatography (silica gel, 0.040–0.063 μm) was performed using *n*-hexane/ethyl acetate as the eluent. The ¹H NMR spectra were recorded on an Agilent VNMRS (400 MHz) spectrometer. The ¹³C NMR spectra were recorded on an Agilent VNMRS (100 MHz) spectrometer. The ¹⁹F NMR spectra were recorded on an Agilent VNMRS

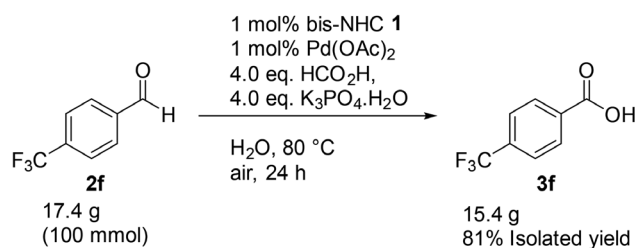
(376 MHz) spectrometer. *J*-values are given in Hz. Tetramethylsilane (δ = 0.00) and chloroform (δ = 7.26) were used as internal standard in the ¹H NMR spectra. The central peak of CDCl₃ (δ = 77.0) was used as internal standard in the ¹³C NMR spectra. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet.

3.2 | General procedure for oxidative transformation of aldehydes

All manipulations were carried out under open air. The round flask was charged with a *bis*-NHC precursor **1** (1 mol%), Pd(OAc)₂ (1 mol%), aldehyde **2** (1 mmol), K₃PO₄·H₂O (4 mmol), HCO₂H (4 mmol), and water (3 ml). The reaction mixture was stirred at 80°C for 24 hr under air. After completion of the reaction (monitored by thin-layer chromatography [TLC]), the reaction was acidified by 1 N HCl (5 ml). The aqueous layer was extracted with EtOAc (5 ml × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and then filtered. The solvent was evaporated under reduced pressure, and the corresponding crude product was purified by column chromatography (if necessary).

3.3 | General procedure for oxidative transformation of aldehydes

A stock solution of Pd(OAc)₂ (0.028 mmol) with *bis*-NHC **1** (0.028 mmol) in H₂O (25 ml) was initially prepared with continuous stirring at room temperature. The stock solution was diluted to 10× work solution (approximately 0.0001 M). The round flask was charged with 10× work solution (1 or 0.5 ml), aldehyde **2f** (1 mmol), K₃PO₄·H₂O (4 mmol), HCO₂H (4 mmol), and water (2 or 2.5 ml). The reaction mixture was stirred at 80°C for 24 hr under air. After completion of the reaction (monitored by TLC), the reaction was acidified by 1 N HCl (5 ml). The aqueous layer was extracted with EtOAc (5 ml × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and then filtered. The solvent was evaporated under reduced pressure.

**FIGURE 2** Gram-scale reaction

4 | CONCLUSIONS

We have successfully developed a highly effective oxidative transformation of aldehydes under air using a *bis*-NHC catalyst (1 mol%) in the presence of Pd(OAc)₂. Several aryl and aliphatic aldehydes have been successfully transformed into the corresponding acids with good-to-excellent yields under open-air conditions in water. This reaction can be carried out with a low loading (0.005 mol%) of *bis*-NHC catalyst, particularly 4-trifluoromethylbenzaldehyde, even in scale-up reactions. The excellent results of the reaction, together with its operational simplicity, make this methodology cost-effective. Water is a cheap, safe, and environment-friendly solvent. The use of water in this transformation is a highlight of the methodology and can be beneficial in the chemical industry.

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