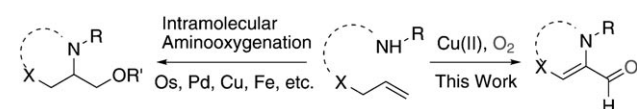


Copper-Catalyzed Intramolecular Dehydrogenative Aminooxygenation: Direct Access to Formyl-Substituted Aromatic N-Heterocycles**

Honggen Wang, Yong Wang, Dongdong Liang, Lanying Liu, Jiancun Zhang,* and Qiang Zhu*

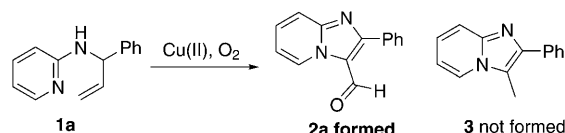
Aminooxygenation of alkenes,^[1–3] a process in which nitrogen and oxygen atoms are added simultaneously across a carbon–carbon double bond, represents one of the most straightforward approaches to prepare vicinal amino alcohol derivatives, which are an important functional motif in many biologically 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 dioxigen. 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.

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-aminopyridine **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 pre-



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

diction, 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.

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

[*] H. Wang, Y. Wang, D. Liang, L. Liu, Prof. Dr. J. Zhang, Prof. Dr. Q. Zhu
State Key Laboratory of Respiratory Disease
Guangzhou Institutes of Biomedicine and Health
Chinese Academy of Sciences
190 Kaiyuan Avenue, Guangzhou 510530 (China)
Fax: (+86) 20-3201-5299
E-mail: zhu_qiang@gibh.ac.cn

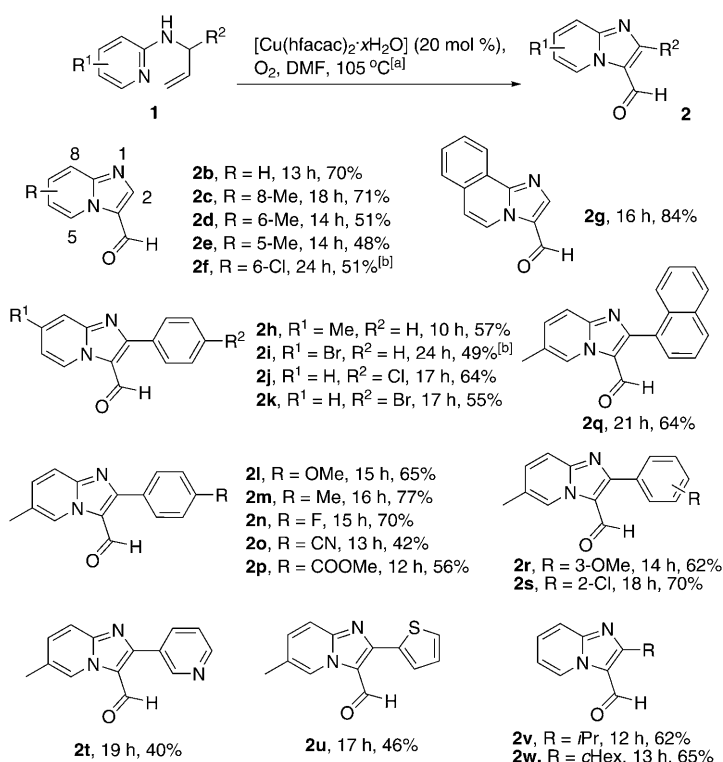
[**] We are grateful for financial support of this work by a Start-up Grant from Guangzhou Institutes of Biomedicine and Health (GIBH), and by the National Science Foundation of China (21072190) and the National Basic Research Program of China (973 Program 2011CB504004 and 2010CB945500). We thank Prof. Jinsong Liu (GIBH) for providing X-ray structural analysis.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201100362>.

unprecedented IDA reaction starting from simple acyclic precursors.

Conditions for the new copper-catalyzed cyclization reaction were explored using *N*-(1-phenylallyl)-2-aminopyridine **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·xH₂O] 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(NO₃)₃·9H₂O 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·xH₂O] 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,



Scheme 3. Synthesis of substituted imidazo[1,2-*a*]pyridine-3-carbaldehydes.

[a] Reaction conditions: **1** (0.50 mmol), [Cu(hfacac)₂·xH₂O] (20 mol %), DMF (1.5 mL), under O₂ (balloon pressure), 105 °C, yield of isolated **2**. [b] 120 °C.

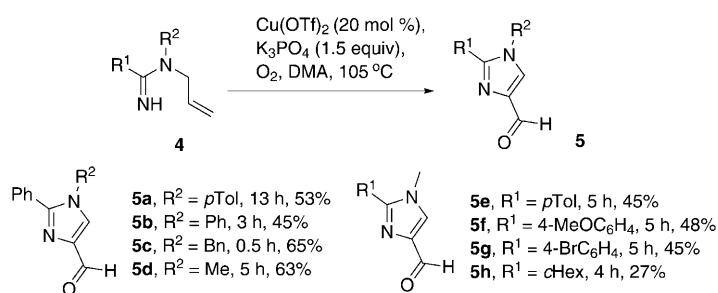
Table 1: Optimization of the reaction conditions.^[a]

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 ·6H ₂ O] (0.2)	DMF	O ₂	20	55
7	[Cu(hfacac) ₂ ·xH ₂ O] (0.2)	DMF	O ₂	6.5	69
8	[Cu(hfacac) ₂ ·xH ₂ O] (0.2)	DMA	O ₂	13	67
9	[Cu(hfacac) ₂ ·xH ₂ O] (0.2)	NMP	O ₂	13	67
10	[Cu(hfacac) ₂ ·xH ₂ O] (0.2)	DMSO	O ₂	20	59
11 ^[c]	[Cu(hfacac) ₂ ·xH ₂ O] (0.2)	DMF	O ₂	9	64

[a] Reaction conditions: **1a** (0.50 mmol), catalyst, solvent (1.5 mL), under air or O₂ (balloon pressure), 105 °C. [b] Yield of isolated **2a**. [c] 10 mol % of [Fe(NO₃)₃·9H₂O] was added. acac = acetylacetonate, DMA = *N,N*-dimethylacetamide, DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide, hfacac = hexafluoroacetylacetonate, NMP = *N*-methyl-2-pyrrolidinone, Tf = trifluoromethanesulfonyl.

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).

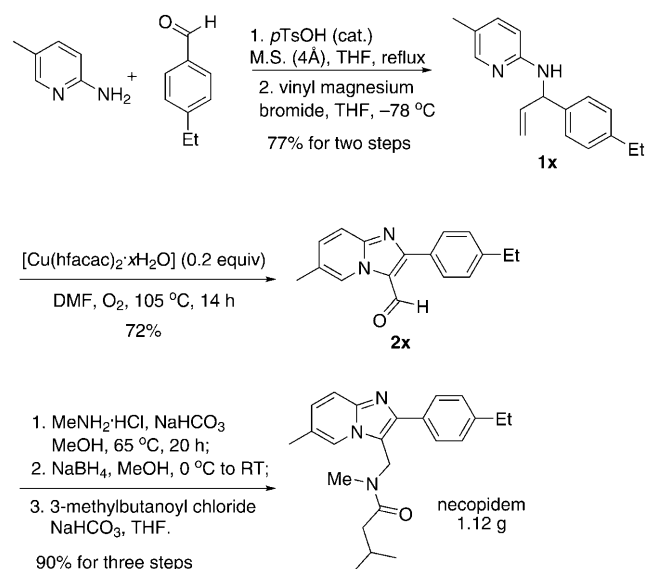
This novel process was also successfully applied to the synthesis of 1,2-disubstituted imidazole-4-carbaldehydes, as summarized in Scheme 4. In this case, modification of the reaction conditions, including an appropriate base (K₃PO₄, 1.5 equiv) together with changing the copper catalyst and solvent, 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 %), K₃PO₄ (1.5 equiv), DMA (1.5 mL), under O₂ (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 anxiolytic drug (Scheme 5).^[12,23] The key intermediate in this pathway, *N*-(1-

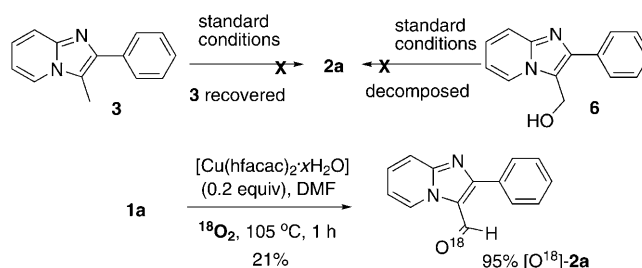


Scheme 5. Synthesis of necopidem. M.S. = molecular sieves.

(*p*-ethylphenyl)allyl)-2-amino-5-methylpyridine **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]

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.

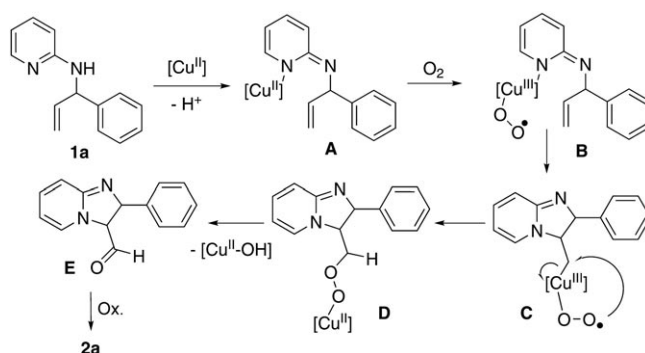
Moreover, when **1a** was subjected to the reaction conditions employing an argon rather than oxygen atmosphere, formation of **2a** did not take place even when 2.0 equivalents of the copper catalyst were present. In addition, an experiment was performed under ¹⁸O₂ atmosphere in anhydrous DMF. About 95% of the product had O¹⁸ 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 O₂ to generate the peroxy-copper(III) intermediate **B**, which undergoes insertion into the carbon-carbon double bond to form an 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·xH₂O] (47.8 mg, 0.1 mmol, 20 mol %) in DMF (1.5 mL) was stirred at 105 °C under O₂ (balloon pressure). The reaction was cooled to room temperature after complete consumption of the starting material (as evident by TLC). Saturated aqueous NaHCO₃ (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 Na₂SO₄ 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 %), K₃PO₄ (0.75 mmol, 1.5 equiv) in DMA (1.5 mL) was stirred at 105 °C under O₂ (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**.

Received: January 15, 2011

Revised: March 23, 2011

Published online: May 4, 2011

Keywords: aldehydes · aminooxygenation · dehydrogenation · N-heterocycles · synthetic methods

- [1] For reviews of aminohydroxylation, see a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) D. Nilov, O. Reiser, *Adv. Synth. Catal.* **2002**, *344*, 1169; c) J. A. Bodkin, M. D. McLeod, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2733; d) K. Muniz, *Chem. Soc. Rev.* **2004**, *33*, 166.
- [2] For recent examples of aminoacetoxylation and aminobenzoxylation, see D. E. Mancheno, A. R. Thornton, A. H. Stoll, A. Kong, S. B. Blakey, *Org. Lett.* **2010**, *12*, 4110.
- [3] For recent examples of aminoalkoxylation, see a) D. V. Liskin, P. A. Sibbald, C. F. Rosewall, F. E. Michael, *J. Org. Chem.* **2010**, *75*, 6294; b) P. Szolcsanyi, T. Gracza, *Chem. Commun.* **2005**, 3948; c) P. H. Fuller, J.-W. Kim, S. R. Chemler, *J. Am. Chem. Soc.* **2008**, *130*, 17638.
- [4] a) L. Albrecht, H. Jiang, G. Dickmeiss, B. Gschwend, S. G. Hansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 9188; b) C. Stephen, *Tetrahedron* **2000**, *56*, 2561.
- [5] The formation of oxygen-containing heterocycles through intramolecular aminooxygenation is less common. For recent examples, see a) L. V. Desai, M. S. Sanford, *Angew. Chem.* **2007**, *119*, 5839; *Angew. Chem. Int. Ed.* **2007**, *46*, 5737; b) J. M. Mahoney, C. R. Smith, J. N. Johnston, *J. Am. Chem. Soc.* **2005**, *127*, 1354.
- [6] a) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690; b) P. Szolcsanyi, T. Gracza, *Chem. Commun.* **2005**, 3948.
- [7] M. C. Paderes, S. R. Chemler, *Org. Lett.* **2009**, *11*, 1915.
- [8] K. S. Williamson, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 4570.
- [9] a) T. J. Donohoe, G. H. Churchill, K. M. P. Wheelhouse, P. A. Glossop, *Angew. Chem.* **2006**, *118*, 8193; *Angew. Chem. Int. Ed.* **2006**, *45*, 8025; b) T. J. Donohoe, M. J. Chughtai, D. J. Klauber, D. Griffin, A. D. Campbell, *J. Am. Chem. Soc.* **2006**, *128*, 2514; c) T. J. Donohoe, C. J. R. Bataille, W. Gattrell, J. Kloesges, E. Rossignol, *Org. Lett.* **2007**, *9*, 1725; d) T. J. Donohoe, C. K. A. Callens, A. L. Thompson, *Org. Lett.* **2009**, *11*, 2305.
- [10] Chiba reported a similar example of dehydrogenative intramolecular aminooxygenation as a side reaction of the copper-catalyzed synthesis of azaspirocyclohexadienones, see: S. Chiba, L. Zhang, J.-Y. Lee, *J. Am. Chem. Soc.* **2010**, *132*, 7266.
- [11] A. R. Katritzky, Y.-J. Xu, H. Tu, *J. Org. Chem.* **2003**, *68*, 4935, and references therein.
- [12] N. Chernyak, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 2803; *Angew. Chem. Int. Ed.* **2010**, *49*, 2743.
- [13] H. Wang, Y. Wang, C. Peng, J. Zhang, Q. Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217.
- [14] For a multistep synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes, see: a) L. Almirante, A. Mugnaini, N. D. Toma, A. Gamba, W. Murmann, J. Hidalgo, *J. Med. Chem.* **1970**, *13*, 1048; b) C. E. McKenna, et al., *J. Med. Chem.* **2010**, *53*, 3454, see the Supporting Information for the full citation.
- [15] a) A. R. Katritzky, A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, 2nd ed., Pergamon, Amsterdam, **2000**; b) L. De Luca, *Curr. Med. Chem.* **2006**, *13*, 1.
- [16] For recent examples of imidazole synthesis, see: a) L. Liu, M. Frohn, N. Xi, C. Dominguez, R. Hungate, P. J. Reider, *J. Org. Chem.* **2005**, *70*, 10135; b) A. V. Gulevich, E. S. Balenkova, V. G. Nenajdenko, *J. Org. Chem.* **2007**, *72*, 7878; c) R. B. Sparks, A. P. Combs, *Org. Lett.* **2004**, *6*, 2473; d) S. Zaman, K. Mitsuru, A. D. Abell, *Org. Lett.* **2005**, *7*, 609.
- [17] a) J. Kerhervé, C. Botuha, J. Dubois, *Org. Biomol. Chem.* **2009**, *7*, 2214; b) B. L. Eriksen, P. Vedsø, M. Begtrup, *J. Org. Chem.* **2001**, *66*, 8344; c) C. Madsen, A. A. Jensen, T. Liljefors, U. Kristiansen, B. Nielsen, C. P. Hansen, M. Larsen, B. Ebert, B. Bang-Andersen, P. Krogsgaard-Larsen, B. Frølund, *J. Med. Chem.* **2007**, *50*, 4147; d) B. H. Lipshutz, B. Huff, W. Hagen, *Tetrahedron Lett.* **1988**, *29*, 3411.
- [18] M. Webel, A. M. Palmer, C. Scheufler, D. Haag, B. Müller, *Org. Process Res. Dev.* **2008**, *12*, 1170.
- [19] For preparation of substrates **1** and **4**, see the Supporting Information.
- [20] Recent examples on functionalization of terminal alkynes and alkenes under Cu^{II}/O₂: a) C. Zhang, N. Jiao, *J. Am. Chem. Soc.* **2010**, *132*, 28; b) L. Huang, H. Jiang, C. Qi, X. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 17652.
- [21] For details in optimizing the reaction conditions, see the Supporting Information.
- [22] a) W. C. Pringle, J. M. Peterson, L. Xie, P. Ge, Y. Gao, J. W. Ochterski, J. Lan, WO2006/089076, **2006**; b) E. Dubost, D. Le Nouen, J. Streith, C. Tarnus, T. Tschamber, *Eur. J. Org. Chem.* **2006**, 610; c) E. Dubost, T. Tschamber, J. Streith, *Tetrahedron Lett.* **2003**, *44*, 3667.
- [23] J. P. Sauvanet, S. Z. Langer, *Imidazopyridines in Sleep Disorders: A Novel Experimental and Therapeutic Approach*, L. E. R. S. Monograph Series, Vol. 6 (Ed.: P. L. Morselli) Raven Press, New York, **1988**.
- [24] H. Depoortere, P. George, US 5064836, **1991**.
- [25] A mechanism involving initial formation of aminyl radical is unlikely, see: O. B. H. Ila, H. Junjappa, *J. Org. Chem.* **2000**, *65*, 1583.
- [26] a) C. J. Cramer, W. B. Tolman, *Acc. Chem. Res.* **2007**, *40*, 601; b) P. J. Donoghue, A. K. Gupta, D. W. Boyce, C. J. Cramer, W. B. Tolman, *J. Am. Chem. Soc.* **2010**, *132*, 15869, and references therein.