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Copper-Catalyzed Aerobic Oxygenation of Benzylpyridine *N*-oxides and Subsequent Post-Functionalization

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Abstract. A copper-catalyzed aerobic oxidation of benzylpyridine *N*-oxides is reported. The *N*-oxide moiety acts as a built-in activator for the benzylic methylene oxidation, without requirement of additives. Reaction conditions were identified which suppress undesired benzoylpyridine formation *via N*-deoxygenation involving intermolecular oxygen transfer. The versatility of the *N*-oxide group of the benzylpyridine *N*-oxide reaction products for post-functionalization of the pyridine ring is demonstrated through efficient C-C, C-N, C-O and C-Cl

bond forming procedures, with both nucleophiles and electrophiles. Finally, the applicability of the new synthetic methodology is demonstrated in an alternative route towards the anti-histaminic drug Acrivastine *via* three consecutive *N*-oxide activated C-H functionalization processes, starting from picoline *N*-oxide.

Keywords: C-H functionalization; pyridine-*N*-oxide; aerobic oxidation; molecular oxygen; copper catalysis

Introduction

Oxidase and oxygenase types of reactions are now acquiring increasing importance from both an academic and industrial perspective. These aerobic oxidation processes do not require the use of (over)stoichiometric reagents, which result in large amounts of often toxic waste, and generally produce only water as by-product.^{[1],[2]} Although safety issues concerning the use of oxygen as oxidant have hampered its use at an industrial level for fine chemicals synthesis, the development of efficient flow processes have now provided a safe solution to work with oxygen as reactant or reagent.^[3]

In 2012 our group reported the aerobic copper and iron catalyzed methylene oxidation of substituted benzylpyridines and analogues.^{[4],[5]} The aroylpyridine products and their derivatives are important intermediates in the synthesis of pharmaceuticals,^[6] and the method has found application in metabolite studies.^[7] The methylene C(sp³)-H bond cleavage in this process is promoted by stoichiometric acid *via N*-protonation of the substrate.^[8] In 2015 Zhuo and Lei published an alternative Cu-catalyzed aerobic oxidation protocol, which employed ethyl chloroacetate as a stoichiometric activator through *in situ* pyridine *N*-alkylation.^[9] While this work was in progress, Stahl reported a procedure using phthalimido *N*-oxyl radical (PINO) as co-catalyst (20 mol%) to cleave the C(sp³)-H bond, generated *in situ* from *N*-

hydroxyphthalimide (NHPI) by a cobalt catalyst and O₂.^[10] From a synthetic point of view, the main limitation of these important oxidation procedures is that the acyl-substituted pyridines obtained upon methylene oxidation are deactivated toward further functionalization of the pyridine moiety (Scheme 1). While the electron-withdrawing acyl substituent and azine nitrogen both inhibit electrophilic aromatic substitutions, nucleophilic substitutions do not occur unless a leaving group, *e.g.* halogen, is present in the substrate. Pre-installing the substituent in the substrate upfront is not a solution, as it does not provide a protocol applicable in library synthesis, typically involving late stage functionalization. Moreover, we previously have shown the oxidation protocol of benzylpyridines to be very sensitive towards the pyridine substitution pattern requiring reoptimization.^[4b] These aspects prompted us to develop a new versatile strategy by considering pyridine *N*-oxides as alternative substrates for the oxidation. The *N*-oxide functionality would have a double function in the process: 1) act as an unprecedented built-in activator for the methylene oxidation without requiring any additive,^[11] and 2) allow further decoration of the pyridine ring *via* post-functionalization. Due to its unique electronic properties, the *N*-oxide can activate the alpha position of the pyridine ring for reactions with both nucleophiles and electrophiles^[6a, 12] (Scheme 1). While in reaction with nucleophiles the *N*-oxide moiety is typically removed, reactions with electrophiles usually leave this moiety intact, which

can be easily removed at a later stage.^[6a] Cheap and commercially available picoline *N*-oxides or (chloro)pyridines *N*-oxides, obtained from the corresponding pyridine derivatives by oxidation with sustainable H₂O₂ oxidant,^[6a, 13] can be used to synthesize the required substituted benzylpyridine *N*-oxides *via* directed Pd catalyzed C-H bond functionalization^[11a, b, 14] or cross-coupling reactions^[6b, 15] (Scheme 1). Herein we report the aerobic Cu-catalyzed oxygenation of substituted benzylpyridine *N*-oxides and subsequent post-functionalization on the pyridine ring with both nucleophiles and electrophiles.

Scheme 1. Classical *versus* new approach towards benzoylpyridines allowing to perform smooth pyridine post-functionalization.

Results and Discussion

Optimization and substrate scope. The benzylic oxidation of the unsubstituted model substrate 2-benzylpyridine *N*-oxide **1a** proceeded with CuI (10 mol%) as catalyst in DMSO at 100°C using a balloon of O₂. However, while little oxidation of 2-benzylpyridine (**2a**) occurred without AcOH,^[4] **1a** was smoothly oxidized in the absence of the acid additive. In fact, addition of either acids or bases proved to have an inhibiting effect on the oxidation of **1a** (Figure 1a). Screening of a number of Cu salts revealed that CuI is by far the best in terms of reaction rate (Figure 1b), whereas the use of Fe salts generally resulted in lower yields and mass-balance. The oxidation performed well in both DMSO and BuOAc, although the use of DMSO results in more homogeneous reaction mixtures and no metal deposition was observed. This solvent was therefore chosen for further experiments. A temperature of 120°C was selected to allow the use of a lower catalyst loading (5%).

Figure 1. Effect of different Cu sources and additives on the conversion of **1a** versus time (FT-IR). Reaction conditions: **1a** (5 mmol), catalyst (10 mol%), DMSO (10 mL), O₂ (balloon), 100°C; a) 1 eq. of CsOAc or AcOH added; b) anhydrous CuCl₂ was used.^[2i]

With the optimized conditions in hand (5% CuI, DMSO [1.0M], O₂ balloon, 120°C, 24h), we then set out to explore the scope of this methodology. 2-Benzylpyridine *N*-oxide (**1a**) gave in these conditions 64% yield of the corresponding benzoyl product **3a** (Scheme 2, Method 1; *vide infra* for discussion on Method 2). The 4-benzyl regioisomer **6a** could be obtained in 71% yield, although a longer reaction time was required (48h); 3-benzylpyridine *N*-oxide **8a** proved instead not reactive in these conditions. Both phenyl and pyridine substituted 2-benzylpyridine *N*-oxides **1** were then subjected to these conditions to get an idea on the sensitivity of the oxidation reaction *versus* azine substitution pattern. The benzylic oxidation occurred smoothly in most cases, however, the formation of the corresponding aroylpyridines **4** was also observed to a considerable extent. While *N*-deoxygenated side-product **4a** was only observed in trace amounts (≤ 5%) for the unsubstituted substrate **1a**, the ratio of **3/4** for pyridine- and phenyl- substituted substrates proved strongly substituent-dependent, and fell in the range of 2/1 to 1/1 (see ESI for details).

Scheme 2. Comparison of the aerobic Cu-catalyzed and aerobic Co/NHPI-catalyzed^[10] oxygenation of regioisomeric benzylpyridine *N*-oxides; reactions on 1 mmol scale; a) 48h.

In order to increase the selectivity by reducing the formation of the undesired deoxygenation product **4**, we performed further optimization studies on both a phenyl and pyridine substituted model substrate, to identify the reaction parameters suppressing its formation. Selected optimization data for 2-(4-chlorobenzyl)pyridine *N*-oxide (**1b**) are reported in Table 1. While in our initial conditions a **3b/4b** ratio of ~2/1 was obtained (entry 1, overall yield 79%), decreasing the temperature to 100°C improved the selectivity to ~4/1, although with considerably reduced conversion (entry 2). Reduction of the substrate concentration from 1.0M to 0.5M, improved the yield and increased the **3b/4b** ratio (~5/1). To keep the concentration of copper constant, 10% CuI was used in this experiment (entry 3). Reaction in BuOAc gave a reduced mass balance and slightly lower yield of target compound **3b** (entry 4). On 2-benzyl-5-cyanopyridine *N*-oxide **1g** the same reaction conditions as for **1b** proved optimal (Table 2, entry 3).

Table 1. Selected optimization results for substrate **1b**^a

Entry	Solvent [1b]	T (°C)	% CuI	% Yield (3b/4b/1b)
1	DMSO [1.0M]	120	5	54/25/0
2	DMSO [1.0M]	100	5	41/13/22
3	DMSO [0.5M]	120	10	75/16/0
4	BuOAc [0.5M]	120	10	67/11/0

a) Yields of isolated products are reported

Table 2. Selected optimization results for substrate **1g**^a

Entry	Solvent [1g]	T (°C)	% CuI	% Yield (3g/4g/1g)
1	DMSO [1.0M]	120	5	28/33/0
2	DMSO [1.0M]	100	5	61/<23/0
3	DMSO [0.5M]	120	10	74/16/0
4	BuOAc [0.5M]	120	10	51/12/0 ^b

a) Yields of isolated products are reported. b) 18% of the corresponding benzylic alcohol, 5-cyano-2-[hydroxy(phenyl)methyl]pyridine *N*-oxide, was obtained

Based on these results, 0.5M concentration, 10 mol% CuI, and 120°C were selected as new reaction conditions to suppress, to some extent, *N*-deoxygenation. Both DMSO and BuOAc were employed to evaluate the 2-benzylpyridine *N*-oxide scope (Scheme 3). A range of electron-withdrawing and electron-donating substituents on either the pyridine or the phenyl ring were well tolerated in the reaction, and much better selectivity than with the original conditions was observed (Scheme 3 and ESI). The amount of deoxygenated products **4** was reduced to 7-16% for the solvent giving the highest yield, except for 4-chloropyridine substrate **1k** (21% of **4k** in BuOAc). The desired *N*-oxides **3** were generally isolated in moderate to good yields (56-81%), apart from **3d** (39%), for which a low mass balance was noted (see ESI, Figure S1). 6-(4-Methylbenzyl)-2-methylpyridine *N*-oxide (**1m**) was tested to investigate the chemoselectivity of the oxidation process as it features three potential reaction sites (benzyl, benzhydryl and picolinyl). Only benzhydryl oxidation was observed in our conditions;^[16] **3m** was formed in a 48% yield. It is worth noting that the CuI catalyzed oxidation of 6-(4-methylbenzyl)-2-methylpyridine using AcOH as an activator resulted in additional oxidation of the 2-methyl group at the same reaction temperature in the same solvent.^[4a] Ketone **3n**, from 2-benzylquinoline *N*-oxide, was obtained in DMSO in 64% yield, together with 28% of the corresponding deoxygenation product **4n**. Similar results were obtained in BuOAc. Benzo annulated systems seem to be more sensitive towards deoxygenation.

Scheme 3. Scope of substituted 2-benzylpyridine *N*-oxides **1**. Yield of deoxygenated products **4** in round brackets and remaining **1** in square brackets. Reaction conditions: **1** (0.5 mmol), CuI (10 mol%), DMSO or BuOAc (1 mL), O₂ (balloon), 120°C, 24h.

A range of 4-benzylpyridine *N*-oxides **5** was subsequently tested under the optimized conditions (Scheme 4). Oxidation of the unsubstituted **5a** was slower than its regioisomer **1a**, but afforded **6a** in good yield in DMSO over 48h (Scheme 2). Electron-withdrawing substituents on the phenyl and the pyridine rings promoted the reaction, furnishing moderate to good yields (59–88%) of **6b–d**, **6f** in 24h. On the other hand, electron-donating substituents considerably inhibited the process, and products **6e** and **6g** were obtained with max. 52% and 24% yield respectively, with (a large amount of) unreacted substrate remaining. Increasing the reaction time to 48h was fruitless in these cases, as only lower mass balance or larger amounts of degradation products were observed. Finally, 4-benzoylquinoline *N*-oxide **6h** was obtained in 41–47% yield, with about 20% of the deoxygenated side product. As observed for the 2-regioisomer benzo annulated systems are more deoxygenation sensitive.

The generally lower reactivity of 4-benzylpyridine *N*-oxides **5** compared to the corresponding 2-benzyl *N*-oxide isomers **1** is in contrast with what observed with analogous benzylpyridines in our previous work

(see Figure 2), suggesting a considerable difference in the reaction mechanism for the two substrate types.

Scheme 4. Scope of substituted 4-benzylpyridine *N*-oxides **5**. Yield of deoxygenated products **7** in round brackets and remaining **5** in square brackets. Reaction conditions: **5** (0.5 mmol), CuI (10 mol%), DMSO or BuOAc (1 mL), O₂ (balloon), 120°C, 24h.

The recently published protocol by Stahl and co-workers was subsequently tested on the 3 regioisomeric benzylpyridine-*N*-oxides (**1a**, **5a**, **8a**) for comparison (Scheme 2, Method 2).^[10] Using substrate **1a** 35% of the 2-benzoyl *N*-oxide product **3a** and also some *N*-deoxygenated side product **4a** (15%) was isolated. Besides, a considerable amount of unreacted starting material (35%) remained. This result did not change when a double amount of Co catalyst was used. Better results were obtained on substrate **5a**, which gave 67% of the desired **6a**, together with 11% of the *N*-deoxygenated side product **7a**, and no remaining substrate over a 24h period. On 3-benzylpyridine *N*-oxide (**8a**) a low conversion and yield but no *N*-deoxygenation was observed (Scheme 2). The same reaction conditions on the corresponding benzylpyridines resulted in full conversion and 93%, 89% and 92% yield of the corresponding benzoylpyridine as reported by Stahl.^[10] While these conditions have not been optimized for *N*-oxide substrates, the difference in performance between the two classes of substrates underpin the challenging nature of the azine *N*-oxides *versus* the corresponding azines for oxygenation, and the suppression of the *N*-deoxygenation as a general challenge.

Pyridine ring functionalization on benzoylpyridine *N*-oxides. As mentioned above, while pyridine ring functionalization of benzoylpyridines is a non-viable synthetic approach, the use of the corresponding *N*-oxide analogues would allow such decoration, both with electrophiles and nucleophiles. Compounds **3** (**3a**, **3e** and **3m**) and **6a** were selected as model systems to demonstrate the utility of the *N*-oxide moiety for post-functionalization. A variety of functionalization reactions could be efficiently performed on 2-benzoylpyridine *N*-oxides (**3**) (Scheme 5). Boekelheide rearrangement on **3a** using trifluoroacetic anhydride resulted in 68% of pyridinone **9**.^[17] Closely related 6-methylated substrate **3m** gave 77% of the picolinyl alcohol **10**.^[18] Amination was possible *via* reaction of **3a** with Ts₂O and *t*-butylamine followed by de-*t*-butylation with TFA (**11**, 67%).^[19] Cyanation and chlorination, using respectively TMSCN/Me₂NCOCI^[20] and POCl₃,^[21] occurred with 79% and 47% yield (**12** and **13**). The formation of **13** is of particular importance, as the aerobic oxidation of 2-benzyl-6-chloropyridine was not successful with our initially reported method.^[4b]

Finally, Pd-catalyzed directed arylation^[11b] with *p*-tolyl bromide resulted in product **14** with 59% yield, while Pd-catalyzed cross-dehydrogenative olefination^{[22],[23]} on substrate **3e** with methyl acrylate provided **15** in 53% yield. Complete regioselectivity at the *alpha* position of the pyridine was achieved in all transformations on **3**.

Next we turned our attention to regioisomer 4-benzoylpyridine *N*-oxide (**6a**) (Scheme 6). This proved to be easily functionalized with a range of O- and N-nucleophiles using PyBroP (bromotripyrrolidinophosphonium hexafluorophosphate) as activating reagent in mild conditions,^[24] giving products **16–22** in 45–97% yield. It is worth noting that this procedure proved completely ineffective for the 2-benzoyl substrate **3a**. Cyanation, chlorination, directed arylation and cross-dehydrogenative olefination on 4-benzoylpyridine *N*-oxide (**6a**) were performed under the same conditions used for the 2-benzoyl regioisomer. Generally higher yields of the final products (**23–26**), in comparison with the 2-benzoyl analogues, were obtained.

Figure 2. Kinetic profiles for the oxidation of a) 2- and 4-benzoylpyridine *N*-oxides, and b) corresponding benzoylpyridines (FT-IR). Reaction conditions: substrate (5 mmol), CuI (10 mol%), DMSO (10 mL), O₂ (balloon), 100°C.

Scheme 5. Functionalization of 2-benzoylpyridine *N*-oxides **3a**, **3e** and **3m**. **Scheme 6.** Functionalization of 4-benzoylpyridine *N*-oxide (**6a**); a) Et₂NH used as base and reactant.

Apart from functionalization of the pyridine ring, the removal of the *N*-oxide moiety can also be easily performed by reaction with PCl₃ as exemplified on **3a** and **6a**, giving the corresponding benzoylpyridines **4a** and **7a** (Scheme 7).^[25] Interestingly, the use of Zn/NH₄Cl^[26] results in the formation of benzylic alcohols **27** and **28**.^[27] Alcohols of type **27** find applications in the synthesis of APIs (active pharmaceutical ingredients) such as Carbinoxamine and Bepotastine (antihistaminic drugs). To our knowledge, the direct reduction of aroylpyridine *N*-oxides to the corresponding benzhydrylic alcohols has not been reported before.^[28]

Scheme 7. Reduction of 2- and 4-benzoylpyridine *N*-oxides **3a** and **6a**. Method A: *N*-oxide (0.5 mmol), PCl₃ (3 eq.), CHCl₃ (1.5 mL), 80°C, 1h. Method B:

N-oxide (1 mmol), Zn (4.5 eq.), NH₄Cl (15 mL), THF (15 mL), r.t., 1h (50°C, 2h for **27**).

Acrivastine synthesis. A concrete example of the use of the *N*-oxides for oxidation/post-functionalization processes is the formal synthesis of the antihistamine Acrivastine (Scheme 8). The classical routes for the synthesis of Acrivastine start from 2,6-dibromopyridine using Li-Br exchange with BuLi and quenching with 4-cyanotoluene to install the 2-benzoyl moiety. The acrylate moiety is introduced *via* formylation, through Li-Br exchange with BuLi and quenching with DMF, followed by Wadsworth–Emmons reaction with a phosphonate,^[29] alternatively a Pd-catalyzed Heck coupling with ethyl acrylate can be used which does not require ketone protection,^[30] obtaining intermediate **29**. Here, the synthesis of **29** starts from a much cheaper starting material, 2-picoline-*N*-oxide, which was transformed into intermediate **15** *via* three consecutive atom-economic, *N*-oxide activated C-H functionalization processes (Pd-catalyzed directed arylation of the picoline methyl,^[11a, b] Cu-catalyzed benzylic oxidation,^[31] and Pd-catalyzed cross-dehydrogenative olefination of the pyridine C6-H). As expected (Scheme 1), no functionalization occurred using 2-benzoylpyridines in the same reaction conditions. Deoxygenation of **15** with PCl₃ finally leads to **29**. Transformation into Acrivastine by reaction with triphenyl[2-(pyrrolidin-1-yl)ethyl]phosphonium bromide has been reported in the classical routes (Scheme 8).^[29-30]

Scheme 8. Synthesis of the antihistaminic drug Acrivastine based on our new strategy *versus* classical routes.^[29-30]

Formation of benzoylpyridines *via* N-O cleavage.

Intrigued by the unexpected formation of benzoylpyridine side-products (**4** and **7**), beside the desired benzoylpyridine *N*-oxides (**3** and **6**), we performed a series of control experiments on the 2-regioisomers to ascertain the nature of this transformation. The reductive cleavage of the N-O bond in pyridine *N*-oxides is typically achieved by reaction with main-group oxophilic species such as P,^[25] Al^[32] and B^[33] reagents. On the other hand, a variety of transition metal salts have also been used, either alone or in combination with reducing agents,^[34] to promote cleavage. Therefore, we suspected this process to be related to the presence of the copper catalyst in the reaction. We envisaged two main pathways which could lead to the benzoylpyridine side-products **4** under our reaction conditions: *path a*) benzylic oxidation of benzylpyridine *N*-oxide **1**, followed by *N*-deoxygenation of **3**; *path b*) *N*-deoxygenation of **1**, followed by oxidation of the benzylpyridine intermediate **2** (Scheme 9). To discriminate between the two pathways control experiments were undertaken on **3b** and **2b**.

When the reaction product **3b** was submitted to the aerobic reaction conditions no deoxygenation was observed (Scheme 9, eq. 1). Instead, reaction of **2b** under the same conditions furnished 34% of product **4b** (eq. 2), suggesting *path b* as the reaction route. The formation of only traces of **4a** when starting from unsubstituted *N*-oxide **1a** is in accordance with this, as 2-benzylpyridine (**2a**) was previously found to not give oxidation into **4a** in the absence of AcOH.^[4a]

Scheme 9. Possible *N*-deoxygenation pathways (top) and aerobic control experiments (bottom, reactions on 0.5 mmol scale).

Scheme 10. Control experiments under anaerobic conditions to rationalize *N*-deoxygenation; anhydrous CuCl₂ was used.^[2i] Reactions on 0.5 mmol scale.

To get more insight into the deoxygenation pathway, the effect of a Cu(I) and a Cu(II) species on compounds **1b** and **3b** under anaerobic conditions (argon atmosphere) was tested. Product **3b** again proved unreactive in the deoxygenation process with both CuI and CuCl₂ (Scheme 10, eq. 1). On the contrary, compound **1b**, although not reactive in DMSO in the presence of CuI (eq. 2), with CuCl₂ led to a number of compounds (eq. 3). Although benzylpyridine **2b** was not observed, 24% of 2-[1-(4-chlorophenyl)-1-hydroxymethyl]pyridine *N*-oxide (**30**) and 11% of 2-(4-chlorobenzoyl)pyridine (**4b**) were detected. As DMSO can act as an anaerobic oxygen donor,^[35] the products observed after the aerobic reaction can be the results of a mixture of two simultaneous processes. This reaction was therefore repeated in inert solvents; reactions in BuOAc and toluene resulted in the formation of 2-benzylpyridine (**2b**) in 40–46% yield, and comparable amounts of the corresponding ketone **4b** (eq. 3). The formation of considerable amount of ketone **4b** and the absence of doubly-oxygenated compound **3b** made us consider

the possibility of an oxygen transfer from the *N*-oxide to the benzylic carbon.^[12d, 36] An experiment with a mixture of equal amounts of *N*-oxide **1b** and benzylpyridine **2a** resulted in the formation, among others, of 4-benzoylpyridine (**4a**) in 35% yield, proving the intermolecularity of the process (eq. 4). Importantly, this result also rationalizes the positive effect of lowering the concentration in inhibiting the de-oxygenation process (Tables 1 and 2). Further proof was obtained by the reaction between 2-benzylpyridine (**2b**) and pyridine *N*-oxide, yielding 58% of ketone **4b** (eq. 5). Replacement of CuCl₂ by CuI completely suppressed the *N*-oxide transfer (eq. 5). These results suggest that oxidized Cu(II) species (formed *in-situ* during the reaction under oxygen) are responsible for both *N*-deoxygenation of substrates **1** and intermolecular oxygen transfer from the *N*-oxide moiety to the benzylic carbon, leading to the ketone side product **4**.

Conclusion

In summary, we reported the Cu-catalyzed oxidation of benzylpyridine *N*-oxides using molecular oxygen. This reaction occurs without the use of additives, typically required for the corresponding benzylpyridines. 2-Benzylpyridine *N*-oxides **1** proved generally more reactive than their 4-benzyl isomers **5**, although considerable differences are observed depending on the electronic properties of the substrate. In particular, differences are observed in the amount of *N*-deoxygenation side products **4** and **7** formed, occurring by competitive anaerobic intermolecular oxygen transfer between the *N*-oxide moiety and the benzylic methylene (*N*-oxide as oxidant). This anaerobic process could be suppressed by reducing the concentration of the substrate in the reaction.

The *N*-oxide moiety in the substrates has a triple role: 1) it allows smooth synthesis of starting materials **1** from cheap and commercially available pyridine *N*-oxide (or derivatives); 2) it promotes the Cu-catalyzed benzylic oxidation with O₂; and 3) its presence allows smooth post-functionalization of the pyridine ring in reaction products **3** and **6**, which is not feasible on the corresponding deactivated benzoylpyridines **4** and **7**. A variety of such post-functionalization procedures with both nucleophiles and electrophiles (C-C, C-O, C-N and C-Cl bond formation) was demonstrated. Finally, the triple role of the *N*-oxide was demonstrated in a new formal synthesis of Acrivastine, involving three consecutive C-H functionalization processes.

Experimental Section

General considerations

Infrared reaction monitoring experiments were performed on a ReactIR spectrometer using a custom made (DST, Ø 6.35 mm) DiComp AgX probe. All the chemicals used were commercially available. Crude materials were purified by flash chromatography on silica gel if not otherwise specified. NMR spectra were recorded at 400 MHz (^1H), 100 MHz (^{13}C) and 376 MHz (^{19}F) on a Bruker AVANCE II 400 spectrometer in CDCl_3 at ambient temperature if not otherwise specified. For ^{13}C -NMR spectra descriptions, CH_3 , CH_2 and CH signals were attributed using DEPT experiments. Chemical shifts (δ) were reported in parts per million (ppm) from the residual solvent peak with tetramethylsilane (TMS) as internal standard. Coupling constants (J) were expressed in Hz. Melting points were measured on a Büchi Melting Point B-545 apparatus. Positive ion mode accurate mass spectra (electrospray) were acquired using a QTOF II instrument (Waters, Manchester, UK). The MS was calibrated prior to use with a 0.1% H_3PO_4 solution. The spectra were lock mass corrected using the known mass of the nearest H_3PO_4 cluster. LC-MS samples were prepared in MeCN at a concentration of 10^{-5}M , and injected on a Waters AcQuity UPLC system equipped with a HALO C_{18} column (2.1 x 30 mm, 2.7 μm). The samples were eluted with $\text{H}_2\text{O}/\text{MeCN}$ (gradient: 90/10 to 5/95, flow rate: 0.5 mL/min), and analyzed with a Waters micromass ZQ (ESI+ and ESI-) with a Photo Diode Array (PDA) detector. The starting materials needed for this investigation were prepared from the corresponding picoline *N*-oxides, pyridine *N*-oxides or 2-chloro- or 4-chloro-pyridine *N*-oxides *via* respectively $\text{C}(\text{sp}^3)\text{-H}$ bond arylation,^[11a] $\text{C}(\text{sp}^2)\text{-H}$ bond benzylation,^[14] and cross-coupling reactions with benzylzinc derivatives,^[6b, 15] using previously reported procedures. All reactions were performed under magnetic stirring.

General procedure for the Cu-catalyzed aerobic benzylic oxidation

A 10 mL vial was charged with the *N*-oxide (0.5 mmol), CuI (0.05 mmol, 10mol%) and DMSO (1 mL) or BuOAc (1 mL). The vial was flushed with O_2 , capped with an aluminum crimp cap with septum, and an oxygen balloon was inserted through the septum. The reaction mixture was stirred for 24 h at 120 °C. After completion the reaction mixture was transferred to a separation funnel, 20 mL of brine were added, and the mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried on MgSO_4 , filtered, and concentrated. The crude material was purified using a semi-automated flash chromatography system on silica gel cartridges (12g) using mixtures of heptane, EtOAc and MeOH as eluents (gradient: 100% heptane to EtOAc/MeOH: 80/20 over 30 min, flow rate: 25-30 mL/min).

2-(4-Methylbenzoyl)pyridine 1-oxide (3e, Acrivastine synthesis intermediate): The general method was applied using 2-(4-methylbenzyl)pyridine 1-oxide (0.100 g, 0.5 mmol).

The crude material was purified with silica gel flash chromatography (Heptane/EtOAc/MeOH) to afford 2-(4-methylbenzoyl)pyridine 1-oxide in 55 % yield (0.059 g, 0.275 mmol) in DMSO and 81 % yield (0.086 g, 0.406 mmol) in *n*-BuOAc. **^1H -NMR (CDCl_3 , 400 MHz)** δ_{H} : 8.25 (d, 1H, $J = 5.2$ Hz), 7.75 (d, 2H, $J = 8.0$ Hz), 7.46-7.34 (m, 3H), 7.29 (d, 2H, $J = 7.9$ Hz), 2.43 (s, 3H). **^{13}C -NMR (CDCl_3 , 100 MHz)** δ_{C} : 188.9 [C], 147.3 [C], 145.4 [C], 140.1 [CH], 132.7 [C], 129.6 [CH], 129.5 [CH], 126.8 [CH], 125.6 [CH], 125.5 [CH], 21.8 [CH_3]. HRMS (ESI) for $\text{C}_{13}\text{H}_{12}\text{NO}_2$ [$\text{M}+\text{H}$] $^+$, calcd 214.0868, found 214.0874; yellow solid; mp: 124 °C.

Synthesis of 6-Benzoylpicolonitrile (12)^[20]

An oven dried 10 mL vial was charged with 2-benzoylpyridine 1-oxide (0.199 g, 1 mmol), 100mg MS (powder) and 2 mL DCM. Under Ar (balloon), trimethylsilylcyanide (0.150 mL, 1.200 mmol) and dimethylcarbonyl chloride (0.110 mL, 1.200 mmol) were added to the mixture through syringe. The vial was sealed with an aluminum crimp cap and a pressure cap, and the mixture was stirred at 100 °C for 24h. At the end of the reaction, the mixture was diluted with 20 mL DCM, 20 mL NaHCO_3 (sat. solution) were added, and the mixture stirred for 20 min. The mixture was then extracted with DCM (3x20 mL), organic fractions dried over MgSO_4 , filtered and concentrated. The crude material was purified using a semi-automated flash chromatography system on silica gel cartridges (12g) using mixtures of heptane, EtOAc and MeOH as eluents (gradient: 100% heptane to EtOAc/MeOH: 80/20 over 30 min, flow rate: 25-30 mL/min). The product was obtained in 79% yield (165 mg, 0.792 mmol). **^1H -NMR (CDCl_3 , 400 MHz)** δ_{H} : 8.28 (d, 1H, $J = 8.0$ Hz), 8.14 (d, 2H, $J = 8.0$ Hz), 8.08 (t, 1H, $J = 7.9$ Hz), 7.90 (d, 1H, $J = 7.7$ Hz), 7.66 (t, 1H, $J = 7.4$ Hz), 7.53 (t, 2H, $J = 7.7$ Hz). **^{13}C -NMR (CDCl_3 , 100 MHz)** δ_{C} : 191.3 [C], 156.3 [C], 138.4 [CH], 135.1 [C], 133.7 [CH], 132.5 [C], 131.2 [CH], 130.5 [CH], 128.4 [CH], 127.6 [CH], 116.7 [C]. HRMS (ESI) for $\text{C}_{13}\text{H}_9\text{N}_2\text{O}$ [$\text{M}+\text{H}$] $^+$, calcd 209.0715, found 209.0719; white fluffy solid; mp: 113 °C.

Synthesis of (6-Chloropyridin-2-yl)(phenyl)methanone (13)^[21]

A round-bottom flask was charged with 2-benzoylpyridine 1-oxide (0.199 g, 1 mmol), then phosphorus oxychloride (0.918 mL, 10.00 mmol) was slowly added. The mixture was refluxed (set temperature oil bath 110 °C) under Ar for 24h. At the end, the reaction was placed in an ice bath, and 10 mL of water were slowly added, while stirring. The resulting solution was slowly poured into a 50 mL aq. NaHCO_3 saturated solution. The mixture was then extracted with DCM (4x20mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated. The crude material was purified using a semi-automated flash chromatography system on

silica gel cartridges (12g) using mixtures of heptane, EtOAc and MeOH as eluents (gradient: 100% heptane to EtOAc/MeOH: 80/20 over 30 min, flow rate: 25-30 mL/min). The product was isolated in 47% yield (103 mg, 0.47 mmol). **¹H-NMR** (CDCl₃, 400 MHz) δ_{H} : 8.14-8.10 (m, 2H), 7.96 (dd, 1H, J = 0.6 Hz, 7.6 Hz), 7.87 (t, 1H, J = 7.8 Hz), 7.62 (t, 1H, J = 7.4 Hz), 7.54-7.48 (m, 3H). **¹³C-NMR** (CDCl₃, 100 MHz) δ_{C} : 191.8 [C], 155.3 [C], 150.3 [C], 139.6 [CH], 135.6 [C], 133.3 [CH], 131.1 [CH], 128.3 [CH], 127.1 [CH], 123.1 [CH]. HRMS (ESI) for C₁₂H₉NOCl [M+H]⁺, calcd 218.0367, found 218.0380; green oil.

Synthesis of 2-Benzoyl-6-(*p*-tolyl)pyridine 1-oxide (14)^[11b]

A 10 mL vial was charged with 2-benzoylpyridine 1-oxide (0.797 g, 4.00 mmol), palladium(II)acetate (0.011 g, 0.05 mmol), potassium carbonate (0.276 g, 2 mmol), tri(*tert*-butylphosphonium)tetrafluoroborate (0.044 g, 0.15 mmol), 4-bromotoluene (0.171 g, 1.0 mmol) and 3.33 mL of toluene. The vial was flushed with Ar, sealed with an aluminum crimp cap with septum and stirred at 120 °C for 24h. At the end of the reaction the mixture was cooled to room temperature, then filtered through celite, washed with DCM and evaporated. Further purification was achieved via column chromatography with an automated chromatography system using a Silica Flash Cartridge applying a heptane-EtOAc-MeOH gradient (from 50% heptane to 100% EtOAc in 15 minutes to 80% EtOAc, 20% MeOH in 15 minutes, 30 mL/min). 2-Benzoyl-6-(*p*-tolyl)pyridine 1-oxide was obtained in 59% yield (174 mg, 0.601 mmol). **¹H-NMR** (CDCl₃, 400 MHz) δ_{H} : 7.84 (d, 2H, J = 7.4 Hz), 7.77 (d, 2H, J = 8.1 Hz), 7.55 (t, 2H, J = 7.8), 7.46-7.36 (m, 3H), 7.29 (dd, 1H, J = 7.6, 1.7 Hz), 7.24 (d, 2H, J = 7.8 Hz), 2.37 (s, 3H). **¹³C-NMR** (CDCl₃, 100 MHz) δ_{C} : 189.7 [C], 149.7 [C], 147.9 [C], 140.2 [C], 135.5 [C], 133.8 [CH], 129.3 [CH], 129.1 [CH], 128.9 [CH], 128.8 [CH], 128.6 [C], 127.7 [CH], 125.6 [CH], 123.4 [CH], 21.4 [CH₃]. HRMS (ESI) for C₁₉H₁₆NO₂ [M+H]⁺, calcd 290.1181, found 290.1183; white solid; mp: 154 °C.

Synthesis of (*E*)-2-(3-Methoxy-3-oxoprop-1-en-1-yl)-6-(4-methylbenzoyl)pyridine 1-oxide (15, Acrivastine synthesis intermediate)^[22]

A 10 mL vial was charged with 2-(4-methylbenzoyl)pyridine 1-oxide (0.426 g, 2.000 mmol), palladium(II)acetate (0.017 g, 0.075 mmol), silver(I)carbonate (0.207 g, 0.750 mmol), methyl acrylate (0.045 mL, 0.5 mmol), pyridine (0.040 mL, 0.500 mmol) and 1 mL of dioxane. The vial was sealed with an aluminum crimp cap with septum, and stirred at 120 °C for 24h. At the end of the reaction the mixture was cooled to room temperature, then filtered through celite, washed with DCM and evaporated. The crude material was purified using a semi-automated flash

chromatography system on silica gel cartridges (12g) using mixtures of heptane, EtOAc and MeOH as eluents (gradient: 100% heptane to EtOAc/MeOH: 80/20 over 30 min, flow rate: 25-30 mL/min). The product was obtained in 53% yield (157 mg, 0.53 mmol). **¹H-NMR** (CDCl₃, 400 MHz) δ_{H} : 8.00 (d, 1H, J = 16.2 Hz), 7.70 (d, 2H, J = 8.0 Hz), 7.65 (dd, 1H, J = 2.8 Hz, 7.1 Hz), 7.39-7.31 (m, 2H), 7.26 (d, 2H, J = 8.3 Hz), 7.09 (d, 1H, J = 16.2 Hz), 3.79 (s, 3H), 2.40 (s, 3H). **¹³C-NMR** (CDCl₃, 100 MHz) δ_{C} : 188.6 [C], 166.6 [C], 148.2 [C], 145.4 [C], 145.3 [C], 133.4 [CH], 132.6 [C], 129.6 [CH], 129.2 [CH], 126.7 [CH], 125.1 [CH], 125.0 [CH], 124.8 [CH], 52.0 [CH₃], 21.8 [CH₃]. HRMS (ESI) for C₁₇H₁₆NO₄ [M+H]⁺, calcd 298.1079, found 298.1087, yellow oil.

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FULL PAPER

Copper-Catalyzed Aerobic Oxygenation of Benzylpyridine *N*-oxides and Subsequent Post-Functionalization

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