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Copper-catalyzed direct α-peroxidation of nitrogen heterocycles

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Dedicated to Prof. Léon Ghosez, an outstanding and passionate chemist

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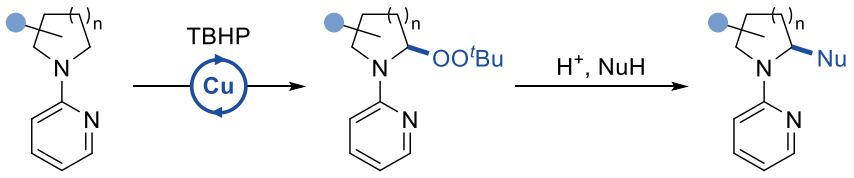
Abstract

Functionalized, saturated nitrogen heterocycles form the core structures of many molecules that have an impact on our daily lives, including natural products and pharmaceuticals. An efficient and general method for the direct α-peroxidation of saturated nitrogen heterocycles is reported. Upon simple reaction with *tert*-butyl hydrogen peroxide in the presence of catalytic amounts of copper(II) chloride and 1,10-phenanthroline, a broad range of nitrogen heterocycles equipped with a 2-pyridyl directing group are readily peroxidized at room temperature to the corresponding stable hemiaminals with full regioselectivity. These hemiaminals were, moreover, shown to be remarkably efficient precursors of the corresponding iminium ions upon simple treatment with citric acid, enabling, overall, the introduction of a series of nucleophiles at the α-position of the starting nitrogen heterocycles.



Keywords: Nitrogen heterocycles, peroxidation, C-H functionalization, copper catalysis, α-aminoalkyl radicals, iminium ions, directing groups

Introduction

Functionalized, saturated nitrogen heterocycles are essential molecules which are at the core structure of a myriad number of molecules that have a deep impact on our daily life. α-Functionalized ones are among the most important and iconic examples, including blockbuster drugs such as ramipril **1** (Altace®), an antihypertensive developed by Sanofi; Novartis's vildagliptin **2** (Galvus®), utilized as an oral treatment for type-2 diabetes; the anticancer drug acalabrutinib **3** (Calquence®) marketed by AstraZeneca; and Pfizer's SARS-CoV-2 medication nirmatrelvir **4** (utilized in combination with ritonavir and commercialized under the brand name Paxlovid®) which generated 19 billion dollars in 2022 alone (Figure 1). Such heterocycles are also commonly found in an array of natural products, the most famous examples certainly being nicotine **5**, quinine **6** and morphine **7**.

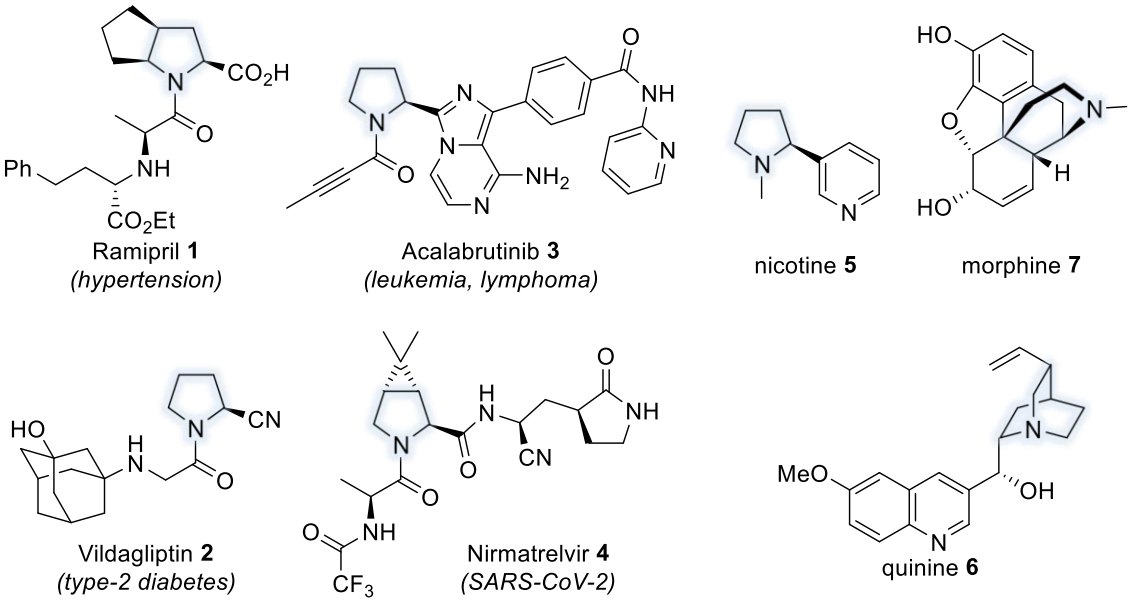
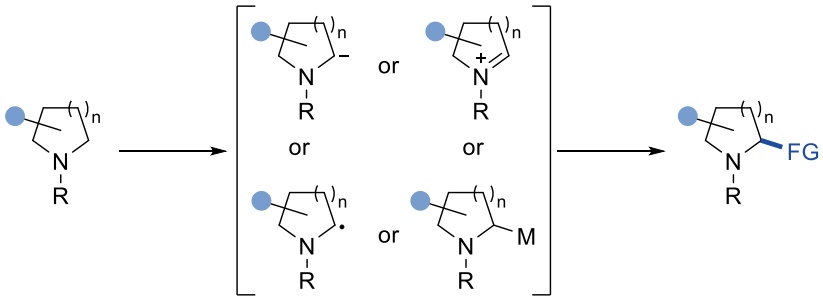


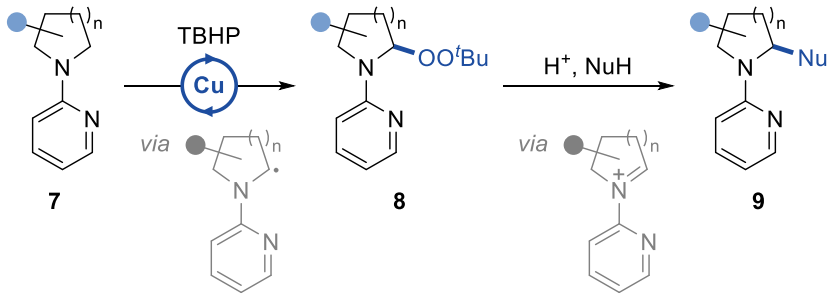
Figure 1. Representative drugs and natural products featuring an α-substituted, saturated nitrogen heterocycle.

Due to the importance of α-functionalized, saturated nitrogen heterocycles, a variety of strategies have been investigated for their syntheses, the majority of these involving the formation of the heterocyclic cores via the formation of C-C and/or C-N bond(s).[1,2] A more appealing approach involves the direct functionalization of unsubstituted nitrogen heterocycles by (formal) C-H functionalization,[3,4,5,6] which typically relies on anionic, cationic, radical or metallic intermediates (Scheme 1).



Scheme 1. Strategies for the direct α-functionalization of saturated nitrogen heterocycles.

While the frontier between radical and cationic approaches can be blurred since the direct generation of an iminium ion from an amine typically involves a transient amine radical cation, examples of purely radical processes - which involve intermediate α-aminoalkyl radical species generated from the corresponding amines by hydrogen atom abstraction or transfer - are still scarce. They do, however, have an important synthetic potential since they are not limited to activated benzylic positions, as is often the case with cationic processes.[7,8,9,10] Based on our long-standing interest in copper-catalyzed oxidative[11,12,13,14,15,16] and C-H functionalization[17,18,19] reactions, and inspired by a pioneering study of the Klussmann group,[20,21] we became interested in the development of a copper-catalyzed direct α-peroxidation of saturated nitrogen heterocycles **7**. This reaction would indeed enable the direct introduction of a peroxide α to the nitrogen atom (**8**),[20,22,23,24] a versatile functional group that could be further replaced by a variety of nucleophiles (**9**) through a transient iminium ion. For this direct oxidation not to be limited to activated substrates, we envisioned the use of a 2-pyridyl directing group (Scheme 2). We report in this manuscript the full development of this reaction.



Scheme 2. Our strategy for the copper-catalyzed direct α-functionalization of saturated nitrogen heterocycles.

Results and Discussion

With this basic strategy in mind, we first focused our efforts on the validation of our working hypothesis, and on the optimization of this copper-catalyzed direct α-peroxidation of saturated nitrogen heterocycles from *N*-(2-pyridyl)-pyrrolidine **7a** which was selected as model substrate. A variety of copper(II) sources, ligands and solvents was evaluated and results from this study are shown in Figure 2.

A series of copper(II) salts was first evaluated to promote the desired α-peroxidation of **7a** using an excess of *tert*-butyl-hydroperoxide TBHP in combination with 1,10-phenanthroline in dichloromethane, which were arbitrarily selected as ligand and solvent, respectively, at room temperature for 2 hours. While the reaction was totally ineffective in the absence of a copper(II) salt, we were delighted to note that the α-peroxidation to **8a** was operative in the presence of 10 mol % of such salts, thereby validating our working hypothesis even if low conversions were observed in most cases. While a better yield of **8a** was obtained with copper(II) triflate, significant degradation was observed, and we, thus, selected copper(II) chloride, which gave a 55% yield (by ^{1}H NMR) of **8a** together with 40% of unreacted **7a**, for the next step of the optimization. A set of representative bidentate ligands typically used in copper catalysis was evaluated at this stage. These ligands were found to have a dramatic impact on the efficiency and selectivity of the process, over oxidation to *N*-(2-pyridyl)-pyrrolidin-2-one **10a** being observed in the absence of a ligand or with *N*,*N*,*N'*,*N'*-tetramethyl-ethylenediamine (TMEDA) and acetylacetone (acac). The best compromise in terms of reactivity, efficiency and selectivity was obtained with 1,10-phenanthroline. Therefore, its use in combination with copper(II) chloride was next assessed in different solvents. These solvents were also found to have a strong impact on the efficiency of the reaction;

dichloromethane was found to be superior to all other solvents evaluated. Finally, in order to boost the conversion, longer reaction times were evaluated. While the reaction was almost complete after only 4 hours, full conversion was obtained after 16 hours, resulting in a 78% isolated yield of **8a**.

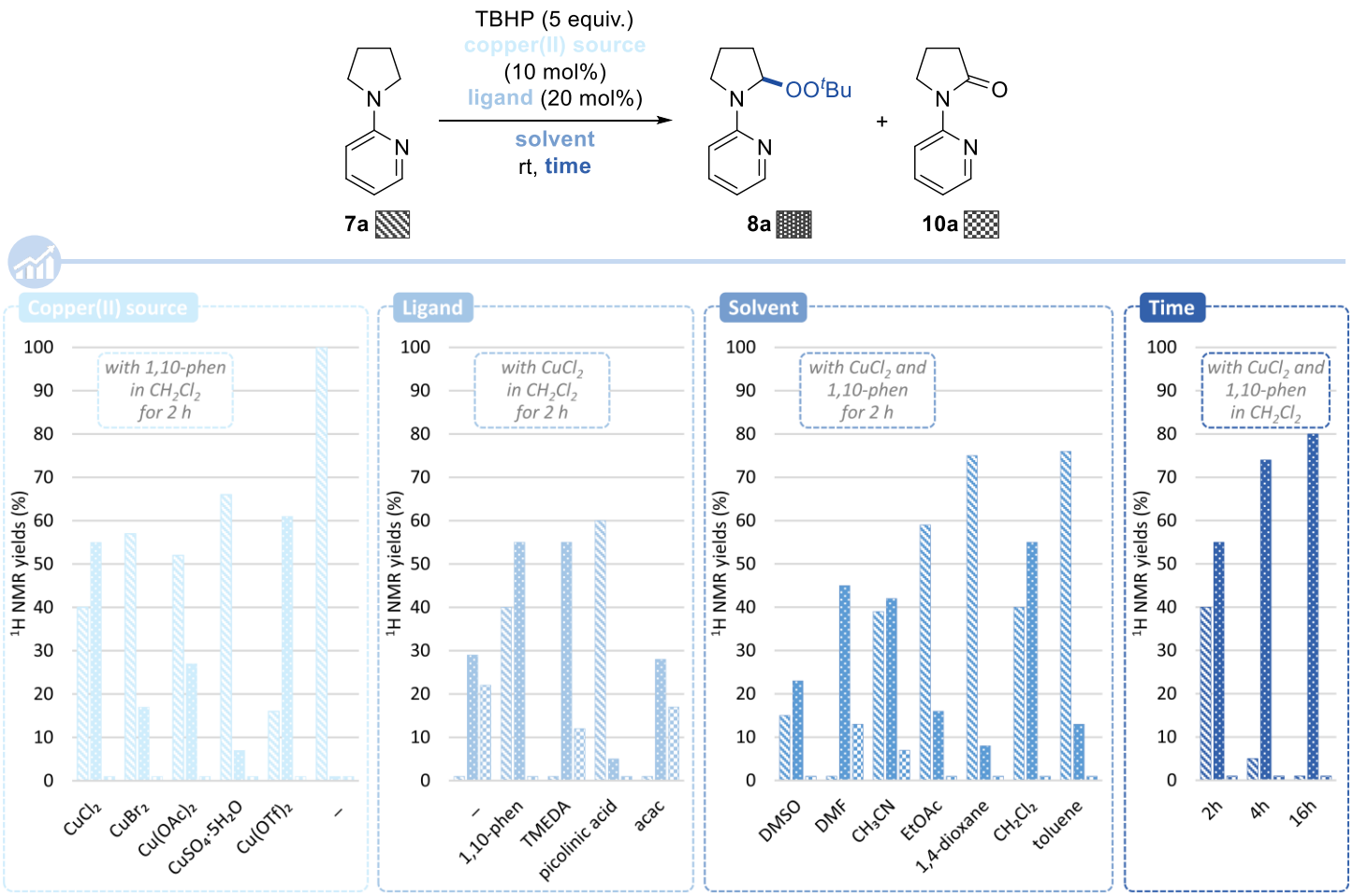


Figure 2. Optimization of the copper-catalyzed direct α-peroxidation of saturated nitrogen heterocycles. *^{1}H NMR yields determined using DMF as an internal standard.*

With these optimized conditions, relying on simple, readily available and cheap copper(II) chloride and 1,10-phenanthroline at room temperature, in hand, we next focused our efforts on the study of the scope and limitations of this copper-catalyzed, direct α-peroxidation of saturated nitrogen heterocycles, which first involved the synthesis of a library of these starting materials with representative ring sizes and substitution patterns. The starting materials, equipped with a *N*-(2-pyridyl) directing group, were readily prepared by either nucleophilic aromatic substitution starting with the corresponding secondary amines **11** and 2-fluoro-pyridine $\mathbf{12_F}$, in the presence of sodium carbonate in acetonitrile at 150 °C[25] (Figure 3, procedure A) or by a Buchwald-Hartwig arylation with 2-bromo-pyridine $\mathbf{12_{Br}}$ using catalytic amounts of $Pd_2(dba)_3$ and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[26] (Figure 3, procedure B), 1,3-bis(diphenylphosphino)propane (dppp)[27] (Figure 3, procedure C) or IPr·HCl[28] (Figure 3, procedure D). These arylations proceeded well in most cases, with lower yields being obtained in the presence of a substituent α to the nitrogen atom or starting from acyclic amines.

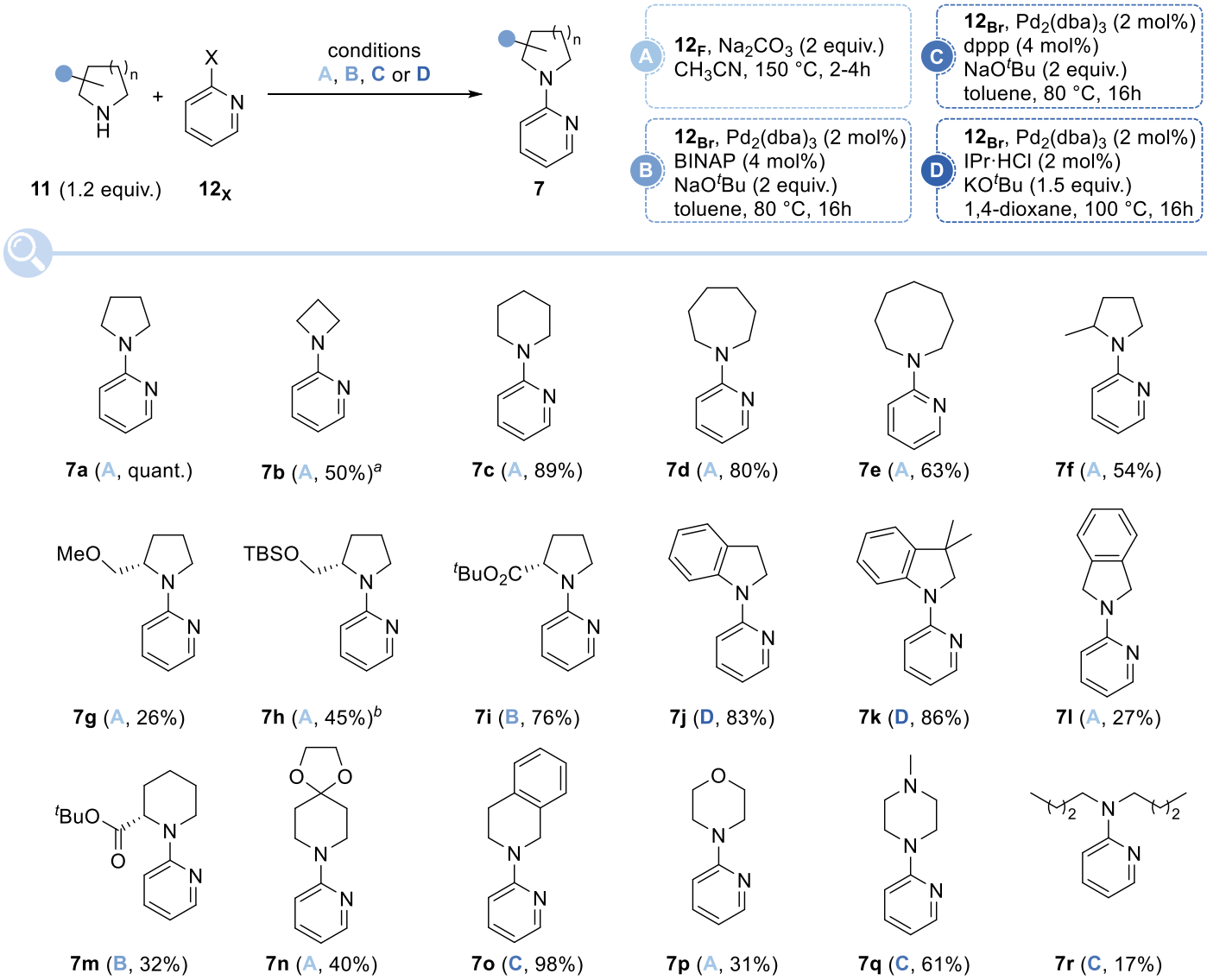


Figure 3. Synthesis of the starting *N*-(2-pyridyl)-amines by nucleophilic aromatic substitution or Buchwald-Hartwig arylation. [a] *Reaction performed at rt for 5 days.* [b] *Arylation performed on L-prolinol at 160 °C without Na_2CO_3 and neat, followed by TBS protection.*

With this collection of *N*-(2-pyridyl)-amines **7** now at our disposal, they were next subjected to the copper-catalyzed direct α-peroxidation under our optimized conditions. As evidenced by results collected in Figure 4, the reaction was found to be fairly general since a broad variety of nitrogen heterocycles **7** could be readily peroxidized to the corresponding stable hemiaminals **8** under mild conditions with high efficiency. Importantly, double peroxidation at the α and α' position, a side reaction that is frequently encountered when using a directing group, was never observed. The efficiency of the peroxidation was found to be directly correlated to the size of the ring, pyrrolidine being readily oxidized to **8a** in 78% yield while its lower azetidine homologue **8b** was isolated in 28% yield. The piperidine derivative **8c** could not be obtained with extensive degradation being noted in this case. Since these nitrogen heterocycles have close bond-dissociation energies,[29] this striking difference in reactivity can be attributed to both steric factors disfavoring the formation of a radical species from **8b**, and to limited stability of **8c**, since the corresponding enamine could be detected in the crude reaction

mixture together with traces of **8c**. Moving to azepane **7d** and azocane **7e** restored reactivity, with the corresponding peroxidized products **8d** and **8e** being obtained in 61% and 31% yields, respectively.

In the presence of a substituent α to the pyrrolidine nitrogen atom, such as in **7f**-**I**, the peroxidation systematically occurred at the less substituted α' position, and the diastereoselectivity was actually found to depend on the nature of the substituent. A methyl group, indeed, yielded the *cis* peroxide **8f**, while the *trans* isomers were predominantly obtained from prolinol and proline-derived substrates **7g**, **7h** and **7i**. The bigger the substituent, the better the diastereoselectivity, and the formation of the *trans* isomers can certainly be attributed to a peroxidation from the less hindered face. The reason for the reversed diastereoselectivity obtained with **7f** is unclear; an isomerization of the kinetic *trans* isomer to the more stable *cis* one[30] being potentially operative in this case. Similar isomerizations were observed over time with **7g**, **7h** and **7i**.

Starting from indoline **7j**, the peroxidation was followed by a spontaneous elimination, affording indole **8j'**, a reaction that could be suppressed in the absence of hydrogen atoms at the β position, as in **7k**. The corresponding hemiaminal **8k** was obtained in 66% yield, provided that the reaction was performed in 1,2-dichloroethane at 60 °C; however, the presence of the *gem* dimethyl groups hindering the α position.

Limitations were met with isoindoline, piperidine and piperazine derivatives, decomposition being observed with **7l**, **7m**, **7n** and **7q** as well as when starting from acyclic amines such as **7r**. Tetrahydroisoquinoline **7o** and morpholine **7p** were, however, successfully transformed to the corresponding hemiaminals **8o** and **8p**, with 85% and 35% yields, respectively.

Importantly, the reaction is not limited to the small scale utilized for the scope and limitation studies, with peroxidations performed on gram scales from **7a**, **7d**, **7i** and **7o** being more efficient.

After carefully studying the scope and limitations of our copper-catalyzed direct α-peroxidation of nitrogen heterocycles, which enables an easy access to a variety of stable hemiaminals, we next focused our attention on their functionalization, such hemiaminals being well-known precursors of iminium ions under acidic conditions.[21] While a range of conditions relying, for example, on the use of stoichiometric acetic acid or catalytic methanesulfonic acid were actually found to be suitable to promote the generation of these iminium ions, we were delighted to note that simple citric acid was efficient, provided that the reaction was run in ethanol at 80 °C. Using these simple conditions, we briefly evaluated the scope of both hemiaminals **8** and nucleophiles which could be employed to generate the corresponding α-functionalized nitrogen heterocycles **9**. As highlighted in Figure 5, the displacement of the peroxide in **8a** was found to be quite efficient, provided, however, that relatively strong nucleophiles, such as *N*-methyl-indole or 1,3,5-trimethoxybenzene were used.

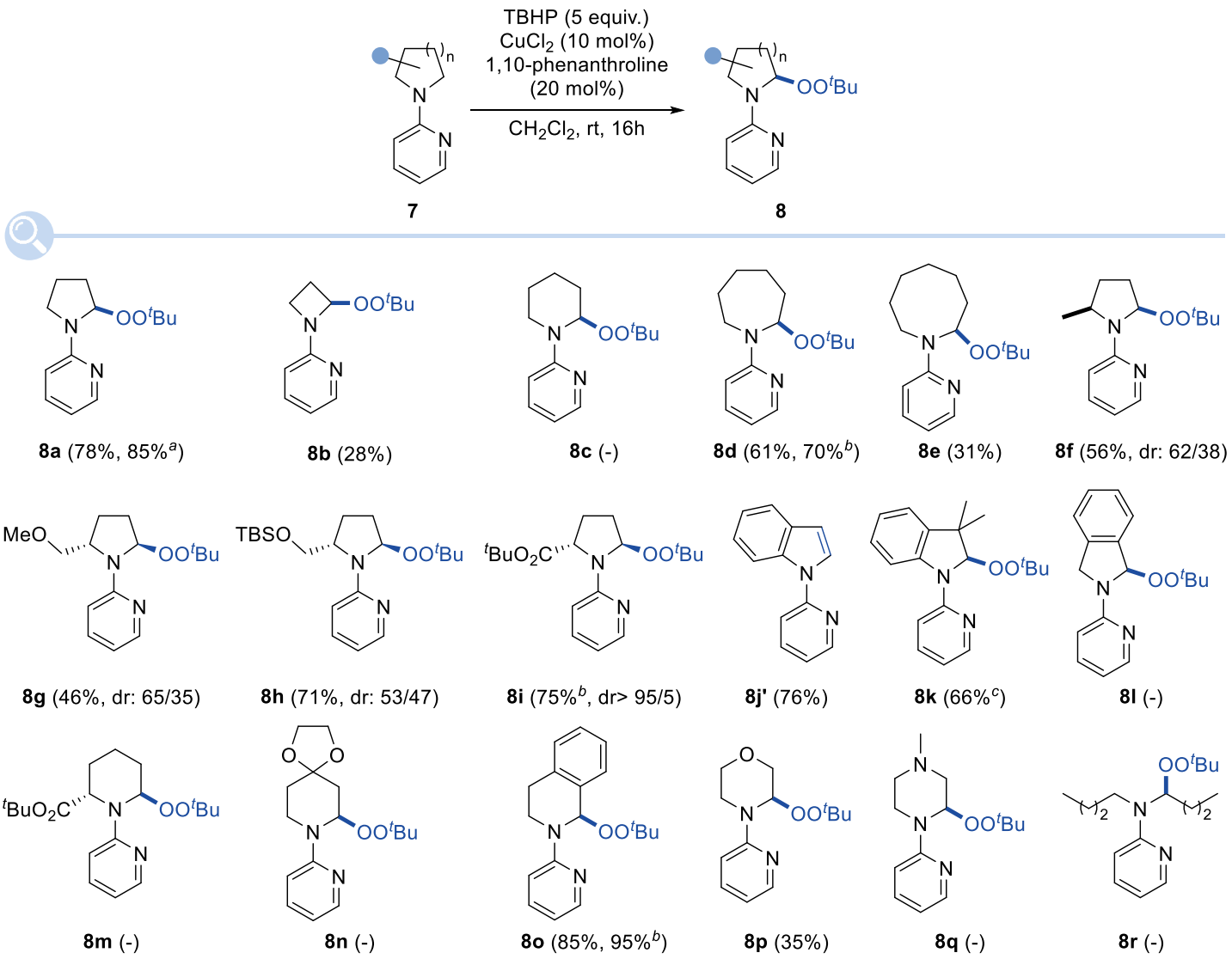


Figure 4. Scope and limitations of the copper-catalyzed direct α-peroxidation of nitrogen heterocycles. [a] *Reaction performed on a 4 gram scale.* [b] *Reaction performed on a 1 gram scale.* [c] *Reaction performed in 1,2-dichloroethane at 60 °C.*

Less reactive nucleophiles, such as allyltrimethylsilane, diethylphosphite, dimethyl malonate, trimethylsilyl cyanide and thiophenol were indeed not suitable, even when replacing citric acid by a range of Lewis acids. Other hemiaminals could be functionalized, including chiral ones such as **8h** and **8i** (which, however, gave varying levels of diastereoselectivity), and indoline- or tetrahydroisoquinoline-derived ones **8k** and **8o**, whose corresponding adducts **9e** and **9f** were obtained in good yields.

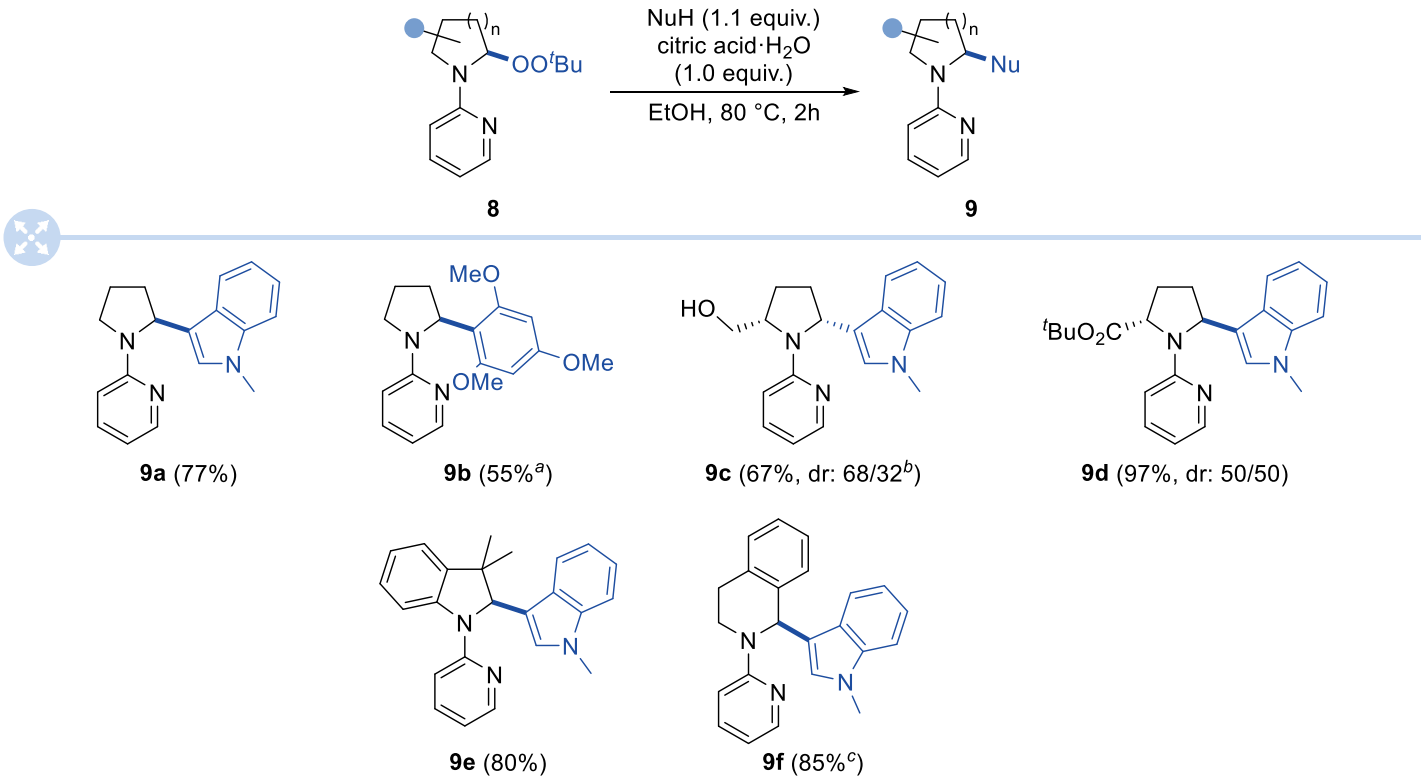


Figure 5. Hemiaminals **8** as precursors of iminium ions: displacement of the peroxide by nucleophiles under acidic conditions. [a] *Reaction performed with 3 equivalents of the nucleophile.* [b] *Reaction performed from TBS ether* ***8h****.* [c] *Reaction performed at rt.*

Once the synthetic usefulness of the hemiaminals obtained by our copper-catalyzed, direct α-peroxidation of nitrogen heterocycles was demonstrated, we finally addressed the catalytic cycle associated with this selective oxidation. In this perspective, a series of control experiments were first performed to get insights into both the reaction intermediates, and the catalytic cycle. The intermediacy of a radical species could be evidenced since the peroxidation of **7a** to **8a** was totally inhibited in the presence of the radical trap, galvinoxyl, under our standard conditions (Figure 6, left). As for the potential generation of an iminium ion from **7a**, it seems rather unlikely since its reaction in the presence of excess nucleophiles, such as *N*-methyl-indole or 1,3,5-trimethoxybenzene, resulted in the exclusive formation of peroxide **8a** with no traces of **9a**-**c**, which should be formed if a transient iminium ion was involved. Finally, the key role of the 2-pyridyl directing group could be demonstrated since the 3-pyridyl- **13** analogue of **7a** failed to undergo peroxidation.

Based on these experiments, and on studies from the Klussmann group on a related peroxidation of *N*-aryl-tetrahydroisoquinolines,[31] the catalytic cycle shown on the right in Figure 6 can be proposed.

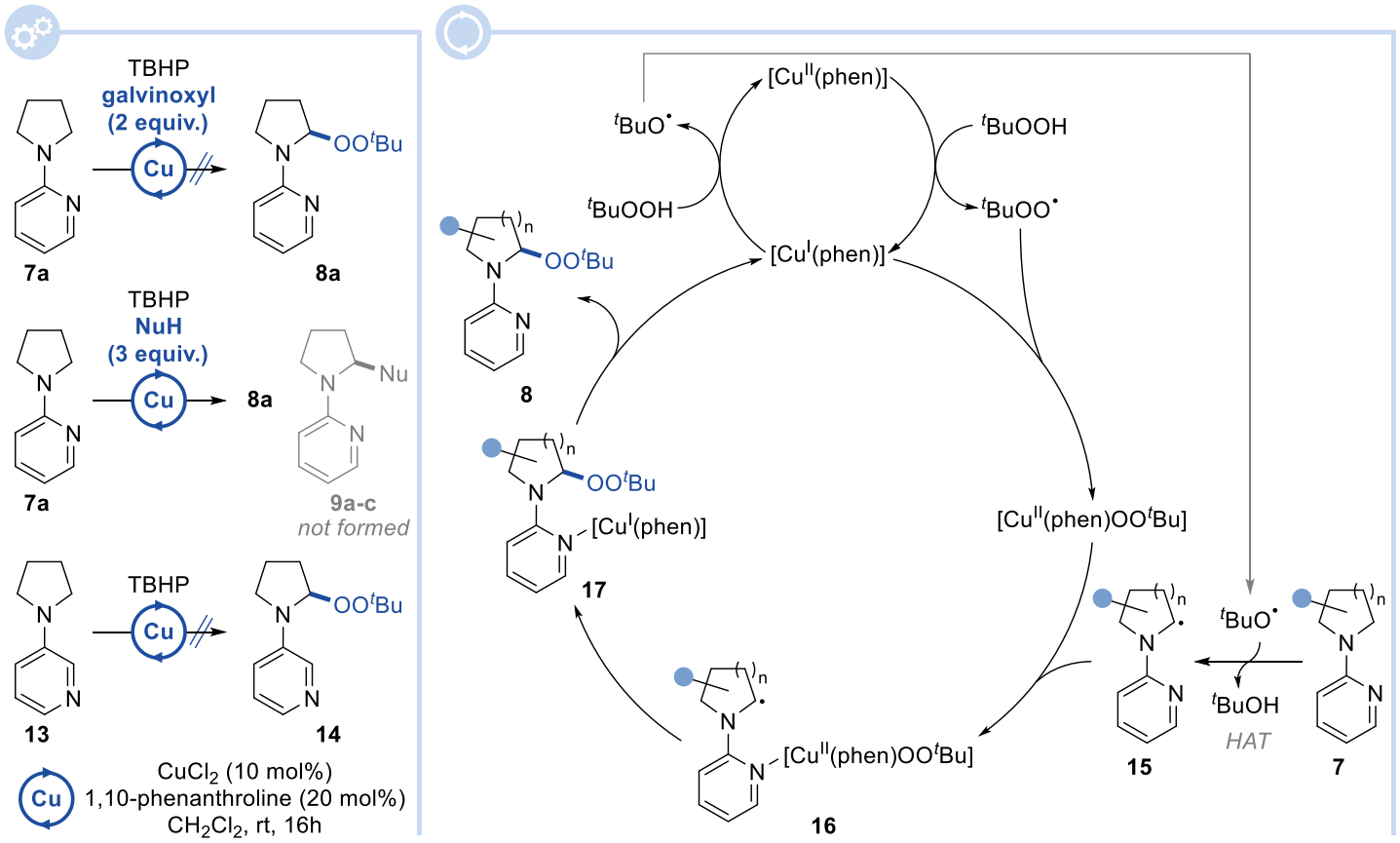


Figure 6. Mechanistic studies and catalytic cycle of the copper-catalyzed direct α-peroxidation of nitrogen heterocycles.

The reaction would be initiated by the reduction of the copper(II)-phenanthroline catalyst by TBHP, generating the corresponding copper(I) complex and a *tert*-butylperoxyl radical species ^{t}BuOO$^•$. This copper(I) complex could then be oxidized either by ^{t}BuOO$^•$, resulting in the generation of a copper(II) peroxide complex as proposed by Kochi,[32] or by TBHP, regenerating the copper(II) catalyst and releasing a *tert*-butoxyl radical species ^{t}BuO$^•$. The latter would then engage in a hydrogen atom transfer with the starting amine **7**, generating the corresponding α-aminoalkyl radical intermediate **15**, an intermediate that could also be formed by hydrogen-atom transfer with ^{t}BuOO$^•$, a radical species which can be generated through a fast hydrogen-atom transfer between ^{t}BuO$^•$ and *tert*-butanol.[31,33] Coordination of **15** with the copper(II) peroxide complex would yield **16**, facilitating the peroxidation that could proceed either directly or via a copper(III) complex (not shown). De-coordination of the peroxidized product would finally yield hemiaminal **8** and close the catalytic cycle.

Conclusions

We have developed an efficient and general method for the direct α-peroxidation of saturated nitrogen heterocycles equipped with a 2-pyridyl directing group. Upon simple reaction with *tert*-butyl hydrogen peroxide in the presence of catalytic amounts of copper(II) chloride and 1,10-phenanthroline, a broad range of nitrogen heterocycles, including unactivated ones, are selectively peroxidized at room temperature to the corresponding stable hemiaminals without over-oxidation. These hemiaminals were shown to be remarkably efficient

precursors of the corresponding iminium ions upon simple treatment with citric acid, overall enabling the introduction of a series of nucleophiles at the α-position of the starting nitrogen heterocycles.

Experimental Section

General. All reactions were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials unless otherwise stated. All reagents and solvents were reagent grade. Acetonitrile and dichloromethane were freshly distilled from calcium hydride under argon. 1,4-Dioxane (99.5%, Extra Dry over Molecular Sieve, AcroSeal®) and toluene (99.5%, Extra Dry over Molecular Sieve, AcroSeal®) were purchased from ACROS Organics and used as supplied. Absolute ethanol was purchased from Fischer Chemical and distilled over magnesium/iodine. Starting *N*-(pyridin-2-yl)heterocycles **7c**,[25] **7d 7l**[34]and **7n**[25] had been previously reported.

Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kiesegel 60F254 plates. Flash chromatography was performed with silica gel 60 (particle size 35-70 μm) supplied by Merck. Yields refer to chromatographically, and spectroscopically, pure compounds.

Proton NMR spectra were recorded using an internal deuterium lock at ambient temperature on a Bruker 300 MHz spectrometer. Internal reference of δ_H 7.26 was used for $CDCl_3$. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sept. = septuplet, sext. = sextuplet, oct. = octuplet, m = multiplet, br. = broad, app. = apparent), coupling constant (J/Hz) and integration. Carbon-13 NMR spectra were recorded at 150, 100 or 75 MHz using $CDCl_3$ (δ_C 77.16) as internal reference.

Melting points were recorded on a Stuart Scientific Analogue SMP11. Infrared spectra were recorded on a Bruker Alpha (ATR). High-resolution mass-spectra were obtained on an Agilent QTOF 6520 spectrometer.

General Procedure I. nucleophilic aromatic substitution.[25] A pressure tube was charged with 2-fluoropyridine **12$_F$** (1.0 equiv.), the amine **11** (1.2 equiv.), Na_2CO_3 (2.0 equiv.) and acetonitrile (10 M). The pressure tube was sealed with a Teflon stopper, and the mixture was heated at 150 °C for 2-4 hours. The crude reaction mixture was then cooled to room temperature and diluted with ethyl acetate. The solids were removed by filtration through a pad of Celite®, which was washed three times with ethyl acetate, and the filtrate was concentrated to dryness. The crude residue was finally purified by flash chromatography over silica gel to give the desired compound **7**, or used without further purification.

General Procedure II. Buchwald-Hartwig arylation using BINAP.[26] A pressure tube was charged with 2-bromopyridine **12$_{Br}$** (1.0 equiv.), the amine **11** (1.2 equiv.), $Pd_2(dba)_3$ (2 mol %), (±)-BINAP (4 mol %) and sodium *tert*-butoxide (2 equiv.). The pressure tube was fitted with a rubber septum, evacuated under high vacuum, and backfilled with argon three times. Degassed 1,4-dioxane (0.25 M) was then added and the rubber septum was replaced by a Teflon stopper. The reaction mixture was then heated to 80 °C overnight, cooled to room temperature and diluted with ethyl acetate. The solids were removed by filtration through a pad of Celite®, which was washed three times with ethyl acetate, and the filtrate was concentrated to dryness. The crude residue was finally purified by flash chromatography over silica gel to give the desired compound **7**.

General Procedure III. Buchwald-Hartwig arylation using dppp.[27] A pressure tube was charged with 2-bromopyridine **12$_{Br}$** (1.0 equiv.), the amine **11** (1.2 equiv.), $Pd_2(dba)_3$ (2 mol %), (±)-1,3 bis(diphenylphosphine)propane (dppp, 4 mol %) and sodium *tert*-butoxide (2 equiv.). The pressure tube was fitted with a rubber septum, evacuated under high vacuum, and backfilled with argon three times. Degassed

toluene (0.25 M) was then added, and the rubber septum was replaced by a Teflon stopper. The reaction mixture was then heated to 80 °C overnight, cooled to room temperature and diluted with ethyl acetate. The solids were removed by filtration through a pad of Celite®, which was washed three times with ethyl acetate, and the filtrate was concentrated to dryness. The crude residue was finally purified by flash chromatography over silica gel to give the desired compound **7**.

General Procedure IV. Buchwald-Hartwig arylation using IPr.[28] A pressure tube was charged with 2-bromopyridine **12$_{Br}$** (1.0 equiv.), the amine **11** (1.2 equiv.), $Pd_2(dba)_3$ (2 mol %), 1,3-bis-(2,4,6-tribenzhydrylphenyl)-1*H*-imidazol-3-ium chloride (IPr·HCl, 2 mol %) and potassium *tert*-butoxide (1.5 equiv.). The pressure tube was fitted with a rubber septum, evacuated under high vacuum, and backfilled with argon three times. Degassed toluene (0.25 M) was then added, and the rubber septum was replaced by a Teflon stopper. The reaction mixture was then heated to 100 °C overnight, cooled to room temperature and diluted with dichloromethane. The solids were removed by filtration through a pad of Celite®, which was washed three times with dichloromethane, and the filtrate was concentrated to dryness. The crude residue was finally purified by flash chromatography over silica gel to give the desired compound **7**.

***N*-(Pyridin-2-yl)pyrrolidine** (**7a**). Prepared according to general procedure I (starting from 3.5 mL (41 mmol) of 2-fluoropyridine **12$_F$**). No purification required, used without further purification. Yield: quant. (6.1 g, 41 mmol). This compound had been previously reported using the same procedure.[25]

***N*-(Pyridin-2-yl)azetidine** (**7b**). Prepared according to general procedure I at room temperature for 5 days (starting from 1.0 mL (11.8 mmol) of 2-fluoropyridine **12$_F$**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 50% (785 mg, 5.8 mmol). This compound had been previously reported using a related procedure.[35]

***N*-(Pyridin-2-yl)piperidine** (**7c**). Prepared according to general procedure I (starting from 3.5 mL (41 mmol) of 2-fluoropyridine **12$_F$**). No purification required, used without further purification. Yield: 88% (5.8 g, 36 mmol). This compound had been previously reported using the same procedure.[25]

***N*-(Pyridin-2-yl)azepane** (**7d**). Prepared according to general procedure I (starting from 2.7 mL (31 mmol) of 2-fluoropyridine **12$_F$**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 80% (4.4 g, 25 mmol). This compound had been previously reported using the same procedure.[36]

***N*-(Pyridin-2-yl)azocane** (**7e**). Prepared according to general procedure I (starting from 175 mL (2.0 mmol) of 2-fluoropyridine **12$_F$**). No purification required, used without further purification. Yield: 63% (235 mg, 1.25 mmol). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (ddd, *J* 4.9, 1.8 and 0.9 Hz, 1H), 7.40 (ddd, *J* 8.5, 7.2 and 1.8 Hz, 1H), 6.54-6.39 (m, 2H), 3.60 (t, *J* 5.7 Hz, 4H), 1.83-1.71 (m, 4H), 1.65-1.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 148.2, 137.1, 110.9, 105.8, 49.0, 27.4, 26.9, 26.7; IR (ATR) ν_{max} 2921, 1594, 1493, 1439, 1374, 1161, 767, 732 cm^{-1}.

***N*-(Pyridin-2-yl)-2-methylpyrrolidine** (**7f**). Prepared according to general procedure I (starting from 340 mL (3.9 mmol) of 2-fluoropyridine **12$_F$**). No purification required, used without further purification. Yield: 54% (339 mg, 2.09 mmol). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (ddd, *J* 5.1, 1.9 and 0.7 Hz, 1H), 7.40 (ddd, *J* 8.9, 7.1 and 1.9 Hz, 1H), 6.49 (ddd, *J* 7.1, 5.1 and 0.7 Hz, 1H), 6.35 (d, *J* 8.5 Hz, 1H), 4.21 – 4.04 (m, 1H), 3.64 – 3.44 (m, 1H), 3.44 – 3.24 (m, 1H), 2.20 – 1.86 (m, 3H), 1.83 – 1.62 (m, 1H), 1.22 (d, *J* 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 148.4, 136.9, 111.0, 106.8, 53.0, 47.3, 33.1, 23.4, 19.6; IR (ATR) ν_{max} 2968, 1703, 1595, 1471, 1436, 1383, 1300, 771 cm^{-1}.

(*S*)-*N*-(Pyridin-2-yl)-2-(methoxymethyl)pyrrolidine (**7g**). Prepared according to general procedure I (starting from 385 mL (4.4 mmol) of 2-fluoropyridine **12$_F$**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 26% (217 mg, 1.13 mmol). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (ddd, *J* 5.0, 1.9 and 0.8 Hz, 1H), 7.41 (ddd, *J* 8.5, 7.1 and 1.9 Hz, 1H), 6.52 (ddd, *J* 7.1, 5.0 and 0.8 Hz, 1H), 6.42 (d,

J 8.5 Hz, 1H), 4.29 – 4.13 (m, 1H), 3.60 (dd, *J* 9.2 and 3.5 Hz, 1H), 3.57 – 3.45 (m, 1H), 3.37 (s, 3H), 3.34 – 3.20 (m, 2H), 2.17 – 1.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 157.6, 148.4, 137.0, 111.7, 106.9, 73.2, 59.3, 57.2, 47.7, 28.7, 23.6; IR (ATR) ν_{max} 2947, 1708, 1596, 1476, 1440, 1377, 1111, 769, 734 cm^{-1}.

(*S*)-*N*-(Pyridin-2-yl)-2-(hydroxymethyl)pyrrolidine. Prepared according to a modification of general procedure I (starting from 1.5 g (14.8 mmol) of (*S*)-2-hydroxymethyl-pyrrolidine, 2.1 mL (22.2 mmol) of 2-fluoropyridine **12$_F$** without Na_2CO_3 and neat at 160 °C for 4h). Solvent system for flash chromatography: dichloromethane/methanol: gradient from 98/2 to 95/5. Yield: 47% (1.24 g, 6.9 mmol). This compound had been previously reported using a related procedure.[37]

(*S*)-*N*-(Pyridin-2-yl)-2-(*tert*-butyldimethylsilyloxymethyl)pyrrolidine (**7h**). A solution of *tert*-butyl-dimethylsilyl chloride (1.49 g, 9.9 mmol, 1.1 equiv.) in 4 mL of dichloromethane was added to a stirred solution of (*S*)-2-(hydroxymethyl)-1-(pyridin-2-yl)pyrrolidine (1.62 g, 9.0 mmol, 1 equiv.) and triethylamine (2.5 mL, 18 mmol, 2 equiv.) in dichloromethane (9 mL) at 0 °C *via* cannula. The resulting mixture was stirred at room temperature overnight, then washed with brine. The organic layer was separated, and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was finally purified by flash chromatography over silica gel (petroleum ether/ethyl acetate: 90/10) to afford the desired protected alcohol **7h** as a yellow oil (2.51 g, 8.6 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.14 (ddd, *J* 5.0, 1.9 and 0.8 Hz, 1H), 7.41 (ddd, *J* 8.6, 7.1 and 2.0 Hz, 1H), 6.50 (ddd, *J* 7.1, 5.0 and 0.8 Hz, 1H), 6.41 (d, *J* 8.6 Hz, 1H), 4.16 – 4.05 (m, 1H), 3.79 (dd, *J* 9.9 and 3.6 Hz, 1H), 3.56 (dd, *J* 9.9 and 7.4 Hz, 1H), 3.52 – 3.44 (m, 1H), 3.41 – 3.26 (m, 1H), 2.15 – 2.01 (m, 4H), 0.88 (s, 9H), 0.02 (d, *J* 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 157.5, 148.3, 137.0, 111.5, 106.8, 63.3, 59.2, 47.8, 28.2, 26.1, 23.5, 18.4, -5.2, -5.2; IR (ATR) ν_{max} 2954, 1600, 1491, 1442, 1252, 834, 769 cm^{-1}.

***Tert*-Butyl (*S*)-*N*-(pyridin-2-yl)prolinate** (**7i**). Prepared according to general procedure II (starting from 1.9 mL (20.0 mmol) of 2-bromopyridine **12$_{Br}$**). Solvent system for flash chromatography: cyclohexane/ethyl acetate: 80/20. Yield: 76% (3.8 g, 15.3 mmol). This compound had been previously reported using the same procedure.[26]

***N*-(Pyridin-2-yl)indoline** (**7j**). Prepared according to general procedure IV (starting from 1.9 mL (20.0 mmol) of 2-bromopyridine **12$_F$**). Solvent system for flash chromatography: cyclohexane/ethyl acetate: 80/20; Yield: 83% (3.3 g, 16.6 mmol). This compound had been previously reported using a related procedure.[38]

***N*-(Pyridin-2-yl)-3,3-dimethyl-indoline** (**7k**). Prepared according to general procedure IV (starting from 270 mL (2.81 mmol) of 2-bromopyridine **12$_F$**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 86% (543 mg, 2.42 mmol). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.35 (ddd, *J* 4.9, 1.9 and 0.8 Hz, 1H), 8.13 (d, *J* 7.9 Hz, 1H), 7.58 (ddd, *J* 8.6, 7.2 and 1.9 Hz, 1H), 7.23 – 7.10 (m, 2H), 6.91 (td, *J* 7.4 and 1.0 Hz, 1H), 6.81 (d, *J* 9.1 Hz, 1H), 6.76 (ddd, *J* 7.2, 4.9 and 0.8 Hz, 1H), 3.79 (s, 2H), 1.40 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 155.7, 148.2, 143.8, 140.7, 137.4, 127.5, 122.0, 120.8, 114.6, 113.2, 109.0, 64.3, 39.6, 28.8; IR (ATR) ν_{max} 2959, 1886, 1485, 1437, 1303, 769, 748 cm^{-1}.

***N*-(Pyridin-2-yl)isoindoline** (**7l**). Prepared according to general procedure I (starting from 480 mL (5.6 mmol) of 2-bromopyridine **12$_F$**). Solvent system for flash chromatography: cyclohexane/ethyl acetate: 70/30. Yield: 27% (297 mg, 1.51 mmol). This compound had been previously reported using a related procedure.[39]

***Tert*-Butyl (*S*)-*N*-(pyridin-2-yl)pipecolinate** (**7m**). Prepared according to general procedure II (starting from 440 mL (4.6 mmol) of 2-bromopyridine **12$_{Br}$**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 32% (388 mg, 1.5 mmol). Beige solid; Mp = 58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.14 (ddd, *J* 4.9, 1.9 and 0.7 Hz, 1H), 7.46 (ddd, *J* 8.7, 7.1 and 2.0 Hz, 1H), 6.63 (d, *J* 8.7 Hz, 1H), 6.59 (ddd, *J* 7.1, 4.9 and 0.7 Hz, 1H), 5.19 (dd, *J* 6.0 and 2.2 Hz, 1H), 3.93 – 3.76 (m, 1H), 3.18 (td, *J* 12.3 and 3.5 Hz, 1H), 2.34 – 2.19 (m, 1H), 1.87 – 1.60 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 172.5, 160.2, 147.7, 137.4, 113.2, 107.0, 80.9, 55.6, 42.9, 28.2, 27.6, 25.4, 20.9; IR (ATR) ν_{max} 2940, 1726, 1597, 1482, 1437, 1139, 769 cm^{-1}.

***N*-(Pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane** (**7n**). Prepared according to general procedure I (starting from 1.7 mL (20 mmol) of 2-fluoropyridine **12$_F$**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 40% (1.8 g, 8 mmol). This compound had been previously reported using the same procedure.[25]

***N*-(Pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline** (**7o**). Prepared according to general procedure III (starting from 1.9 mL (20 mmol) of 2-bromopyridine **12$_F$**). Solvent system for flash chromatography: cyclohexane/ethyl acetate: 80/20. Yield: 98% (4.1 g, 19.5 mmol). This compound had been previously reported using a related procedure.[40]

***N*-(Pyridin-2-yl)morpholine** (**7p**). Prepared according to general procedure I (starting from 3.4 mL (40.0 mmol) of 2-fluoropyridine **12$_F$**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 31% (2.1 g, 12.4 mmol). This compound had been previously reported using a related procedure.[41]

***N*-Methyl-*N'*-(pyridin-2-yl)piperazine** (**7q**). Prepared according to general procedure III (starting from 1.9 mL (20.0 mmol) of 2-bromopyridine **12$_F$**). No purification required, used without further purification. Yield: 61% (2.15 g, 12.2 mmol). This compound had been previously reported using a related procedure.[42]

***N*-(Pyridin-2-yl)dibutylamine** (**7r**). Prepared according to general procedure III (starting from 1.9 mL (20.0 mmol) of 2-bromopyridine **12$_F$**). Solvent system for flash chromatography: cyclohexane/ethyl acetate: 90/10. Yield: 17% (728 mg, 3.5 mmol). This compound had been previously reported using a related procedure.[43]

General Procedure V: copper-catalyzed direct α-peroxidation. In a 5 mL round bottom flask, the *N*-(pyridin-2-yl)-amine **7** (0.50 mmol), copper(II) chloride (6.7 mg, 0.10 mmol, 10 mol %) and 1,10-phenanthroline (18.0 mg, 0.20 mmol, 20 mol %) were dissolved in dichloromethane (1 mL). *tert*-Butylhydroperoxide (5.89 M in decane, 430 μL, 2.5 mmol, 5 equiv.) was then added and the resulting blue-green solution was stirred at room temperature overnight. The reaction mixture was then quenched with water (1 mL) and a few drops of a 1:1 mixture of an aqueous solution of ammonia (25%) and a saturated aqueous solution of ammonium chloride were added. The organic layer was separated, and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was finally purified by flash chromatography over silica gel to afford the desired □-peroxidized product **8**.

***N*-(Pyridin-2-yl)-2-(*tert*-butylperoxy)pyrrolidine** (**8a**). Prepared according to general procedure V (starting from 4.1 g (28.9 mmol) of **7a**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 85% (5.8 g, 24.6 mmol). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.18 (dd, *J* 4.8 and 1.0 Hz, 1H), 7.46 (ddd, *J* 8.7, 7.5 and 1.9 Hz, 1H), 6.80 (d, *J* 8.5 Hz, 1H), 6.63 (t, *J* 5.8 Hz, 1H), 5.66 (d, *J* 4.9 Hz, 1H), 3.69 (t, *J* 9.0 Hz, 1H), 3.48 (td, *J* 9.9 and 6.9 Hz, 1H), 2.33 (dd, *J* 12.0 and 6.7 Hz, 1H), 2.27 – 2.03 (m, 1H), 2.03 – 1.78 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 156.8, 147.9, 137.0, 113.5, 108.6, 91.5, 80.1, 47.3, 31.3, 26.8, 22.2; IR (ATR) ν_{max} 2977, 1598, 1478, 1440, 1381, 1197, 995, 772 cm^{-1}; ESIHRMS *m/z* calcd. for $C_{13}H_{21}N_2O_2$ $[M+H]^+$ 237.1598, found 237.1601.

***N*-(Pyridin-2-yl)-2-(*tert*-butylperoxy)azetidine** (**8b**). Prepared according to general procedure V (starting from 67 mg (0.50 mmol) of **7b**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 28% (31 mg, 0.14 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.17 (ddd, *J* 5.0, 1.8 and 0.9 Hz, 1H), 7.45 (ddd, *J* 8.5, 7.2 and 1.9 Hz, 1H), 6.86 (dd, *J* 8.4 and 0.8 Hz, 1H), 6.65 (ddd, *J* 7.1, 5.1 and 0.9 Hz, 1H), 5.56 (dd, *J* 7.1 and 4.7 Hz, 1H), 3.91 (ddd, *J* 8.6, 7.6 and 4.9 Hz, 1H), 3.81 – 3.69 (m, 1H), 2.69 – 2.40 (m, 2H), 1.27 (s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 159.4, 148.1, 137.1, 114.3, 107.8, 94.3, 80.8, 43.6, 26.6, 23.9; IR (ATR) ν_{max} 2977, 1754, 1591, 1478, 1439, 1380, 1156, 775 cm^{-1}.

***N*-(Pyridin-2-yl)-2-(*tert*-butylperoxy)azepane** (**8d**). Prepared according to general procedure V (starting from 1.05 (6.0 mmol) of **7d**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield:

70% (1.1 g, 4.2 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.16 (dd, *J* 4.6 and 1.2 Hz, 1H), 7.42 (ddd, *J* 8.7, 6.9 and 1.8 Hz, 1H), 6.85 (d, *J* 8.7 Hz, 1H), 6.57 (dd, *J* 6.9 and 5.2 Hz, 1H), 5.95 (dd, *J* 9.3 and 6.9 Hz, 1H), 4.03 (d, *J* 14.6 Hz, 1H), 3.45 – 3.21 (m, 1H), 2.37 (quint., *J* 7.2 Hz, 1H), 1.89 – 1.57 (m, 7H), 1.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 158.5, 147.6, 137.0, 112.8, 107.0, 89.0, 80.1, 42.0, 31.9, 30.4, 27.3, 26.6, 23.2; IR (ATR) ν_{max} 2928, 1594, 1486, 1440, 1363, 1190, 941, 771 cm^{-1}.

***N*-(Pyridin-2-yl)-2-(*tert*-butylperoxy)azocane** (**8e**). Prepared according to general procedure V (starting from 86 mg (0.45 mmol) of **7e**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 31% (39 mg, 0.14 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.18 (ddd, *J* 4.9, 2.0 and 0.8 Hz, 1H), 7.43 (ddd, *J* 9.1, 7.1 and 2.0 Hz, 1H), 6.72 (d, *J* 8.7 Hz, 1H), 6.58 (ddd, *J* 7.1, 4.9 and 0.8 Hz, 1H), 6.22 (dd, *J* 10.8 and 4.0 Hz, 1H), 3.78 – 3.43 (m, 2H), 2.13 – 1.83 (m, 2H), 1.72 – 1.37 (m, 8H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 158.3, 147.8, 136.9, 112.8, 107.2, 87.8, 80.0, 27.3, 26.8, 26.7, 26.6, 26.0, 24.9, 24.7; IR (ATR) ν_{max} 2930, 1605, 1518, 1476, 1362, 1289, 1154, 770 cm^{-1}.

***N*-(Pyridin-2-yl)-2-(*tert*-butylperoxy)-5-methylpyrrolidine** (**8f**). Prepared according to general procedure V (starting from 81 mg (0.50 mmol) of **7f**). Two *cis*- and *trans*- diastereoisomers are obtained with a 62/38 ratio as determined by ^{1}H NMR; the stereochemistry of these diastereoisomers has been assigned on the basis of NOE experiments. Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 56% (70.3 mg, 0.28 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.24 –8.13 (m, 1H), 7.53 – 7.37 (m, 1H), 6.90 (d, *J* 8.6 Hz, 0.62H), 6.71 (d, *J* 8.6 Hz, 0.38H), 6.65 (ddd, *J* 7.1, 5.0 and 0.9 Hz, 0.62H), 6.60 (ddd, *J* 7.1, 5.0 and 0.9 Hz, 0.38H), 5.71 (d, *J* 4.7 Hz, 0.38H), 5.51 (d, *J* 4.5 Hz, 0.62H), 4.36 (quint., *J* 6.3 Hz, 0.38H), 4.22 (sex., *J* 6.4 Hz, 0.62H), 2.42 – 2.19 (m, 1H), 2.19 – 1.97 (m, 1H), 1.97-1.73 (m, 1.24H), 1.69 – 1.52 (m, 0.76H), 1.40 (d, *J* 6.0 Hz, 1.86H), 1.27 (s, 5.58H), 1.20 (d, *J* 6.8 Hz, 1.14H) 1.19 (s, 3.42H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 148.0 (minor diastereoisomer), 147.8 (major diastereoisomer), 137.0 (major diastereoisomer), 136.7 (minor diastereoisomer), 113.7 (major diastereoisomer), 113.1 (minor diastereoisomer), 109.5 (minor diastereoisomer), 109.4 (major diastereoisomer), 94.7 (major diastereoisomer), 90.3 (minor diastereoisomer), 80.0 (minor diastereoisomer), 79.9 (major diastereoisomer), 54.3 (major diastereoisomer), 53.5 (minor diastereoisomer), 31.3 (major diastereoisomer), 30.1 (major diastereoisomer), 29.7 (minor diastereoisomer), 29.0 (minor diastereoisomer), 26.9 (major diastereoisomer), 26.8 (minor diastereoisomer), 21.3 (major diastereoisomer), 18.9 (minor diastereoisomer); IR (ATR) ν_{max} 2973, 1595, 1479, 1438, 1373, 1189, 873, 772 cm^{-1}.

(2*R*,5*S*)- and (2*S*,5*S*)- *N*-(Pyridin-2-yl)-2-(*tert*-butylperoxy)-5-(methoxymethyl)pyrrolidine (**8g**). Prepared according to general procedure V (starting from 96 mg (0.50 mmol) of **7g**). Two *trans*- and *cis*- diastereoisomers are obtained with a 65/35 ratio as determined by ^{1}H NMR; the stereochemistry of these diastereoisomers has been assigned on the basis of NOE experiments. Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 46% (64.0 mg, 0.23 mmol). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.21 – 8.12 (m, 1H), 7.50 – 7.36 (m, 1H), 6.90 (d, *J* 8.5 Hz, 0.35H), 6.75 (d, *J* 8.6 Hz, 0.65H), 6.68 – 6.57 (m, 1H), 5.68 (d, *J* 4.6 Hz, 0.65H), 5.57 (dd, *J* 5.5 and 1.4 Hz, 0.35H), 4.47 – 4.33 (m, 1H), 3.95 (dd, *J* 8.7 and 3.9 Hz, 0.35H), 3.66 (dd, *J* 9.1 and 2.9 Hz, 0.65H), 3.38 (s, 1.05H), 3.39 – 3.22 (m, 1.35H), 3.32 (s, 1.95H), 2.31 – 1.92 (m, 3.65H), 1.24 (s, 3.15H), 1.16 (s, 5.85H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 157.0, 155.8 (major diastereoisomer), 147.9 (major diastereoisomer), 147.8 (minor diastereoisomer), 137.1 (minor diastereoisomer), 136.7 (major diastereoisomer), 114.0 (minor diastereoisomer), 113.5 (major diastereoisomer), 109.6 (major diastereoisomer), 109.0 (minor diastereoisomer), 94.2 (minor diastereoisomer), 90.5 (major diastereoisomer), 79.9 (minor diastereoisomer), 79.9 (major diastereoisomer), 75.4 (minor diastereoisomer), 72.2 (major diastereoisomer), 59.2 (minor diastereoisomer), 59.2 (major diastereoisomer), 57.4, 29.8 (minor diastereoisomer), 29.5 (major diastereoisomer), 27.4 (minor diastereoisomer), 26.8 (minor diastereoisomer), 26.7 (major diastereoisomer), 25.8 (major diastereoisomer).

(2*R*,5*S*)- and (2*S*,5*S*)- *N*-(Pyridin-2-yl)-2-(*tert*-butyldimethylsilyloxymethyl)-5-(*tert*-butylperoxy)pyrrolidine (**8h**). Prepared according to general procedure V (starting from 115 mg (0.39 mmol) of **7h**). Two *trans*- and *cis*-diastereoisomers are obtained with a 53/47 ratio as determined by ^{1}H NMR; the stereochemistry of these diastereoisomers has been assigned on the basis of NOE experiments. Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 71% (70.3 mg, 0.28 mmol). Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 8.19 – 8.13 (m, 1H), 7.48 – 7.40 (m, 1H), 6.89 (d, *J* 8.5 Hz, 0.47H), 6.75 (d, *J* 8.6 Hz, 0.53H), 6.64 (dd, *J* 7.1 and 5.0 Hz, 0.47H), 6.60 (dd, *J* 7.1 and 5.1 Hz, 0.53H), 5.66 (d, *J* 4.8 Hz, 0.53H), 5.57 (d, *J* 5.6 Hz, 0.47H), 4.36 – 4.26 (m, 1H), 4.16 (dd, *J* 9.5 and 4.0 Hz, 0.47H), 3.83 (dd, *J* 9.9 and 2.7 Hz, 0.53H), 3.68 (dd, *J* 9.9 and 6.4 Hz, 0.53H), 3.51 (t, *J* 9.0 Hz, 0.47H), 2.31 – 1.87 (m, 4H), 1.25 (s, 4.23H), 1.17 (s, 4.77H), 0.90 (s, 4.23H), 0.85 (s, 4.77H), 0.07 – -0.09 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 157.2 and 156.0 (diastereoisomers), 147.81 and 147.78 (diastereoisomers), 137.0 and 136.7 (diastereoisomers), 114.0 and 113.3 (diastereoisomers), 109.5 and 109.0 (diastereoisomers), 94.4 and 90.9 (diastereoisomers), 79.9, 65.4 and 62.7 (diastereoisomers), 59.6 and 59.5 (diastereoisomers), 32.1 and 29.8 (diastereoisomers), 29.7, 29.7 and 29.5 (diastereoisomers), 26.9, 26.8 and 26.8 (diastereoisomers), 26.1 and 26.1 (diastereoisomers), 25.7, 22.8 and 18.5 (diastereoisomers), 18.4 and 14.3 (diastereoisomers), -5.0 and -5.1 (diastereoisomers), -5.3; IR (ATR) ν_{max} 2928, 1595, 1479, 1439, 1363, 1253, 1093, 836, 773 cm^{-1}.

***Tert*-Butyl (2*S*,5*R*)-*N*-(pyridin-2-yl)-5-(*tert*-butylperoxy)prolinate** (**8i**). Prepared according to general procedure V (starting from 1.0 g (4.0 mmol) of **7i**). Obtained as a single *trans*- diastereoisomer as determined by ^{1}H NMR; the stereochemistry of this diastereoisomer has been assigned on the basis of NOE experiments. Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 75% (1.0 g, 3.0 mmol). Pale yellow solid; Mp = 43 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10 (dd, *J* 5.0 and 0.9 Hz, 1H), 7.46 (ddd, *J* 8.7, 7.3 and 1.9 Hz, 1H), 6.87 (d, *J* 8.5 Hz, 1H), 6.64 (dd, *J* 7.1 and 5.1 Hz, 1H), 5.68 (d, *J* 5.2 Hz, 1H), 4.53 (d, *J* 8.9 Hz, 1H), 2.55 – 2.39 (m, 1H), 2.33 – 2.14 (m, 2H), 1.94 (dd, *J* 12.5 and 7.2 Hz, 1H), 1.39 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 173.2, 155.8, 147.5, 136.9, 114.1, 108.4, 91.9, 80.6, 80.0, 61.3, 29.9, 28.0, 27.2, 26.7; IR (ATR) ν_{max} 2979, 1732, 1595, 1480, 1442, 1365, 1154, 771 cm^{-1}; ESIHRMS *m/z* calcd. For $C_{18}H_{29}N_2O_4$ $[M+H]^+$ 337.4395, found 337.4397.

***N*-(Pyridin-2-yl)indole** (**8j'**). Prepared according to general procedure V (starting from 98 mg (0.50 mmol) of **7j**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 95/5. Yield: 76% (74 mg, 0.38 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.59 (ddd, *J* 4.9, 1.9 and 0.8 Hz, 1H), 8.26 (dq, *J* 8.3 and 0.9 Hz, 1H), 7.80 (ddd, *J* 8.3, 7.4 and 2.0 Hz, 1H), 7.75 (d, *J* 3.5 Hz, 1H), 7.71 (ddd, *J* 7.7, 1.3 and 0.8 Hz, 1H), 7.49 (dt, *J* 8.3 and 0.9 Hz, 1H), 7.35 (ddd, *J* 8.4, 7.2 and 1.3 Hz, 1H), 7.26 (ddd, *J* 8.2, 7.2 and 1.1 Hz, 1H), 7.16 (ddd, *J* 7.4, 4.9 and 0.9 Hz, 1H), 6.76 (dd, *J* 3.5 and 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 152.6, 149.0, 138.5, 135.2, 130.5, 126.1, 123.2, 121.4, 121.2, 120.1, 114.6, 113.1, 105.6. This compound had previously been reported.[44]

***N*-(Pyridin-2-yl)-2-(*tert*-butylperoxy)-3,3-dimethyl-indoline** (**8k**). Prepared according to general procedure V in 1,2-dichloroethane at 60 °C (starting from 112 mg (0.50 mmol) of **7k**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 66% (103.7 mg, 0.33 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.31 (ddd, *J* 4.9, 1.9 and 0.7 Hz, 1H), 8.07 (d, *J* 8.0 Hz, 1H), 7.59 (ddd, *J* 9.1, 7.2 and 2.0 Hz, 1H), 7.27 (d, *J* 8.6 Hz, 1H), 7.21 (td, *J* 7.8 and 1.4 Hz, 1H), 7.11 (dd, *J* 7.3 and 1.1 Hz, 1H), 6.95 (td, *J* 7.4 and 1.0 Hz, 1H), 6.83 (ddd, *J* 7.2, 4.9 and 0.8 Hz, 1H), 5.49 (s, 1H), 1.51 (s, 3H), 1.22 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 156.0, 147.6, 142.7, 139.7, 137.2, 127.3, 121.6, 121.3, 115.8, 115.7, 111.0, 101.3, 80.9, 45.1, 29.9, 26.6, 19.7; IR (ATR) ν_{max} 2929, 1588, 1485, 1437, 1364, 1194, 1023, 770, 748 cm^{-1}.

***N*-(Pyridin-2-yl)-1-(*tert*-butylperoxy)-1,2,3,4-tetrahydroisoquinoline** (**8o**). Prepared according to general procedure V (starting from 1.0 g (4.6 mmol) of **7o**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 95% (1.3 g, 4.4 mmol). Pale orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.23 (dd, *J* 5.0 and 1.1 Hz, 2H), 7.51 (ddd, *J* 8.8, 7.1 and 2.0 Hz, 1H), 7.46 (dd, *J* 7.1 and 1.4 Hz, 1H), 7.31 – 7.17 (m, 2H),

7.20 (d, *J* 7.3 Hz, 1H), 7.06 (d, *J* 8.7 Hz, 1H), 6.68 (s, 1H), 6.66 (ddd, *J* 7.0, 5.1 and 0.5 Hz, 1H), 4.27 (dt, *J* 11.8 and 5.6 Hz, 1H), 3.76 (dt, *J* 12.7 and 6.7 Hz, 1H), 3.00 (t, *J* 6.1 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 157.5, 146.5, 136.2, 131.1, 128.4, 127.8, 127.3, 125.1, 112.8, 107.4, 86.3, 79.4, 38.3, 27.2, 25.6; IR (ATR) ν_{max} 2973, 1709, 1666, 1601, 1468, 1435, 1299, 1083, 742 cm^{-1}.

***N*-(Pyridin-2-yl)-3-(*tert*-butylperoxy)-morpholine** (**8p**). Prepared according to general procedure V (starting from 80 mg (0.48 mmol) of **7p**). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 35% (44 mg, 0.17 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.20 (dd, *J* 4.8 and 1.7 Hz, 1H), 7.50 (ddd, *J* 8.7, 7.3 and 1.9 Hz, 1H), 6.78 (d, *J* 8.5 Hz, 1H), 6.70 (dd, *J* 7.1 and 5.0 Hz, 1H), 5.80 (s, 1H), 4.32 (d, *J* 12.2 Hz, 1H), 4.04 (dd, *J* 11.1 and 3.4 Hz, 1H), 3.82 (d, *J* 12.3 Hz, 1H), 3.75 – 3.57 (m, 2H), 3.47 (td, *J* 12.0 and 3.6 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 158.9, 147.6, 137.4, 114.9, 108.1, 83.6, 80.6, 66.9, 66.6, 40.5, 26.5; IR (ATR) ν_{max} 2972, 1649, 1593, 1478, 1439, 1194, 1076, 771 cm^{-1}.

General Procedure VI: post-functionalization of hemiaminals (**8**)**.** In a 15 mL pressure tube, hemiaminal **8** (0.5 mmol) was dissolved in ethanol (2 mL) before adding the nucleophile (1.1 equiv. or 3.0 equiv.) and citric acid monohydrate (105 mg, 0.5 mmol, 1.0 equiv.). The pressure tube was closed with a Teflon stopper and the reaction mixture was then heated at 80 °C for 2 hours, and then cooled to room temperature. The reaction mixture was diluted with dichloromethane and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude residue was finally purified by flash chromatography over silica gel to afford the desired functionalized product **9**.

***N*-(Pyridin-2-yl)-2-(*N*-methyl-indol-3-yl)pyrrolidine** (**9a**). Prepared according to general procedure VI (starting from 1.2 g (5.2 mmol) of **8a** and 750 mg of *N*-methyl-indole (5.7 mmol, 1.1 equiv.)). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 77% (1.1 g, 4.0 mmol). Beige solid; Mp = 146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.18 (ddd, *J* 5.0, 1.8 and 0.6 Hz, 1H), 7.65 (d, *J* 7.9 Hz, 1H), 7.35 – 7.19 (m, 3H), 7.14 (ddd, *J* 8.0, 6.7 and 1.4 Hz, 1H), 6.74 (d, *J* 0.5 Hz, 1H), 6.49 (ddd, *J* 7.0, 5.1 and 0.7 Hz, 1H), 6.30 (d, *J* 8.6 Hz, 1H), 5.18 (d, *J* 7.4 Hz, 1H), 3.91 (tt, *J* 7.2 and 2.6 Hz, 1H), 3.69 (s, 3H), 3.74 – 3.57 (m, 1H), 2.36 (tt, *J* 10.7 and 7.7 Hz, 1H), 2.24 – 1.92 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 157.4, 148.1, 137.7, 136.6, 126.5, 126.0, 121.7, 119.1, 119.0, 116.6, 111.4, 109.5, 107.9, 55.4, 47.5, 34.2, 32.7, 23.3; IR (ATR) ν_{max} 2928, 1601, 1493, 1443, 1387, 1298, 988, 735 cm^{-1}; ESIHRMS *m/z* calcd. for $C_{18}H_{20}N_3$ $[M+H]^+$ 278.1652, found 278.1655.

***N*-(Pyridin-2-yl)-2-(2,4,6-trimethoxyphenyl)pyrrolidine** (**9b**). Prepared according to general procedure VI (starting from 123 mg (0.49 mmol) of **8a** and 247 mg of 1,3,5-trimethoxybenzene (1.47 mmol, 3.0 equiv.)). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 70/30. Yield: 55% (86 mg, 0.27 mmol). Yellow solid; Mp = 114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.07 (ddd, *J* 5.0, 1.2 and 0.7 Hz, 1H), 7.16 (ddd, *J* 8.8, 7.0 and 2.0 Hz, 1H), 6.33 (ddd, *J* 6.8, 5.3 and 0.6 Hz, 1H), 6.12 (d, *J* 8.7 Hz, 1H), 6.09 (s, 2H), 5.27 (dd, *J* 7.9 and 6.5 Hz, 1H), 3.92 (ddd, *J* 9.7, 8.0 and 3.0 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 6H), 3.70 – 3.59 (m, 1H), 2.45 – 2.21 (m, 1H), 2.21 – 1.98 (m, 2H), 1.98 – 1.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 160.1, 159.0, 156.7, 147.9, 136.2, 111.5, 110.1, 106.6, 91.3, 56.1, 55.3, 52.5, 47.8, 33.5, 25.2; IR (ATR) ν_{max} 2969, 1359, 1598, 1498, 1442, 1207, 1123, 767 cm^{-1}.

(2*S*,5*R*)-*N*-(Pyridin-2-yl)-2-(hydroxymethyl)-5-(*N*-methyl-indol-3-yl)pyrrolidine (**9c**). Prepared according to general procedure VI (starting from 194 mg (0.51 mmol) of **8h** and 73 mg of *N*-methyl-indole (0.56 mmol, 1.1 equiv.)). Two *cis*- and *trans*- diastereoisomers are obtained with a 68/32 ratio, as determined by ^{1}H NMR and the major *cis*- diastereoisomer could be separated by flash column chromatography and fully characterized; the stereochemistry of this major diastereoisomer has been assigned on the basis of NOE experiments. Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield for the mixture of

diastereoisomers: 67% (104 mg, 0.34 mmol); Yield of isolated *cis*-diastereoisomer: 49% (76 mg, 0.25 mmol). Beige solid; Mp = 198 °C. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 8.09 (dd, *J* 5.1 and 1.1 Hz, 1H), 7.68 (d, *J* 7.9 Hz, 1H), 7.33 (d, *J* 8.2 Hz, 1H), 7.29 (ddd, *J* 8.6, 7.3 and 1.9 Hz, 2H), 7.18 (ddd, *J* 7.9, 7.0 and 0.9 Hz, 1H), 6.91 (s, 1H), 6.58 (ddd, *J* 6.9, 5.4 and 0.5 Hz, 1H), 6.36 (d, *J* 8.7 Hz, 1H), 5.14 (dd, *J* 7.8 and 3.2 Hz, 1H), 4.41 (qd, *J* 6.9 and 1.4 Hz, 1H), 3.95 (dd, *J* 11.0 and 1.6 Hz, 1H), 3.85 (dd, *J* 11.0 and 8.8 Hz, 1H), 3.71 (s, 3H), 2.47 – 2.35 (m, 1H), 2.19 – 2.07 (m, 2H), 1.81 – 1.70 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 157.9, 146.3, 137.8, 126.4, 125.9, 121.9, 119.1, 118.8, 116.4, 112.7, 109.6, 109.0, 69.1, 63.6, 58.4, 33.0, 32.8, 28.0; IR (ATR) ν_{max} 2966, 1603, 1489, 1443, 1096, 1062, 769, 750, 728 cm^{-1}; ESIHRMS *m/z* calcd. for $C_{19}H_{22}N_3O$ $[M+H]^+$ 308.4045, found 308.4041.

(2*S*,5*R*)- and (2*S*,5*S*)- *tert*-Butyl *N*-(pyridin-2-yl)-5-(*N*-methyl-indol-3-yl)prolinate (**9d**). Prepared according to general procedure VI (starting from 83 mg (0.25 mmol) of **8i** and 36 mg of *N*-methyl-indole (0.27 mmol, 1.1 equiv.)). Two *cis*- and *trans*- diastereoisomers are obtained with a 50/50 ratio, as determined by ^{1}H NMR and the two diastereoisomers could be separated by flash column chromatography and fully characterized; the stereochemistry of these diastereoisomers has been assigned on the basis of NOE experiments. Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 97% (82 mg, 0.24 mmol).

(2*S*,5*R*)-*tert*-Butyl *N*-(pyridin-2-yl)-5-(*N*-methyl-indol-3-yl)prolinate (**9d**). Pale yellow solid; Mp = 114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.12 (ddd, *J* 5.0, 1.7 and 0.7 Hz, 1H), 7.65 (d, *J* 7.8 Hz, 1H), 7.50 (s, 1H), 7.36 – 7.11 (m, 4H), 6.51 (ddd, *J* 7.0, 5.1 and 0.6 Hz, 1H), 6.27 (d, *J* 8.5 Hz, 1H), 5.19 (d, *J* 7.7 Hz, 1H), 4.44 (dd, *J* 9.5 and 6.5 Hz, 1H), 3.71 (s, 3H), 2.50 – 2.23 (m, 2H), 2.23 – 2.00 (m, 2H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 173.8, 156.4, 147.8, 137.7, 136.7, 128.5, 126.1, 121.5, 118.9, 118.6, 116.0, 112.4, 109.6, 107.7, 80.6, 62.1, 56.6, 33.6, 32.9, 28.5, 28.3; IR (ATR) ν_{max} 2940, 1746, 1596, 1484, 1443, 1144, 775, 742, 733 cm^{-1}.

(2*S*,5*S*)-*tert*-Butyl *N*-(pyridin-2-yl)-5-(*N*-methyl-indol-3-yl)prolinate (**9d**). Pale yellow solid; Mp = 137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.13 (ddd, *J* 5.0, 1.9 and 0.6 Hz, 1H), 7.66 (d, *J* 7.9 Hz, 1H), 7.35 – 7.21 (m, 3H), 7.17 (ddd, *J* 8.0, 6.6 and 1.5 Hz, 1H), 6.75 (s, 1H), 6.52 (ddd, *J* 7.1, 5.0 and 0.7 Hz, 1H), 6.34 (d, *J* 8.5 Hz, 1H), 5.34 (d, *J* 8.2 Hz, 1H), 4.81 (d, *J* 8.4 Hz, 1H), 3.69 (s, 3H), 2.75 – 2.57 (m, 1H), 2.47 – 2.32 (m, 1H), 2.13 – 2.03 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 173.7, 156.6, 147.6, 137.7, 136.7, 126.4, 126.0, 121.8, 119.1, 119.0, 116.6, 112.3, 109.5, 108.1, 80.5, 61.4, 55.8, 32.8, 32.4, 28.1, 27.8; IR (ATR) ν_{max} 2942, 1733, 1599, 1481, 1443, 1155, 774, 746 cm^{-1}.

***N*-(Pyridin-2-yl)-2-(*N*-methyl-indol-3-yl)-3,3-dimethyl-indoline** (**9e**). Prepared according to general procedure VI (starting from 78 mg (0.25 mmol) of **8k** and 36 mg of *N*-methyl-indole (0.27 mmol, 1.1 equiv.)). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 80% (71 mg, 0.20 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.47 (d, *J* 8.0 Hz, 1H), 8.36 (ddd, *J* 4.9, 1.9 and 0.7 Hz, 1H), 7.60 (d, *J* 7.6 Hz, 1H), 7.39 – 7.21 (m, 4H), 7.20 – 7.11 (m, 2H), 7.01 (td, *J* 7.4 and 1.0 Hz, 1H), 6.75 (s, 1H), 6.71 (ddd, *J* 7.2, 4.9 and 0.7 Hz, 1H), 6.59 (d, *J* 8.5 Hz, 1H), 5.31 (s, 1H), 3.65 (s, 3H), 1.55 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 155.7, 147.7, 144.2, 139.7, 137.2, 137.1, 127.6, 127.6, 127.0, 122.3, 121.7, 121.1, 119.5, 119.3, 114.6, 114.1, 112.7, 110.2, 109.5, 70.0, 45.4, 32.9, 31.5, 23.4; IR (ATR) ν_{max} 2959, 1586, 1485, 1454, 1437, 1379, 1303, 769, 748 cm^{-1}.

***N*-(Pyridin-2-yl)-1-(*N*-methyl-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline** (**9f**). Prepared according to general procedure VI (starting from 77 mg (0.26 mmol) of **8o** and 38 mg of *N*-methyl-indole (0.29 mmol, 1.1 equiv.) at room temperature). Solvent system for flash chromatography: petroleum ether/ethyl acetate: 90/10. Yield: 85% (73 mg, 0.22 mmol). Pale yellow solid; Mp = 72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.28 (ddd, *J* 4.9, 1.9 and 0.7 Hz, 1H), 7.67 (d, *J* 8.0 Hz, 1H), 7.46 (ddd, *J* 8.8, 7.1 and 2.0 Hz, 1H), 7.36 – 7.10 (m, 7H), 7.04 (ddd, *J* 8.0, 6.9 and 1.2 Hz, 1H), 6.76 (d, *J* 8.7 Hz, 1H), 6.57 (ddd, *J* 7.0, 5.0 and 0.4 Hz, 1H), 6.56 (s, 1H), 4.07 – 3.93 (m, 1H), 3.67 (s, 3H), 3.74 – 3.57 (m, 1H), 3.13 (ddd, *J* 16.4, 10.9 and 5.7 Hz, 1H), 2.82 (dt, *J* 16.2 and 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 158.1, 148.3, 137.8, 137.6, 137.4, 135.7, 129.1, 129.0, 128.5, 127.3, 126.7, 125.8, 121.8, 120.5, 119.3,

118.0, 112.1, 109.2, 106.5, 52.3, 39.0, 32.8, 27.2; IR (ATR) ν_{max} 2940, 1593, 1474, 1437, 1223, 938, 771, 740, 651 cm^{-1}; ESIHRMS *m/z* calcd. for $C_{23}H_{22}N_3$ $[M+H]^+$ 340.4495, found 340.4493.

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Supplementary Material

Copies of ^1H and ^{13}C NMR spectra are presented in the Supplementary Material file associated with this manuscript.

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