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Aminofluorene-Mediated Biomimetic Domino Amination−Oxygenation of Aldehydes to Amides

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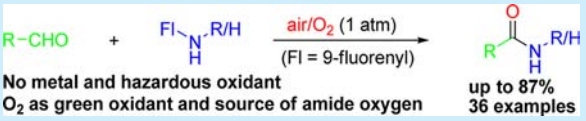
Supporting Information

ABSTRACT: A conceptually novel biomimetic strategy based on a domino amination−oxygenation reaction was developed for direct amidation of aldehydes under metal-free conditions employing molecular oxygen as the oxidant. 9-Aminofluorene derivatives acted as pyridoxamine-5′-phosphate equivalents for efficient, chemoselective, and operationally simple amine-transfer oxygenation reaction. Unprecedented RNH transfer involving secondary amine to produce secondary amides was achieved. In the presence of $^{18}O_2$, ^{18}O-amide was formed with excellent (95%) isotopic purity.

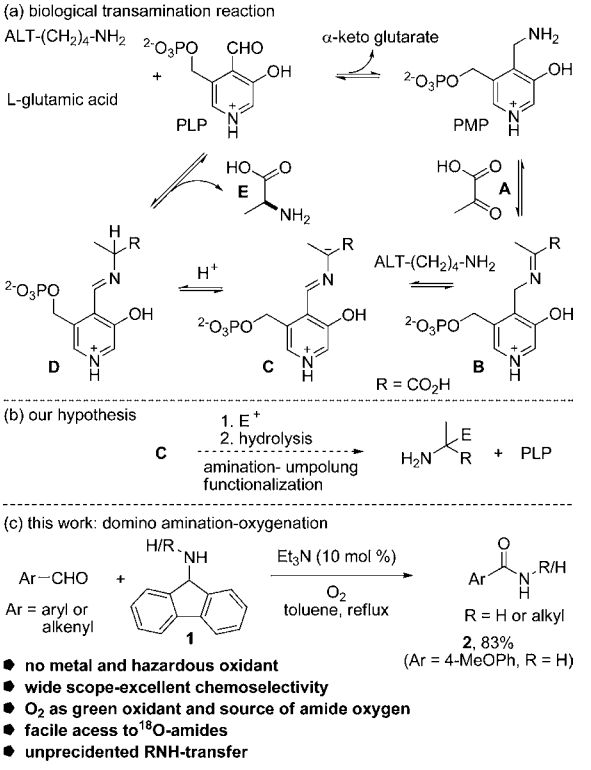


Amide is a ubiquitous functionality of organic molecules and forms an essential part of many natural products, medicinal drugs, and functional materials.[1] The primary way to form an amide bond is the classical condensation of a carboxylic acid with an amine. The reactions are promoted by coupling reagents, which produce superstoichiometric amounts of waste.[2] To circumvent this, different methods using catalytic amounts of coupling reagents, which are primarily based on boron and other metal-based complexes, have been developed.[3] Alternatively, oxidative coupling of an aldehyde/alcohol with an amine is one of the elegant approaches that have been developed as a direct method for amide synthesis.[4,5] Other direct alternatives include amidation involving α-keto acids,[6] α-bromo nitroalkanes,[7] and Staudinger ligation.[8,9] However, the practicability of these methods was reduced due to the involvement of metallic reagents and hazardous oxidants (e.g., hypervalent iodine, $KMnO_4$, etc.). In addition, most often these methods require sensitive reaction conditions. Molecular oxygen has been used as a viable alternative to hazardous oxidants; however, this worked only in the presence of metallic reagents/catalyst.[4h,i] On the other hand, carbene-catalyzed direct amidation of aldehydes was achieved under metal-free conditions.[10] However, prefunctionalized aldehydes, stoichiometric organic oxidants (e.g., nitroxides and quinones), or electrochemical oxidation were essential for the reactions. Herein, we present a mechanistically different metal-free approach for direct amidation of aldehydes via biomimetic domino amination−oxygenation reactions, which uses molecular oxygen as the oxidant (Scheme 1c).

In an aminotransferase-catalyzed transamination, coenzyme pyridoxyl-5′-phosphate (PLP) is aminated, producing pyridoxamine-5′-phosphate (PMP) which subsequently transfers the amine group to keto acid **A** to provide amino acid **E** (Scheme 1a).[11] Ketamine **B**, which is formed in a reaction of PMP with the keto acid, undergoes deprotonative isomerization to anion **C**. Protonation of **C** produces the corresponding aldimine **D**, which after hydrolysis provides alanine (**E**) and PLP.

Various suitable amines, which mimic the activity of PMP, were developed for the transamination reactions to produce chiral or achiral amines and amino acids.[12] Currently, our group is working on the development of metal- and hazardous oxidant-

Scheme 1. (a) Alanine Aminotransferase (ALT) Catalyzed Transamination. (b) Our Hypothesis for Biomimetic Amination−Umpolung Functionalization of Carbonyls. (c) This Work: Metal-Free Biomimetic Amination−Oxygenation of Aldehydes to Amides



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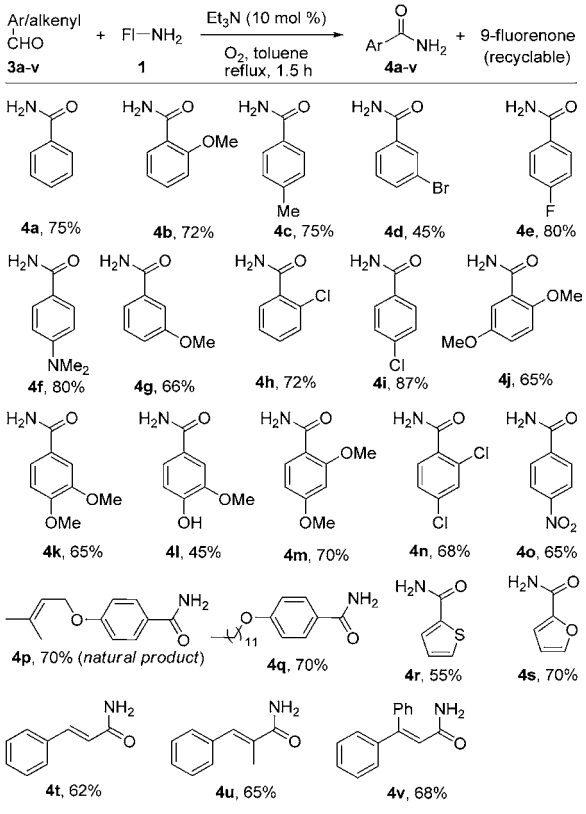
free organic transformations.[13] Along that line, we thought that the reaction of the anion in **C** with any other electrophile except proton would lead to the amination−umpolung functionalization of carbonyl carbon of **A** (Scheme 1b).[14] Therefore, we anticipated that molecular oxygen would be a suitable electrophile to test our hypothesis because oxygen was found to oxidize the related azomethine anion in lucifarase-catalyzed biological reactions (Scheme S1).[15] We decided to employ commercially available 9-aminofluorene (**1**) as the PMP analogue to ease the deprotonative isomerization through a stabilized aromatic anion (**13**, see Scheme 5).[13] Surprisingly, 9-aminofluorene was not known as a transaminating agent despite of its potential.

Our investigation started with a reaction of 4-methoxybenzaldehyde and 9-aminofluorene in the presence of triethylamine under oxygen atmosphere (Table S1). The desired 4-methoxybenzamide (**2**) was produced with 50% isolated yield. Different reaction conditions, such as varying solvents, temperatures, reactant stoichiometry, etc., were evaluated to optimize the reaction (Table S1). The best result (83% of **2** in 1.5 h) was obtained in a triethylamine-catalyzed reaction of **1** and aldehyde in refluxing toluene under oxygen atmosphere. The use of benzylamine and 4-fluorobenzylamine, replacing 9-aminofluorene, did not yield the desired amide under the same conditions. However, a trace amount of **2** was identified using diphenylmethylamine (entry 10).

The scope of the metal-free and biomimetic amination−oxygenation of aldehydes using oxygen as the ecologically viable oxidant was tested next. Different aryl, heteroaryl, and alkenyl aldehydes **3a−v** reacted smoothly to produce the corresponding primary carboxamides **4a−v** with good to excellent yields (Scheme 2). Various functional groups were tolerated under the reaction conditions. The functional groups (e.g., OR, NR_2, OH, Ar−Br, alkene), which are sensitive to oxidizing agent and transition-metal-mediated reaction, were found to be well accepted in this reaction. Substrates having both electron-donating (e.g., OH, OMe, NMe_2) and electron-withdrawing (e.g., NO_2, F, Cl) groups were efficiently reacted to produce the desired amides. The oxidizable heteroaromatic thiophene ring also remained intact during the reaction to yield **4r**.

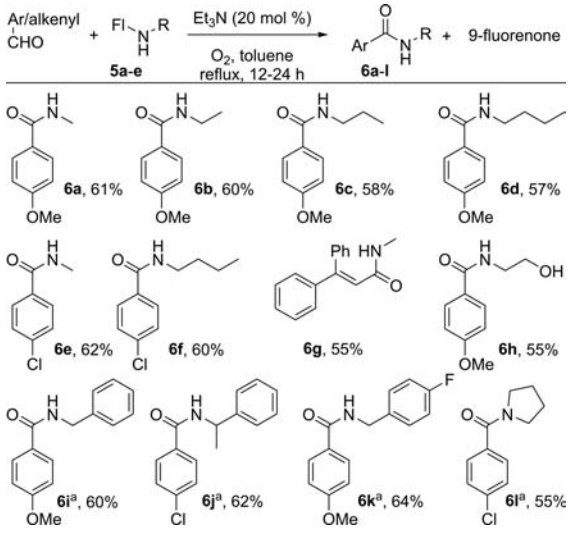
Scheme 2. Scope in NH_2-Transfer Oxygenation Forming Primary Carboxamides



The amination−oxygenation reaction was also applied for the synthesis of natural amide **4p** (Scheme S2). Additionally, the reaction was found to be effective in gram-scale synthesis, which indicated its potential for practical application (Scheme S3). Moreover, the byproduct 9-fluorenone can be recycled after conversion to the corresponding 9-aminofluorene derivative.

Although there have been several reports on the transamination (NH_2 transfer) using primary amine,[12] to our surprise, there was no example where RNH was transferred involving secondary amine. Therefore, we were interested in investigating the possibility of RNH transfer involving secondary amines to obtain the corresponding secondary amides. Accordingly, different secondary amines **5a−e** were reacted with various aldehydes under the standard reaction conditions to afford the corresponding secondary amides **6a−h** with good yields (Scheme 3).[16] Under these conditions, 9-(*N*-benzylamino)-

Scheme 3. Scope in RNH-Transfer Oxygenation



[a]Obtained from one-pot amidation−transamidation reaction.

fluorene was unable to provide corresponding amide **6i** with isolable yields. However, the desired benzyl amides **6i−k** along with tertiary amides **6l** were also obtained directly from the corresponding aldehydes via a one-pot current amidation to primary amide and its subsequent transamidation[17] reaction with suitable primary and secondary amines (Scheme S4).

Several additional experiments were carried out to better understand the mechanism and chemoselectivity of the amine-transfer−oxygenation reaction (Scheme 4).[16] Reaction of benzoic acid and 9-aminofuorene under the standard reaction conditions did not yield the desired benzamide (eq 1). This ruled out the possibility of amide formation via thermal condensation of amine with carboxylic acid that can be formed in situ by oxidation of aldehyde. On the other hand, the desired benzamide **2** (60%) was isolated from the reaction of preformed aldimine **7** (eq 2). This observation suggested azomethine **7** or its derivative

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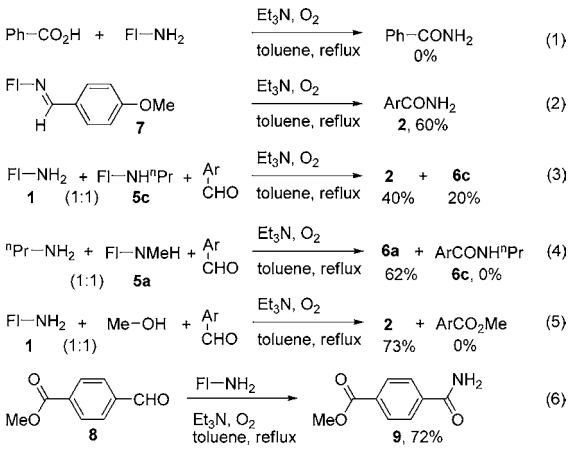
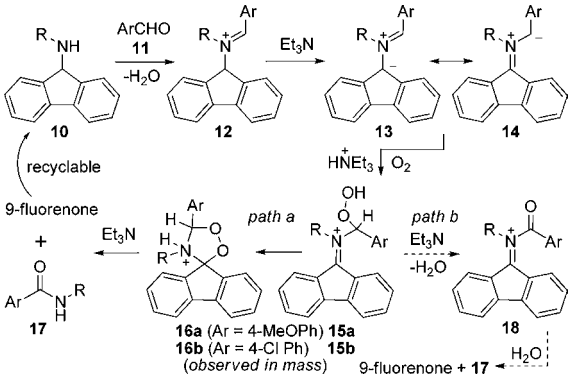
Scheme 4. Investigations on Chemoselectivity and Mechanism of the Reaction



12 (Scheme 5) as a possible intermediate of the reaction. The reduced yield of benzamide obtained from the reaction, which was carried out without an oxygen balloon, indicated the necessity of molecular oxygen for the reaction (Table S1, entry 7). A competition experiment was performed to investigate the relative reactivity of primary and secondary amines (eq 3). Expectedly, a lower yield (20%) of secondary amide **6c** (vs 40% of primary amide **2**) was obtained due to the reduced reactivity of the corresponding bulky secondary amine **5c** as compared to primary amine **1**. Other experiments were carried out to test the chemoselectivity of the reaction (eqs 4−6). The amides **6a** and **2** were isolated from the reactions shown in eqs 4 and 5, respectively. Amide **6c** and methyl ($ArCO_2Me$) ester were not formed. Thus, the results demonstrated the excellent chemoselectivity of this coupling reaction in the presence of other potential coupling partners like alcohol (eq 5) and amine (eq 4). Similarly, the aldehyde functionality in **8** reacted selectively in the presence of ester moiety to obtain corresponding amide **9** with very good yield (72%, eq 6). Further, the results from the reactions shown in eq 4 and 5 suggested that amines, which are attached with a fluorenyl moiety, were specifically transferred to form corresponding amides.

On the basis of the experimental evidence, a plausible mechanism for the base-catalyzed metal-free biomimetic amine transfer and subsequent molecular oxygen mediated oxidation of aldehydes to amides is proposed in Scheme 5. Condensation of aldehyde **11** and 9-aminofluorenyl derivative **10** occurred to provide corresponding aldimine **12**. Triethylamine promoted

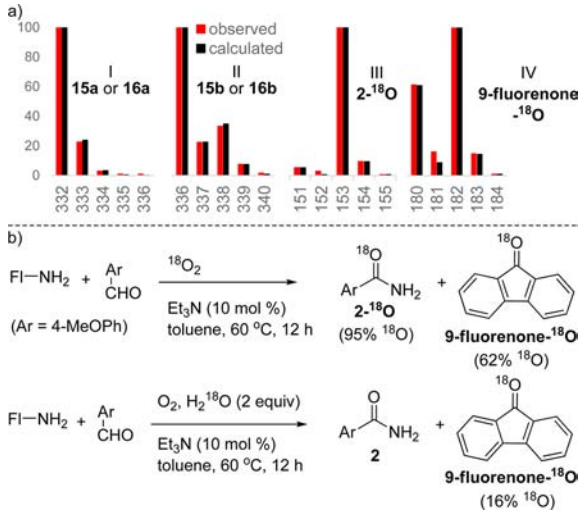
Scheme 5. Proposed Reaction Mechanism



deprotonation of **12** and furnished stabilized azomethine anion **13**. Anion **13** or its mesomer **14** reacted with molecular oxygen to provide hydroperoxide **15** or its regioisomer. Hydroperoxide **15** could react further to furnish the corresponding dioxazolidine **16**, which on subsequent thermal decomposition would provide the desired amide **17** and 9-fluorenone (path a). However, the base-mediated O−O bond cleavage of hydroperoxide **15** followed by hydrolysis of resulting imine **18** could also provide the desired products (path b).

Mass spectrometric analysis of the reaction mixture identified peroxide derivatives **15a** (R = H) or **16a** (R = H) (Scheme 6a I).

Scheme 6. (a) Observed and Calculated Mass with Isotopic Pattern for Compound 15a or 16a (I), 15b or 16b (II), 2-^{18}O with 95% ^{18}O (III), and 9-Fluoreneo-^{18}O with 62% ^{18}O (IV). (b) Amination−oxygenation Reaction in the Presence of $^{18}O_2$ (Preparation of ^{18}O-Amide) and $H_2{}^{18}O$



The mass of a similar species **15b** (R = H) or **16b** (R = H) was also found in the reaction with 4-chlorobenzaldehyde (Scheme 6a, II). This observation suggested that the reaction occurs through the peroxide intermediate **15** or **16**. However, the mass corresponding to compound **18** was not observed.

The reaction was also performed in the presence of $^{18}O_2$ to gain further insights into the mechanism (Scheme 6b). Amide **2-^{18}O** was formed having 95% of ^{18}O incorporation, which was observed from mass spectrometric analysis (Scheme 6a, III). At the same time, incorporation of 62% of ^{18}O was observed in 9-fluorenone (Scheme 6a, IV).[18] However, incorporation of ^{18}O did not occur in amide **2** when the reaction was carried out in the presence of $H_2{}^{18}O$ (Scheme S5). In contrast, 9-fluorenone formed in the reaction was found to have 16% of ^{18}O.[18] Therefore, in the presence $^{18}O_2$, formation of amide **2** and 9-fluorenone, both with high levels of ^{18}O, indicated that the reactions proceed via dioxazolidine **16** (path a). Importantly, the observations also revealed that the ^{18}O-labeled amides with excellent isotopic purity can be prepared by this method just by performing the reaction in the presence of $^{18}O_2$.

We have disclosed an unprecedented approach for chemoselective direct amidation of aldehydes based on a biomimetic amination−oxygenation. This environmentally benign method used triplet molecular oxygen as the oxidant without the aid of metallic reagents and other hazardous oxidants. In addition to the facile synthesis of primary amides via NH_2 transfer, RNH transfer involving secondary amine was also achieved for the first time,

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providing corresponding secondary amides. Mass spectrometric and isotope-labeling studies revealed that the oxygenation of azomethine ylide occurred through the dioxazolidine intermediate. ^{18}O-Amides can be prepared easily by performing this reaction in the presence of $^{18}O_2$. The proposed amination−umpolung functionalization strategy can also be applied for direct derivatization of carbonyl compounds employing other (e.g., carbon-based) electrophiles. The results of the ongoing related investigations will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02465.

Additional schemes and table and experimental procedure (PDF)

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Reduced ^{18}O levels in 9-fluorenone in the presence of $^{18}O_2$ and incorporation of ^{18}O in the presence of $H_2{}^{18}O$ were observed due to the formation of 9-fluorenone from the other side reactions (see the Supporting Information, Scheme S5).

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