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Zinc(II)-catalyzed oxidative amidation of arylaldehydes with alkylamines under solvent-free conditions

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ABSTRACT

The first zinc-catalyzed oxidative amidation of arylaldehydes has been developed. Various amides were prepared in good yields under solvent-free and mild reaction conditions.

Drawing from the significant advantages of zinc salts including inexpensiveness, abundance, and low toxicity, the exploration of zinc derivatives as environmentally benign catalysts in organic reactions has attracted considerable attention in the past decades. In some aspects, zinc is considered as a desired alternative for toxic or expensive transition-metal catalysts.[1]

Carboxamides constitute a significant important class of compounds found in numerous bioactive products, polymers, and pharmaceuticals.[2] In addition, amides serve as useful building blocks for the preparation of pharmaceuticals, agrochemicals, polymers, etc.[3] Owing to these extensive functions of amides, the development of efficient methodologies for the construction of amide skeleton has attracted significant interests from organic chemists. Generally, amides can be prepared by conventional substitution reactions of amines with carboxylic acid derivatives, or by the coupling of aryl/alkyl halides with amides.[4] Additionally, the classical name reactions (i.e., Ritter,[5a] Schmidt,[5b] Beckmann,[5c] Ugi,[5d] Wolff,[5e] etc.) have also provided alternative routes to the same end. During the past decades, a number of elegant methodologies were also developed to afford new accesses for amide elaborations.[6]

Comparing to these significant contributions, the oxidative amidation processes in which amines reacted with different aldehydes[7] represent more directly and interesting unconventional routes for the synthesis of carboxamides. Owing to the starting materials that are widely available, these procedures are of potential value in industrial applications. However, many of these processes require a key pre-treatment step to convert amines into their salts owing to the nitrogen atom of amines which may competitively occupy the coordination sites of metals that could decrease the catalyst activity.[8] In some cases, these synthetic protocols need high temperature or excessive amount of reagents including organic solvents that would lead to tedious laboratory procedures. Clearly, from the viewpoint of atom economy and environmental concerns, the development of efficient and direct methods for amide syntheses under mild conditions by using amine compatible catalysts and meanwhile minimizing the waste generation is of highly importance.

Considering various advantages of zinc catalysis and our continuous research interests in developing zinc-catalyzed oxidation reactions,[9] we became interested in exploring a zinc catalyst for direct oxidative amidation of aldehydes. Herein, for the first time we present an efficient zinc-catalyzed oxidative amidation of arylaldehydes with alkylamines under solvent-free conditions.

Based on our previous investigations in zinc-catalyzed oxidative esterification of aromatic aldehydes[10a,b] and some other oxidation reactions, we initiated our studies by employing the standard reaction conditions [catalyst: 10 mol % of $ZnBr_2$; temperature: 80 °C; reaction time: 16 h; solvent: pyridine; oxidant: 3 equiv of *tert*-butyl hydroperoxide (TBHP)] in the synthesis of *N*-phenethylbenzamide **3a** from benzaldehyde **1a** and 2-phenylethanamine **2a**. Gratifyingly, an almost quantitative yield was obtained upon GC-analysis (Scheme 1, Eq. 1). Interestingly, the reaction under

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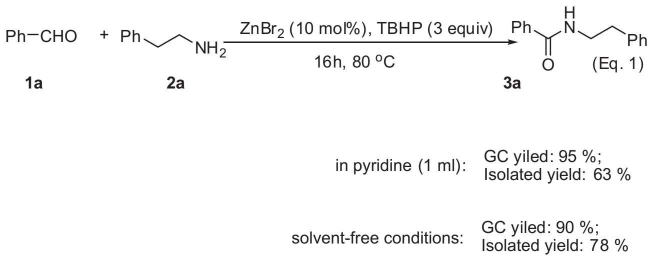
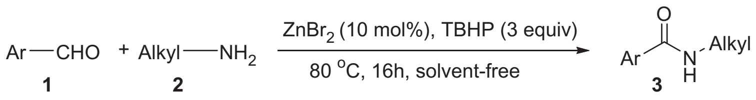


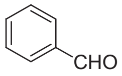
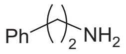
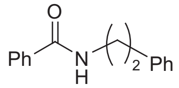
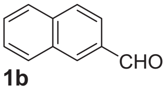
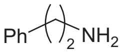
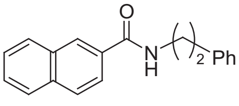
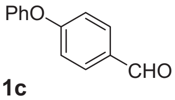
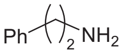
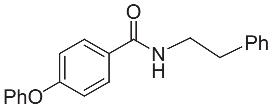
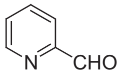
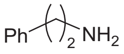
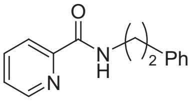
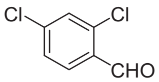
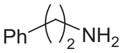
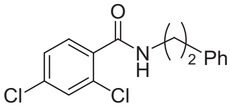
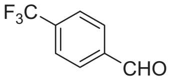
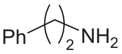
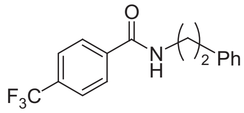
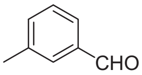
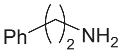
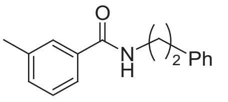
Scheme 1. Result comparison using solvent and solvent-free conditions.

solvent-free conditions can still afford an excellent GC yield of **3a** (Scheme 1, Eq. 2). However, the isolated yield of **3a** using solvent-free conditions is much higher than the former manipulation which is due to the product loss during the work-up procedure for removing organic solvent. No amide was produced in the absence of $ZnBr_2$, but only the oxidation of aldehyde occurred. H_2O_2 as the oxidant was tested as well, unfortunately, no desired amide was detected.

Inspired by the above-described results, we then examined the generality and limitation of this zinc-catalyzed oxidative amidation protocol under solvent-free conditions. Initially, 2-phenylethanamine **2a** was employed in combination with various aryl

Table 1
Zinc-catalyzed oxidative amidation of aldehydes into carboxamides[a]



Entry	Aldehyde **1**	Amine **2**	Amide **3**, yield[b] (%)
1	 **1a**	 **2a**	 **3a,** 78
2	 **1b**	 **2a**	 **3b**, 66
3	 **1c**	 **2a**	 **3c,** 70
4	 **1d**	 **2a**	 **3d,** 71
5	 **1e**	 **2a**	 **3e,** 66
6	 **1f**	 **2a**	 **3f,** 82
7	 **1g**	 **2a**	 **3g,** 55