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Access to Amide from Aldimine via Aerobic Oxidative Carbene Catalysis and LiCl as Cooperative Lewis Acid

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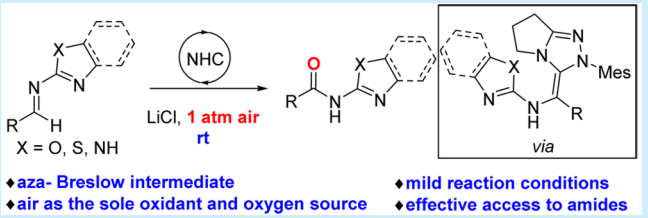
Supporting Information

ABSTRACT: Herein, an efficient route to amides from aldimines via aza-Breslow intermediates through aerobic oxidative carbene catalysis with LiCl as a cooperative Lewis acid is described. Many of the obtained *N*-heteroarylamides feature biological activity. Ambient air was used as the sole oxidant and source of oxygen in this catalytically oxidative amidation. This method allows for a broad substrate scope and mild conditions. The aza-Breslow intermediate derivative was isolated and its crystal structure confirmed.



Biological processes in nature often inspire chemists to discover new organic reaction modes, for example, the biological pathway by which thiamine (vitamin B1) activates pyruvic acid or aldehyde units in biological systems.[1] Breslow revealed that N-heterocyclic carbene[2] (NHC), a thiazolium moiety in vitamin B1, which behaves as the active site, could reverse the reactivity of the formyl group of an aldehyde from an electrophilic carbonyl to a nucleophilic acyl anion equivalent.[3] With the pioneering discovery by Breslow, umpolung of aldehydes under NHC catalysis has been further advanced, predominantly focused on benzoin condensations[4] and Stetter reactions.[5]

Umpolung of electrophiles other than aldehydes under NHC catalysis is very rare.[6−10] In particular, it is difficult to reverse the reactivity of unactivated imines owing to their lower reactivity compared with that of aldehydes. In 2009, the Douthwaite group[7a] reported pioneering work on NHC-catalyzed intramolecular reactions of unactivated imines and imidazoliums, which allowed access to six- and seven-membered ring aza-heterocycles through aza-Breslow intermediates (Figure 1a). Subsequently, the Rovis group[7b] has described successful isolation and full characterization of aza-Breslow intermediates, which were generated from intermolecular reactions of triazolium NHC precatalysts with iminium salts (Figure 1b). These two examples have clearly demonstrated the existence of aza-Breslow intermediates from a mechanism perspective. Very recently, the Biju group[7c] reported on the use of NHC-catalyzed umpolung of imines to synthesize 2-(hetero)arylindole-3-acetic acid derivatives via an intramolecular aza-Stetter reaction at a higher temperature (up to 100 °C, Figure 1c). Despite this progress, further development of NHC-catalyzed mild and efficient umpolung of imines access to useful molecules is highly desirable. Moreover, developing oxidative reactions with the direct use of

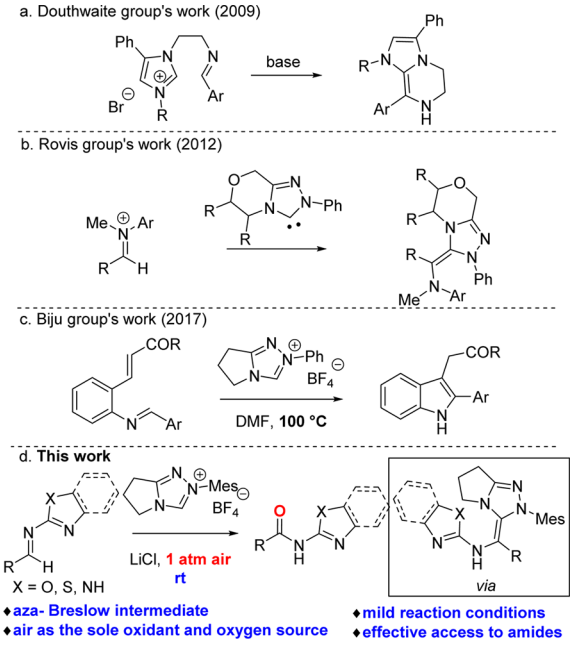


Figure 1. Umpolung of imines by NHC.

molecular dioxygen, and in particular, ambient air as the sole oxidant, is one of the most critical challenges to academic research and industrial application.[11] In fact, ambient air or O_2 as the sole oxidant in NHC-catalyzed reactions is mainly limited in the transformation of aldehydes to corresponding carboxylic acids and esters.[12] Considering these two fundamental requirements,

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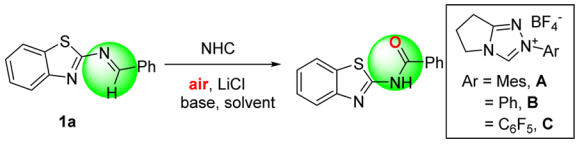
herein we present a highly efficient aerobic oxidative amidations[13] of aldimines under NHC and LiCl cooperative catalysis[14] via aza-Breslow intermediates in the presence of ambient air (Figure 1d). Compared to the traditional approach for amides from carboxylic acids and their derivatives, our method possesses high atom-economical, mild conditions and no need for stoichiometric amounts of coupling reagents. The use of ambient air as the sole oxidant and source of oxygen has no associated costs and avoids generation of stoichiometric amounts of hazardous byproducts. Thus, our considerably enhanced transformation shows potential feasibility for application in industry.

Key results of our initial studies and optimization of the reaction conditions based on **1a** as a model aldimine are summarized in Table 1. When the achiral triazolium *N*-Mes NHC

Table 1. Screening Reaction Conditions for Reaction of 1a[a]



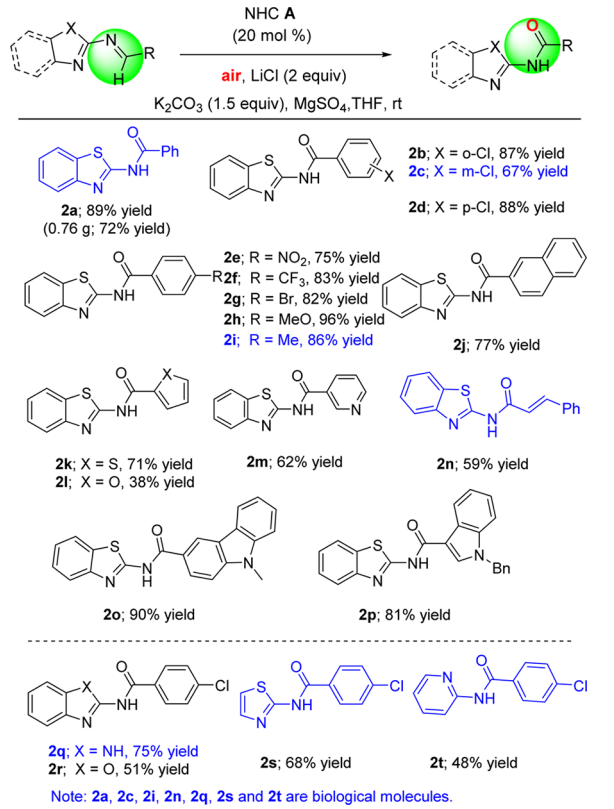
entry[a]	NHC	solvent	base	yield[b] (%)
1	**A**	THF	Cs_2CO_3	81
2	**A**	THF	K_2CO_3	83
3	**A**	THF	DBU	80
4	**A**	THF	Et_3N	77
5	**A**	THF	NaOAc	37
6	**A**	toluene	K_2CO_3	76
7	**A**	DCM	K_2CO_3	79
8	**A**	CH_3CN	K_2CO_3	56
9[c]	**A**	THF	K_2CO_3	89
10	**B**	THF	K_2CO_3	40
11	**C**	THF	K_2CO_3	33
12[d]	**A**	THF	K_2CO_3	24
13[e]	**A**	THF	K_2CO_3	trace
14	-	THF	K_2CO_3	nd
15[f]	**A**	THF	K_2CO_3	69
16[g]	**A**	THF	K_2CO_3	59
17[h]	**A**	THF	K_2CO_3	68

[a]Standard conditions: aldimine (0.2 mmol), NHC precursor (15 mol %), base (1.5 equiv), solvent (0.1 M), LiCl (2.0 equiv), $MgSO_4$ (20 mg), rt, 48 h. [b]Isolated yields after column chromatography. [c]20 mol % NHC precursor was used. [d]1.0 equiv LiCl was used. [e]Without LiCl. [f]10 mol % NHC precursor was used. [g]1.0 equiv K_2CO_3 was used. [h]Without $MgSO_4$.

precatalyst **A** was used with Cs_2CO_3 as a base and LiCl as an additive in THF, the desired amidation product **2a** was obtained in 81% yield (entry 1). We next evaluated bases, and K_2CO_3 proved to be the most effective choice (entries 2−5). This reaction also worked efficiently in other solvents (entries 6−8). When the NHC loading was increased to 20 mol %, the yield of amide **2a** increased to 89% (entry 9). The product yield decreased considerably when triazolium NHC precatalyst **B** or **C** was used (entries 10 and 11). The Lewis acid LiCl played a critical role in this transformation. In the absence of LiCl, only traces of the desired product **2a** were found (entry 13). Without NHC, none of the desired product **2a** was found (entry 14). Reducing the amount of base or omitting the drying agent decreased the product yield considerably.

With acceptable optimized conditions in hand (Table 1, entry 9), we next evaluated the scope of the reaction for aldimine substrates (Scheme 1). For aldimine aldehyde moieties with aromatic rings bearing electron-donating groups or electron-

Scheme 1. Scope of Reaction[a]



[a]Reaction conditions as in Table 1, entry 9; yields (after SiO_2 chromatography purification) were based on aldimine **1**.

withdrawing groups, all of the reactions proceeded smoothly to generate the corresponding amide products with good to excellent yield (**2a−j**). Aldmine aldehyde moieties bearing heteroaromatic rings (such as 2-furyl, 2-thienyl, and 3-pyridinyl) also worked efficiently (**2k−m**). The enal-derived aldimine also gave amide product **2n** in acceptable yield. Imines from noncommercially aldehydes, which were easily formed by installation a formyl group into electron-rich heteroarenes (i.e., indole and carbazole) via Vilsmeier−Haack reaction, also gave the desired products **2o** and **2p** in high yield. Other heteroaryl amine-derived aldimines, such as **1q**, **1r**, **1s**, and even **1t**, also underwent oxidative amidation reactions to afford the corresponding amides. It is worth mentioning that this aerobic oxidative reaction could be readily scaled-up. One gram of the aldimine **1a** could be converted to the amide **2a** in 72% yield under the conditions shown in Table 1, entry 3. Notably, among the obtained *N*-heteroarylamides, **2a**,[15] **2c**,[16] **2i**,[17] **2n**,[18] **2q**,[19] **2s**,[20] and **2t**[21] are biological molecules.

We then attempted one-pot aerobic oxidative amidation directly starting from the aldehyde and amine (Scheme 2). The aldimines generated from the reactions of 1:1 molar ratio of amines and aldehydes were used directly in the next aerobic oxidative step without purification. Finally, the corresponding amides **2** were generated efficiently in similar yields to those of the reactions starting from corresponding aldimine.

To probe the reaction pathway, control experiments were performed as shown in Scheme 3. Both Schiff base **3** and *N*-Ts-

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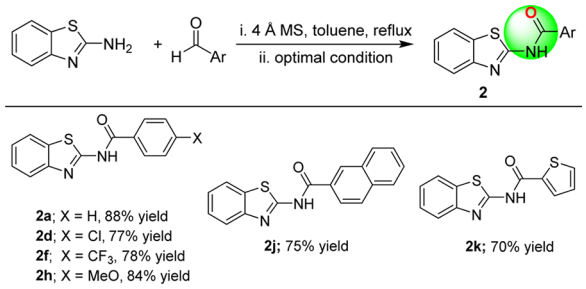
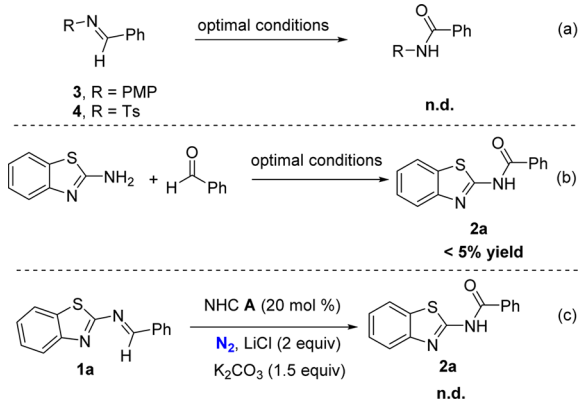
Scheme 2. Scope of One-Pot Reaction[a]



[a]Reaction conditions: (i) amine (0.5 mmol), aldehyde (1.0 equiv), 4 Å MS, toluene, reflux; (ii) same as in Table 1, entry 9; yields (after SiO_2 chromatography purification) were based on amine.

Scheme 3. Control Experiments[a]



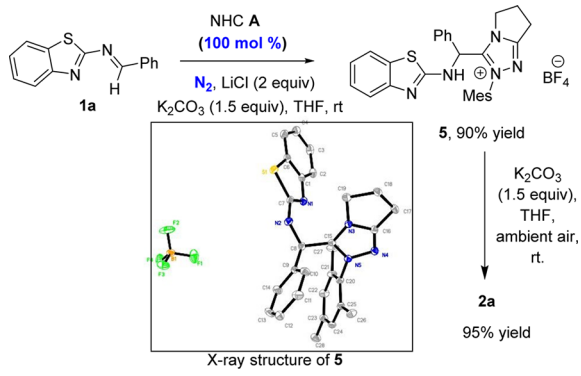
[a]PMP = 4-methoxyphenyl.

aldimine **4** were ineffective, and the raw material remained for **3** or decomposed for **4**, respectively (Scheme 3a). The direct use of an amine and aldehyde under the optimal conditions gave the desired amide **2a** in lower yield (<5% yield) (Scheme 3b). This result indicates that a pathway involving formation of a Breslow intermediate from the aldehyde which was generated from hydrolysis of the aldimine could be ruled out. When the reaction of the aldimine was performed under a nitrogen atmosphere, rather than air, none of the desired amide **2a** was found (Scheme 3c). Furthermore, product **2a** could be obtained in the presence of both bases and solvents that did not contain oxygen, as shown in Table 1, entries 3, 4, and 6−8. These results clearly confirmed that the oxygen atoms of the resulting amides derived from molecular dioxygen in air rather than from the base or solvent.

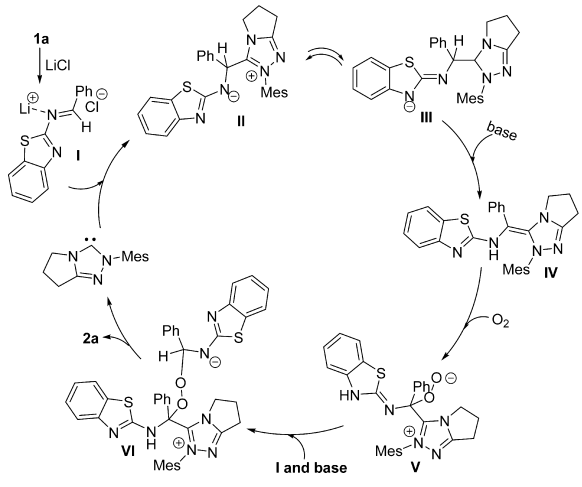
Gratifyingly, when the aldimine **1a** was treated with 1 equiv of NHC **A** in the presence of LiCl and K_2CO_3 in THF under nitrogen atmosphere at room temperature, expected intermediate **5** was successfully captured.[22] This intermediate could be separated in 90% yield, and its structure was confirmed by X-ray diffraction analysis (Scheme 4). Furthermore, intermediate **5** could be converted to **2a** in 95% yield in the presence of K_2CO_3 in THF and ambient air at room temperature. This is direct evidence that our transformation proceeded through an aza-Breslow intermediate.

On the basis of previous work and the current results, a proposed reaction pathway for the formation of amides from aldimines under aerobic oxidative NHC catalysis is illustrated in Scheme 5. With the assistance of the Lewis acid LiCl, the addition of NHC to aldimine **1a** produces the NHC-bounded aldimine

Scheme 4. Mechanistic Study



Scheme 5. Proposed Mechanism



intermediate II, the structure of which was confirmed by X-ray diffraction analysis. Intermediate II undergoes the dearomatization of benzothiazole ring to give intermediate III, the structure of which could significantly increase the acidity of hydrogen on the carbon bounded to NHC. This might be the reason why both Schiff base **3** and *N*-Ts-aldimine **4** were not effective. Intermediate III undergoes deprotonation to form an imine-derived Breslow intermediate IV, which then adds to dioxygen from the air to generate intermediate V.[23] Further addition of oxygen anion in intermediate V to intermediate I leads to the formation of intermediate VI, which undergoes O−O bond cleavage under basic conditions resulting in the formation of two amide molecules **2a** and regeneration of the free carbene.

In summary, we have developed a mild and efficient method for the synthesis of amides from aldimines via aerobic oxidative NHC catalysis. As a crucial step, NHC can activate aldimines with the assistance of LiCl to afford imine-derived Brelow intermediates. This transformation required only air as the sole oxidant to oxidize the aldimine-derived Breslow intermediates and furnished the desired amide products in excellent yields. This economical and environmentally friendly approach may be applied to other types of NHC-activated aldimine reactions, and further investigations are undergoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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