Oxygen Activation

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Copper-Catalyzed Intramolecular Dehydrogenative Aminooxygenation: Direct Access to Formyl-Substituted Aromatic N-Heterocycles**

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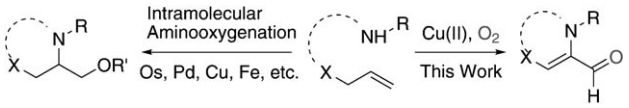
Aminooxygenation of alkenes,[1–3] a process in which nitrogen and oxygen atoms are added simultaneously across a carbon–carbon double bond, represents one of the most straightforward approaches to prepare vicinal amino alcohol derivatives, which are an important functional motif in many biologically active compounds.[4] The regioselective intramolecular version of this process leads to a variety of nitrogen-containing heterocycles,[5] in which an exocyclic oxygenated methylene group is present for further elaboration. In studies focusing on the development of this method, less-toxic metal catalysts, including palladium,[6] copper,[7] and iron,[8] in addition to the toxic osmium salts have been explored.[9] To elaborate the N-heterocycles formed in this fashion, deprotection ($R' \neq H$) and oxidation strategies have been probed. In these efforts, oxidation of the exocyclic primary alcohols to form aldehydes, among the most versatile functional groups in chemical transformations, was found to be a general strategy.[3c,7] Herein, we describe the results of an investigation that has led to the discovery of an unexpected and novel intramolecular dehydrogenative aminooxygenation (IDA) reaction, catalyzed by copper and occurring under dioxygen. The process results in the direct formation of aromatic N-heterocycles substituted with a formyl group (Scheme 1).[10]

The presence of the imidazo[1,2-*a*]pyridine scaffold in many biologically active compounds has stimulated the development of numerous methods for their preparation.[11]



Scheme 1. Intramolecular dehydrogenative aminooxygenation.

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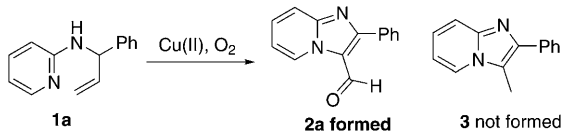
Recently, Chernyak and Gevorgyan[12] described a new copper-catalyzed, three-component coupling reaction that was used to generate an impressive array of imidazo[1,2-*a*]pyridine derivatives. By considering features of our recent synthesis of pyrido[1,2-*a*]benzimidazoles through copper-catalyzed aromatic C–H amination of *N*-aryl-2-aminopyridines,[13] we hypothesized that 3-methyl-2-phenylimidazo[1,2-*a*]pyridine **3** would be formed under the developed reaction conditions when *N*-(1-phenylallyl)-2-aminopyrine **1a** is employed as substrate. We envisaged that this transformation would take place either by direct amination of the vinyl C–H bond in **1a** and subsequent double bond migration or through intramolecular hydroamination of **1a** followed by dehydrogenative aromatization (Scheme 2). In contrast to this prediction, the copper-catalyzed reaction of **1a** actually formed 2-phenylimidazo[1,2-*a*]pyridine-3-carbaldehyde **2a**, which is a potentially versatile synthetic intermediate.[14] In this unexpected process, the terminal carbon atom of the monosubstituted olefin moiety in **1a** is transformed into the formyl group with concurrent formation of the N-heterocyclic ring in **2a**. Although imidazo[1,2-*a*]pyridine-3-carbaldehydes can be prepared through Vilsmeier–Haack formylation of the corresponding imidazo[1,2-*a*]pyridines,[14] the extremely low yields (20–30%) and harsh reaction conditions limits the application of this approach.



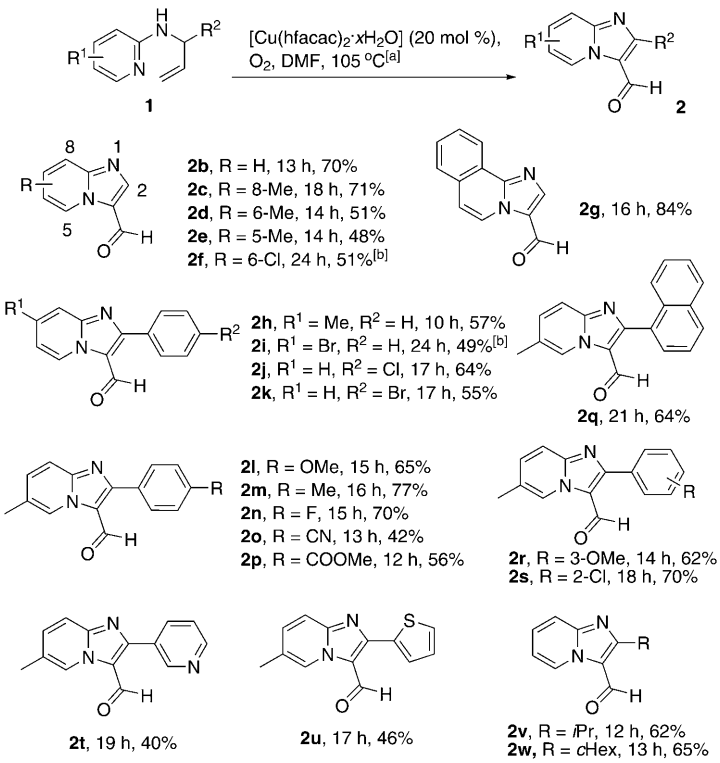
Scheme 2. Unexpected formation of **2a**.

The widespread distribution of substituted imidazoles in biologically active natural products and synthetic drugs or drug candidates makes them important synthetic targets.[15,16] Owing to the electron-deficient nature of imidazole, its formylation cannot be realized through Vilsmeier–Haack reaction. An alternative deprotonation with BuLi and subsequent nucleophilic addition to DMF at low temperature is accessible.[17] However, deprotonation of 1,2-disubstituted imidazole occurs at the 5-position exclusively, and no direct formylation at the 4-position of 1,2-disubstituted imidazoles has been reported in the literature.[18] Herein, we report the synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes as well as 1,2-disubstituted imidazole-4-carbaldehydes through the

unprecedented IDA reaction starting from simple acyclic precursors.

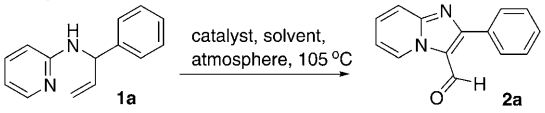
Conditions for the new copper-catalyzed cyclization reaction were explored using *N*-(1-phenylallyl)-2-aminopyrine **1a** as the substrate.[19] With 20 mol% of $Cu(OAc)_2$ as the catalyst and DMF as the solvent, **1a** was converted into aldehyde **2a** in respective yields of 13% and 18% under air or dioxygen (Table 1, entries 2–3). $Pd(OAc)_2$ did not serve as a suitable catalyst for the reaction of **1a** because no separable product was formed in this case (entry 1). Interestingly, screening other copper(II) sources led to the observation that $[Cu(hfacac)_2{\cdot}x\,H_2O]$ promoted a high-yielding conversion (69%) of **1a** into **2a** (entries 4–7). Switching the reaction solvent from DMF to DMA, NMP, and DMSO proved to be unfruitful (entries 8–10). In addition, inclusion of 10 mol% of $Fe(NO_3)_3{\cdot}9\,H_2O$ in the reaction mixture, a pivotal feature in aromatic C–H amination reactions of *N*-aryl-2-aminopyridines,[13] had no beneficial effect on the efficiency of the process (entry 11).[20]

The generality of this process was explored using simple substituted *N*-allyl-2-aminopyridines and the optimal reaction conditions involving 20 mol% of $[Cu(hfacac)_2{\cdot}x\,H_2O]$ in DMF under dioxygen at 105 °C. These processes generated the corresponding imidazo[1,2-*a*]pyridine-3-carbaldehydes **2b–2f** (Scheme 3) in moderate to good yields. Interestingly, reaction of *N*-allyl-1-isoquinoline produced imidazo-[2,1-*a*]isoquinoline-3-carbaldehyde **2g** in 84% yield. *N*-(1-phenylallyl)-2-aminopyridines substituted with electron-donating (Me, OMe) and -withdrawing (F, Cl, Br, COOMe, CN) groups also underwent this oxidative cyclization to form the respective products **2h–2p** and **2r–2s** (Scheme 3) in acceptable to good yields (42–77%). Notably, the introduction of functional groups, such as Br, COOMe, and CN, adds flexibility to further elaborate the aldehyde products that are formed. Moreover, incorporation of the sterically bulky naphthyl substituent does not hamper the efficiency of the process (**2q**; Scheme 3). Furthermore, heteroaromatic-substituted *N*-allyl-2-aminopyridines also underwent this transformation, albeit in lower yields (**2t–2u**; Scheme 3). The nature of the substituents on the allylic position of the substrates can include alkyl groups, as exemplified by the formation of the isopropyl- and cyclohexyl-substituted imidazo[1,2-*a*]pyridine-3-carbaldehydes **2v–2w** (Scheme 3).



Scheme 3. Synthesis of substituted imidazo[1,2-*a*]pyridine-3-carbaldehydes. [a] Reaction conditions: **1** (0.50 mmol), $[Cu(hfacac)_2{\cdot}x\,H_2O]$ (20 mol%), DMF (1.5 mL), under O_2 (balloon pressure), 105 °C, yield of isolated **2**. [b] 120 °C.

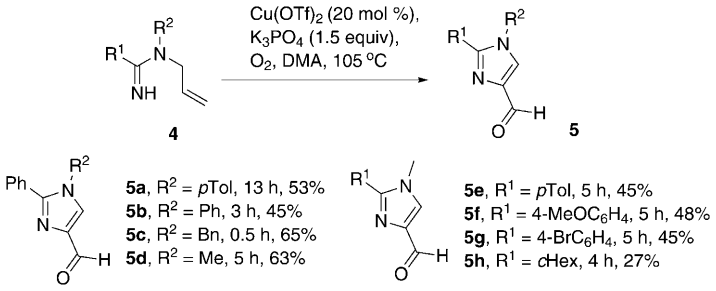
Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst (equiv)	Solvent	Atmos.	*t* [h]	Yield [%][b]
1	$Pd(OAc)_2$ (0.1)	DMF	air	16	0
2	$Cu(OAc)_2$ (0.2)	DMF	air	16	13
3	$Cu(OAc)_2$ (0.2)	DMF	O_2	16	18
4	$Cu(OTf)_2$ (0.2)	DMF	O_2	13	60
5	$[Cu(acac)_2]$ (0.2)	DMF	O_2	12	61
6	$[Cu(ClO_4)_2{\cdot}6H_2O]$ (0.2)	DMF	O_2	20	55
7	**$[Cu(hfacac)_2{\cdot}x\,H_2O]$ (0.2)**	**DMF**	**O_2**	**6.5**	**69**
8	$[Cu(hfacac)_2{\cdot}x\,H_2O]$ (0.2)	DMA	O_2	13	67
9	$[Cu(hfacac)_2{\cdot}x\,H_2O]$ (0.2)	NMP	O_2	13	67
10	$[Cu(hfacac)_2{\cdot}x\,H_2O]$ (0.2)	DMSO	O_2	20	59
11[c]	$[Cu(hfacac)_2{\cdot}x\,H_2O]$ (0.2)	DMF	O_2	9	64

[a] Reaction conditions: **1a** (0.50 mmol), catalyst, solvent (1.5 mL), under air or O_2 (balloon pressure), 105 °C. [b] Yield of isolated **2a**. [c] 10 mol% of $[Fe(NO_3)_3{\cdot}9\,H_2O]$ was added. acac = acetylacetonate, DMA = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, hfacac = hexafluoroacetylacetonate, NMP = 1-methyl-2-pyrrolidinone, Tf = trifluoromethansulfonyl.

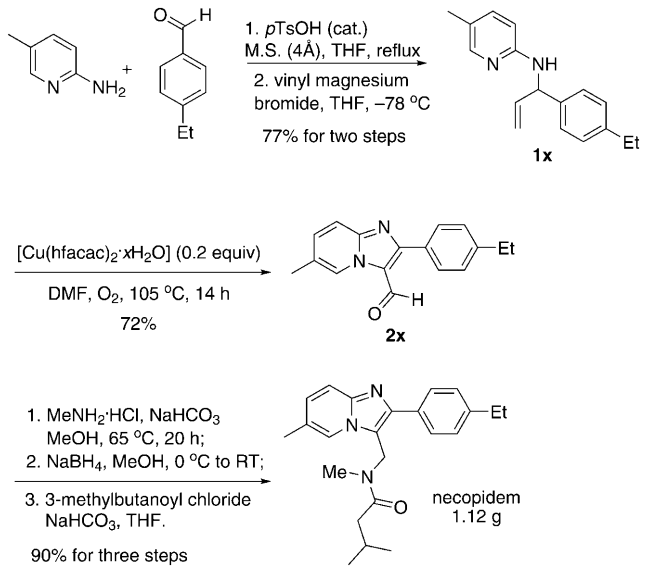
This novel process was also successfully applied to the synthesis of 1,2-disubstituted imidazole-4-carbaldehydes, as summarized in Scheme 4. In this case, modification of the reaction conditions, including an appropriate base (K_3PO_4, 1.5 equiv) together with changing the copper catalyst and solvent, was necessary.[21] The substituted *N*-allylamidines **4** starting materials were prepared readily.[19] 1,2-Diaryl-imidazole-4-carbaldehydes **5a–b** were obtained in moderate yields favoring an electron-donating group on the *N*-aryl ring. *N*-Benzyl- and *N*-methyl-*N*-allylphenylamidines **4c–d** were converted into the corresponding 1,2,4-trisubstituted imidazole aldehydes **5c–d** in high yields (63–65%). Phenylamidines substituted with electron-donating (Me, MeO) and -withdrawing (Br) groups were compatible with the reaction conditions, albeit in low yields (**5e–g** vs. **5d**). In addition, formation of the 2-alkyl-substituted variant **5h** was also achieved in diminished yield. Considering the fact that multistep procedures are usually necessary for the synthesis



Scheme 4. Synthesis of 1,2-disubstituted imidazo-4-carbaldehydes. Reaction conditions: **4** (0.50 mmol), $Cu(OTf)_2$ (20 mol%), K_3PO_4 (1.5 equiv), DMA (1.5 mL), under O_2 (balloon pressure), 105 °C, yield of isolated **5**. Bn = benzyl.

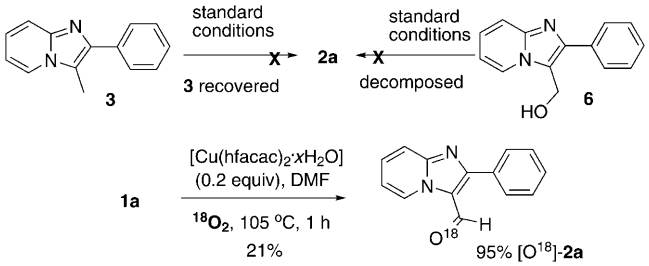
of 1,2-disubstituted imidazole-4-carbaldehydes,[22] these moderate yields are still acceptable. The current method paves the way to a fast assembly of diversified 1,2,4-trisubstituted imidazoles.

The synthetic utility of the process described in this study was demonstrated by its use in a concise route for the preparation of necopidem, an anxyolytic drug (Scheme 5).[12,23] The key intermediate in this pathway, *N*-(1-(*p*-ethylphenyl)allyl)-2-amino-5-methylpyrine **1x**, was generated by using a two-step sequence, starting with 5-methyl-2-aminopyridine and *p*-ethylbenzaldehyde, in 77% yield. The IDA reaction of **1x** provided the key aldehyde intermediate **2x**, which was subjected to reductive amination with methylamine. N acylation of the resulting secondary amine with 3-methylbutanoyl chloride provided necopidem in about 50% overall yield in four one-pot operations (the last three steps are actually two operations), compared with the reported 21% overall yield in five steps.[24]



Scheme 5. Synthesis of necopidem. M.S. = moleacular sieves.

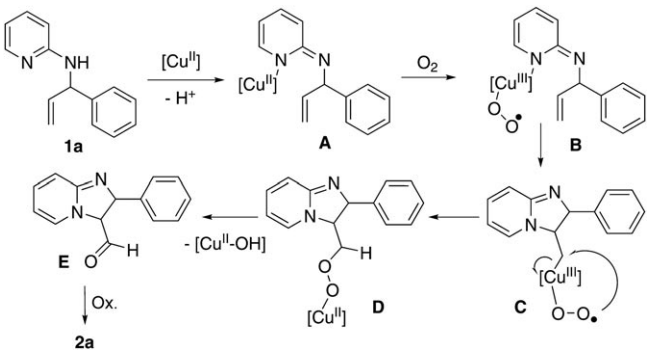
Studies were undertaken to probe a possible mechanism for the IDA reaction (Scheme 6). Upon exposure of **3** and **6**, possible intermediates in this pathway, to the reaction conditions, no detectable quantities of **2a** were formed. Moreover, when **1a** was subjected to the reaction conditions employing an argon rather than oxygen atmosphere, formation of **2a** did not take place even when 2.0 equivalents of the copper catalyst were present. In addition, an experiment was performed under $^{18}O_2$ atmosphere in anhydrous DMF. About 95% of the product had O^{18} incorporated, thus indicating that the carbonyl oxygen in the aldehyde product derives from dioxygen rather than adventitious water in DMF. When the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) was included, no carbon–TEMPO adduct was detected.[25]



Scheme 6. Mechanistic studies.

The findings described above suggest that the IDA reaction mechanism displayed in Scheme 7 is plausible.[10,26] The process is initiated by coordination of **1a** with the copper(II) catalyst to form complex **A**. Single-electron transfer then occurs from Cu to O_2 to generate the peroxy–copper(III) intermediate **B**, which undergoes insertion into the carbon–carbon double bond to form a alkyl copper(III) species. Isomerization of the resulting exocyclic peroxy–copper(III) intermediate **C** yields the copper(II) species **D** with concurrent formation of a carbon–oxygen bond. Elimination of Cu^{II}-OH releases aldehyde **E**, which undergoes spontaneous aromatization to produce **2a**.

In summary, our studies have led to the development of an unprecedented IDA process that produces imidazo[1,2-*a*]pyridine-3-carbaldehydes and 1,2-disubstituted imidazole-4-carbaldehydes from readily available *N*-allyl-2-aminopyridines and substituted *N*-allylamidines, respectively. The reaction, carried out by using 20 mol% of Cu^{II} catalyst in DMF or DMA under dioxygen, is efficient and environmentally benign because it does not require additional organic or



Scheme 7. Plausible mechanism.

inorganic oxidants. Substituted imidazo[1,2-*a*]pyridine-3-carbaldehydes and imidazole-4-carbaldehydes, which can serve as versatile synthetic intermediates, are obtained in moderate to good yields by a reaction that possesses a broad substrate scope and good functionality tolerance. The process opens a new path towards direct formation of aromatic N-heterocycles substituted with a formyl group from acyclic substrates. Mechanistic studies directly show that the carbonyl oxygen in the aldehyde products is derived from dioxygen by a pathway that takes place via a peroxy–copper(III) intermediate.

Experimental Section

General procedure for the synthesis of **2**: A mixture of substrate **1** (0.5 mmol), $[Cu(hfacac)_2 \cdot x H_2O]$ (47.8 mg, 0.1 mmol, 20 mol%) in DMF (1.5 mL) was stirred at 105 °C under O_2 (balloon pressure). The reaction was cooled to room temperature after complete consumption of the starting material (as evident by TLC). Saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added to the reaction mixture successively. The organic phase was separated, and the aqueous phase was further extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate 3:1) to provide the desired product **2**.

General procedure for the synthesis of **5**: A mixture of substrate **4** (0.5 mmol), $Cu(OTf)_2$ (36.2 mg, 0.1 mmol, 20 mol%), K_3PO_4 (0.75 mmol, 1.5 equiv) in DMA (1.5 mL) was stirred at 105 °C under O_2 (balloon pressure). The reaction was cooled to room temperature after complete consumption of the starting material (as evident by TLC). Similar workup and purification procedures as those mentioned above were applied to provide the desired product **5**.

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